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AMYOTROPHIC LATERAL SCLEROSIS – MOTOR NEURON DISEASE

R. H. Brown, Charlestown, MA, USA

MITOCHONDRIAL RESPIRATORY CHAIN AND NEURODEGENERATION

Stefano Di Donato, MD, I

Oxidative Phosphorylation

Most human cells contain hundreds of mitochondria, the cytoplasmic double-membrane organelles that are essentially devoted to generate cellular energy in the form of ATP by the process of oxidative phosphorylation (OXPHOS)[1]. OXPHOS is carried out and brought to completion at the level of the respiratory chain (RC), a supramolecular structure embedded in the inner mitochondrial membrane. From a genetic standpoint, the RC is unique as it is formed by means of the complementation of two separate genetic systems: the nuclear genome and the mitochondrial genome (mtDNA). The nuclear genome encodes most of the protein subunits of the respiratory complexes and most of the mtDNA replication and expression systems, whereas the tiny mitochondrial genome only encodes 13 OXPHOS polypeptides, 22 tRNAs, and 2 RNA components of the mitochondrial translational apparatus. Accordingly, mitochondrial disorders due to defects in OXPHOS include both mendelian-inherited and cytoplasmic-inherited diseases.

In terms of function, the RC carries out two main reactions, which operate in an integrated fashion: the exoergonic transfer of electron equivalents from the reduced electron carriers NADH and FADH2 to molecular oxygen, a process coupled to proton translocation across the inner membrane, and the endoergonic ATP synthesis, driven by the energy primarily stored as an electrochemical proton gradient. In addition, the RC contains two highly hydrophobic, mobile, small electron carriers, coenzyme Q 10 and cytochrome c, both encoded by nuclear DNA[2].

OXPHOS and Neurodegeneration

Because OXPHOS is the essential reaction of life and mitochondria are ubiquitous, mitochondrial pathology is generally multisystemic, though it involves most frequently and more heavily the organs with the highest aerobic demand, such as brain, skeletal muscle, and heart. In addition, since these organs are composed of highly-specialized, post-mitotic cells, negative selection against cells containing faulty mitochondria is impossible, making these organs particularly sensitive to OXPHOS mutations. Each among these tissues can be affected alone ("pure" mitochondrial myopathies, encephalopathies or cardiomyopathies), or more often in combination with each other (mitochondrial encephalo-myopathies and encephalo-cardio-myopathies).

A number of OXPHOS diseases due to mtDNA deletions and duplications, or mutations in mitochondrial tRNA genes have been reported since 1988, when the first two human diseases due to mtDNA mutations were described[3–5]. By contrast, mutations in nuclear-encoded components of the RC have only recently come to age, and include both mutations in genes encoding structural subunits of RC subcomplexes, and mutations in genes with general regulatory properties affecting the efficiency, homeostasis, and assembly of the RC[6–8]. Simple and unique phenotypes are rarely associated with OXPHOS deficiency: *CNS symptomatology* includes stroke-like episodes, generalized seizures, myoclonus, ataxia, extrapyramidal signs, optic atrophy, central weakness and mental deterioration; whereas *Neuromuscular symptomatology* includes CPEO, proximal myopathy, hypotonia, muscle fatigue, peripheral neuropathy, and sensorineural deafness. Some complex phenotypes are, however, relatively common: among Mendelian diseases, Leigh's subacute necrotizing encephalomyelitis is considered a prototypic form of mitochondrial neurodegeneration characterized by extensive periventricular and periependimal neuronal loss, and multiple symmetric foci of spongy degeneration and microscopic vascular proliferation in the basal ganglia, thalamus, cerebellum, brain stem tegmentum, and the spinal cord. These lesions can be evidenced in vivo by imaging techniques such as MRI, whereas MRI spectroscopy shows an increase in brain lactate in the very same areas. Core symptoms of LS include hypotonia and developmental arrest in infancy, oculomotor palsy and optic atrophy, weakness, dystonia and incoordination, peripheral neuropathy, seizures, intellectual and psychomotor decline, respiratory abnormalities with irregular breathing and apnea[9].

I will review some recent concepts about human diseases due to mutations of the structural components of the RC, focusing particularly on the disorders caused by mutations in nuclear genes affecting the functional efficiency, homeostasis, and assembly of RC subcomplexes[10].

Mutations in structural genes of RC Complexes I-V

Most of the mutations in complex I structural genes have been reported in ND1-ND4 mtDNA genes and are associated with one disease, Leber's hereditary optic neuropathy, LHON, a maternally-inherited disorder characterized by optic atrophy, retinal microangiopathy, and cardiac conduction defects. More recently, *bona fide* mutations in nuclear-encoded structural genes for complex I have been described in patients with clinical phenotypes of Leigh's syndrome (LS) or Leigh's-like syndromes (LL)[7].

Likewise, two siblings with marked deficiency of RC complex II, or succinate dehydrogenase, had a clinical phenotype characterized by leukodystrophy and Leigh's-like syndrome[11]. A few mutations in the cytochome *b* component of complex III (the only structural subunit encoded by mtDNA) have been found in patients with neurodegenerative syndromes including LHON[5, 12]. More recently, mutations in cytochrome *b* have been described in patients with exercise intolerance, muscle fatigue, and myoglobinuria: the mutation could be detected only in patients' skeletal muscle. Also, family studies failed to evidence maternal transmission. Accordingly, muscle-specific pathology is thought to be due to somatic mutations ensuing during embryogenesis[13].

Complex IV, or cytochrome *c* oxidase (COX), deficiency is one of the most common biochemical defects associated with LS; however, in LS patients no pathological mutations in structural COX subunits have been identified to date[14–15]. By contrast, a few mutations in mtDNA-encoded complex IV subunits have been reported in patients with variable phenotypes characterized by neurodegeneration but without features of LS[16]. As far as Complex V, or ATPase, no mutations of the nuclear-encoded structural genes are known to date, but mutations in the ATPase 6 mitochondrial subunit have been reported in maternally-inherited LS and NARP, an allelic maternally-inherited disorder characterized by neurogenic weakness, ataxia, and retinitis pigmentosa[17–18].

Mutations in RC genes involved in complex assembly and OXPHOS homeostasis

As previously mentioned, the nucleus provides genetic information not only for the 70 or so essential proteins that make up, together with the 13 proteins encoded by the mitochondrial genome, the five respiratory chain subcomplexes, but also codes for a still undefined number of regulatory polypeptides essential for RC assembly, homeostasis and function[19–20]. A few of these genes have been recently identified and found to carry mutations that cause common neurodegenerative disorders, including LS with COX deficiency, Friedreich's ataxia, and Hereditary Spastic Paraplegia.

Notably, after the nuclear origin of LS with COX deficiency was proven, it became clear that most patients with this disease appeared to pertain to a single complementation group[21]. This evidence prompted cellular and genetic strategies that allowed the identification of a new gene, dubbed SURF–1, which was mutated in patients with the disease[22–23]. SURF–1 encodes a mitochondrial protein involved in COX assembly[19–22]. Interestingly, another human gene involved in COX assembly, dubbed SCO2 for "synthesis cytochrome c oxidase", has been recently identified[24]. This gene, together with the homologous gene SCO1, is involved in assembling Cox I and Cox II mitochondrial subunits into the COX holoenzyme[25]. SCO2 pathogenic mutations were demonstrated in three independent patients with a phenotype of progressive cardioencephalomyopathy[24].

Friedreich's ataxia (FA) is an autosomal recessive neurodegenerative disorder characterized by onset before age 25, progressive gait and limb ataxia, dysarthria, absent deep tendon reflexes, sensory loss and pyramidal weakness. Cardiomyopathy is present in the majority of patients and its severity marks prognosis[25]. The disease has been associated with a GAA trinucleotide repeat expansion in the first intron of the *X25* gene on chromosome locus 9q13–21.1 The cloned *X25* gene encodes a 210 aminoacid protein of unknown function, dubbed *frataxin*[26]. Further studies suggested that frataxin is a mitochondrial protein which putatively regulates iron content in mitochondria[27]. Accordingly, low levels of functional frataxin could lead to an increase of intramitochondrial iron, causing damage to iron-sulphur clusters-contain-

ing enzymes, OXPHOS deficiency, excessive ROS generation, and cell death[28-29].

Hereditary spastic paraplegia (HSP) is genetically heterogeneous[30]. An autosomal recessive form of HSP mapping to chromosome 16 is due to mutations in a gene encoding a large protein of 795 amino acids, dubbed *paraplegin*[31]. Immunofluorescence localization and protein import experiments demonstrated that human paraplegin had a cleavable leader peptide, and localized to mitochondria. Moreover, muscle biopsy from patients carrying paraplegin mutations demonstrated typical signs of OXPHOS defects, such as ragged-red fibres, COX-negative fibres, and SDH-positive hyperintense fibres, suggesting that autosomal recessive HSP is a mitochondrial disease due to impaired cellular respiration[31].

I conclude that defective mitochondrial respiration is a common cause of neurodegeneration, and protocols aimed at the study of OXPHOS physiopathology are needed tool to investigate and to diagnose genetic-degenerative disorders of the brain, nerve, and skeletal muscle.

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Anita Harding lecture: POLYGLUTAMINE EXPANSION NEURODEGENERATIVE DISEASES

K. H. Fischbeck, Bethesda, USA

Symposium 1: TRANSLATIONAL NEUROSCIENCE: FROM LABORATORY TO CLINIC AND BACK. Chairpersons: J. van Gijn, Utrecht; DAS Compston, Cambridge, UK

NEUROPROTECTION FOR STROKE: INSIGHTS FROM NEUROIMAGING

Jean-Claude Baron. INSERM U320, University of Caen, France

According to the experimental literature, four main mechanisms are thought to underlie the deterioration of the ischaemic penumbra and its subsequent infarction: glutamate excitotoxicity, peri-infarct depolarisations, inflammation, and programmed cell death (apoptosis). However, the relationships among these mechanisms remain unclear, each seemingly operating through a distinct cascade of deleterious biochemical events. Although blocking each of these cascades separately with specific pharmacological agents consistently reduces infarct size after focal cerebral ischaemia in the laboratory animal, so far this has not translated into significant beneficial effects in clinical trials. This worrying state of affairs may stem from two (possibly additive) reasons, *firstly* that the animal models of neuroprotective agents may not be predictive of the human situation; and *secondly* that the clinical trials do not reproduce well enough the experimental conditions of the animal studies. Regarding the former, several potential problems have been identified in the laboratory work based on which clinical trials are launched, such as *i)* publication bias in favour of positive studies, *ii)* lack of duplication of positive effects, *iii)* lack of randomised, intention-to-treat and blinded experimental design, *iv)* variability in the effects of the agent on infarct volume from strain to strain, *v)* administration of the agent before or minutes only after the arterial occlusion, *vi)* determination of 'infarct volume' based on early instead of chronic stage histology, *vii)* termination of the experiment while the animal is still being treated, such that the deleterious cascade may have resumed had the animal been allowed to survive, and *viii)* inappropriate stroke model (*e.g.*, global ischemia, stroke complicated by seizures). A different issue relates to the targeting of a mechanism not documented in man, which may be an epiphenomenon, or which may set in too late when necrosis is established. For instance, reperfusion injury has not been documented in man so far, and physiologic imaging has indicated that post-ischemic hyperperfusion is not deleterious. Regarding the latter reason, it has been argued that the stroke population of most clinical trials is pathophysiologically heterogeneous, with only a fraction of the enrolled patients matching the targeted mechanism of the agent being tested (*e.g.*, agents directed at reperfusion injury given to patients with persistent occlusion). Physiologic imaging with PET, confirmed recently with diffusion- and perfusion-weighted MRI, indeed documents that even within the range of neurological deficit typical of most trials, there is a marked pathophysiological heterogeneity among the patients. Other problems may relate to the treatment being given too late, typically later than 3 hours after clinical onset, whereas both the animal literature and the rt-PA trials tend to suggest that little salvageable tissue would still be present at this stage. However, both PET and MR-based physiologic imaging suggest that salvageable tissue may still be present as late as 16 hrs after stroke onset at least in a fraction of the patients. Thus, neuroprotective agents should ideally be given only to that subgroup of cases in whom the targeted tissue is identified by neuroimaging. Additional potential problems in clinical trials include *i)* too short a duration of treatment, *ii)* intolerable side effects, *iii)* deleterious interaction between the mechanisms, such that acting on one cascade negatively influences another, *iv)* untoward reductions in systemic blood pressure, and *v)* inadequate doses. In addition to incorporating physiologic imaging in order to select the most appropriate patients, future trials of neuroprotection should consider the fundamental mechanism which sets off all of the secondary mechanisms, namely the inadequacy of the oxygen supply-to-demand ratio clearly demonstrated by PET in acute stroke. Improving the oxygen supply would clearly afford the most straightforward neuroprotection, and this can be achieved either by restoration of the perfusion (*via* thrombolysis or pharmacologically-controlled arterial hypertension) or by increasing the arterial oxygen content *via e.g.* hyperbaric oxygen. An alternative approach would be to reduce the oxygen needs of the brain cells, *via* hypothermia or CNS depressants such as GABA agonists. Finally, preventing secondary neuronal damage due to complications such as vasogenic edema and systemic hypoxia should also be considered as potentially effective neuroprotection. Though most of these approaches have been tested in the past with equivocal results, they now deserve to be tested again with present-day state-of-the-art therapeutic trial methodology, including neuroimaging-based pathophysiological diagnosis.

HETEROGENEITY IN COMPLEX GENETIC TRAITS.

DAS Compston, Cambridge, UK

RESTORING STRUCTURE AND FUNCTION OF THE NIGROSTRIATAL SYSTEM IN PARKINSON'S DISEASE

Olle Lindvall, Lund, Sweden

Nigral dopamine (DA) neurons are important regulators of cortico-striatal neurotransmission. Impairment of striatal DA function, which is the principal deficit underlying the hypokinetic symptoms in PD, leads to increased threshold for activation of the striato-pallido-thalamic output pathway and impaired movement-related activation of frontal motor cortical areas. Intrastriatal dopaminergic grafts may improve striatal function by at least three different mechanisms: non-regulated DA release, synaptic DA release, and regulated DA neuron function. In patients with advanced PD, human embryonic nigral DA neurons implanted ectopically in the striatum can give long-lasting and therapeutically valuable symptomatic relief. Survival of the grafted DA neurons, reinnervation of the striatum, and formation of synaptic connections have been shown in two autopsy cases. A recent study demonstrated, using positron emission tomography (PET), that in the best cases, intrastriatal transplants of nigral DA neurons had normalized both DA synthesis and storage (as assessed by striatal 18F-dopa uptake) as well as spontaneous and drug-induced DA release (measured as DA D2 receptor occupancy in the grafted putamen). Interestingly, the gradual onset of substantial clinical improvement seen in grafted PD patients correlates with the recovery of movement-related cortical activation. This suggests that integration into the host cortico-striatal circuitry may be necessary for the full expression of the functional capacity of the grafted DA neurons.

AUTOIMMUNE T-CELLS AND ACTIVATED MACROPHAGES ARE NEEDED FOR CNS POST AXOTOMY MAINTENANCE AND REGENERATION

M. Schwartz, Rehovot, Israël

Symposium 2: BORDERLAND BETWEEN NEUROLOGY AND PSYCHIATRY Chairpersons: P. Scheltens; J. O'Brien, Newcastle-upon-Tyne

FUNCTIONAL MRI IN NEUROLOGY AND PSYCHIATRY

P. Scheltens, Vrije Universiteit (Amsterdam, NL)

Functional magnetic resonance imaging (fMRI) is an imaging modality to detect areas of metabolic change resulting from neuronal activity. With fMRI, individual subjects can be studied non-invasively using the blood oxygen level dependent (BOLD) technique. Recently, fMRI experiments were performed in which brain activation during higher cognitive tasks was studied in healthy individuals. Fusiform, lingual and parahippocampal gyri were shown to be activated during encoding of novel coloured pictures and visual associations of line drawings. Others have shown that performing a sequential-letter memory task activates dorsolateral prefrontal cortex, more posterior and inferior regions of the frontal cortex and posterior parietal cortex. Besides cognitive function, studies of the motor and sensory system have been performed with success. For detection of language dominance fMRI may soon replace the Wada test. In psychiatry studies are going on in obsessive compulsive behaviour and schizophrenia.

So far, the number of reported patient studies has been limited. Since fMRI is non-invasive and has high spatial resolution, the technique could be an appropriate method to investigate patients. Recently, we performed a study of encoding, in which both healthy elderly controls and patients with

Alzheimer's disease (AD) were studied. Studies that include patients with other types of dementia will soon follow.

In this presentation some examples of fMRI studies in neurology, psychiatry and the borderland between these two will be highlighted and the place of fMRI in clinical practice will be outlined.

Neuroimaging Findings In Dementia With Lewy Bodies

John T O'Brien, Professor of Old Age Psychiatry, University of Newcastle upon Tyne, UK. Correspondence c/o Wolfson Research Centre, Newcastle General Hospital, Newcastle, UK, NE4 6BE.Tel: 44(0)191 256 3323. Fax: 44(0)191 219 5051. Email: j. t.o'brien@ncl.ac.uk

Dementia with Lewy bodies (DLB) has been recognised as a common form of dementia in late life which is clinically and pathologically separate from Alzheimer's disease (AD). However, neuroimaging changes in DLB have not been well characterised, nor has it been clearly established whether there are differences with AD which may prove helpful in clinical differential diagnosis or in understanding underlying neurobiology. We undertook both cross sectional and longitudinal structural MRI and blood flow SPET studies in DLB and in AD.

Twenty-seven subjects with consensus criteria DLB, 25 with NINCDS/ADRDA AD, and 26 controls were matched for age and (where appropriate) dementia severity. Subjects were scanned using 1.0 Tesla T1 (1mm slices), proton density and T2-weighted MRI and Tc-HMPAO SPET using a single-headed gamma camera. Volumetric and visual MRI analysis of temporal lobe structures, caudate volume, white matter lesions and region of interest SPET analysis were performed to investigate differences between groups. Where possible, repeat MRI scans were performed one year later and change in whole brain volume between scans (% loss/year) was calculated for each subject by analysis of shifts in the brain/CSF boundary following brain segmentation and registration.

Dementia subjects had reduced temporal lobe volume on MRI and regional (parietal) hypoperfusion on SPET compared to controls. DLB and AD had similar degrees of parietal hypoperfusion on SPET but those with DLB had significantly larger temporal lobe, hippocampal and amygdala volumes compared to AD, with higher blood flow on SPET in the same structures. On MRI, 40% of DLB subjects compared to 0% of those with AD had normal hippocampi on visual inspection. Neither white matter lesions nor caudate volumes differed between AD and DLB, though hyperintensities in the caudate were associated with hypotensive episodes in those with DLB. From the longitudinal study mean changes in brain volume were significantly greater in AD than controls, though rates for DLB subjects were not significantly different from controls.

DLB was found to be associated with less atrophy of medial, but not lateral, temporal lobe structures on MRI than AD though overall atrophy (as assessed by ventricular volume) was similar. Perfusion changes as assessed by SPET showed a similar pattern, with differences between DLB and AD in temporal but not parietal lobes. On serial MRI scanning, progressive brain atrophy may be greater in AD than DLB. These findings, together with reports suggesting loss of the dopamine transporter in DLB, may have important implications both for differential diagnosis and understanding clinical and neuropsychological differences between DLB and AD.

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Symposium 3: NEUROLOGY OF SENSORY-MOTOR CONTROL Chairpersons: Th. Brandt, Munich; A. Berthoz, Paris

FROM SPINAL SHOCK TO SPASTICITY

V. Dietz, A. Curt and L. P. Hiersemenzel; Paraplegic Centre, University Hospital Balgrist, Zürich

The term "spinal shock" was introduced to describe the clinical state in patients with acute spinal cord injury (SCI) presenting muscle paralysis with flaccid muscle tone and loss of tendon reflexes below the level of lesion (1). During the following months after SCI a "spastic syndrome" develops with exaggerated tendon reflexes, increased muscle tone and muscle spasms. In order to explain these changes several hypotheses were put forward. A change from hypoexcitability of alpha-motoneurons (alpha-MN) during spinal shock to hyperexcitability during spasticity was presumed (2). According to this concept the alpha-MN hypoexcitability in spinal shock is due to an acute loss of supraspinal excitatory input resulting in a hyperpolarized alpha-MN (3). Such a hyperpolarization of spinal MN was observed in spinalized cats (4).

Here we describe the changes in excitability of some spinal neuronal mechanisms after SCI and their relationship to the clinical signs from spinal shock to spasticity. We are aware that the electrophysiological recordings applied here (i. e. F-wave, H-reflex, flexor reflex) reflect only a restricted part of spinal neuronal mechanisms. These can be related only with caution to clinical signs (i. e. tendon reflexes, muscle tone, spasms). Given this reservation, the evolution of clinical signs and electrophysiological measures over time might, however, provide some information about the neuronal background of the changes that take place in the clinical state. Futhermore, by comparing mono- and polysynaptic (flexor) reflex activity a better knowledge about interneuronal (IN) activity following an SCI might be achieved.

Over six months after an acute SCI clinical follow-up examinations were paralleled by electrophysiological recordings with tibial nerve stimulation (M-wave, F-wave, H-reflex and flexor reflex) (5).

During spinal shock the loss of tendon tap reflexes and flaccid muscle tone are associated with low persistence of F-waves and loss of flexor reflexes, while H-reflexes are already elicitable. During the transition to spasticity the reappearance of tendon tap reflexes and muscle tone and the occurrence of spasms is associated with the recovery of F-waves and flexor reflex excitability, while H/M-ratio remained about stable over months. At later stages (two to six months after SCI) when clinical signs of spasticity become established the electrophysiological measures show little change.

During the spastic stage, both M-wave and flexor reflex amplitudes remain about stable in tetraplegic or decrease in amplitude in paraplegic patients, i. e. develop even opposite to the clinical signs. The slight increase of H/M-ratio, which is in line with an earlier study (6), might contribute to exaggerated tendon tap reflexes. However, this increase which was thought to be well correlated with the spastic state (for review see 7) must be considered cautiously: 1. In paraplegic patients the increase in H/M-ratio might express rather a decrease of M-wave than an increase in reflex excitability. 2. Short latency reflex hyperexcitability was shown to be little related to spastic muscle tone (8).

The fact that the decrease of flexor reflex amplitude is more pronounced in paraplegic than in tetraplegic patients, i. e. depends on the level of lesion, indicates that several weeks after an SCI secondary degeneration of spinal tracts occurs including pre-motoneuronal circuits and alpha-MN. For the time period and the measures described here, this presumed tract degeneration obviously becomes less effective in patients with high compared to those with a low level of SCI. One may argue that some of the tetraplegic patients were sensory incomplete. However, there is no difference in flexor reflex amplitudes between sensory complete and incomplete, and chronic complete tetraplegic patients.

On the basis of the observations made, clinical signs of increasing spasticity, such as muscle tone and spasms, can hardly be related to the electrophysiological recordings. Secondary changes of motor units might contribute to the syndrome of spasticity, especially in respect to muscle tone and spasms. This is in line with observations showing that following a central motor lesion changes in mechanical muscle fiber properties occur with the consequence of a significant contribution to muscle tone in the active (9, for review see 10) and passive muscles (11; for review see 8).

Conclusion: The late decrease in M-wave and flexor reflex amplitude in paraplegic patients suggests a secondary impairment/degeneration of premotoneuronal circuits and of motoneurons. The divergent course of clinical signs of spasticity and their probable neuronal correlates indicates the occurrence of non-neuronal changes contributing to spasticity.

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Symposium 4: PATHOPHYSIOLOGY OF DEMYELINATING DISORDERS
Chairpersons: A. Steck, Basel; G. Said, Paris.

THE PATHOPHYSIOLOGY OF DEMYELINATING NEUROPATHIES

Gérard Said, Paris, France

Demyelination of the nervous system occurs in a number of conditions. The causes of primary demyelination of axons in the peripheral nervous system occurs include abnormalities of genes coding for myelin proteins, cell and/or antibody mediated immune responses, infection of Schwann cells, toxic and mechanical processes. The functional consequences of demyelination are extremely variable. In some cases, demyelination of peripheral nerves remains clinically silent in spite of slowed nerve conduction velocity, for example in some patients carrying duplication of the PMP 22 gene, or in some cases of chronic inflammatory neuropathy. The question then is to understand what leads to clinical manifestations in patients with demyelinating polyneuropathy?

It is clear that acute focal or multifocal demyelination, as it occurs in the Guillain-Barré syndrome, induces nerve conduction blocks, with subsequent neurological deficit in corresponding territory. Macrophage mediated acute demyelination is usually followed by remyelination within a few weeks, with disappearance of the conduction block and clinical recovery. Experimental models of acute, focal demyelination support these views. However, in a number of cases, the axons are damaged during the inflammatory-immune process, leading to prolonged or permanent deficits. The mechanism of axonal damage in this setting is probably not unique. Both a bystander effect in foci of inflammation (Asbury et al., 1969, Madrid and Wisniewski, 1977) and a specific action of antibodies on epitopes located on the axolemma may play a role (Griffin et al., 1996). The length of fiber demyelinated does not seem to cause axonal damage per se, at least when of short duration (Said et al., 1981; England et al., 1988). Endoneurial oedema, perineurial compression with subsequent nerve ischemia have also been suggested to play a role in secondary axonal damage (Berciano et al., 1999). In the Campylobacter jejuni infection associated Guillain-Barré syndrome, the incidence of axonal degeneration seems higher, but most studies on the subject have been based on neurophysiological data, which often lack sensitivity and specificity as recently stressed again (Cros and Triggs, 1994; Hartung et al., 1998).

In chronic demyelinating disorders of the PNS, such as Charcot-Marie-Tooth type 1, the functional naturopathic deficits are not a result of slowing of conduction but a consequence of progressive axonal degeneration (Dyck et al., 1989). In chronic inflammatory demyelinating polyneuropathy we recently showed that axonal loss had the major long term prognostic impact, much more than active demyelination, inflammatory infiltrates or onion bulb formations (Bouchard et al., 1999). It is thus obvious that in demyelinating disorders of the peripheral, the long term prognosis depends more on the amplitude of axonal loss than on demyelination. The recent recognition that axonal damage occurs in multiple sclerosis and has a major prognostic impact is in keeping with observations made in the peripheral nervous system (Trapp et al., 1998; Revesz, 2000).

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ACQUIRED DEMYELINATING NEUROPATHIES: MOLECULAR MECHANISMS AND NOVEL THERAPEUTICAL APPROACHES

A. J. Steck, Department of Neurology, Kantonsspital, University of Basel, Switzerland

Major advances have been made in elucidating the pathogenesis of acquired demyelinating inflammatory neuropathies. By performing detailed studies using ultrastructural and modern immunohistochemical techniques combined with immunologic assays, such as ELISA and Western blot, new insights have been gained in the cellular and molecular mechanisms leading to demyelination in immune mediated neuropathies. Recent investigations into the role of auto-antibodies against myelin proteins or glycolipids have helped identify the molecular mechanisms that lead to demyelination.

Autoimmune reaction against myelin constituents

In the peripheral nervous system, the paranodal loops and the Schmidt-Lanterman incisures form gap junctions. While these structures have largely been neglected in research because their function was not known, recent data suggest that they form a radical pathway for the diffusions of ions and small molecules. Membranes of paranodes and Schmidt-Lanterman incisures are similar and both contain different protein to those of compact myelin, such as myelin associated glycoprotein (MAG) and connexin 32. On the other hand, myelin proteins, such as PMP22, myelin protein 0 and myelin basic protein, are localized in compact myelin. It has been suggested that many of these molecules are associated with intercellular and intracellular adhesive processes. MAG and myelin protein 0 carry the L2-HNK–1 epitope which is a target for auto-antibodies in a subset of patients with anti-MAG auto-immune chronic demyelinating neuropathy. Recent studies have shown that immunoglobulin M auto-antibody deposits in the anti-MAG neuropathy are localized in Schmidt-Lanterman incisures and paranodal loops. The nodal and paranodal membrane have complementary specialization that have been thought to be sites of adhesion but that could also serve as centers of intercellular signaling. The former is disturbed in the anti-MAG neuropathy while the latter may be compromised in CMTX.

Immunotherapeutic strategies targeting B-cell

Rapid progress in recombinant biotechnology and protein engineering techniques has allowed the design of specific therapeutic strategies, replacing conventional immunosuppression and are being applied to motor neuropathies with serum IgM-antibodies to GM1-ganglioside or MAG. Previous experience, by the use of conventional immunosuppression, has shown that reduction of polyneuropathy associated antibody titers usually leads to an amelioration of the neuropathy with quantitative improvement in strength. Rituximab, a new drug for the treatment of B-cell lymphoma, is a chimaeric mouse – human monoclonal antibody directed against CD20 protein. CD20 is widely expressed in B-cell membranes. Rituximab treatment has been shown to eliminate more than 80 % of circulating B-cells in patients with lymphoma. Preliminary results have shown improved function correlating with reduced titers of serum auto-antibodies following Rituximab treatment in patients with anti-GM1 ganglioside or MAG antibody associated polyneuropathies. Though these results are still preliminary, they suggest that Rituximab may be a well-tolerated, relatively efficient therapy for patients with IgM-antibody related polyneuropathies.

Matrix metalloproteinases in CIDP:

Matrix metalloproteinases are a family of endopeptidases with substrate affinities against extracellular matrix components. MMPs are upregulated in acute experimental allergic neuritis, a model of inflammatory demyelinating polyneuropathy. We quantitated MMPs in nerve biopsy from patients with CIDP by immunohistochemistry and correlated the expression levels with clinical and electrophysiologic findings. We found an increased production of MMP2 and MMP9 in nerve tissue in CIDP with T-cells as the predominant source. Our results stress the pathophysiologic role of MMPs in inflammatory neuropathies.

Novel immunomodulatory treatment for CIDP

Steroids and interferon-β are drugs that suppress the production of MMP9 and this mechanism may be responsible for their therapeutic effects. A few uncontrolled studies have shown a beneficial response of interferon-β in CIDP or GBS. We found an interesting and significant effect of interferon-β1a when combined with IvIg infusions. This combination therapy could induce a synergistic effect. It is also conceivable that the direct inhibition of MMP-activity by hydroxamic acid type MMP inhibitor would be more effective and could be an improvement over current approaches.

Conclusion

Based on a better understanding of the pathogenesis of immune mediated neuropathies, new immunomodulatory drugs are currently in clinical trials.

Neurophysiology of Demyelinating Disease

Kenneth J. Smith, London, UK

Diseases such as multiple sclerosis (MS) and Guillain-Barré syndrome (GBS) result in inflammatory demyelinating lesions within the central and peripheral nervous systems (CNS, PNS) respectively. The lesions cause a range of conduction abnormalities and these lead directly to the symptoms characteristic of the disorders. Perhaps the most prominent conduction deficit is conduction block and this is responsible for the most disabling, 'negative' symptoms such as blindness, paralysis and numbness. A number of events conspire to promote conduction block. The most studied has been demyelination, which will block conduction (11) even if only a single whole internode of myelin is lost (i. e. segmental demyelination). Indeed, partial loss of an internode can also block conduction, especially if the loss is focussed at the paranodes. The block results primarily from two factors. First, a reduction in the safety factor for conduction at affected nodes, which arises from the spread and dispersal of action currents away from the excitable nodal membrane, and a decreased internodal resistance and increased membrane capacitance of the demyelinated axolemma (2;15). Secondly, block results from the initially unsuitable density and distribution of the appropriate types of sodium channel along the demyelinated axolemma (22). However, the block is not necessarily permanent since, in some axons at least, conduction can be restored despite the persistence of demyelination (3;19). It seems likely that such conduction will make a valuable contribution to remission, despite the fact that it occurs with a much reduced velocity. This reduction leads to diagnostically valuable conduction delays (7), and it can be expected to disturb sensations dependent upon the precise timing of impulses. Demyelinated axons also have a much reduced ability to conduct closely spaced impulses (5;11), and impulse trains, and these deficits can be expected to contribute to weakness and sensory disturbances. The insecurity of conduction in demyelinated axons means that its success can be modulated by subtle influences in the environment of the axons. Temperature is one such influence (4;13), and, particularly with lesions in the CNS, even subtle changes in body temperature can result in profound changes in the expression of symptoms (Uhthoff's phenomenon).

Apart from acquiring sufficient excitability to conduct, demyelinated regions can also become hyperexcitable (20) such that they can generate impulses ectopically for many hours, apparently spontaneously. The impulses can be generated in regular or bursting discharges, and they conduct away from their site of initiation in both directions along the axon (1;21). Sensory axons are especially prone to such activity, and so the ascending impulses can result in the expression of "positive" symptoms such as tingling sensations and perhaps pain. Such phenomena might also arise from the triggering of additional, spurious impulses at damaged regions by the transmission of normal impulses through these regions (9). Suspected ephaptic interactions involving demyelinated axons may also induce the formation of spurious impulses (14). Hyperexcitability can also manifest as a marked mechanosensitivity of axons, which underlies movement-induced sensations such as Lhermitte's phenomenon (21).

Where remyelination occurs it typically not only reduces or eliminates hyperexcitability, but also restores secure conduction, with a normal or near normal ability to conduct closely spaced impulses. Remyelination by either oligodendrocytes (18), Schwann cells (even in the CNS) (6) or transplanted cells (8) is effective in this respect, and such repair is believed to make a major contribution to the remission of symptoms.

It is becoming clear that some of the conduction abnormalities attributed to demyelination may also arise as a consequence of accompanying inflammation (11;23). Nitric oxide is produced at sites of inflammation and it has been shown to promote conduction block (16;17), especially in demyelinated axons (16). Nitric oxide can also slow conduction, and impair the ability of axons to conduct closely spaced impulses and impulse trains. These effects are reversible upon removal of the nitric oxide and so they may contribute to the temporary expression of symptoms associated with inflammation. Permanent loss of function, such as is associated with progressive MS or severe GBS, may arise from persistent conduction block in demyelinated axons, but another important factor is axonal degeneration. The mechanisms causing such degeneration are starting to be explored, and sustained impulse conduction either in the presence of nitric oxide (10), or along early remyelinated axons (V. Samtani, K. J. Smith, unpublished observations), has recently been shown to result in degeneration.

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HEREDITARY DEMYELINATING DISORDERS OF THE CENTRAL NERVOUS SYSTEM. O. Boespflug-Tanguy (Clermont-Ferrand, F)

(the complete abstract is on page 217, because it arrived after the editorial deadline).

Oral sessions

Oral session 1

Cerebrovascular disorders – 1

1
HISTOPATHOLOGICAL CORRELATE OF SILENT INTRACEREBRAL HAEMORRHAGES DETECTED BY MRI. S. M. Schade van Westrum, J. M. Rozemuller, C. B. L. M. Majoie, M. Vermeulen, Academic Medical Center (Amsterdam, NL)

In contrast to patients with atrial fibrillation and transient ischemic attacks (TIA) or non-disabling ischemic strokes, patients without atrial fibrillation have a high risk of developing a fatal intracerebral haemorrhage when given anticoagulants to prevent secondary ischemia. One of the hypotheses to explain this discrepancy is that patients with TIA's or infarcts, but without atrial fibrillation, have a type of cerebral vascular pathology leading to clinically silent haemorrhages, which have been detected by MRI. These haemorrhages become symptomatic when treatment with anticoagulants is given. Before embarking on a study on this type of cerebral vascular pathology, we investigated what the pathological correlate is of these silent haemorrhages demonstrated by MRI.

METHODS: We selected from our pathology archive 10 brains with a cerebral vascular disorder (CVD) leading to an increased probability of developing silent haemorrhages and 3 normal brains not having any CVD. These brains, cut in coronal slices, have been stored in 4 % formaldehyde. After rinsing with water, the brains were imaged with an 1.5 Tesla MR scan to detect microhaemorrhages. These are defined as local hypointense signals on the T2-weighted spin-echo images, which are more pronounced on the T2-weighted gradient-echo images and with a corresponding slightly hypointense or normal signal on the T1 weighted images. The sections containing the lesions, the cases, were cut into 6 micrometer thin paraffin embedded slices. Corresponding sections in brains without any suspect lesions, the controls, were also sliced. We stained the slices with Haematoxillin-Eosin, Perl's blue, Congo red and Schmorrl. In addition we also used antibodies against CD68 and Glial Fibrillary Acidic Protein (GFAP). We compared the histopathological morphology of areas containing local hypointensities on MR images with the same areas from brains with CVD but without hypointensities and with areas from brains not containing any CVD. Criteria to define microhaemorrhages were formulated on features unique to the cases.

RESULTS The pathological correlate of silent haemorrhages demonstrated on MRI will be presented at the meeting.

CONCLUSION: Using the histopathological criteria of silent haemorrhages detected by this study, it is possible to explore which type of cerebral vascular pathology is associated with silent intracerebral haemorrhages as detected by MRI.

2
ESPRIT: MILD ANTICOAGULATION, ACETYLSALICYLIC ACID PLUS DIPYRIDAMOLE OR ACETYLSALICYLIC ACID ALONE AFTER CEREBRAL ISCHAEMIA OF ARTERIAL ORIGIN. G. J. Biessels, E. L. L. M. De Schryver, University Medical Center Utrecht (Utrecht, NL)

On behalf of the European / Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) Study Group

Low-dose aspirin (ASA) of at least 30 mg/day prevents only 13 % of the subsequent vascular events after minor cerebral ischaemia of arterial origin. Anticoagulation (AC) has been proven highly effective in preventing vascular events after myocardial infarction and after cerebral ischaemia in patients with atrial fibrillation. SPIRIT showed that high intensity AC (INR 3.0 to 4.5) is not safe after cerebral ischaemia of arterial origin, but also that mild AC (INR 2.0 to 3.0) was. ESPS–2 reported a 22 % relative risk reduction of the combination of ASA and dipyridamole (DIP) above that of ASA only; its results, however, are controversial.

The objective of ESPRIT is to compare the efficacy and safety of mild AC, combination treatment of ASA and DIP, or treatment with ASA alone after cerebral ischaemia of arterial origin. Study design: ESPRIT is designed to randomise 4500 patients between oral AC (INR 2.0 to 3.0), the combination of DIP (400 mg daily) plus ASA (30–325 mg/day) and ASA only (same dose). Randomisation between two treatment arms (ASA + DIP vs ASA or AC vs ASA) is also possible. Primary outcome is the composite event of vascular death, stroke, myocardial infarction or major bleeding; outcome assessment will be blinded. The mean follow-up will be three years. By now over 90 hospitals in Europe and Australia participate and more are invited to follow. As of January 2000 more than 800 patients from 58 hospitals had been included and a total of 45 outcome events had been reported, including only one intracranial (subdural) bleed.

3
ANTI-THROMBIN III, A NOVEL RISK FACTOR FOR CEREBRAL WHITE MATTER LESIONS. F.-E. de Leeuw, J. C. de Groot, A. Hofman, J. van Gijn, M. M. B. Breteler (Utrecht, Rotterdam, NL)

We studied the relation between anti-thrombin III activity and cerebral white matter lesions. Cerebral white matter lesions are frequently found on MRI scans of healthy, non-demented elderly. They play a role in cognitive decline, eventually resulting in dementia. Atherosclerosis plays an important role in the pathophysiology of white matter lesions. Procoagulatory clotting factors are related to atherosclerosis, eventually resulting in cerebrovascular disease. Anti-thrombin III is the most important coagulation inhibitor under physiological circumstances. Previous studies on the relation between anti-thrombin III activity and cardiovascular disease and stroke showed conflicting results in a way that both linear and curvilinear relations were found. The relation between anti-thrombin III activity and white matter lesions has never been examined. Methods: This study is based on the Rotterdam Study, a prospective population-based cohort study among 7983 subjects aged 55 years or older with baseline datacollection between 1990–1993. Anti-thrombin III activity was determined during the baseline data collection by a chromogenic method as heparin cofactor in a random sample of 1656 persons. In 1995/1996 563 randomly selected subjects from the Rotterdam Study participated in the Rotterdam Scan Study, a prospective study of determinants and consequences of age-related cerebral changes, and underwent 1.5T MRI scanning of the brain. There were 244 individuals who had a MRI scan made and their anti-thrombin III activity assessed. Anti-thrombin III deficiency was defined as anti-thrombin III activity < 80 %. White matter lesions were rated in the deep subcortical and periventricular region separately. We compared the degree of both types of white matter lesions between anti-thrombin III deficient and non-deficient subjects, and per tertile of the anti-thrombin III distribution. The analyses were performed using age, sex and vascular factors adjusted linear regression.

Results: Anti-thrombin III activity was determined in 244 out of 563 subjects who underwent MRI scanning and there was no difference in clinical parameters between the groups in which the anti-thrombin III activity was and was not determined. Mean activity of anti-thrombin was 105.3 % (SD17.7). Mean age was 73.9 years (SD 7.3) and 57 % was female. Of all individuals

20% and 8% were without any periventricular and deep subcortical white matter lesions respectively. Individuals with anti-thrombin III deficiency had more subcortical white matter lesions (mean volume 3.2 ml vs. 1.5 ml, p=0.03 and more periventricular white matter lesions (mean grade 3.0 vs. 2.5, p=0.2). When we looked in tertiles of anti-thrombin III activity we saw a U-shaped relation between anti-thrombin III activity and degree of white matter lesions suggesting that also subjects with higher activity are at increased risk for subcortical white matter lesions (pquadratic=0.07) and periventricular white matter lesions (pquadratic=0.21).

Conclusion: Both individuals who are anti-thrombin III deficient and subjects with a high activity of anti-thrombin III are at increased risk of white matter lesions.

4
PREDICTION OF CLINICAL OUTCOME AFTER CARDIO-PULMONARY RESUSCITATION USING TRANSCRANIAL DOPPLER SONOGRAPHY. C. Klötzsch, C. Jacke, O. S. Popescu, J. Noth, Universitätsklinikum der RWTH, Klinikum, Dept. Neurology (Aachen, Saarbrücken, D)

Decrease of cerebral flow velocity and insufficient cerebral autoregulation in the early phase after cardio-pulmonary resuscitation (CPR) are well known phenomena. The aim of the present study was to estimate the ability of transcranial Doppler sonography (TCD) to predict the clinical outcome of patients after CPR on the basis of systolic and diastolic flow velocity changes. Methods: Thirty-one patients (24 men, 7 women) aged 64±15 years (±SD) who had undergone CPR were involved. Serial TCD-examinations (MDX–4, DWL, Germany) of the circle of Willis were performed after 4, 8, 16, 24 and 72 hours. Ventilation parameters (pH, pO2, pCO2) and hemodynamic parameters (heart rate, blood pressure) were recorded together with the TCD-curve at each examination.

Results: Eleven patients (group 1.) survived without moderate or severe neurological deficits. Twenty patients (group 2.) either died (n=19) within 8±10 days or remained in a vegetative state (n=1). Postanoxic myoclonus was observed in one patient (9%) of group 1. and in 10 patients (50%) of group 2. The neuron specific enolase (NSE) level in plasma ranged from 9–29 mg/l in group 1. and 22–1242 mg/l in group 2. A comparison of the flow velocities in the middle cerebral artery (MCA) 4 and 24 hours after CPR revealed an increase of the peak systolic velocities of 10% in group 2. and 67% in group 1. while diastolic velocities increased 17% in group 2. and 108% in group 1. Similar changes were found in the remaining intracranial vessels (anterior/posterior cerebral artery, basilar artery).

Conclusions: The present study reveals a significant increase of systolic and diastolic flow velocity within the first 24 hours in patients who subsequently survive cardio-pulmonary arrest without neurological deficits. Independent of medication and ventilation parameters, serial TCD-examinations are able to support the early prediction of the clinical outcome in patients after CPR.

5
3D-POWER-MODE SONOGRAPHY AND ANGIOGRAPHY IN HIGH-GRADE STENOSES OF THE INTERNAL CAROTID ARTERY. G. Lammers, S. Stetter, K. Hegener, M. Mull, C. Klötzsch, Dept. of Neurology, RWTH, Dept. of Neuroradiology, RWTH (Aachen, D)

The advantages of a personal-computer based three-dimensional reconstruction system for color-coded sonography (CCS) were evaluated in patients with severe stenoses of the internal carotid artery. Methods: Twenty-two patients [16 men, 6 women; mean age 65±12years (±SD)] with 30 severe stenoses of the ICA were involved in the study. The stenoses were detected by frequency-based 2D-CCS and confirmed by digital subtraction angiography (DSA). Power-based CCS-examinations were performed for subsequent 3D-reconstruction. A personal computer (3D-Echotech, Germany) connected with a magnetic sensor to enable spatial localisation of the probe was used to reconstruct a 3D-image of the carotid bifurcation from serial 2D-CCS images. For 3D-sonography the investigator was blinded in respect to the results of CCS and DSA. Results: In 30 ICA-stenoses DSA estimated a mean degree of stenosis of 86±8% (±SD). In 27 of 30 (90%) ICA-stenoses 3D-sonography was able to visualize exactly the length and minimum diameter of the stenosis. The remaining 3 (10%) patients revealed a pseudoocclusion of the ICA with severe reduction of the flow velocity (n=2) or circular calcifications (n=1) of the vessel wall with echo shadows. Conclusions: 3D-CCS enables the investigator to reconstruct virtually any arbitrary view angle. Compared to conventional 2D-CCS the spatial assessment of extracranial stenoses is easier and yields a sufficient correlation with angiography. Since the same 3D-data can be post-processed by different investigators these additional informations may be useful for vascular surgeons, especially if carotid surgery is done without DSA.

6
WERE PATIENTS ADMITTED ACCORDING TO THE STROKE PROGRAM IN THE LILLE STROKE UNIT IN 1998? D. Leys, H. Hénon, C. Gautier, C. Lucas, X. Leclerc, O. Godefroy, D. Guerouaou, Ph. Lestavel, C. Dekluder, J. P. Pruvo, University Hospital Roger Salengro (Lille, F)

Stroke units (SU) decrease mortality and handicap. The aim of this study was to evaluate if the SU of the Lille University Hospital was able to admit all stroke patients of the hospital in 1998.

Methods. The SU consists of acute 45 beds, and is part of the department of neurology (157 beds), in the only University hospital for 4 million inhabitants, acting as primary care hospital for 0.8 million inhabitants. Criteria to be admitted are to have a presumed acute stroke and a bed available.

Results. Of 1704 patients, 1402 (82.3%) were admitted in the SU, 249 (14.6%) in other parts of the neurological department and 53 (3.1%) elsewere. The mean age was 61.8 years; 2/3 of patients lived in the city of Lille; 1/3 of patients were fully independent at admission (Barthel = 100); 2/3 were discharged at home; the in-hospital mortality rate was 7.2%. The mean length of stay was 10.1 days, 1/4 being discharged < 3 days. The mean delay for discharge in post acute units (including rehabilitation) was 12 days; 4/10 of patients were fully independent at discharge; Barthel scores improved in 41% and worsened in 8% of patients in the SU. The rate of misdiagnoses was 9.1%.

Conclusion. The primary objective of the Lille Stroke Program was not achieved in 1/6 of patients, because of a too high occupancy rate. The main reasons are the lack of other stroke units, and the delay of discharge for patients requiring admission in post-acute care, rather than the rate of misdiagnoses.

Oral session 2

Cerebrovascular disorders – 2

7
STENOSIS OF THE MIDDLE CEREBRAL ARTERY: LONG TERM OUTCOME, ROLE OF TRANSCRANIAL DOPPLER ULTRASOUND AND CORRELATION WITH MR-ANGIOGRAPHY. N. Niedermaier, O. Jansen, B. Rundler, K. Lowitzsch, R. Winter, Klinikum Ludwigshafen, University of Heidelberg (Ludwigshafen, Heidelberg, D)

Arteriosclerotic disease of the intracranial cerebral vessels with stenosis of the middle cerebral artery (MCA) is a well known cause for ischemic stroke. The long term outcome of stenosis of the MCA is nonetheless discussed partly inconsistently, and little is known about the correlation of transcranial doppler (TCD) ultrasound with magnetic resonance angiography (MRA) in diagnosis of MCA stenosis. Methods: The medical records of 74 patients with MCA stenosis, that were routinely followed up both clinically and with TCD for 2–6 years, were analyzed and the patients included in the study. 33 of these patients were then examined again physically, with TCD and MR-angiography.

Results: One patient died of MCA stroke and one patient had multiple transitory ischemic attacks over the surveillance period of 2–6 years, the remaining patients were clinically stable. The degree of MCA stenosis as diagnosed by TCD did not significantly change. TCD and MRA correlated in 90% with regard to detection of MCA stenosis in general and in 77% with regard to detection of the grade of the stenosis.

Conclusion: Our study demonstrates a surprisingly good long term outcome of MCA stenosis with stable TCD results over the period of surveillance. It also shows a good correlation of TCD and MRA in the diagnosis of MCA stenosis.

8
CEREBRAL BLOOD FLOW AND VASCULAR RISK FACTORS IN 81-YEARS OLD MEN. A. Siennicki-Lantz, F. Reinprecht, E. Ryding, J. Axelsson, O. Thorsson, S. Elmståhl, Division of Geriatric medicine, Dept. of Neurophysiology, Dept. of Clinical Physiology (Malmö, Lund, S)

Vascular risk factors are correlated with dementia and occlusion in carotid and peripheral arteries. The aim of the study was to prove the association between the peripheral vascular changes and cerebral blood flow (CBF), as a sensitive method for detecting brain dysfunction, in a cohort of men born 1914.

METHODS: The prospective population study "Men born in 1914" in

progress since 1968 with re-examination at the age of 69. Of the 281 men alive at follow-up at the age of 81–82, 186 agreed to participate, and as 14 years earlier, all with carotid ultrasound and ankle/brachial blood pressure index, which together with hypertension were defined as markers of vascular disease (MVD). 129 subjects had CBF examined with 99mTc-HMPAO SPECT. All subjects were non-demented (MMSE ≥ 24) except one with MMSE=18.

RESULTS: The Chi-squared test between dichotomized groups with CBF in lowest tertile and in median/high tertile versus presence of MVD, showed significant association between low CBF in right temporal (p=0.04), right parietal (p=0.001), occipital (p=0.01) ROI and MVD at 69 years of age, but not for MVD data collected at 81 years of age. The multiple logistic regression analysis showed the predictive values of hypertension at 69 years of age on low CBF in right parietal (p=0.01) and occipital (p=0.03) lobes, and moderate but non-significant predictive value of carotid stenosis on low CBF in right frontal lobe (p=0.07).

CONCLUSIONS: An association was observed between accumulated MVD at the age of 69 and CBF during follow-up 14 years later in a cohort of preferentially non-demented men. The results indicate a potential for prophylactic activities to prevent cognitive decline in the elderly.

9

A MAGNETIZATION TRANSFER IMAGING STUDY OF INDIVIDUALS WITH CADASIL. G. Iannucci, M. Dichgans, M. Rovaris, R. Brüning, T. Gasser, L. Giacomotti, T. Yousry, M. Filippi, Neuroimaging Research Unit, Klinikum Grosshadern, Neuroimaging Research Unit Scientific Institute Ospedale San Raffaele (Milan, I; Muenchen, D)

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant disorder leading to cerebrovascular manifestations, including abnormalities on T2-weighted magnetic resonance imaging (MRI) scans of the brain.

In this study, we obtained magnetization transfer imaging (MTI) scans from individuals with CADASIL: a) to investigate the presence, extent and nature of pathology in white and gray matter outside T2-visible lesions; b) to quantify the degree of tissue damage occurring in lesions seen on T2-weighted scans; c) to correlate MTI-derived measures of disease burden with age, physical disability and cognitive performance. We obtained dual echo, T1-weighted and MT scans of the brain from 33 individuals with CADASIL and 12 sex- and age-matched controls. After image co-registration, MTR values from T2-visible lesions, normal-appearing white (NAWM), and normal-appearing gray (NAGM) matter in different regions were measured; MTR values from the same brain regions in controls were measured. Histograms of MTR from the whole brain and normal-appearing brain tissue (NABT) were also produced. All MTR values from NAWM and NAGM regions studied were significantly lower for individuals with CADASIL than in controls with the exception of those obtained from the NAWM of the infratentorial structures and those obtained from the NAGM of the occipital cortex. Average lesion MTR in individuals with CADASIL was 39 % (range=33.5–44.2 %). It was significantly lower than the average MTR from all the NAWM regions studied. All MTR histogram-derived measures from whole brain and NABT were significantly lower for individuals with CADASIL than for controls, with the exception of histogram peak heights. Average MTR of NAWM was strongly correlated with macroscopic lesion extent and severity. Apart for NAGM, average MTR from all other tissues studied significantly decreased with increasing age, physical disability and cognitive impairment.

This study shows that T2 lesions of individuals with CADASIL have variable degrees of tissue destruction and that brain tissue outside T2 abnormalities (both gray and white matter) is also diffusely damaged. It also indicates that the amount and the severity of the affected brain tissue are critical factors in determining clinical status in CADASIL.

10

CAROTID ARTERY DAMAGE: A COMMON COMPLICATION OF INTERNAL JUGULAR VENOUS CANNULATION? M. Reuber, L. A. Dunkley, J. M. Bamford, United Leeds Teaching Hospitals Trust (Leeds, UK)

The use of central venous catheters continues to increase. The internal jugular vein (IJV) is one of the most popular routes for central venous access. Stroke is a rare but recognised complication of attempted cannulation of this vein. Most of the 18 strokes reported in the medical literature were thought to be caused by arterial puncture during insertion and compression of the cannulation site. In most patients there was evidence of coexisting atherosclerosis. Rarer causes include iatrogenic arterio-venous fistula (1 case), head positioning for cannulation (2 cases) and intimal injury causing local thrombus formation with embolisation / occlusion (3 cases).

We report three further patients who suffered strokes following IJV-line insertions complicated by carotid intimal injury. Cases: Case 1: 74-year-old female, IJV-insertion for peri-operative fluid optimisation, immediate stroke due to intimal injury, thrombo-embolism, atherosclerosis. Treated with anticoagulation. Survived with moderate disability. Case 2: 31-year-old male, IJV-line insertion for parenteral feeding, delayed stroke with stuttering course after 2 days due to intimal injury, thrombo-embolism. Treated with anticoagulation. Survived with moderate disability. Case 3: 73-year-old male, IJV-line for peri-operative fluid optimisation, delayed stroke after one day due to intimal injury, thrombo-embolism, atherosclerosis. Treated with endarterectomy. Survived with moderate disability.

Discussion: Whilst IJV-line insertion has rarely been reported as a cause of stroke, carotid artery injury is relatively common. Prospective studies of over 4500 IJV-line cannulations using the landmark technique found rates of inadvertent carotid injury of between 0.5 and 11.4 % (average 5.8 %). It is impossible to say how many of these carotid punctures caused significant damage to the arterial wall including dissection since no studies included ultrasonography or angiography. However, 3 cases of Horner's syndrome, well recognised as an isolated sign of carotid artery dissection, were observed in these studies. In the single prospective study designed to look for neurological complications of IJV-line insertion, Horner's syndrome was found in one of 66 patients. There are 14 other reports of Horner's syndrome caused by IJV-line insertion.

Conclusions: Although carotid injury occurs in 5.8 % of IJV-line insertions using the landmark technique, IJV-cannulation rarely causes clinically apparent stroke or Horner's syndrome. It is unclear how often arterial damage causes clinically silent arterial dissection or thrombus formation at the site of intimal disruption. It seems prudent to avoid carotid artery injury during IVJ-line insertion. Several prospective studies have proven that ultrasound guidance reduces the risk of artery damage by over two thirds.

11

INCIDENCE OF DEMENTIA AFTER STROKE: INFLUENCE OF PRE-STROKE COGNITIVE DECLINE. H. Henon, I. Durieu, O. Godefroy, G. Guerouaou, C. Lucas, F. Pasquier, D. Leys, Hopital Roger Salengro (Lille, F)

Objective: to evaluate the 3-year incidence of post-stroke dementia and the influence of pre-stroke cognitive decline. Background: the risk of dementia is increased after stroke. The mechanisms underlying the occurrence of dementia after stroke remain uncertain. Preexisting cognitive decline is frequent in stroke patients.

Methods: in 202 consecutive stroke patients (177 infarcts, 25 hemorrhages) older than 40 years, pre-stroke cognitive functions were evaluated using the Informant Questionnaire on Cognitive decline in the elderly (IQ CODE) (Jorm et al., 1988), using a cut-off of 104 for the diagnosis of pre-existing dementia. Six months and then annually after stroke, survivors underwent neurological, neuropsychological and functional examinations: the diagnosis of dementia was based on ICD–10 criteria. In survivors who did not undergo the visits, the diagnosis of dementia was based on the IQCODE score obtained by telephone contact with the family or the general practitioner, with a cut-off of 104. Life-table methods were used to estimate the cumulative proportion of demented patients at the end of the 3-year follow-up period. Cox proportional hazards analysis was used to determine independent predictors of dementia within 3 years after stroke.

Results: 33 patients were excluded because of pre-stroke dementia. In the 169 remaining patients, the cumulative proportion of demented patients was 28.5 % at the end of the 3-year follow-up period, most of post-stroke dementia occurring during the first 6 months. Multivariate analysis revealed that independent predictors of post-stroke dementia were aging, preexisting cognitive decline, severity of neurological deficit at stroke onset, diabetes mellitus and presence of silent infarcts.

Conclusion: the risk of dementia after stroke is high. The influence of preexisting cognitive decline suggests that an underlying degenerative pathology may play a role in the development of post-stroke dementia.

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TREATMENT AND OUTCOME AFTER EXTRACRANIAL INTERNAL CAROTID ARTERY DISSECTION: A SYSTEMATIC REPORT OF A CASE SERIES. P. A. Lyrer, S. T. Engelter, E. C. Kirsch, A. J. Steck, Neurology Dept., Neuroradiology (Basel, CH)

Despite widely used anticoagulation, treatment recommendations for extracranial internal carotid artery dissection (eICAD) are not based on proven evidence. Although anticoagulation might have harmful effects in a disorder associated with primary (intramural) hemorrhage, there is no controlled trial comparing anticoagulation versus antiplatelets in eICAD.

Objective: Systematic and standardized evaluation of benefits and risks of anticoagulation versus antiplatelets in a case series of eICAD patients. Meth-

ods: Among 33 consecutive eICAD patients initially treated either with anticoagulation (n=25) or with antiplatelets (n=8) a standardized interview was performed after 28 ± 22.1 months. Ischemic and hemorrhagic complications, occurrence of seizure, and rates of arterial recanalization were compared and long-term clinical outcome was assessed using modified Rankin Scale (mRS) and Barthel-Index (BI).

Results: Among anticoagulated patients, one died due to brain herniation. In 3 patients stroke (n=2) or TIA (n=1) recurred. In the antiplatelet group none died and no subsequent ischemic events happened. Hemorrhagic complications were noted in neither treatment group. Functional outcome among anticoagulated patients was BI 92±21.6 and mRS 1.48±1.50, which did not differ from patients initially treated with antiplatelets (BI 89±18.9, mRS 1.50±1.41, p> 0.05). Four anticoagulated patients developed seizures, compared to 2 patients with antiplatelets (p> 0.05). Arterial recanalization occurred in 16 of 22 anticoagulated patients (73 %) with ultrasound follow-up, compared to 5 of 6 patients with antiplatelets (83 %) (p> 0.05).

Conclusion: In the absence of hemorrhagic side effects, anticoagulation and antiplatelets were safe for eICAD in our series. The rates for death and stroke were low and outcome ratings did not differ between both agents. Thus, a controlled randomized trial comparing anticoagulation and antiplatelets is mandatory and ethically justified.

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WHAT DO STROKE RISK PATIENTS KNOW ABOUT STROKE? S. T. Engelter, P. A. Lyrer, S. Papa, A. J. Steck, Neurology Dept. (Basel, CH)

Management of stroke risk factors is important in primary and secondary stroke prevention. Further, emerging stroke treatment options like thrombolysis have been shown beneficial only if applied very early. Therefore, public perception of stroke is crucial in reducing the burden of stroke, most notable for patients with considerably high stroke risk. We assessed the level of knowledge about which organ is involved in stroke, about stroke risk factors, stroke symptoms, and the presumed action taken in case of stroke for patients with high stroke risk.

Methods: Among all patients who were transferred for doppler/duplex-sonography between June and December 1999 those with high stroke risk were asked to complete an open questionnaire. High stroke risk was defined as prior TIA or non-disabling stroke, and/or occlusive disease of at least one major cerebral artery. Patients with disabling aphasia, dementia, or recent stroke (< 2 weeks), and those, who did not speak the local language, were excluded.

Results: The questionnaire was completed by 145 patients. Mean age was 69± 10.6 years. Forty-five were women. Seventy-two patients (49 %) did not know that a stroke occurs in the brain. Seventy patients (48 %) could not name at least one of their own stroke risk factors. Only 78 (54 %) patients mentioned at least one common stroke symptom. Although 132 patients (91 %) considered stroke as treatable, only 50 (34 %) patients would call for immediate in-hospital care, if they, friends, or relatives suffered from an acute stroke.

Conclusion: Among patients with high stroke risk, there is a lack of relevant knowledge about stroke. This population is an important target for improved educational efforts.

Oral session 3

Higher function disorders – 1

14
PRESENILIN–1 POLYMORPHISMS AND ALZHEIMER'S DISEASE: INTERACTION WITH APOE? G. Roks, B. Dermaut, J. Tol, R. Rademakers, A. J. C. Slooter, S. Serneels, A. Hofman, M. Breteler, M. Cruts, J. J. Houwing-Duistermaat, C. Van Broeckhoven, C. M. Van Duijn, Epidemiology & Biostatistics, VIB, BBS, Department of Biochemistry (Rotterdam, NL; Antwerp, B)

Mutations in the Presenilin–1 gene (PSEN–1) on chromosome 14 cause an autosomal dominant form of Alzheimer's disease (AD). Polymorphisms in this gene have been found to be associated with sporadic AD. We studied the intron–8 and the –48C/T and D14S1028 promotor polymorphisms of PSEN–1. Furthermore, we reanalyzed all published studies on intron–8 in a meta-analysis. The study population consisted of 356 late-onset AD patients and 230 controls derived from a population-based follow-up study (the Rotterdam Study). No association between AD and the 3 polymorphisms was found. However, in a stratified analysis we found a statistically significant (p=0.02) interaction between the –48C/T and the E4 allele of the apolipoprotein E gene (APOE). There was an increased risk for homozygotes of the 2 allele (odds ratio of 4.2, 95 % CI 1.2–14.6). This interaction was caused by a genotype frequency shift in the E4 positive controls. Because the E4 positive controls is a small group we genotyped 56 additional controls. The association disappeared with this extended control group (p=0.12, odds ratio of 1.8, 95 % CI 0.85–3.8) suggesting the interaction in the initial analysis was false positive. In the meta-analysis 24 studies were included. In this total sample of 4286 cases and 3759 controls no association was found (odds ratio 1.10, 95 % CI 0.99–1.12). There was no difference in association between Caucasian and Asian populations. Together, these results suggest that genetic variation at the PSEN1 locus does not influence the risk of developing AD. Furthermore, care should be taken if interactions are caused by genotype frequency shifts in a small group, and no firm conclusions can be drawn without genotyping additional subjects.

15
A PRELIMINARY STUDY OF DIFFUSION-WEIGHTED AND MAGNETIZATION TRANSFER IMAGING IN PATIENTS WITH ALZHEIMER'S DISEASE. M Filippi, M. Bozzali, M. Cercignani, G Magnani, M. Zuffi, G. Comi, M. Franceschi, Neuroimaging Research Unit, Clinical Trials Unit, Neuropsychology Unit (Milan, I)

This study was designed to quantify the extent of tissue loss and disorganization in the brain of patients with Alzheimer's disease (AD), using diffusion-weighted (DWI) and magnetization transfer (MTI) imaging. We studied nine patients with AD and nine sex- and age-matched healthy controls. The following pulse sequences were acquired for each subject: a) dual echo turbo spin echo; b) 2D gradient echo (GE) with and without an off resonance saturation pulse, c) spin-echo echo-planar with diffusion-weighting along 8 directions. From the two GE images, maps of the MT ratio (MTR) were derived. Similarly, maps of the mean diffusivity (D) and fractional anisotropy (FA) were calculated. After image co-registration, white matter (WM) and grey matter (GM) were segmented from 10 supratentorial slices using fractional anisotropy (FA) thresholds. Then, histograms of the MTR and D were created for the whole brain tissue, WM and GM of all subjects. Finally, the frontal, parietal, temporal and occipital lobes were segmented and their MTR and D characteristics analyzed separately. MTR and D histogram-derived metrics from the entire brain tissue were significantly different between AD patients and normal controls (p values ranging from 0.04 to 0.007). MTR (p=0.02) and D (p=0.04) peak height of the histograms from GM were reduced in AD patients compared to controls. MTR histograms of WM were similar between AD patients and controls, whereas significant diffusivity changes were noted (p values ranging from 0.05 to 0.02). The MTR and D metrics of the GM of the temporal lobes were all significantly different than those from normals (p values ranging from 0.05 to 0.004). This was not the case for GM of all the other lobes. In AD patients, a strong correlation between D metrics and disease duration was found (r values ranging from 0.76 to 0.90).

This study indicates that MTR and D changes can be detected in the GM and in the WM of AD patients, thus suggesting a role for quantitative MR techniques to monitor disease evolution objectively and accurately. GM changes are likely due to neuronal loss, whereas WM changes might be the result of Wallerian degeneration.

16
THE LEVELS OF TAU AND 14–3–3 PROTEINS ARE ELEVATED IN CEREBROSPINAL FLUID OF CREUTZFELDT-JAKOB DISEASE PATIENTS CARRYING THE E200K MUTATION IN THE PRP GENE. Z. Meiner, H. Rosenmann, O. Abramsky, H. Ovadia, R. Gabizon, Hadassah University Hospital (Jerusalem, IL)

Objective. To examine whether elevated levels of tau and 14–3–3 proteins are found in cerebrospinal fluid (CSF) of Libyan Jews patients with Creutzfeldt-Jakob disease (CJD) carrying the E200K mutation in the PrP gene. Background. CJD is a prion disease that can manifest as sporadic, inherited or infectious forms. The diagnosis of CJD is based on clinical signs, periodic EEG pattern and spongiform changes in brain biopsy. One of the largest clusters of inherited CJD is found among Jews of Libyan origin. The disease in this community is linked to the E200K mutation in the PrP gene (CJDE200K). Recently, high levels of the proteins 14–3–3 and tau were found in the CSF of sporadic CJD patients. The significance of these proteins in CSF of inherited CJD patients is unknown. Methods. Tau protein levels were examined in CSF of 11 CJDE200K patients, 2 carriers of the E200K mutation with other neurological diseases, 5 patients with sporadic CJD. 14–3–3 levels were examined in CSF of 29 CJDE200K patients, 3 carriers of the E200K mutation with other neurological diseases, and 19 patients with sporadic CJD. As controls

we examined CSF of patients with Alzheimer's disease (AD) and CSF of patients with other neurological diseases (OND) without dementia. Tau levels in CSF were examined using sandwich ELISA techniques (Innotest hTAU-Ag Innogenetics NV) and 14–3–3 protein was detected using immunoblotting. Results. The mean level of tau in CSF of CJD patients with the E200K mutation was 1210±441 pg/ml, similar results were found in the five sporadic cases that were examined. Tau levels in CSF of the two asymptomatic E200K carriers were similar to OND patients. Tau levels in CSF of AD patients were elevated in range of 389± 148 pg/ml but were significantly lower than tau levels of CJD patients. However, high levels of tau were found also in 2 patients with viral encephalitis. 14–3–3 protein was detected in CSF of 26 out of 29 CJDE200K patients and in CSF of 18 out of 19 sporadic CJD. It was not found in CSF of the three asymptomatic E200K carriers as well as in CSF of 38 out of 45 OND patients. As previously described, 14–3–3 protein was found in CSF of patients with viral encephalitis and recent cerebrovascular accidents.

Conclusions. High tau levels and 14–3–3 protein can be found in the CSF of CJD patients carrying the E200K mutation as in sporadic CJD patients. These high tau levels can be distinguised from the elevated tau levels in CSF of AD patients. Tau and 14–3–3 proteins levels are not elevated in CSF of asymptomatic carriers of the E200K mutation and therefore can be used to distinguish between CJD breakout and another neurological disease in these patients.

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THE EPISODIC MEMORY EVALUATION IN INCIPIENT ALZHEIMER'S DISEASE. A Ivanoiu, S Adam, M Van der Linden, AC Juillerat, A Jacquemin, G Godfrind, C Prairial, R Mulligan, M George, S Bechet, E Salmon, X Seron, Memory Clinic, Cliniques Universitaires Saint Luc (Brussels, Liège, B; Geneva, CH)

Episodic memory (EM), that is memory for events personally experienced in spatio-temporal context, is the cognitive domain which seems to be first and foremost impaired in Alzheimer's disease (AD). As clinical diagnosis of incipient AD is difficult and biological markers are not yet available, the EM evaluation by neuropsychological tests is central to the diagnostic procedure. We aimed at evaluating the usefulness of four EM tests as diagnostic tools in incipient AD: a test of delayed cued recall using semantic cues (DCR) (Adam and Van der Linden, unpublished), a ten word-list recall (TWR) from the CERAD battery (Morris et al., 1988), the "doors" test (DT) and the "shapes" test (ST) from "The Doors and People Test Battery" (Baddeley et al., 1994). 72 consecutive patients consulting one of three Memory Clinics (Brussels, Liege, Geneva) were included in the study. All were evaluated by trained clinicians, underwent CT-scan or MRI, and were re-examined one year later to confirm the initial diagnosis (probable AD according to the NINCDS-ADRDA criteria or absence of dementia). Three groups of patients were considered: 25 with Incipient AD (MMSE 26.8±1.7), 22 with Mild AD (MMSE 23.4±2.4) and 25 not demented Clinical Controls (MMSE 28.5±1.3). They were also compared with a group of 27 normal elderly. There were no significant differences between the four groups in age or education. The difference between the performances of normal elderly and Clinical Controls on the four EM tests was not statistically significant. Incipient AD patients were impaired on all four EM tests, compared to both Clinical Controls and normal elderly ($p < 0.001$, ANOVA, post-hoc comparisons). However, an analysis of the diagnostic value in terms of sensibility / specificity showed that the DCR test was clearly the most discriminant measure between the Incipient AD and the Clinical Controls (sensibility 93% / specificity 96%, by the ROC curve method). In conclusion, EM tests may prove sensible but differ in their diagnostic value for detecting the Incipient AD. DCR test, which is based on a procedure that maximises learning by controlling the subject's processing and by co-ordinating encoding and retrieval, have much more chance to disclose real memory impairment associated with AD.

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AN ANALYSIS OF WORD DYSLEXIA IN PATIENTS WITH RIGHT HEMISPHERIC STROKE. M. Rousseaux, D. Busch, C. Lavaud, Y. Martin, T. Bernati, CHRU Hopital Swynghedauw, Centre l'Espoir (Lille, Lille-Hellemmes, F)

Dyslexia is an important consequence of spatial neglect. Few studies have suggested that most errors are omissions, and are more frequent in the initial part of words. However, other errors are possible, such as additions or substitutions. The aim of this study was to investigate the frequency of errors according to their category, place, and the influence of specific factors such as the lexicality, affixation, word length, and frequency of use. Fifty-four right-handed patients presenting with a unilateral right hemisphere injury were evaluated at the secondary phase post-stroke (M: 28; F: 26; mean age: 53 years). Aphasia and dementia were excluded by conventional assessment. About 40% of patients presented with spatial neglect in visuo-motor testing. Lecture of words and non-words was assessed using a specific battery. Words (96) were concrete substantives, balanced following 3 main variables: word type (full, composed, prefixed, suffixed), length (5–6, 7–8, 9–10 letters), frequency of use (high, low). Non-words (72) were constructed from high frequency real words, following the same 2 first variables, type, and length. Errors were classified as left- or right-sided, and as omissions, substitutions, additions, inversions, shifting. Results. An ANOVA ($p < .05$) was performed to assess the effect of 4 variables, category and side of errors, type and length of words, on the relative frequency of errors. The category had a significant influence (omissions> > substitutions> > additions> inversions> shifting), and errors were significantly more frequent on the left than on the right side of words. The word type had a significant influence (errors for full non-words> for composed non-words> for prefixed words> for suffixed words> for composed words> for full words). The length also had a significant influence (errors for 9–10> 7–8> 5–6 letters). Some interactions were significant: – side x category of errors, as the difference between right and left errors was more severe for omissions than substitutions, and was absent for other errors – word type x category of errors, as the influence of the word type was more marked for omissions than substitutions, and absent for other errors – word lenght x category of errors, as the length had a severe effect on omissions only. Furthermore, omissions but not other errors were higher for low frequency words.

Discussion. This represents the first global study of words dyslexia following right hemisphere injury. It clearly demonstrated that the most frequent errors are omissions and substitutions, which are more frequent on the left than on the right side. Other errors are much less frequent and of similar frequency on both sides. These errors are also more frequent for non-words than real words, and for affixed than non-affixed words. They are also influenced by the length of the stimuli. Then, words dyslexia is clearly influenced by the perceptive characteristics of words, but also by their syntactic and semantic properties.

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ALZHEIMER'S DISEASE: INFLUENCE OF COMT VAL108MET POLYMORPHISM IN COMT ACTIVITY. M. M. Monteiro Grazina, F. M. Pereira da Silva, I. Santana, M. T. Proença, L. M. Oliveira, B. Santiago, L. Cunha, C. Oliveira, Faculty of Medicine, University Hospital, Centre for Neurosciences (Coimbra, P)

The mechanisms generating Alzheimer's disease (AD) are not completely understood. One mechanism might be related with the APOE genotype (alleles – e2, e3, e4 – on chromosome 19), which encodes a polymorphic apolipoprotein with three common isoforms: apoE2, apoE3, and apoE4. ApoE 4 (e4) allele appears to confer substantial risk for late-onset AD, either sporadic or familial. However, the mechanism(s) by which the APOE e4 allele is associated with AD and the role of apo E in AD is not clear. Catechol-O-methyltransferase (COMT) is an ubiquitous enzyme that catalyses the transfer of the methyl group from the coenzyme S-adenosyl-L-methionine (SAM) to one of the hydroxyl groups of catechols in the presence of Mg2+. Altered COMT activity levels at different physiological status were observed both in animal and human studies. We have reported earlier that COMT activity levels in erythrocytes of AD patients and age-matched controls with the e4 allele, were significantly lower than those observed in controls without e4 allele. In order to clarify the possible association between AD, e4 allele and COMT activity levels, we have genotyped COMT Val108Met polymorphism in AD patients and age-matched controls; furthermore we have studied the influence of this polymorphism in COMT activity levels. We have found that COMT Val108Met polymorphism is not associated to risk for AD, not even considering age of onset or gender. However, heterozygous patients with early age of onset may have increased COMT activity levels when compared with age-matched heterozygous controls and that male AD patients may have decreased COMT activity levels. We also have found that COMT activity in AD patients is only based on the COMT Val108Met polymorphism as it has been reported to the general populations.

Oral session 4

Dementia and higher function disorders – 2

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CEREBROSPINAL FLUID PATTERN IN PATIENTS WITH DEFINITE CREUTZFELDT-JAKOB DISEASE. C. Jacobi, I. Zerr, S. Arlt, A. Schröter, M. Otto, S. Poser, Neurology, Georg-August University, Neurology, Georg-August University (Göttingen, D)

Creutzfeldt-Jakob disease (CJD) is a rare neurodegenerative disease caused by the pathologic form of prionprotein. Patients can be clinically classified as probable, possible and other cases. Definite diagnosis can only be made by neuropathological examination. 4–14 % of patients classified as other cases suffered from acute and chronic inflammatory diseases of the nervous system. These patients usually have typical findings like pleocytosis, blood-CSF barrier dysfunction and/or intrathecally synthesized immunoglobulins in CSF. In literature CSF pattern of cell count, albumin, IgG, IgA, IgM and oligoclonal bands in CJD was examined in small, not well defined groups or single case reports up to now. The aim of this study was to review the CSF pattern of CJD patients and to examine if CSF changes of acute or chronic inflammatory origin can be found.

We analyzed CSF pattern of 148 patients with definite CJD altogether. Patients are devided into two groups. Albumin, IgG, IgA, IgM and oligoclonal bands in CSF/serum pairs of 25 patients were measured in our laboratory (group I). Of the remaining 123 patients CSF/serum pairs were not available and we had to rely on the CSF reports of the external hospitals (group II). CSF/serum pairs of this group were analyzed in different laboratories.

In group I six of 25 cases (24 %) had blood-CSF barrier dysfunction (range Q Alb: 7,8–17,6). Oligoclonal bands, a sensitive sign of intrathecally synthesized IgG, were found in two of 25 patients (8 %). No intrathecally synthesized IgA or IgM was detected. CSF analysis of group II was in accordance with the results of group I. Mild pleocytosis (range: 5–11 cells) was found in 6 of 110 patients (5,4 %). A blood-CSF barrier dysfunction (range Q Alb: 8,0–22,7) could be shown in 27 of 100 cases (27 %). Five of 75 cases (6,7 %) had positive oligoclonal bands in CSF.

We describe the complete CSF pattern of albumin, IgG, IgA, IgM and oligoclonal bands in patients with definite CJD. Apart from blood-CSF barrier dysfunction mild pleocytosis and positive oligoclonal bands are rare findings in CSF of CJD patients and do not exclude this diagnosis. Previous inflammatory disorders of the nervous system may lead to persistent oligoclonal bands in the CSF, as shown in one case with Lyme disease in the medical history.

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14–3–3 PROTEINS IN NEUROLOGICAL DISORDERS. I. Zerr, M. Bodemer, R. Westermann, A. Schröter, C. Jacobi, S. Arlt, M. Otto, S. Poser, Neurology, University of Göttingen (Göttingen, D)

The detection of 14–3–3 proteins in the cerebrospinal fluid (CSF) has been described in Creutzfeldt-Jakob disease (CJD), supporting the clinical diagnosis with a high sensitivity and specificity. These neuronal proteins are believed to be released into the CSF due to rapid neuronal damage in CJD and are therefore likely to be elevated in other neurological diseases, too. The aim of this study was to analyze the presence of 14–3–3 proteins in CSF in CJD and in other neurological diseases. Cerebrospinal fluid and serum samples were obtained in the framework of the epidemiological study on CJD (n = 488). Samples from patients with rapid progressive dementia were sent to our laboratory from neurological and psychiatric hospitals (n = 581). In addition, CSF from patients with meningitis/encephalitis was analyzed (n = 95). The detection of 14–3–3 proteins in the CSF was carried out using a Western blot technique. Patients with suspected CJD were then examined by a study physician and classified according to established clinical and neuropathological criteria. In other patients, clinical and neuropathological information was sought from the notifying physicians.

The analysis for 14–3–3 was carried out in 488 patients with definite or probable CJD and in 676 patients with other neurological disorders. In CJD, the proteins were detected in 454 out of 488 patients (sensitivity 93 %). In patients with other neurological diseases, CSF was positive for 14–3–3 only in 76 patients (55 out of 192 with inflammatory disorders, six out of 51 with hypoxia or ischemia) and four out of 133 patients with Alzheimer's disease. Three out of four patients with later diagnosed cerebral tumor had elevated 14–3–3 levels in the CSF as well as three out of 13 patients with epilepsy. Only single cases have been positive for 14–3–3 in other diseases: each one of Parkinson's disease (out of 34) and para-neoplastic (out of 21). Remaining 14–3–3 positive cases were due to other metabolic or other neurological disorders. In 22 CJD patients and patients with other diseases a second spinal tap was done at least two weeks after the initial one. Twelve out of 13 CJD patients were still positive for 14–3–3. In contrast, all three patients with epilepsy were negative in the second lumbar puncture. Only two out of six patients with inflammatory disorders had detectable 14–3–3 levels in the CSF in the second lumbar puncture. Both patients had still inflammatory CSF changes. The detection of 14–3–3 proteins in the CSF is helpful in the clinical diagnosis of CJD. However, levels of 14–3–3 proteins may be elevated in other neurological disorders, most due to rapid neuronal damage. This could be shown in patients with inflammatory and hypoxic brain damage as well as in patients with cerebral tumors. Therefore, these conditions should be carefully excluded when using 14–3–3 detection in the clinical diagnosis of CJD. In cases of doubt, a second lumbar puncture at least two weeks after the initial one may be helpful: a further increase of 14–3–3 protein levels is likely in CJD. In other diseases with acute neuronal damage, 14–3–3 may not longer be detectable.

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FUNCTIONAL ANALYSIS OF CYTOCHROME C OXIDASE AND ATPASE (ATP SYNTHASE) ACTIVITIES IN PLATELETS MITOCHONDRIA FROM PATIENTS WITH ALZHEIMER'S DISEASE. G. Solaini, G. Siciliano, F. Brizzi, M. Mancuso, G. Tognoni, S. Barogi, L. Murri, Scuola Superiore di Studi Universitari e di Perfez, Dip. Neuroscienze, Università Pisa (PISA, I)

Altered brain energy metabolism is an early and prominent feature of Alzheimer's disease (AD). The activities of two mitochondrial enzymes, playing critical roles in oxidative phosphorylation, cytochrome c oxidase (COX), the terminal enzyme of the electron transport chain, and ATPase (ATP synthase) have been reported to be decreased in autopsy samples of the most affected brain regions of individuals with AD. However, post mortem biochemical results should be corroborated by data obtained on patients. This can be attained on platelets, an easily accessible source of human material that share many similar biochemical features with neurons and have served as clinical markers for numerous neuropsychiatric disorders. Based on this background and to gain further insight into the pathogenesis of mitochondrial dysfunction in AD, we have initiated a study of the properties of the enzymes in platelets mitochondria from patients.

Twelve subjects with Clinical Dementia Rating Scale (CDR) scores of 1 to 3 and twelve aged-matched controls were included in this study. Mitochondria from isolated blood platelets were prepared according to a method recently set up by us and described elsewhere (Baracca et al.; J. Biol. Chem., in press). Mitochondrial rates of cytochrome c oxidation and oligomycin sensitive ATP hydrolysis were recorded by means of a spectrophotometric and a luminometric method, respectively. The data obtained were analyzed and are here presented as mean ± SEM. The significance of differences was evaluated by unpaired t test analysis and accepted when $p < 0.05$.

COX activity was decreased in AD platelets mitochondria relative to controls, whereas the ATPase activity did not change significantly. These enzyme activities varied markedly from subject to subject. COX activity was globally decreased in the AD platelets mitochondria by about 25 % on a mean basis. This decrease in COX activity was significant when compared with control platelets. On the contrary, the oligomycin sensitive ATPase (OS-ATPase) activity appeared slightly increased in AD patients mitochondria (61 vs 48 nmol/min/mg protein), but the difference was not statistically significant. However, if we consider two categories of the patients, based on CDR scores, that category with CDR score 3 (i.e. the most severely affected patients), shows a dramatic decrease of the OS-ATPase activity of 27.7 ± 5.2 nmol/min/mg, a value significantly lower ($p < 0.05$) than that of the controls. This observation, though preliminary, might clarify why the data of the ATPase activity reported in the literature are not homogeneous: it might in fact depend on the choice of the patients analyzed. Moreover, our results as a whole support the view that studies of mitochondrial functions in AD can effectively be performed in platelets.

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ELECTROPHYSIOLOGICAL STUDIES OF WORKING MEMORY IN UNTREATED MAJOR DEPRESSION. L. Pelosi, T. Slade, V. Sharma, L.D. Blumhardt, Clinical Neurophysiology, QMC, Fazakerley Hospital, University of Nottingham (Nottingham, Liverpool, Liverpool, UK)

The mechanisms that account for the commonly observed memory deficits in depression are unknown. We aimed to investigate working memory function by comparing the behavioural performance (reaction times and error scores) and event-related potentials (ERPs) during processing of a digit/probe identification and matching task (Sternberg memory paradigm) of 14 patients with an untreated major depressive illness, with 14 healthy controls. Memory sets and probe digits were presented in auditory and visual modalities under conditions of varying memory load.

Results: patients made more mistakes than healthy controls as memory load was increased from one to five digits. In addition, they had significantly slower reaction times at all levels of memory load. ERPs from patients deviated significantly from controls and showed similar abnormalities for both auditory and visual responses. 157–210 msec after stimulus presentation there was significantly reduced surface negative activity that suggested abnormal sensory/perceptual processing in modality specific cortical areas, possibly due to a failure of selective attention mechanisms. In the 375–840 msec epoch, the patients' responses contained high amplitude sustained negative activity that was sensitive to memory load. This was followed by a significantly reduced late positivity.

The prolonged late negative 'shift' suggests activation of additional neuronal assemblies participating in the processing of the task, which could represent either a compensatory mechanism or a failure or dysfunction of cortical inhibitory systems. The reduced late positivity may suggest dysfunction of both context updating in working memory and cognitive closure of the task.

Conclusions: this study has provided the first objective evidence of working memory impairment in untreated major depression. Both the early and late ERP changes we observed can be accounted for by deficits in the 'central executive system'. Dysfunction of working memory processes may be an important contributing or core factor underlying memory deficits in depression.

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DONEPEZIL PRESERVES FUNCTIONAL STATUS IN ALZHEIMER'S DISEASE PATIENTS: RESULTS FROM A 1-YEAR PROSPECTIVE PLACEBO-CONTROLLED FUNCTIONAL SURVIVAL STUDY. R. Mohs, R. Doody, J. Morris, S. Rogers, J. Ieni, C. Perdomo, R. Pratt, Bronx VA Medical Center, Baylor College of Medicine, Washington University School, Eisai Co. Ltd, Eisai Inc. (New York, Houston, St. Louis, USA; Tokyo, J; Teaneck, USA)

Background: In Alzheimer's disease (AD), deterioration in functional ability results in growing caregiver burden and the eventual need for institutionalization. The impact of treatment with cholinesterase inhibitors on the preservation of function has not been investigated in studies of longer than 6 months. Objective: To examine the effects of donepezil compared with placebo on the preservation of functional status over time in patients with AD in a prospective 1-year double-blind study.

Methods: Patients were required to have a diagnosis of probable AD (NINCDS criteria), Mini-Mental State Examination (MMSE) of 12 to 20 inclusive, Clinical Dementia Rating (CDR) of 1 or 2, and a modified Hachinski ischemia score < /=4. Patients also had to be able to perform five out of six basic Activities of Daily Living (ADLs) and eight out of ten instrumental ADLs (IADLs). Randomized patients received either placebo or donepezil for 1 year. Patients in the donepezil group received 5 mg/day for 28 days and 10 mg daily thereafter. Outcome measures were the Alzheimer's Disease Functional Assessment and Change Scale, MMSE, and the CDR. At each visit, investigators determined whether pre-defined criteria for clinically evident decline in functional status had been reached. Criteria were defined as: (1) a decline in ability to perform one or more basic ADLs present at baseline; (2) a 20 % decline in ability to perform IADLs present at baseline; or (3) a 1 point increase in the global CDR rating. If criteria were met, patients were discontinued from the study.

Results: A total of 431 patients were randomized. In this study of 1-year duration, donepezil treatment extended the median time to clinically evident decline in function by 5 months versus placebo. The probability of patients treated with donepezil remaining in the study with no evident functional loss was 51 % at 48 weeks, compared to only 35 % probability for placebo-treated patients. The Kaplan-Meier survival curves for the two treatment groups were significantly different (p=0.002, log rank test). The most frequent reason for meeting the criteria for functional decline was deterioration in ability to perform IADLs. Cognitive benefits were also observed with donepezil. At endpoint, the donepezil group showed a mean change from baseline in MMSE score of +0.615 compared with –0.593 for placebo (p< 0.001). Conclusion: This is the first 1-year, prospective, placebo-controlled evaluation of the effects of an acetylcholinesterase inhibitor on the maintenance of functional status of patients with AD. The study demonstrated that AD patients continue to show disease progression over time, but that the likelihood of patients treated with donepezil retaining functional capacity was significantly greater over a 1-year period than in the case of placebo-treated patients.

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THE ALPHA–2 MACROGLOBULIN GENE: ITS ROLE IN EARLY AND LATE ONSET ALZHEIMER'S DISEASE. M. N. Koster, B. Dermaut, G. Munteanu, J. J. Houwing-Duistermaat, G. Roks, J. Tol, A. Ott, A. Hofman, M. Cruts, M. M.B Breteler, C. Van Broeckhoven, C. M. Van Duijn, Erasmus Medical Center, Flanders Institute of Biotechnology (Rotterdam, NL; Antwerp, B)

Background: While several groups recently reported a positive association between the alpha–2-macroglobulin gene (A2M) and late-onset Alzheimer's disease (AD), others were unable to replicate these findings. Objective: To evaluate the role of A2M in AD, we conducted a population-based case-control study of early- and late-onset AD as well as a meta-analysis of all studies published to date. Methods: Early-onset AD patients (N=100) were derived from a population-based study of EOAD in four northern provinces of the Netherlands. Late-onset AD patients (N=344) were drawn from the Rotterdam Study. Two polymorphisms were studied, A2M-I/D and A2M-Ile1000Val. For the meta-analysis data of 12 studies were re-analyzed, including 3153 cases and 3299 controls for A2M-I/D and 2185 cases and 2281 controls for A2M-Ile1000Val. Results: No genotypic or allelic association was found for both polymorphisms in the population-based series of patients with LOAD. Overall, no association was found between EOAD and either of the two polymorphisms. However, in patients with EOAD and without APOE*4, a borderline significant increase of carriers of A2M–1000Val was found (OR 1.86, 95 % CI 1.04–3.32, p=0.04). The meta-analysis of available published case/control data on these polymorphisms yielded no significant differences between cases and controls. Conclusions: These results suggest that A2M is not genetically associated with LOAD. The findings on EOAD are equivocal and remain to be confirmed.

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EVALUATION OF COGNITIVE FUNCTION IN PATIENTS WITH ACUTE STROKE AND AFTER THREE MONTHS. S. Riss, D. Bittner, M. W. Riepe, University of Ulm (Ulm, D)

Aged patients have an increased risk prevalence of ischemic stroke and dementia syndrome. However, medical attention for dementia syndrome remains poor on general and even neurological wards. Nevertheless, early detection of dementia syndrome is warranted due to recently emerging pharmacological strategies. The goal of the current study was to investigate whether cognitive impairment can be reliably evaluated with screening tests for memory, orientation, and aphasia in patients with acute stroke within the first 72 hours after admission to an acute stroke ward and whether the results are a valid predictor of cognitive status after three months recovery.

The investigation was performed on an acute stroke ward for stroke patients (stroke unit). 66 consecutive conscious patients (age 34–89 years) were investigated within 72 hours of admittance. The study is ongoing and patients are reevaluated after three months. In addition to routine clinical and imaging studies the cognitive abilities were screened with ADAScog subscales orientation and aphasia, the clock drawing test, a letter-sorting test and Buschke's memory impairment screen. In addition, depressive mood was self-rated on an ordinal scale.

In the acute stage of stroke 50 % of all patients failed on the letter-sorting test. In patients with right and left middle cerebral artery ischemia failure was 60 % and 72 %, respectively (p < 0.05). 33 % of all patients were impaired on the aphasia subscale of the ADAScog with patients suffering from left middle cerebral artery ischemia worst (45 %). 44 % of all patients but 73 % of patients with left middle cerebral artery ischemia showed deficits in the ADAScog subscale orientation. 65 % of all patients were impaired on Buschke's memory impairment screen. With currently 34 patients followed up pathologic results were confirmed in more than 90 % of the patients after three months.

We conclude that cognitive screening tests allow evaluation of cognitive deficits in conscious stroke patients within the first 72 hours of admission. Results are predictive of cognitive function three months after recovery. Cognitive screening therefore should be considered for the routine diagnostic procedure in patients admitted to stroke units.

Oral session 5

Genetics – 1

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A FRAMESHIFT MUTATION OF COX SUBUNIT III LEADING TO A LEIGH-LIKE SYNDROME. P. Corona, G. Uziel, F. Carrara, V. Tiranti, M. Zeviani, Istituto Nazionale Neurologico (Milano, I)

Human Cytochrome c Oxidase, COX, the terminal component of the mitochondrial respiratory chain, is composed of thirteen protein subunits: the three largest are encoded by mtDNA genes, while the remaining subunits are encoded by nuclear genes. Combined or isolated defects of COX account for a number of mitochondrial disorders including severe infantile myopathies, progressive encephalomyopathies, cardiomyopathies, and Leigh syndrome. Genes controlling the assembly of COX are responsible for some of them. Examples are mutations of SURF–1, leading to Leigh syndrome, or SCO2, causing a severe infantile cardiomyopathy. By contrast, in only a few reports have mutations been described in mtDNA-encoded COX structural genes, while no mutations are known in nuclear genes encoding COX subunits. We report here the first frameshift mutation in the mtDNA gene encoding COX subunit III. The proband is a 10 year old girl with a negative family history. Birth weight was 3600 gm; the psychomotor development in the first months of life was normal. However, she walked autonomously at 2 years; since 4 years of age she developed a progressive spastic paraparesis, associated with ophthalmoparesis, convergent strabismus, reduced visual acuity, and moderate mental retardation. The presence of severe lactic acidosis and Leigh-like lesions of putamina prompted us to perform muscle and skin biopsies. In both, a profound, isolated defect of COX was found by histochemical and biochemical assays. To establish whether the gene mutation underlying the disease was carried by a nuclear or a mitochondrial gene, we performed a complementation assay based on the fusion of the proband's fibroblasts with mtDNA-less human cells (rho-zero cells). The resulting hybrids did not show a correction of the COX defect. Contrariwise, full restoration of COX activity was obtained in cybrids of patient-derived rho-zero fibroblasts fused with control cytoplasts. Both results indicate the presence of a deleterious mutation in the mitochondrial genome. Accordingly, sequence analysis of the mtDNA COX genes revealed the presence of a virtually homoplasmic mutation in both muscle and fibroblast mtDNA, consisting in the insertion of an extra C in the midportion of the COIII gene. The frameshift produced by this mutation causes the creation of a stop codon next to it, leading to the synthesis of a prematurely truncated subunit. To understand the consequence of the mutation on the assembly of the holoenzyme, we performed western-blot analysis using anti-COXI antibodies on patient's mitochondrial proteins separated by 2D blue-native electrophoresis. Results showed an accumulation of early-assembly intermediates of COX, while the fully-assembled complex was absent. One of these intermediates had an electrophoretic mobility different from those seen in controls, suggesting the presence of a qualitative abnormality of COX assembly. From a clinical point of view, this is the first case of a Leigh-like syndrome due to a mutation in a structural COX gene. From a biochemical standpoint, it offers the possibility to study the role of COXIII on the structure and function of human COX.

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ALPHA–2 MACROGLOBULIN GENE AND ALZHEIMER'S DISEASE. R. L. Oliveri, R. Cittadella, V. Andreoli, R. Canonaco, I. Manna, G. Nicoletti, A. Quattrone, Clinica Neurologica, Univ. Catanzaro, IMSEB-CNR, CNR-IMSEB (Catanzaro, Cosenza, I)

Alpha–2 macroglobulin is a proteinase inhibitor found in association with senile plaques (SP) in Alzheimer's disease (AD), and recently the alpha–2 macroglobulin gene (A2M) on chromosome 12 has been suggested as a candidate locus for AD. Specifically, two polymorphisms in the A2M gene, the Val1000 (GTC)/Ile1000 (ATC) located in exon 24 and a pentanucleotide deletion Ins/Del located in exon 18, have been associated with the risk of developing AD, but data are still controversial. We determined the allelic frequencies and genotypic distribution of these two polymorphisms in a sample of 132 patients with dementia Alzheimer type (DAT) and 184 normal controls, frequency matched for age. No significant difference was observed in the allelic frequencies and the genotypic distribution between DAT patients and controls with regard to the Ins/Del variant. On the contrary, allelic and genotypic distribution of the Val1000/Ile1000 polymorphism was significantly different between cases and controls (Controls G=26 %, A=74 %; DAT patients G=36 %, A=64 %,chi2=7.03 p=0.008). Subject carrying the G allele had an increased risk of DAT(odds ratio:1.59, 95 % confidence intervals: 1.12–2.23). The present data confirm that genetic variation in the A2M gene may influence the risk of developing AD.

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COGNITIVE IMPAIRMENT IN PURE AUTOSOMAL DOMINANT HEREDITARY SPASTIC PARAPARESIS IS PARTICULAR TO SPG4 MUTATION CARRIERS. P. Mc Monagle, P. Byrne, B. Fitzgerald, N. Parfrey, M. Hutchinson, St Vincent's University Hospital, University College Dublin (Dublin, IRL)

Cognitive impairment occurs more often than expected in families with AD-HSP. It has been reported with paraparesis at the SPG4 locus on chromosome 2p but not at other loci. The SPG4 locus has recently been cloned. Purpose: To compare cognitive status among groups of patients with defined genetic status to identify whether cognitive decline is particular to individuals with SPG4 mutations. Methods: As part of an ongoing survey of HSP in Ireland, affected family members were examined by two neurologists. An assessment of cognitive function was performed using the Cambridge Cognitive examination (CAMCOG) in all over age 40. Maximum score is 107, scores under 80 indicate dementia. Blood was taken for linkage/mutation analysis and based on these results patients were divided into 2 groups. 1) SPG4 mutation carriers and 2) SPG4-excluded individuals. CAMCOG scores were compared using the Mann-Whitney U test. Results: 26 HSP affected individuals over age 40 were identified. 17 patients from 4 families with SPG4 mutations and 9 from 3 SPG4-excluded families. SPG4-carriers had a lower mean CAMCOG score (83.5/107) than the SPG4-excluded individuals (94.9/107, $p = 0.008$). CAMCOG scores < 80/107, indicating dementia, were found in 6 SPG4-carriers and none of the SPG4-excluded individuals. Conclusions: Cognitive impairment in AD-HSP appears to be particular to the SPG4 locus.

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ASSOCIATION BETWEEN 5-HT2A RECEPTOR POLYMORPHISM AND PSYCHOTIC SYMPTOMS IN ALZHEIMER'S DISEASE. B. Nacmias, A. Tedde, G. Marcon, C. Petruzzi, B. Guarnieri, A. Serio, P. Forleo, University of Florence, University of Udine, Casa di Cura Villa Serena (Florence, Udine, Pescara, I)

The first case description of Alzheimer's disease (AD), in 1907, has provided evidence of the risk of psychotic symptoms in patients with Alzheimer's disease. Recent studies reports that some 33 % of AD patients have delusions early in the course of the disease and 28 % have hallucinations. A recent observation has shown that common genetic polymorphisms in the 5-HT2A and 5-HT2C serotonin receptor genes are a risk factor for psychotic symptoms in the course of AD. According to this study, associations were found between the 102T/C polymorphism and the presence of visual and auditory hallucinations for genotypes frequencies. We analyzed the segregation of the polymorphisms in the 5-HT2A serotonin receptor genes in 203 patients affected by sporadic and familial AD with and without psychotic symptoms. A semi-structured interview was used to obtain information about delusions, hallucinations and other specific behavioural signs occurring during the clinical course of the disease. We used the presence of delusions or hallucinations as evidence of psychosis. The distribution of 5-HT2A 102T/C genotypes and allele frequencies in all the studied groups followed Hardy-Weinberg equilibrium and did not significantly differ from that of controls. The main finding of this study is the strong association of 5-HT2A polymorphism with the presence of psychotic symptoms either in Sporadic or in Familial AD. A stratification of the 5-HT2A data, based on the presence or absence of the ApoE e4 allele (patients with one or more e4 alleles were rated as e4 positive and the others were rated as e4 negative), revealed that AD patients, sporadic and familial, within the ApoE e4 carrier group did not show statistically significant differences with respect to e4 not carriers in relation to the C/T allele frequencies. Our data strongly confirm that the genetic variation at the 102T/C locus is associated with prominent psychotic features in AD and that the 102C allele could play an important role in the clinical course of late onset AD. Moreover our study provides evidence that the presence of psychosis is not significantly related to ApoE genotype and that the frequency of ApoE e4 allele is not significantly predictor of the presence of psychosis.

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ANGIOTENSIN CONVERTING ENZYME POLYMORPHISM IN PRESENILIN LINKED ALZHEIMER'S DISEASE FAMILIES AND SPORADIC ALZHEIMER'S DISEASE. A. Tedde, B. Nacmias, P. Forleo, G. Marcon, A. Orlacchio, S. Sorbi, University of Florence, University of Udine (Florence, Udine, I)

A recent study (Kehoe et al. 1999) has shown that genetic variation in the gene encoding Angiotensin converting enzyme (ACE) predisposes to Alzheimer's disease (AD) in a manner that is independent of Apolipoprotein E (ApoE). In this study an excess of ACE I/I and I/D genotypes was found in AD cases with respect to controls. However, different groups have published contrasting re-

sults. In order to investigate the possible implication of ACE gene polymorphism in sporadic (AD) and familial Alzheimer's disease (FAD), we have analyzed the segregation of this polymorphism in 69 mutated subjects (affected patients and at risk subjects) belonging to Italian families bearing pathogenetic mutations in Presenilin (PS) and APP genes: 36 subjects (age at onset, 39.86 ±14.30 years, mean ± SD) with the PS–1 Met146Leu mutation, 13 subjects (mean age, 55 ± 20.77) with the PS–2 Met239Val mutation, 20 subjects (mean age 46.65 ±13.18) carrying the APP Val717Ile missense mutation. Moreover we analyzed 51 patients belonging to 42 autopsy-proven AD families [24 late onset familial AD (mean age 76.15 ± 11.32) and 27 early onset familial AD (mean age 49.32 ± 12.6)] without mutations in the APP, PS–1 and PS–2 genes, but probably with other unknown mutations. In addition we studied 95 sporadic AD patients (age at onset 64.36 ± 8.84 years, mean ± SD) and 192 normal controls. PS–1 mutated subjects showed a higher frequency of the ACE/DD genotype (66.66 % Vs. 42.7 % in the control group, p=0.014) and the ACE/D allele showed the highest frequency compared to the control group (81.9 % Vs 64.5 %, p=0.006). No significant differences were found in the APP, PS–2 mutated and AD groups compared to controls, in particular APP mutated subjects had an overexpression of the ACE/DD genotype but this value was not statistically significant (60 %Vs 42.7 %, p> 0.05). Our data suggest that the ACE polymorphism may play a role in PS–1 mutated families.

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ROLE OF THE TAPASIN GENE IN SUSCEPTIBILITY TO MULTIPLE SCLEROSIS. M.G Marrosu, M.R Murru, G. Costa, R. Murru, E. Solla, C. Mancosu, C. Melis, F. Cucca, Multiple Sclerosis Center University Of Cagliari, Department Of Pediatrics (Cagliari, I)

Tapasin gene, located on the centromeric side of the HLA-DPB1 locus inside the MHC, is believed to have a critical role in the assembly and function of the MHC class I-TAP complexes. Dimorphism at codon 260 of the Tapasin gene determines two alleles, named Tapasin*01 (260 AGA) and Tapasin*02 (260 ACA). In order to evaluate the role of the Tapasin gene in susceptibility to multiple sclerosis (MS), we analyzed the weight of the 260 codon polymorphism on the "high risk" DRB1*0301-DQA1*0501-DQB1*0201 (DR3) and DRB1*0405-DQA1*0501-DQB1*0301 (DR4) Sardinian haplotypes using the transmission disequilibrium test (TDT). DNA was obtained from 200 singleton MS families (both parents, one affected and one healthy sib), all Sardinians. Amplification of the DRB1, DQA1, DQB1 exon 2, of the Tapasin gene exon 4, of the TAP1 and TAP2 gene polymorphism and dot-blot analysis of amplified DNAs with sequence-specific oligonucleotide probes was carried out. The Tapasin gene appears to have a modifying effect on the transmission of the predisposing DR3 haplotype, since the DR3-Tapasin*01 haplotype was preferentially transmitted to MS (%T 63.7, P=0.003) but not to healthy sibs, while the DR3-Tapasin*02 haplotype was neutrally transmitted to both affected and healthy sibs (%T 55.9 and 35.5, respectively). A decrease in the transmission of the DRB1*1601-DQA1*0102-DQB1*0502-Tapasin*02 haplotype (%T 22.9, P=0.00002)was evident in MS, suggesting a protective effect of this haplotype, while the DRB1*1601-DQA1*0102-DQB1*0502-Tapasin*01 was neutrally transmitted to both MS and healthy sibs (%T 52.5 and 60, respectively). In order to exclude that the effect of the Tapasin gene was due to linkage disequilibrium between the Tapasin and the TAP1 and TAP2 gene, we analyzed the extended DRB1, DQA1, DQB1, TAP1, TAP2, Tapasin haplotype. No variation on the results were observed. In conclusion, these data provide consistent and significant evidence that haplotypes identical at the DR/DQ, TAP1 and TAP2 loci but different at the Tapasin locus have different association with MS. In this sense, susceptibility to MS might result from complex interactions between multiple residues affecting various HLA class II molecules.

Oral session 6

Genetics – 2

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HOMOZYGOUS BUT NOT HETEROZYGOUS INTERMEDIATE CAG REPEAT EXPANSION IN THE CACNL1A4 GENE IS ASSOCIATED WITH SPINOCEREBELLAR ATAXIA TYPE 6. C. Mariotti, C. Gellera, M. C. Riggio, M. Grisoli, P. Boffi, D. Vacca, L. Morandi, S. Di Donato, Istituto Nazionale Neurologico, Osp. Inf. "Regina Margherita" (Milano, I)

Spinocerebellar ataxia type 6 is an autosomal dominant cerebellar ataxia (ADCA) clinically characterized by slowly progressive cerebellar ataxia, dysarthria, and impairment of eye movements. The disease is caused by small CAG repeat expansions in the gene coding for the alpha-A voltage-dependent calcium channel (CACNL1A4), on chromosome 19p13. Normal alleles have 7 to 18 repeats, whereas expanded alleles range from 20 to 29 repeats. Homozygous subjects carrying both expanded SCA6 alleles have been shown to present an earlier age of onset and a more severe clinical phenotype than the individuals heterozygous for the same expansion. We studied an Italian family in which the proband developed unsteady gait at age 33. The patient's mother, aged 70, had no neurological symptoms; the father died at age 77, and was referred to have no walking difficulties. A first-degree maternal cousin of the proband, aged 36, presented dysarthria and gait ataxia. The patient, now 43, presents marked cerebellar ataxia of trunk and limbs, mild dysarthria, slow eye movements, horizontal gaze-evoked nystagmus, brisk deep tendon reflexes, bilateral Babinski sign, and decreased vibration sense in lower limbs. Muscle tone and strength are normal. MRI of the brain at age 37 showed a marked atrophy of the cerebellar vermis and hemispheres, while the brainstem was normal. Acrylamide-gel electrophoresis and sequence analysis of the CAG repeats in the SCA6 gene, demonstrated that the proband carried 19 CAG repeats on both alleles; the unaffected mother and one unaffected maternal cousin were both heterozygous for one 11-CAG repeat normal allele, and one 19-CAG repeat "intermediate" allele, while an affected maternal cousin was heterozygous for the 11-CAG repeat normal allele and a pathologically expanded 27-CAG repeat allele.

Our molecular and clinical data suggest that an intermediate SCA6 allele of 19 CAG repeats is associated with progressive cerebellar ataxia in homozygous individuals, while heterozygous subjects for the same repeat length are asymptomatic. This finding is in agreement with the hypothesis of a gene dosage effect in SCA6 phenotype.

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FAMILIAL PARTIAL EPILEPSY WITH VARIABLE FOCI: CLINICAL AND GENETIC ANALYSIS OF A FIVE GENERATION SPANISH FAMILY LINKED TO CHROMOSOME 22Q11-Q12. F. Díaz-Otero, P. Gómez-Garre, M. Martín, R. Peraita, Y. Fernández-Bullido, J.C. Mulley, S.F. Berkovic, M. Pandolfo, J.M. Serratosa, Fundación Jiménez Díaz, Hospital Gregorio Marañón, Women's and Children's Hospital, Austin and Repatriation Med. Centre, Centre Hospitalier de l'Université (Madrid, E; Adelaide, Melbourne, AUS; Montréal, CDN)

Familial partial epilepsy with variable foci (FPEVF) is an idiopathic partial epilepsy characterized by partial seizures originating from variable brain regions in different family members in the absence of detectable structural abnormalities. A gene for FPEVF has been recently mapped to chromosome 22q11-q12 by Xiong et al. (1999). We have identified a five generation Spanish FPEVF family with 14 affected members. Interviews, EEGs, and video-EEG recordings were used to study the phenotype of the 11 living affected family members. Information on the three deceased family members was obtained through interviews. Chromosome 22q11-q12 microsatellite markers were typed in 26 members and linkage analysis was performed in order to confirm or exclude the existence of linkage to this locus. Mean age of onset of seizures was 11.6 years (range 1- 26 years). Seizures occurred exclusively during sleep (4 individuals), exclusively during wakefulness (3 individuals), or both during sleep and wakefulness (4 individuals). Thirteen patients presented secondarily generalized tonic-clonic seizures, some reporting clear partial symptomatology at onset (one patient presented frontal lobe seizures consisting of clonic movements of one side of the face). One individual presented benign epilepsy of childhood with centro-temporal spikes and was given unknown status for linkage analysis purposes. Interictal EEGs showed bursts of bilateral sharp waves in 3 patients and centro-temporal spikes in one patient. Video-EEG recordings demonstrated hypertonia of one limb, sitting up, extension of the head, or search movements during seizures in two patients. No ictal EEG abnormalities were recorded. Response to treatment with antiepileptic drugs was, in general, good. Mode of transmission was consistent with an autosomal dominant model with incomplete penetrance. Linkage analysis resulted in multipoint lod scores of 3.3 (recombination fraction = 0) for marker D22S689. The phenotype of this family is characterized by the presence of secondarily generalized tonic-clonic seizures, both during wakefulness and during sleep, with a nocturnal predominance. Few affected individuals reported characteristic focal onset symptoms at seizure onset, probably due to the nocturnal predominance of seizures or to their low frequency. Our findings confirm an autosomal dominant inheritance with incomplete penetrance and the previously reported chromosome 22q11-q12 locus for FPEVF.

P419
BEHÇET'S DISEASE. D.S Deniz Selçuki, Celal Bayar University (Manisa, TR)

Twenty-four patients diagnosed as neuro-Behçet's disease were surveyed clinically and radiologically (computed tomography, magnetic resonance imagings) in between 1990–1998. The main interval from the onset of Behçet's disease to nervous system involvement was 5.3 years. The most common neurological complication appeared as headache (15 patients). Other symptoms were weakness, forgetfulness, dizziness, speech dysfunction, personality changes and convulsions and peripheral neuropathy. 15 patients had undergone computed tomography (CT) examination. 8 patients had normal appearance at CT, 2 had cerebellar lesions, one had periventricular hypodense lesions, one had subarachnoid bleeding, one had an hypodense lesions in the midbrain area.

At magnetic resonance imagining, 2 patients had sinus thrombosis, 9 patients had periventricular white matter hyperdensity, spinal involvement. These clinical and radiological findings are discussed in concert with the systemic phases and therapies.

P420
SPINAL NEURORADIOLOGICAL FINDINGS IN CSF HYPOTENSION SYNDROME. M. Savoiardo, L. Chiapparini, L. Farina, L. D'Incerti, C. L. Solero, Ist. Naz. Neurologico C. Besta (Milano, I)

Introduction: Brain magnetic resonance imaging (MRI) findings in intracranial cerebrospinal fluid (CSF) hypotension are now well known, while spinal studies have been only rarely and incompletely described. We reviewed all the spinal neuroradiological examinations performed in patients with spontaneous intracranial CSF hypotension (SIH) syndrome looking for possible characteristic features.

Materials and Methods: Of the 17 patients with SIH observed at our Institute in the past 6 years, 9 (6 males, 3 females, aged between 28 and 59) had one or more neuroradiological examinations of the spine. The studies had been performed to complete the neuroradiological work-up or to search for a possible site of CSF leakage; in only one patient was MRI of the cervical segment performed because of local pain. In 4 patients there was history of previous minor trauma, in 2 of previous surgery on the spine and head, while in 3 history was completely unremarkable. All 9 patients had cervical, 6 thoracic, and 5 lumbar spine MRI studies. Some patients had repeated studies. MRI myelograms were obtained in 5 cases. Post-contrast MRI was available in 5 cases. Radioisotope myelocisternograms were obtained in 4 patients; myelo-CT in 4.

Results: In 7 cases, epidural CSF collections, anterior or posterior to the dural sac, with various extension, were found on MRI. In 4 cases, the dural sac was "collapsed" around the spinal cord, with a festooned appearance in axial sections due to tethering to the posterior longitudinal ligament and to the nerve roots exiting through the foramina. On post-contrast studies, intense epidural enhancement demonstrated marked dilatation of the epidural venous plexuses. In 4 cases, a long or irregular root sleeve suggested probable dural tearing, i. e. the probable point of CSF leakage. Myelo-CT demonstrated the CSF fistula in 2 cases, radioisotope myelocisternography in 3.

Conclusions: In spinal MRI studies, the pattern of dural abnormalities is different from that seen in cranial MRI because of anatomical reasons: the dural sac is not adherent to the bone and can, therefore, collapse with consequent dilatation of the epidural space filled by engorged, passively distended veins; enlargement of the venous plexuses should not be interpreted as resulting from increased venous pressure caused by a possible arteriovenous fistula. In most cases, the search for a point of CSF leakage is difficult and different studies need to be performed. MRI, myelo-CT, and radioisotope myelocisternography give complementary information and may suggest or demonstrate the point of CSF fistula.

P421
ANTINEURONAL AUTOANTIBODIES IN MOVEMENT DISORDERS. B. Giometto, M. Vianello, T. Scaravilli, R. Vitaliani, P. Nicolao, C. Betterle, B. Tavolato, Second Neurological Clinic, University of Padova (Padova I)

Background: Although it has been suggested that some neurological disease presenting movement disorders could be mediated by autoantibodies which cross-react with neuronal antigens, the only disease in which antineuronal antibodies have been characterized is the Stiff-Man syndrome (SMS). Recent findings suggest that other neurological conditions presenting movement disorders could be immune-mediated. In Sydenham chorea, it is presumed that neurological symptoms are mediated through induction of antibodies which cross-react with basal ganglia neurons, although no antineuronal antibodies have been so far demonstrated.

Methods and Results: In the group of 980 patients whose sera were examined for antineuronal antibodies according to the standardised procedures, 180 presented movement disorders. We detected antineuronal antibodies in 6 patients with SMS, in 3 with non-paraneoplastic chronic cerebellar ataxia and in 3 with myoclonus. These cases harboured anti-Glutamic Acid Decarboxilase (GAD) antibodies in their serum and cerebrospinal fluid, as tested by immunohistochemistry on rat cerebellum and RIA with recombinant GAD65. The GAD antibody titre was high both in the serum and in the cerebrospinal fluid. Most of these patients in addition to the movement disorders presented an organ-specific autoimmune disease that fulfilled the diagnostic criteria for Polyglandular autoimmunity. No reactivity was detected in cases with chorea and akinetic-rigid syndromes.

Conclusions: The range of movement disorders with antineuronal antibodies was limited in our study to patients with SMS, ataxia and myoclonus, where anti-GAD were the only autoantibodies detected. These data suggest that, in addition to SMS, other patients with movement disorders and Polyglandular Autoimmunity could present these antibodies. Interestingly, in these neurological conditions an alteration of the GABAergic system has been reported.

P422
THE SPECTRUM OF IMAGING FINDINGS IN PATIENTS WITH CEREBROTENDINOUS XANTHOMATOSIS (CTX) AND THE CORRELATION WITH NEUROPATHOLOGY. A. Verrips, F. Barkhof, P. Wesseling, M. S. van der Knaap, B. G. M. van Engelen, F. J. M. Gabreëls, A. Keyser, R. A. Wevers, J. Valk, University Hospital Nijmegen, University of Amsterdam (Nijmegen, Amsterdam, NL)

Objective: To describe the imaging findings and their neuropathological correlate in biochemical and genetically diagnosed patients with cerebrotendinous xanthomatosis (CTX), a rare but treatable inherited disorder of sterol storage, that is often misdiagnosed clinically and radiologically.

Methods: Cerebral CT (4 patients), cerebral MR (24 patients), spinal cord MR (5 patients) and tendon xanthoma MR scans (8 patients) were reviewed for site and frequency of involvement and compared with post-mortem neuropathological findings in 2 patients.

Results: Apart from non-specific brain atrophy and supratentorial deep white matter changes, more typical hyperintense T2 lesions were seen in the dentate nucleus (84%), globus pallidus, substantia nigra, and inferior olive, extending into the adjacent white matter as the disease progresses. In these locations, lipid crystal cleft and perivascular macrophages, neuronal loss, demyelination, fibrosis and reactive astrocytosis are found at microscopy. Sometimes low signal T2 in the dentate was found related to deposition of haemosiderin and calcification. CT showed fewer lesions, mostly hypodense, except for the calcifications. Spinal cord MR may reveal hyperintense signal in the lateral and dorsal columns. Achilles tendon xanthomas produced intermediate signal on T1 and T2 weighted images.

Conclusion: The typical pattern of MR findings reflects the classical histopathological findings and should prompt the diagnosis of CTX.

P423
CYCLOSPORINE NEUROTOXICITY AND STEROL 27-HYDROXYLASE BLOCKADE IN PATIENTS AFTER RENAL TRANSPLANTATION: A PILOT STUDY. A. Verrips, R. G. L. de Sévaux, F. T. M. Huysmans, B. G. M. van Engelen, R. A. Wevers, University Hospital Nijmegen (Nijmegen, NL)

Objective: Cyclosporine is a widely used immunosuppressive drug with several neurotoxic side effects, especially seizures, visual disturbances, headaches and tremor. In vitro, cyclosporine specifically blocks the enzyme sterol 27-hydroxylase (CYP 27), essential for bile acid synthesis from cholesterol. This enzyme is deficient in patients with cerebrotendinous xanthomatosis (CTX). Patients with this latter disease have an increased urinary excretion of bile alcohols and develop neurological symptoms and signs. To investigate whether blockade of CYP 27 also explains cyclosporine-induced central nervous system toxicity, a pilot study was performed.

Methods: Urine bile alcohol excretion was investigated in 12 patients with neurological symptoms and signs who underwent renal transplantation and in 6 healthy controls. Patients were classified according to the serum level of cyclosporine. Urine bile alcohol excretion (5-cholestane–3, 7, 12, 23–25-pentol, 5 -cholestane–3, 7, 12, 24–25-pentol, 5 -cholestane- 3, 7, 12, 27 nor–24–25-pentol) was expressed in mg/mmol creatinine.

Results: Total 24h excretion of bile alcohols was significantly higher in the patients group than in the controls ($p < 0.001$). After subclassification into patients with higher (n=6) and lower (n=6) serum cyclosporine level of 200 ng/ml the differences in total 24h urine bile alcohol excretion compared with the control group was still significant ($p < 0.02$ and $p < 0.003$ respectively).

Conclusions: There is an interference in bile acid synthesis in patients who use cyclosporine after renal transplantation, but the bile alcohol excretion is much lower than in patients with CTX. Therefore, a causal relationship between

increased bile alcohol excretion and cyclosporine-induced neurotoxicity cannot be established in this pilot study. Further research should clarify the possible causative role of other sequelae of CYP 27 blockade (like intracellular cholesterol or cholestanol accumulation) in cyclosporine neurotoxicity

P424
MEDIATION OF THE STROKE RISK FACTORS BLOOD LIPIDS AND COAGULATION THROUGH STRESS COPING STYLES. I. Anders, E. Esterbauer, G. Ladurner, U. Wranek, Christian Doppler Klinik, University of Salzburg (Bürmoos/ Salzburg, A)

Introduction: A pathological concentration of lipoproteins (total cholesterol, LDL- and HDL-cholesterol and triglycerids) as well as pathological values of blood coagulation parameters of (hematocrit, fibrinogen, viscosity) represent considerably high stroke risk factors. Various studies demonstrated relationships between these factors and stress coping styles.

Aim: The aim of this study was to investigate how stroke risk patients with the above mentioned risk factors differ from a risk factor free control group in their ways of stress coping.

Method: 2351 stroke prevention patients participated in a medical-psychological stroke risk investigation at the Christian Doppler Klinik Salzburg. The stress coping styles have been examined with the SVF questionnaire by Janke et al. Statistical analyses have been executed with t-test and U-test.

Results: Patients with pathological total cholesterol concentration showed significantly higher values in the avoidance of stress situations and a stronger tendency towards escapist behaviour. Prevention patients with pathologically high LDL values showed a tendency to higher values in the intake of narcotic substances. Patients with normal HDL cholesterol values indicated a tendency to higher values in positive self-instruction in comparison to patients with reduced HDL cholesterol values. Patients with increased triglycerides indicated significantly higher values in factor 6 of the SVF "alternative reinforcement". Men with normal hematocrit showed significantly higher scores in factor 4 of the SVF "evasive behaviour and distraction" and in the subtests positive self-instruction and resignation. Women with higher hematocrit values demonstrated higher scores in social seclusion. Men with higher fibrinogen values showed higher scores in factor 3 "cognitive coping by change of appraisal" and in the subtests distraction and vacarious satisfaction. Men free of risk factors had higher values in aggression. Women with normal fibrinogen values demonstrated higher scores in self pity and lower scores in minimizing by comparison. Men with normal values in whole blood viscosity showed higher scores in factor 2 "active stress coping" and in the subtest distraction. Healthy women showed higher values in response control attempts and lower scores in intake of narcotic substances than the risk factor group. Men featuring normal plasma viscosity presented tendencially higher values in tendency to flee. Women with normal plasma viscosity demonstrated higher scores in response control attempts than the risk factor group.

Conclusions: Risk patients with higher values showed significantly different coping strategies in comparison to those patients with normal values. Increased avoidance and escapism behaviour and also compensation and the abuse of narcotic substances could be seen in connection to an increase in the risk of a stroke. In contrast, a constructive coping strategy such as positive self-instruction could reduce the risk of a stroke. Positive effects of active stress coping styles on stroke risk factors have been proven. However some passive strategies showed higher scores also in the risk factor free group.

P425
STRESS COPING AS A MEDIATOR OF THE STROKE RISK FACTORS ADIPOSITY, CORONARY HEART DISEASE, NICOTINE AND ALCOHOL ABUSE. E. Esterbauer, I. Andres, M. Gstach, M. Huemer, G. Ladurner, U. Wranek, Christian Doppler Klinik, University of Salzburg (Bürmoos/ Salzburg, A)

Introduction: Coronary heart disease, adiposity, nicotine and alcohol abuse are all well known stroke risk factors. In various studies stress coping has been characterized as a mediator for important stroke risk factors.

Aim: The aim of this study was to investigate how stroke risk patients with the above mentioned risk factors differ from a risk factor free control group in their ways of stress coping.

Method: 1159 stroke prevention patients participated in a medical-psychological stroke risk investigation at the Christian Doppler Klinik Salzburg (neurological department). The risk factor adiposity has been explored by means of three age-related groups: adipose, obese, normal weighted (criteria of Garrow). The remaining risk factors have been investigated in the whole sample. The stress coping styles have been examined with the SVF questionnaire by Janke et al. Statistical analyses have been executed with t-test and ANOVA.

Results: Adipose men showed in comparison to normal weighted men higher values in aggression, desire for social support, vacarious satisfaction and self pity. Obese men demonstrated in comparison to normal weighted men higher scores in desire for social support, vacarious satisfaction and tendency to flee. Adipose and obese men did not differ in stress coping styles. Adipose women indicated in comparison to normal weighted women higher values in vacarious satisfaction and minimizing by comparing with others. Obese women showed in comparison to normal weighted women higher scores in vacarious satisfaction and positive self-instruction. Adipose women demonstrated in comparison to obese women higher values in positive self-instruction and lower scores in attempts to control the situation. Men with coronary heart disease indicated significantly higher values in factor 1 of the SVF "emotional dismay and abandonment" and in the subtest intake of narcotic substances. Women with this risk factor showed significantly lower values in factor 2 "active stress coping" and in the subtest search for assertion and higher values in intake of narcotic substances. Heart complaint free patients showed a tendency to more positive self instruction. Nicotine abusing patients showed significantly higher values in intake of narcotic substances. Men consuming wine showed higher values than non-drinkers in aggression, pharma intake and positive self-instruction. Women consuming wine showed higher values in positive coping styles than women consuming beer or non-drinking women.

Conclusions: Risk patients demonstrated significant differences in coping strategies in comparison to the risk factor free control group. Some strategies like desire for social support, positive self instruction and response control attempts have been recognized as positive coping mechanisms and could have a supportive influence on the decrease of stroke risk. Whereas passive stress coping styles like vacarious satisfaction, intake of narcotic substances, behaviour of escapism and avoidance have been found primarily within risk patients.

P426
A CASE WITH RADICULOPATHY, NEUROPATHY AND TEMPORAL ARTERITIS WITH A SIBLING SUFFERING FROM VASCULITIC NEUROPATHY. DIFFERENT MANIFESTATIONS OF A FAMILIAL VASCULITIC SYNDROME? J. H. M. Anneser, G. D. Borasio, Klinikum Grosshadern (München, D)

Classification of vasculitic disorders is a matter of controversy and various categorisation schemes have been suggested. Nevertheless, overlap syndromes are common and it is sometimes difficult to classify a case into exact disease categories. This might reflect the fact that the pathogenesis and the mutual relationship of vasculitic disorders are poorly understood.

We describe a 72-year-old female patient presenting with the typical symptoms of temporal arteritis. She additionally experienced sudden monoparesis of the left arm and peripheral symmetrical polyneuropathy, suggesting a more widespread inflammatory process. Biopsy of the temporal artery showed non-giant cell, non-specific vasculitis. Intriguingly, her brother had been admitted in our department 3 years earlier at the age of 72 with a diagnosis of symmetrical polyneuropathy which was most likely vasculitic in origin as revealed by sural nerve biopsy. Both patients had an excellent response to steroid treatment. Because of the common features in both cases (involvement of peripheral nerves, age of onset, evidence of a vasculitic process and impressive improvement with steroids) the hypothesis of a familial vasculitic syndrome is discussed.

P427
CHARACTERIZATION OF BRAIN PARENCHYMA LESIONS BY NMR – COMPLEMENTARY INFORMATION OF THE APPARENT DIFFUSION COEFFICIENT (ADC), MAGNETIZATION TRANSFER RATIO (MTR), AND SPECTROSCOPIC IMAGING. T. Beck, R. Möckel, J. Hirsch, J. Gaa, M. Hennerici, A. Gass, Klinikum Grosshadern, Klinikum Mannheim (Munich, Heidelberg, D)

Introduction: Diffusion-weighted MRI differentiates cytotoxic and vasogenic oedema, the magnetization transfer ratio is sensitive to quantify tissue destruction in demyelinating diseases, and proton spectroscopic imaging (MRSI) provides information on various cerebral metabolites. In the present study, the information of those methods was combined in order to obtain an in-vivo profile of various brain pathologies. Methods: Five healthy volunteers and 10 patients (multiple sclerosis [MS], cerebrovascular disorders, leukodystrophy) were investigated with conventional MRI (PD-, T2- and T1-weighted), ADC maps (TR 4000/TE 144 ms, b-values = 0–1000 s/mm2), MTR maps (3D-FLASH, TR 40/TE 5 ms, 1.2 kHz off resonance pulse, bandwidth 500 Hz, *sat = 500°), and MRSI (water-suppressed 1H spectra, TR 1500/TE 10/TM 30 ms; transverse oblique slab containing 10 voxels of 2 cm^3 size). Peaks of N-acetyl-aspartate (NAA), creatine (Cr) and choline (Cho) were expressed as NAA/Cr and Cho/Cr ratios. The ADC and MTR were determined in identical voxels to ensure identical partial volume effects compared to MRSI. Results: Normal values were established for all variables with a 2 standard deviation confidence interval to define significant differences. Most MS lesions showed an increased ADC,

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SCREENING THE CONNEXIN32 GENE IN HMSN PATIENTS, PARTICULARLY HMSN II, REVEALS 23 MUTATIONS OF WHICH 6 ARE NOVEL. H. Houlden, J. Blake, N. Wood, M.M Reilly, Institute of Neurology (London, UK)

Hereditary sensory and motor neuropathy is a heterogeneous condition. The characteristic clinical manifestations include distal muscle wasting and weakness, distal sensory disturbance, foot deformities and hyporeflexia. X-linked HMSN is well recognised. The affected male in the HMSN X family shows slowing of motor conduction velocity, typical for HMSN I; however, the female in the HMSN X family may show reduced amplitude of muscle action potential with normal or near normal motor conduction velocities more like HMSN II. Nevertheless, many patients have variable and overlapping neurophysiology manifestations between demyelinating and axonal neuropathy. Connexin32 mutations are the common cause of X-linked HMSN. We have screened all patients with HMSN type I which are negative for the duplication of 17p11.2 particularly if there was no male-to-male transmission in the family. All the HMSN X and HMSN II families without male-to-male transmission were included as well. Ninety-four patients have a family history. The other thirty patients' family history was not available; but the clinical manifestations such as pes cavus and very long disease history, suggest a genetic cause of neuropathy. After sequencing the connexin32 gene, twenty-three mutations have been detected. Six of them are novel. In these mutant patients, five have a clinical diagnosis of HMSN I, eleven HMSN II and seven HMSN X. In our study, the connexin32 mutation occurred frequently in patients with clinical diagnosis of HMSN II and without male-to-male transmission.

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SCREENING OF TWO CANDIDATE GENES, TRKA AND P75 NGFR IN THE MUTILATED FOOT (MF) RAT. M-J Lee, H. Houlden, M. Groves, N. W. Wood, F. Scaravilli, M. M. Reilly, Institute of Neurology (London, UK)

Mutilated foot rat (mf), which belongs to the Sprague-Dawley (SD) strain, is an autosomal recessive mutant rat. The principal signs in affected animals include ataxia, anesthesia with increased pain threshold, and eventually progressive ulceration with destruction of tissues of the feet. The most striking pathological feature is a markedly reduced number of myelinated and unmyelinated fibers in the lumbar dorsal root, and decreased neuron numbers in cervical and lumbar dorsal root ganglia (DRG). We are studying the mf rat to investigate the causative gene.

Nerve growth factor (NGF) plays an important role in differentiation and mediation of the sensory nervous system development. There are two types of receptors for NGF, i. e. trkA and p75 NGFR. Mutations of trkA gene has been detected in patients with congenital insensitivity to pain and anhidrosis. The trkA knockout mice also have insensitivity to pain. Increased pain threshold, ataxia, mutilated foot, and decreased size of DRG has been detected in p75NGFR knockout mice. Therefore, both trkA and p75 NGFR are candidate genes for the mf neuropathy.

We screened the coding regions of TrkA and p75 NGFR in mf rats, normal SD and Wistar rats. We also checked for deletions or duplications of the p75NGFR gene by southern blotting. Neither of these genes showed any abnormalities in the mf rat as compared to normal SD and Wistar rat. We are now backcrossing the animals to look for linkage by homozygosity mapping.

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MYELIN PROTEIN ZERO MUTATIONS IN TAIWANESE PATIENTS WITH HEREDITARY MOTOR AND SENSORY NEUROPATHY TYPE I. M-J Lee, H. Houlden, N. W. Wood, S-T Hsieh, M. M. Reilly, Institute of Neurology, National Taiwan University Hospital (London, UK)

Hereditary motor and sensory neuropathy (HMSN) is the most common hereditary neuropathy. Due to advances in molecular genetics in recent years, the HMSN type I (demyelinating) is now subdivided into IA, IB, IC, type X and autosomal recessive type. The most common genetic abnormality in HMSN IA is a duplication of chromosome 17p11.2–12, which contains the peripheral myelin protein 22 (PMP22) gene. Mutations in PMP22 itself are also found in a few HMSN IA patients without duplication. HMSN IB links to chromosome 1q22–23 and is caused by mutations in the myelin protein zero (P0) gene. Connexin32 mutations are the most common cause of X-linked HMSN. Early growth response 2 (EGR2) mutations are a recently described rare cause of HMSN I or HMSN III.

Five Taiwanese patients with a demyelinating neuropathy were studied genetically. The duplication of chromosome 17p11.2–12 had been excluded. PMP22, P0, connexin32 and its promotor region were sequenced. Two exons of the EGR2 gene have also been checked by SSCP. Two missense and pathogenic mutations, Ser51Pro and Val58Asp were found in the exon 2 of P0 gene in two patients. These two mutations are novel. This is the first report of P0 mutation in Taiwanese patients.

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JUVENILE, AUTOSOMAL DOMINANT, DISTAL SPINAL MUSCULAR ATROPHY AND NEUROSENSORIAL DEAFNESS NOT LINKED TO CHROMOSOME 12Q24. M. V. De Angelis, L. Stuppia, L. Passamonti, G. Palka, D. Gambi, A. Uncini, Center for Neuromuscular Diseases, Institute of Genetics, Institute of Genetics, Center for Neuromuscular Diseases Clinica Neurologica Ospedale SS Annunziata (Chieti, I)

Distal spinal muscular atrophy, also classified as spinal form of Charcot-Marie-Tooth disease or distal hereditary motor neuropathy, is genetically heterogeneous and both autosomal dominant and autosomal recessive inheritance have been described.

Recently in an autosomal dominant Belgian family with juvenile onset in distal leg muscles a significant linkage was obtained with markers located at chromosome 12q24 (Timmermann et al., 1996).

We described a three generation Italian kindred with distal spinal muscular atrophy showing autosomal dominant inheritance, onset at 8–10 years with leg weakness and atrophy, later involvement of distal arm muscles and eventually proximal muscles. The older patients had also neurosensorial deafness. To confirm the previous genetic findings we used four microsatellite markers located at chromosome 12q23–24: D12S86, D12S1612, D12S1349, PLA2A. No support for linkage with 12q24 was found in this family indicating a genetic heterogeneity in juvenile onset autosomal dominant distal spinal muscular atrophy.

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A NOVEL FORM OF AUTOSOMAL DOMINANT NEUROACANTHOCYTHOSIS WITH EXERTION-INDUCED PAROXYSMAL DYSKINESIAS. H. Lerche, A. Storch, A. Pekrun, Y. G. Weber, A. D. Sperfeld, E. Elitok, S. N. Reske, R. Linke, K. Tatsch, R. Tomczak, H. J. Gaertner, W. Sauermann, H. J. Christen, A. C. Ludolph, F. Lehmann-Horn, University of Ulm, University of Goettingen, University of Munich, Technical University of Dresden, Clinic of Dresden, Neustadt (Ulm, Goettingen, Munich, Dresden, Radebeul, D)

Neuroacanthocytoses are inherited disorders with typical morphological abnormalities of erythrocytes (acanthocytes) and variable movement disorders. Most frequent is a recessive form with chorea linked to chromosome 9q21. Here, we describe a three generation family with four affected individuals suffering from exertion-induced attacks of dystonia and choreoathetosis. The index patient (33 y) complains about a dystonic gait after long walks (> 30 min.) and the occurrence of involuntary choreoathetotic movements after a more heavy work load since the age of 6. Symptoms only occur in used muscles. Interictally, he does not report any neurologic symptoms and the clinical examination was normal. His mother had similar symptoms occurring less frequently beyond the age of 35 years. His 7 year old son has a mild permanent coordination problem and is little mentally retarded, but a reported hypoxia during birth probably complicates his clinical picture. The 1 year old son is neurologically completely normal. All affected family members have a moderate hemolytic anemia and an increased number of acanthocytes. Erythrocytes had a 4-fold increased intracellular Na+ and a decreased K+ concentration. Membrane protein electrophoresis and glycolytic enzymes of the erythrocytes were normal. CSF lactate was decreased. MRI scan of the brain was normal. FDG-PET scan showed a small decrease in glucose utilization in the right thalamus. SPECT scans measuring the pre- and postsynaptic parts of dopaminergic synapses in the striatum showed a borderline decrease in presynaptic signal on the right more than on the left side. EEG, EMG, nerve conduction studies, ischemia and ergometer tests measuring lactate, muscle biopsy, lipoproteins, long chain fatty acids, phytanic acid and amino acids were normal. Altogether a problem of the ionic transport, thus a mutation in a transporter or ion channel gene expressed in erythrocytes and the basal ganglia, seems the most probable cause of this novel form of neuroacanthocytosis.

Oral session 7

Multiple Sclerosis – 1

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CORTICOSTEROIDS OR ACTH FOR ACUTE EXACERBATIONS IN MULTIPLE SCLEROSIS. G. Filippini, F. Brusaferri, A. Citterio, G. Ciucci, R. Midgar, L. Candelise, Neurological Institute "C. Besta", General Hospital, Neurological Institute "Mondino", General Hospital, University of Bergen, University of Milan (Milan, Crema, Pavia, Ravenna, I; Bergen, N)

This review aimed to determine whether corticosteroids or adrenocorticotrophic hormone (ACTH) improve outcome in patients with multiple sclerosis (MS). The primary outcomes were: a) no improvement or worsening in disability grade on Expanded Disability Status Scale (EDSS) or equivalent score within a period no longer than 12 weeks from randomisation; b) proportion of patients who relapsed at 6 months, 1 year, 2 years, 3 years, from randomisation; c) proportion of patients who had disability progression 12 weeks forward till the end of the trial follow-up. Search strategy: The Cochrane MS Group Trials Register (last searched: September 1999) plus hand searching and personal contacts with trialists and pharmaceutical companies marketing steroids. Selection criteria: all completed, unconfounded, randomised controlled trials comparing corticosteroids or ACTH with placebo in patients with MS treated for acute exacerbation. Seven trials that met the inclusion criteria were included in the review. Data collection and analysis: Two authors independently assessed trial quality and extracted data. A third author checked them. The data analysis was made using Cochrane software. Main results: A total of 413 patients with MS were randomised in the seven trials (222 in the treatment and 191 in the control group). The drugs analysed were methylprednisolone (four trials, 140 patients) and ACTH (three trials, 273 patients). Overall, methylprednisolone or ACTH significantly reduced the risk of no improvement or worsening within five weeks from randomisation: relative risk (RR) 0.59 (95 % CI 0.47–0.75); the absolute risk reduction was 24.7 %. For methylprednisolone alone the RR was 0.45 (95 % CI 0.29–0.70) and that for ACTH alone 0.66 (95 % CI 0.50–0.87). There was not a significant difference between short (five days) or long (15 days tapering) treatment with methylprednisolone. For the other two outcomes the results were inconclusive: in one trial the RR for new exacerbations at 6 months from randomisation was 1.7 (95 % CI 0.6–5.2) and that of disability progression at 1 year 0.6 (95 % CI 0.1–3.5). Conclusions: Methylprednisolone or ACTH reduce the proportion of patients with no improvement or worsening early after exacerbations of MS; a short-term treatment with methylprednisolone is equally efficacious as a long-term treatment and may cause fewer side effects. The evidence for reduction of risk of new exacerbations or long-term disability worsening over a 1 year period of follow-up is inconclusive.

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HEALTH-RELATED QUALITY OF LIFE IN MULTIPLE SCLEROSIS PATIENTS: A POPULATION STUDY. A. Solari, D. Radice, Istituto Nazionale neurologico Besta (Milan, I)

Objectives. To assess the health related quality of life (HRQOL) profile of persons with multiple sclerosis (MS) living in Milan and nearby, and the consequences of the disease on social and occupational status, by a cross-sectional mail survey. Design/Methods. We identified 1350 patients with MS of age 318 years, living in the province of Milan from the computer records of the Lombardy Regional Health Service. To a random sample of 400 (34 %) of these we sent out the Multiple Sclerosis Quality-of-Life–54 (MSQOL–54) questionnaire, the proxy version of the Medical Outcome Study Short Form–36 (SF–36) questionnaire, a sociodemographic and medical questionnaire, and a cover letter. Results. We received 256 completed questionnaires (64 %); 163 responders were women (65 %), mean age was 42 years (standard deviation 12.2, range 18–71 years). Responders and non-responders were similar in age, sex and distribution of domicile within the area. Compared to 1636 healthy Italians of 23–68 years, the MS patients had lower scores in all SF–36 scales, differences being greatest for physical functioning, physical role limitations, vitality, and general health perceptions. Unemployment was 109 (42 %) overall, 50 % in women, and 56 % in the less educated. Fifty three patients (21 %) required daily home care and/or nursing services; 44 (17 %) had had their homes adapted; 100 (39 %) had been hospitalised in the previous year. Psychopharmaceuticals were the most commonly prescribed class of symptomatic drugs (25 % out of 160 patients receiving drug treatment over the last month). A proxy informant was available in 245 (96 %) overall, and he was the patient's spouse in 151 (62 %). Reliability between patient and proxy reports on the SF–36 ranged between fair and moderate, with proxies tending to slightly underestimate patient's HRQOL. Conclusions. MS has a substantial impact on MS patients' life, with marked social and economic consequences, that generally make themselves felt in the most active and productive period of life. This especially affects women and less educated patients.

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CHARACTERIZATION OF CCR4+ T CELLS IN MULTIPLE SCLEROSIS. A. Karni, K.E Balashov, W.W Hancock, S.J Khoury, H.L Weiner, Harvard Medical School Brigham and Women's Hospital, Leukosite (Boston, Cambridge, USA)

MS is postulated to be Th1 type cell mediated autoimmune disease of the central nervous system (CNS) associated with increased IFN-gamma production. We have previously shown that the chemokine receptor CCR5 and CXCR3, that are preferentially expressed on Th1 type cells, are detected in the brain lesions of MS. T cells expressing CCR4, which is preferentially expressed on Th2 type cells, were not found in brain specimens from patients with MS. We investigated the frequency of CCR4+ T cells among patients with MS and the effect of therapy with beta-interferon, corticosteroids or pulse cyclophosphamide on chemokine receptors expression and cytokines production. Peripheral blood mononuclear cells were isolated by Ficoll Hypaque centrifugation and were stained by flow cytometry with mouse anti-human CCR4, CCR5 and CXCR3 (Leukosite) and FITC conjugated goat anti-mouse Ig, and by PE or Cy-chrome conjugated mouse anti-human GD3. Intracytoplasmic staining for cytokines was performed using PE conjugated anti-human IL–2, IL–4, IL–10 and IFN-gamma. Purification of CCR4+ and CCR4– T cells was done by high speed flow cytometry, and the purified cells were studied for their cytokine production profile by ELISA after stimulation through the T-cell receptor. For chemokine receptor expression the only significant differences we observed were for CD3+CCR4+ T cells. CCR4 chemokine receptor expression on peripheral blood CD3+ T cells was significantly higher among untreated secondary progressive MS (SP-MS) patients (n=8) (34.0±11.5) and cyclophosphamide treated MS patients (n=16) (39.3±8.28) as compared to untreated relapsing remitting MS patients (n=19) (17.0±4.8), patients treated with beta-interferon (n=19) (24.3±9.6), methylprednisolone (n=9) (24.7±14.0) and healthy controls (n=19) (15.6±4.5). For cytokine production by CD3+ T cell expressing either CCR4, CCR5 or CXCR3, we found that in both MS patients and controls IL–10 was produced almost exclusively by CCR4+ cells, INF-gamma by CCR5+ and CXCR3+ cells and IL–4 by CCR4+, CCR5+ and CXCR3+ with increased frequency by CCR4+ cells. For INF-gamma, CD3+ cells from untreated MS patients had a significantly increased production of INF-gamma (26.1 %) compared to healthy controls (9.6 %) ($p < 0.02$) and there was normalization of raised IFN-gamma in all groups of treated patients, irrespective of treatment. For IL–4 and IL–10, we found a trend for increased production of these cytokines by CD3+CCR4+ cells in patients treated with cyclophosphamide (4 % and 3.8 %, respectively) as compared to the controls (1.3 % and 0.6 % respectively). Purified CD3+CCR4+ cells produced higher amount of IL–4 and IL–5 as compared to CD3+CCR4– cells, and did not produce IFN-gamma. In conclusion: CD3+CCR4+ cells, a subset of Th2 type, were increased in untreated SP-MS patients and in pulse cyclophosphamide treated patients. The latter patients were associated with increased production of IL–4 and IL–10. Differential expression of chemokine receptors was observed depending on cytokines produced by T-cells and may thus be used in future studies to study response of MS patients to immunomodulatory therapy.

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CSF ANTIBODIES TO THE LIGHT NEUROFILAMENT COMPONENT: A POTENTIAL MARKER OF DISEASE PROGRESSION IN MULTIPLE SCLEROSIS? E. Silber, Y.K Semra, N.A Gregson, M.K Sharief, Guy's, King's & St Thomas' Medical School King's College (London, UK)

Axonal loss contributes to disability in patients with multiple sclerosis (MS) however the mechanisms are uncertain. Using an enzyme-linked immunoassay (ELISA), we have recently identified elevated cerebrospinal fluid (CSF) levels of antibodies to the 68kD neurofilament component (NF-L), a major structural protein, in patients with primary and secondary progressive MS. We present further data characterising this immune response. Methods: Using a capture ELISA, NF-L protein in CSF was measured in patients with relapsing-remitting (RR, n=34) and primary (PP, n=10) and secondary (SP, n=14) progressive MS, other inflammatory (n=18) and non-inflammatory (n=35) neurological diseases and controls (n=9). These were compared to the concentration of CSF anti-NF-L specific IgG and an index of intrathecal anti-NF-L antibody production ("NF-L index"). To provide qualitative evidence of intrathecal production of NF-L specific antibodies, isoelectric focusing was

performed on matched CSF and serum from 13 MS patients and 4 controls. After focusing, specimens were adsorbed onto nitrocellulose membranes soaked in NF-L and developed with anti-human IgG to identify oligoclonal CSF IgG reactive with NF-L. Results: Anti-NF-L IgG was significantly elevated in PP and SP MS and other inflammatory diseases ($p< 0.0001$), the NF-L index was elevated in only the PP and SP MS groups ($p< 0.0001$). In contrast, there were no significant differences in levels of CSF NF-L protein between the diagnostic categories ($p=0.13$). There was no correlation between CSF NF-L and either CSF anti-NF-L IgG ($r=-0.06$; $p=0.5$) or the NF-L index ($r=0.04$; $p=0.7$). Independent CSF oligoclonal bands reactive with NF-L were identified in 7/13 MS specimens but in none of the controls. Conclusions: There appears to be an association between antibodies to NF-L and disease progression in MS, which is independent of CSF levels of NF-L, suggesting that this may not be only the result of NF release with axonal breakdown. The presence of independent oligoclonal antibodies reactive with NF-L provides further evidence that the intrathecal response to NF-L in patients with progressive MS is of restricted heterogeneity.

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DEVELOPMENT OF NEW LESIONS ON SERIAL T2-WEIGHTED MRI INCREASES THE RISK OF THE EARLY DEVELOPMENT OF MS FOLLOWING A CLINICALLY ISOLATED SYNDROME. P. A. Brex, K. A. Miszkiel, J. I. O'Riordan, G. T. Plant, I. F. Moseley, A. J. Thompson, D. H. Miller, Institute of Neurology (London, UK)

Many patients who present with clinically isolated syndromes (CIS) will have a relapse leading to the diagnosis of multiple sclerosis (MS). The presence of high signal lesions on T2-weighted magnetic resonance imaging (MRI) of the brain increases this risk. It is hoped that treatment of CIS patients may delay the time to develop MS. However, not all CIS patients do develop MS even amongst those with abnormal brain MRI. Treatment of all such patients would therefore be inappropriate and methods are required to select those at greatest risk. Method: 64 CIS patients (42 optic neuritis, 1 optic tract lesion, 15 brainstem & 6 spinal cord syndromes) had T2-weighted brain imaging at presentation [1.5T GE scanner, fast spin-echo sequence, slice thickness 3mm] and after three months. Brain images were regarded as abnormal if there were T2 lesions suggestive of demyelination and normal if either no lesions or only the symptomatic lesion was detected. A clinical review took place one year after presentation to determine the patients' clinical status. Results: At presentation, 72% (46/64) patients had abnormal baseline T2-weighted imaging and of these 37% (17/46) developed clinically probable (3) or definite (14) MS after one year. 40% (14/35) with four or more T2 lesions at baseline developed MS. In patients with abnormal baseline T2-weighted imaging, the presence of new T2 lesions after 3 months increased the risk of developing MS to 58% (15/26) whereas of those patients with an abnormal baseline T2-weighted image but no new lesions at 3 months follow up, only 5% (1/20) developed MS. In addition, only 5% (1/19) with normal baseline brain T2-weighted imaging and with no new T2 brain lesions at follow up developed MS within the year. Conclusion: The combination of an abnormal brain T2-weighted imaging at baseline and new T2 lesions after 3 months is associated with a high risk (nearly 60% of the early development of clinical MS). Early serial MRI should therefore be a suitable method for selection of patients for inclusion in future treatment trials aimed at delaying the evolution from CIS to established MS.

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CILIARY NEUROTROPHIC FACTOR (CNTF) GENE MUTATION IN A GERMAN POPULATION OF PATIENTS WITH MULTIPLE SCLEROSIS. M. Mäurer, R. Giess, M. Warmuth-Metz, D. Pohl, F. Hanefeld, K. V. Toyka, M. Sendtner, P. Rieckmann, Department of Neurology, Division of Neuroradiology, Department of Neuropediatrics (Würzburg, Göttingen, D)

CNTF promotes oligodendrocyte survival in vivo and protects cultured human oligodendrocytes from tumor necrosis factor-mediated cell death. Recently a G to A transition in the human CNTF gene has been described, which resulted in a truncated protein lacking biological activity. The aim of our study was to investigate the frequency of the CNTF null mutation among patients with multiple sclerosis (MS) and to analyze its relation to clinical characteristics and disease onset. Patients and Methods: 217 German MS patients (relapsing-remitting MS n=139, secondary-progressive MS n=63, chronic progressive MS n=15) were analyzed. The CNTF mutation was identified by RPLF-PCR. Disability was assessed by using Kurtzke's Expanded Disability Status Scale (EDSS), the rate of accumulation of neurological disability was expressed by the progression index (PI). NMR-spectroscopy data from MS patients with the CNTF null mutation and matched controls were collected. Results: Of 217 MS patients 155 (69.8%) were homozygous normal, 57 (25.7%) were heterozygous and 5 (2.3%) were homozygous mutant for the CNTF gene defect. No association of clinical MS subtypes and disease severity and the allelic distribution was found. However, patients with the CNTF null mutation revealed an earlier onset of clinical disease (CNTF -/- 19.2 y, CNTF ± 28.2 y, CNTF +/+ 28.4 y, ANOVA $p = 0.06$) with predominantly motor symptoms. Conclusion: The frequency of the CNTF-/- mutation was not increased in the MS population but patients with the homozygous CNTF mutation show a rather early disease onset in comparison to the majority of MS patients. This study provides evidence for a protective role of this neurotrophic factor in chronic inflammatory CNS disease.

Oral session 8

Multiple Sclerosis – 2

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MULTIPLE SCLEROSIS IS ASSOCIATED TO A FUNCTIONALLY ACTIVE PROMOTER ELEMENT OF THE T CELL SPECIFIC ADAPTER PROTEIN GENE SH2D2A. K-Z. Dai, H. F. Harbo, E. G. Celius, A. Oturai, L. P. Ryder, P. S. Sørensen, A. Svejgaard, J. Hillert, S. Fredrikson, M. Sandberg-Wollheim, K. M. Myhr, H. Nyland, M. Laaksonen, O. P. Dahl, F. Vartdal, A. Spurkland, Inst. of Immunology, Nath. Hospital, Dept. of Neurology, Ullevål Hospital, Dept. of Neurology, Rigshospitalet, Dept. of Clin. Immunology, Rigshospitalet, Inst. of Clin. Immunol, Rigshospitalet, Dept. of Neurology, Karolinska Inst., Dept. of Neurology, Lund Univ. Hosp., Dept. of Neurology, Haukeland Hosp., Turku Immunology Centre, Dept. of Neurology, Namdal Hospital (Oslo, N; Copenhagen, Denmark, DK; Huddinge, Lund, S; Bergen, N; Turku, FIN; Namsos, N)

The SH2D2A gene encoding the T cell specific adapter protein (TSAd) is involved in the control of the early T cell activation. It is located in the 1q21 region close to the CD1 gene cluster. This chromosomal region has been implicated in the susceptibility to experimental encephalomyelitis in the mouse. A polymorphic GA repeat (allele lengths ranging from 13 to 30 GA repeats) is located in the promoter region of the SH2D2A gene. We analyzed whether this marker on the SH2D2A gene confers susceptibilty to multiple sclerosis (MS). Results: The distribution of the GA repeat alleles was examined in a total of 309 Norwegian unrelated MS patients and 276 Norwegian controls, using an ABI fluorescent scanner and the Genotyper software. In two repeated experiments we found that the combined gene frequency of the two short alleles (GA13 and GA16) was increased among MS patients compared with controls, the GA13 significantly so (0.097 versus 0.053, $p=0.0052$). To evaluate a possible contribution of other genes in this region, we performed linkage analysis in 150 Nordic sib pair MS families, using markers spanning 25 cM around the SH2D2A locus. No evidence of linkage of MS to genes in this region was observed. However, transmission disequilibrium analysis of the same data revealed association of the short GA16 allele to MS ($p=0.0002$). Since the GA repeat is located in the promoter region of the SH2D2A gene, it may influence the transcriptional avtivity of the gene. Three different 1kb fragments of the promoter representing the GA13, GA16 and the GA23 alleles, were therefore assessed for transcriptional activity in Jurkat cells using a luciferase reporter system. The MS associated alleles GA13 and GA16 showed markedly lower basal and induced transcriptional activity compared to the GA23 allele, which was not associated with MS.

Conclusion: MS is associated to short alleles in the promoter of the SH2D2A gene. Since we observed no evidence of linkage, the primary association is probably to the SH2D2A gene itself or a gene in the vicinity. Interestingly, we have shown that the associated alleles are less transcriptionally active than the alleles not associated with MS, suggesting a mechanism by which the SH2D2A gene may confer disease susceptibility.

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LONG-TERM EFFICACY OF INTERFERON BETA–1A (REBIF) IN RELAPSING MS: 4-YEAR PRISMS RESULTS. J. McLeod, The PRISMS Group, University of Sydney (Sydney, AUS)

Previously reported data from the PRISMS trial involving 560 Relapsing Remitting Multiple Sclerosis (RRMS) patients treated for two years with Rebif® doses of 22mcg tiw or 44mcg tiw or placebo demonstrated a statistically significant benefit of both doses over placebo on multiple clinical and MRI outcome measures. Objectives: The PRISMS trial, a double-blind, multinational study, was extended two years. Placebo patients were randomized to receive either Rebif 22mcg tiw or 44mcg tiw in years 3 and 4 but remained blinded

to dose as did the patients originally assigned to active drug. The objectives of the extension phase were to assess 1) whether efficacy was sustained beyond two years, 2) whether a clinical dose-response was apparent after 4 years therapy and, 3) whether early treatment (years 1 to 4) produced greater benefit on disability than delayed treatment (years 3 and 4 only). Methods: Ninety percent (506/560) of the original PRISMS cohort continued in the extension phase. Patients had neurological assessments every 6 months and annual PD/T2 MRI scans during the extension. Patients were examined by a treating physician who supervised drug administration, monitored safety, and managed adverse events and an evaluating physician who conducted neurological assessments. Results: Patients converting to Rebif from placebo demonstrated 52–54% reduction in relapse rate compared to placebo years ($p = 0.0001$) with significantly reduced MRI activity and accumulation of lesion burden ($p < 0.0001$). Rebif 44 tiw (132mcg weekly) reduced relapses better than Rebif 22 tiw ($p = 0.07$) while both doses were superior to placebo/treatment arms ($p < 0.005$). Relapse rate was significantly lower in years 3–4 in the Rebif 44 tiw group then Rebif 22 tiw ($p=0.02$). During years 3–4, when all patients were on active drug, there was evidence of a carry-over benefit of early therapy compared to later therapy (Rebif 44 tiw vs Placebo/44, $p = 0.01$). High dose Rebif significantly prolongs time to first progression compared to the placebo/treatment group ($p = 0.01$) and reduces the total number of progressions compared to Rebif 22 tiw ($p = 0.05$) and placebo/treatment arms ($p = 0.001$). Both doses strongly diminish the MRI active lesion development and the accumulation of lesion burden over time compared to placebo ($p < 0.001$). Rebif 44 tiw is more effective on MRI outcomes than Rebif 22 tiw ($p < 0.001$). Rebif at both doses is safe and well tolerated as less than 10% of patients treated with active therapy withdrew for adverse events over 4 years. Conclusions: The data demonstrate a continued benefit of Rebif 22 and 44 tiw therapy up to 4 years. Dose-effect was noted with Rebif 44 tiw having greater benefit on both clinical and MRI parameters. The true effect of Rebif on relapses may be greater than previously thought. Finally, patients treated early attain more benefit on all outcome measures than those delaying treatment.

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A PROSPECTIVE, OPEN-LABEL TREATMENT TRIAL TO COMPARE THE EFFECT OF AVONEX (IFNB–1A), BETASERON (IFNB–1B), AND COPAXONE (GLATIRAMER ACETATE) ON THE RELAPSE RATE IN RELAPSING-REMITTING MULTIPLE SCLEROSIS: RESULTS AFTER 18 MONTHS OF THERAPY. O Khan, A Tselis, J Kamholz, J Garbern, R Lewis, R Lisak, Wayne State University (Detroit, Michigan, USA)

We previously reported the results of a prospective, non-randomized, open-label treatment trial in patients with relapsing-remitting multiple sclerosis (RRMS) with follow up for 12 months. Our primary objective was to prospectively compare the effect of Avonex', Betaseron', and Copaxone' on the relapse rate in patients with RRMS. We now report the results of an additional six months of follow up with the total duration of prospective follow up reaching 18 months per patient. Prior 2-year relapse history and available chart information was carefully reviewed at the time of enrollment. Thirty three of 156 elected no treatment (mean age 32.5 years; mean EDSS 2.64) at enrollment; 40 elected Avonex' (mean age 32.4 years; mean EDSS 2.69), 41 Betaseron' (mean age 32.1 years; mean EDSS 2.56), and 42 chose Copaxone' (mean age 31.5 years; mean EDSS 2.57). Annual relapse rate based upon the 2 years prior to enrollment was 1.08 in the Untreated group, 1.20 in the Avonex' group, 1.21 in the Betaseron' group, and 1.10 in the Copaxone' group. There were no statistically significant differences among the four groups at enrollment. After 12 months of treatment, patients in the untreated groups had a relapse rate of 0.97, whereas patients in the Avonex', Betaseron', and Copaxone' groups had relapse rates of 0.85, 0.61, and 0.62, respectively. Compared to the untreated group, reduction in the relapse rate was statistically significant only in the Copaxone' ($p=0.003$) and IFNb–1b ($p=0.002$) groups in contrast to the Avonex' treated patients who did not show a significant reduction ($p=0.309$). Compared to the untreated patients, mean EDSS was significantly reduced only in the Copaxone' ($p=0.001$) and Betaseron' ($p=0.01$) treated patients in contrast to patients treated with Avonex' ($p=0.51$). As reported previously, compared to untreated patients, treatment with only Copaxone and Betaseron significantly reduced the relapse rate in contrast to patients treated with Avonex who did not demonstrate a significant reduction in the relapse rate. Our results are similar to the observations made after 12 months of therapy in phase III studies of Avonex 'Betaseron' and Copaxone. Final analysis of the 18 month follow up will be available on March 1, 2000 and presented at the meeting. Despite some limitations of the study design, the results provide helpful clinical information regarding the relative efficacy of each therapy in mildly affected treatment naive RRMS patients.

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MICROGLIAL SUPPORT IS RECRUITED THROUGH CHEMOTACTIC SIGNALS RELEASED BY STRESSED OLIGODENDROCYTES. R. S. Nicholas, M. G. Wing, D. A. S. Compston, Addenbrooke's Hospital (Cambridge, UK)

Background: Activated microglia are toxic for oligodendrocytes through a cell contact dependent mechanism. We have in addition determined that soluble microglial factors have effects other than cell injury on oligodendrocytes. They promote oligodendrocyte precursor survival and maturation, survival of differentiated oligodendrocytes and exert autocrine inhibition of microglial-derived tumour necrosis factor alpha toxicity in monolayer culture. Aim: If microglia have beneficial as well as toxic effects on oligodendrocytes do oligodendrocytes actually recruit microglia when they are under stress?

Methods: Microglia and oligodendrocytes were sequentially derived from rat mixed glial cultures. Oligodendrocytes were grown in insulin and serum-free, insulin ± serum supplemented media and oligodendroglial death was quantified at 48 hours. At time points up to 48 hours media was removed from oligodendrocyte cultures for use in a chemotaxis assay. The migration of non-activated or interferon gamma treated microglia towards oligodendrocyte conditioned media was quantified.

Results: Conditioned media derived from 48-hour-old insulin and serum-free oligodendrocyte cultures where 75% oligodendrocytes die are chemotactic for microglia. The chemotactic effect is reduced in the less stressful conditions of insulin (70% oligodendrocyte death) and serum (10% oligodendrocyte death). The chemotactic factor production by oligodendrocyte cultures peaks after 8 hours in stressed cultures. The signal is not dependent on cell death, as oligodendroglial lysis does not reproduce the effect. Interferon gamma activation of microglia enhances their sensitivity to the chemotactic effects of oligodendroglia.

Discussion: Stressed oligodendrocytes are actively chemotactic for microglia. This property could potentially allow microglia selectively to target and determine the fate of oligodendrocytes that are acutely stressed or damaged.

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COGNITIVE DEFICITS IN PATIENTS WITH MULTIPLE SCLEROSIS AND CORRELATING NEURONAL DYSFUNCTION AS REVEALED BY LOW RESOLUTION ELECTROMAGNETIC TOMOGRAPHY – LORETA. S. Mientus, J. Gallinat, R. Pascual-Marqui, J. Haas, University Hospital of Psychiatry Benjamin Franklin, Key Institute for Brain Mind Research, Jewish Hospital (Berlin, D; Zurich, CH)

Cognitive impairments in Patients with Multiple Sclerosis (MS) have frequently been reported since the first works of Charcot (1877) and add considerably to the distress and disability of the patients. Different components of the executive function including working memory, selective and focused attention and strategic planning are impaired. Even though it could be shown that there is a significant correlation between number and volume of lesions and neuropsychological test performance, evidence for focused cortical dysfunction is missed. We set out to elucidate the correlation between cognitive performance deficit in patients with MS and cortical dysfunction by applying LORETA to electrophysiological data obtained simultaneously to the neuropsychological test. Methods: 24 unmedicated MS Patients, diagnosed according to Poser-criteria, and 14 healthy controls underwent simultaneous evaluation of neuropsychological test performance, realised by repetitive (3 times) tracing trials of a multiple t-junction maze, and corresponding brain electric activity as given by EEG. Applying LORETA-analysis, that allows for frequency selective source estimation and statistical group comparison, results were calculated and visualized based on anatomical information of the Talairach Atlas. Results: All subjects successfully performed the maze-test. With repetitive tracing trials healthy controls as well as patients improved test-performance, which was measured by a significant reduction of tracing-times, even though patients were significantly slower than control subjects. LORETA-analysis revealed significant group differences especially in the theta-frequency band (4–7.5Hz). Patients showed less activation in precisely circumscribed cortical regions of the frontal cortex, i. e. Brodmann Area 9 (BA 9) and the anterior parts of the cingulate. Posterior cingulate areas (BA 7) developed a significant deficit with repetitive tracing-trials, while the anterior pattern especially in BA 9 remained unaffected by repetition. Conclusion: Applying LORETA-analysis to electrophysiological data obtained during a neuropsychological test we could provide, to our knowledge the first time, evidence for a direct correlation between deficits in cognitive performance and cortical dysfunction in Multiple Sclerosis. Previous work about functional organization of cognitive processes has shown that BA 9 acts as a region of executive processes. Considering the unchanged pattern of deficient activation of BA 9 we can confirm the assumption that processes localized in

this region maintain a key position for cognition. Since BA 9 maintains reciprocal connection with the cognitive effector region of the anterior cingulate and since BA 7, which represents the sensory component of the extrapersonal attentional network, receives open efferents from the cognitive effector region and maintains connections with BA 9 we assume that we found components of the functional network that mediates attention- and working memory processes. Being able to detect components of attentional network structures by applying LORETA-analysis possibly might lead to a powerfull tool of therapy-prediction.

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ECHO PLANAR IMAGING – FAST FLUID-ATTENUATED INVERSION RECOVERY (EPI-FLAIR) IMAGING IN MULTIPLE SCLEROSIS. M. Rovaris, G. Iannucci, C. Pereira, G. Comi, M. Filippi, Neuroimaging Research Unit, Clinical Trials Unit, IRCCS HSR, Neuroimaging Research Unit Scientific Institute Ospedale San Raffaele (Milan, I)

Fast fluid-attenuated inversion recovery (fast-FLAIR) sequences are very sensitive for detecting lesions of patients with multiple sclerosis (MS). Echo planar imaging allows to obtain FLAIR images (EPI-FLAIR) with significantly shorter scanning times. EPI-FLAIR images obtained with 10 measurements are as sensitive as fast-FLAIR for the detection of large MS lesions, but their acquisition time is similar to that of fast spin echo T2-weighted images. We compared the numbers of MS lesions seen on EPI-FLAIR images with fewer measurements (and, as a consequence, very short scanning times) with those seen on EPI-FLAIR images with 10 measurements, to assess their sensitivity for MS lesion detection. EPI-FLAIR scans with 2 (EPI–2), 4 (EPI–4), 6 (EPI–6), 8 (EPI–8) and 10 (EPI–10) measurements were obtained in a single session using a 1.5 Tesla scanner. Twenty-four, 5-mm thick contiguous axial slices were obtained. The total acquisition times were 32 seconds for EPI–2, 1 minute and 4 seconds for EPI–4, 1 minute and 36 seconds for EPI–6, 2 minutes and 8 seconds for EPI–8 and 2 minutes and 40 seconds for EPI–10 scans. Lesions seen using each of the five approaches were counted by agreement by two observers. EPI–10 images were used as the "gold standard" for pairwise comparisons. Twenty-nine MS patients were studied. Their mean age was 39.2 years (range: 22–65 years), median disease duration 7.0 years (range: 2–28 years) and median expanded disability status scale (EDSS) score 2.0 (range: 1–6). The disease course was relapsing-remitting in 20 cases and secondary progressive in 9 cases. EPI-FLAIR scans with fewer measurements (EPI–2, –4, –6, –8) were all significantly less sensitive than EPI–10 for the detection of small, intermediate and large MS lesions. Susceptibility and chemical shift artifacts were evident on all the scans. The severity of artifacts and the subjective scores for rating image quality were similar for the EPI-FLAIR scans obtained with different numbers of measurements. All the scans obtained with the five EPI-FLAIR acquisition schemes fulfilled the criteria for a definite MR diagnosis of MS. When rapid MR scanning of uncooperative MS patients is needed, EPI-FLAIR images covering the entire brain in less than one minute may be considered. Acknowledgements. Supported by a grant from the Istituto Superiore di Sanità (National Ministry of Health, Rome, Italy; contract n. 96/J/T49).

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A PILOT STUDY OF RECOMBINANT INSULIN-LIKE GROWTH FACTOR–1 (RHIGF–1) IN SEVEN MULTIPLE SCLEROSIS PATIENTS. T. Leist, N. Richert, B. Lewis, T. Howard, R. Stone, J. Eaton, H. McFarland, J. Frank, Neuroimmunology Branch, Laboratory of Diagnostic Radiology Research, Laboratory of Diagnostic Radiology Research National Institutes of Health (Bethesda, USA)

Insulin-like growth factor (IGF)–1 is a cytokine that has been shown to reduce the number of Blood Brain Barrier (BBB) defects and both the numbers and sizes of inflammatory, demyelinating, and demyelinated lesions in the experimental autoimmune encephalomyelitis (EAE) in the rat and mouse. rhIGF-I treatment was well tolerated and that the anti-inflammatory effects of IGF-I have a major role in reducing clinical deficits and lesion severity in these EAE models. The purpose of this cross-over study was to determine the safety and potential effect of recombinant Insulin Like Growth Factor–1 (rhIGF–1) on various MRI and clinical measures of disease activity in Relapsing Remitting (RR) and Secondary Progress (SP) Multiple Sclerosis (MS) Patients. Methods: 7 Patients (3 SP and 4RR) of age between 32–55 years old and Expanded Disability Status Scores of 1–8.5 were enrolled in this study. None of the MS patients had received any immunomodulating therapy within 6 months of starting the baseline period of the study. Monthly clinical and MRI examinations were performed during 6 month baseline and 6 month of rhIFG–1 treatment periods. MRI was preformed at 1.5 Tesla. Primary outcome measure was a decrease in contrast enhancing lesion (CEL) frequency on treatment compared to baseline. Secondary outcome measures were changes in EDSS, exacerbartion rate, White Matter Lesion Load, Magnetization Transfer Ratio (MTR) T1-Hypointensity volume, and proton MRS imaging. rhIGF–1 (Cephalon, Inc) was administered at 50 mg subcutaneously twice a day for 6 months. Results: In these 7 patients, rhIGF–1 was safe and well tolerated with no severe adverse reactions. There was no significant difference between baseline and treatment periods for CEL or any other MRI or clinical measures of disease activity. In addition, there was no change in metabolite ratio on proton MRSI of MS lesions with rhIFG–1 treatment or in global MTR metrics. Conclusion: rhIGF–1 was safe, well tolerated without at injection site reactions, and did not result in an increase in MS disease clinical or MRI activity in this small cohort of MS patients. In future studies, the effects of long-term administration of the medication on disease activity and repair of myelin should be studied in a larger cohort of patients.

Oral session 9

Motor neuron disease and motor neuropathy – 1

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MULTIFOCAL MOTOR NEUROPATHY: CLINICAL AND IMMUNOLOGICAL FEATURES AND RESPONSE TO IVIG IN PATIENTS WITH DEFINITE, PROBABLE OR NO OVERT CONDUCTION BLOCK. E. Nobile-Orazio, N. Meucci, M. Carpo, F. Terenghi, A. Bersano, A. Cappellari, S. Barbieri, G. Scarlato, IRCCS Ospedale Maggiore Policlinico (Milan, I)

Multifocal motor neuropathy (MMN) is characterized by progressive asymmetric limb weakness usually predominant in the upper limbs associated with conduction block (CB) in motor but not sensory nerves. There are however occasional patients with clinically typical MMN in whom no overt or definite CB can be detected. Whether these patients differ from patients with MMN and definite CB remains unclear. Since 1991 we observed 24 patients with the typical clinical features of MMN. In 15 of them (10 men, 5 women) electrophysiological studies disclosed the presence of definite CB (> 40 % amplitude reduction with < 15 % increased duration of proximal versus distal CMAP) in at least one motor nerve. Five patients (4 men, 1 woman) had probable CB [> 30 % proximal versus distal CMAP amplitude reduction with (4 patients) or without (1 patient) increased temporal dispersion] in at least two motor nerves. In four patients (all women) no evidence of CB could be detected in examined nerves, even if three had some features of demyelination including asymmetric reduction of motor conduction velocities (1 patient) or prolonged or absent F-wave latencies (3 patients); three of them had markedly decreased or absent proximal and distal CMAP amplitudes in some nerves. The mean age of onset of MMN was similar in patients with definite (41.5 years, range 21–55), probable (41.8 years, range 25–70), or no CB (41.5 years, range 24–57). The mean duration of the disease at the time of our first evaluation was longer in patients without CB (18.5 years, range 13–25) than in those with definite (6.7 years, 3 months–21 years) or probable CB (8.4 years, 1–25) with only two patients with definite and one with probable CB having a disease duration longer than 10 years. All patients without CB had a predominant or exclusive impairment of upper limbs as compared to 11 (73 %) with definite and 4 (80 %) with probable CB. The median Rankin score before therapy was worse in patients without (3) than with definite (2) or probable (2) CB. Anti-ganglioside antibodies were found in one patient (25 %) without CB, six (40 %) with definite and 2 (40 %) with probable CB. All but two patients with definite (87 %) and all those with probable CB consistently improved with IVIg. All patients without CB also improved with IVIg but only two did so consistently. MMN patients with probable CB are clinically and immunologically indistinguishable from those with definite CB. The longer duration and higher severity of disease and frequent axonal impairment in patients with clinically typical MMN but no overt CB may explain the lower efficacy of IVIg in these patients than in those with definite or probable CB.

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MULTIFOCAL MOTOR NEUROPATHY: DIAGNOSTIC CRITERIA AND RESPONSE TO IMMUNOGLOBULIN TREATMENT. R. M. Van den Berg-Vos, H. Franssen, J. H. J. Wokke, H. W. Van Es, L. H. van den Berg, UMCU, St. Antonius Hospital (Utrecht, Nieuwegein, NL)

Background: Multifocal motor neuropathy (MMN) is a rare immune-mediated treatable neuropathy. As most previously published studies on MMN were relatively small and patients underwent variable (electro)diagnostic ex-

amination and immunologic therapy, diagnostic criteria for MMN have not been defined.

Goal of the study: To propose diagnostic criteria for MMN and evaluate the response to therapy with intravenous immunoglobulins (IVIg).

Methods: In a prospective study, 37 patients with an asymmetric lower motor neuron disorder and features compatible with segmental demyelination on electrophysiologic examination were included. All patients were investigated using a standardized clinical and electrodiagnostic examination and were treated with IVIg.

Results: Conduction block (CB) was found in 33 patients and features compatible with demyelination other than CB in 4 patients. Twenty-three patients responded favourably to IVIg. Age at onset of disease, the number of affected limb regions before treatment and the number of patients with an elevated CK were significantly lower in the responders than in the non-responders and the number of patients with elevated anti-GM1 antibodies, the finding of CB and the mean distal amplitude on electrophysiological examination were significantly higher in responders than in non-responders. On the basis of these clinical, laboratory and electrophysiologic findings and the comparison of the electrophysiological criteria for CB used in the present study and those proposed by others, we propose diagnostic criteria for MMN that were verified by follow-up and response to IVIg treatment.

Conclusion: Based on our criteria, 21 patients had definite MMN (17 responders), seven patients had probable MMN (5 responders) and nine patients possible MMN (1 responder). These criteria may help early diagnosis of this treatable disorder.

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APOLIPOPROTEIN E EPSILON–4 GENOTYPE IN AMYOTROPHIC LATERAL SCLEROSIS. M. Birnbaum, V. E. Drory, J. Chapman, A. D. Korczyn, Tel-Aviv Sourasky Medical Center, Sieratzky Chair of Neurology, Tel-Aviv University (Tel-Aviv, IL)

OBJECTIVE: To examine the frequency of the Apolipoprotein E allele epsilon–4 (APOE epsilon–4) allele in a large group of ALS patients and correlate its presence to relevant clinical features. BACKGROUND: APOE epsilon–4 influences the age of onset of Alzheimer's disease, and affects the prognosis and clinical features of other neurodegenerative disorders. In amyotrophic lateral sclerosis (ALS), APOE genotyping revealed inconclusive results. DESIGN/METHODS: DNA samples of 93 ALS patients were amplified by PCR and digested by restriction enzyme to identify specifically the APOE allele. For comparison we used a previously described group of 148 normal controls of similar ethnicity. For statistical analysis we used x2 and Kaplan-Meier survival curves. RESULTS: The frequency of APOE epsilon–4 allele in ALS patients was 16.5 %, which was significantly higher than in controls (8.7 %; p=0.01). The survival of patients with one epsilon–4 allele was significantly shorter than that of patients without epsilon–4 allele (p=0.01), and the rate of progression (defined as time from disease onset to ALS Functional Rating Scale 20) of patients with one epsilon–4 allele was faster than that of patients with no epsilon–4 allele (p=0.05) CONCLUSIONS: The APOE epsilon–4 allele seems to have a deleterious effect on the clinical expression and progression of ALS. Our results can be explained by an impaired axon repair process in patients with APOE epsilon–4.

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CORTICAL ABNORMALITIES ARE MORE EXTENSIVE IN PRIMARY LATERAL SCLEROSIS THAN IN AMYOTROPHIC LATERAL SCLEROSIS: A [11C] FLUMAZENIL PET STUDY. I. Bonnaud, L. Spelle, F. Salachas, N. Le Forestier, J. Moret, J. Salama, Y. Samson, V. Meininger, Hôpital Avicenne, Fondation Rothschild, Hôpital De La Salpêtrière, Fondation Rothschild (Bobigny, Paris, F)

Objectives: To evaluate structural cortical abnormalities in Amyotrophic Lateral Sclerosis (ALS) and in Primary Lateral Sclerosis (PLS). Background: Motor neuron diseases are characterized by a degeneration of cortical pyramidal motor neurons, associated – in ALS – with a degeneration of lower motor neurons. [11C] Flumazenil (CFLU) PET studies allow to quantify Benzodiazepine receptors (BZR) loss which may reflect cortical structural changes such as neuronal loss.Using this method, it is possible to compare cortical changes in ALS and in PLS. Methods: Ten patients with clinically definite ALS, six patients with definite PLS and ten controls were studied with CFLU PET. BZR loss was assessed on B'max dependent images and data were analyzed with the SPM 96 software. Each group of patients was compared to the control group. Results: In patients with ALS, highly significant (p< .001) BZR loss was restricted to the bilateral sensori-motor cortex and the motor cingulate gyrus. In patients with PLS, significant BZR loss extended to large cortical regions including the frontal opercular regions, the sensori-motor cortex, the prefrontal cortex, the insula and the cingulate gyrus. Conclusions: Structural cortical abnormalities are more extensive in PLS than in ALS. CFLU PET can be used to study in vivo cortical neuronal degeneration in motor neuron diseases.

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MOLECULAR SCREENING OF SOD1 GENE IN ITALIAN PATIENTS WITH FAMILIAL AND SPORADIC ALS: IDENTIFICATION OF THREE NOVEL MISSENSE MUTATIONS. C. Gellera, C. Riggio, B. Castellotti, L. Morandi, M. Carriero, C. Casali, M. Zeviani, C. Mariotti, Istituto Nazionale Neurologico, Università Statale La Sapienza (Milano, Roma, I)

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disorder of upper and lower motor neurons. The incidence is about 1/100.000; approximately 90 % of the cases are sporadic, the rest being inherited as autosomal dominant or, less frequently, recessive traits. Mutations in the gene encoding the cytoplasmic Cu/Zn superoxide dismutase (SOD1), located on chromosome 21q22.1, have been identified in 20 % of patients with familial amyotrophic lateral sclerosis (FALS). We have screened by SSCP and direct sequence analysis the five exons of the SOD1 gene in 32 FALS and in 42 apparently sporadic ALS patients. We identified a molecular defect in 4/32 families (12.5 %): in two we found a heterozygous A4V mutation, the most frequent mutation reported in the US. In two other families we found two new heterozygous missense mutations: G12R and F45C. As previously, the A4V mutation was associated with a severe and rapidly progressive form, while the new mutations were both associated with slowly progressive FALS. The patient carrying the G12R mutation presented the first symptoms at age 63; at age 67 he was still able to walk unaided and had no sign of bulbar involvement. The F45C proband presented mild distal weakness of the upper limbs at age 59. The patient, now 65 years old, is still able to walk with assistance. His mother died at age 73, after 10 years of illness. Molecular analysis of the SOD1 gene in the sporadic cases led to the identification of three mutated patients (3/42, 7.1 %). In two patients we found a homozygous D90A mutation and a heterozygous I113T, respectively. Both mutations have already been reported. In the third patient we identified a new heterozygous mutation, A95T, associated with early-onset ALS. This proband developed progressive weakness in the lower limbs at age 26. At age 28, the neurological examination showed mild weakness and wasting of lower limb muscles, a Babinski sign on the left, and absent ankle jerk, while the patellar and upper-limb reflexes were slightly increased. Cranial nerves and sensation were both normal. To establish the origin and pathogenicity of the A95T mutation, segregation analysis on numerous unaffected family members is currently underway. In contrast with previous studies, our results demonstrate that the frequency of SOD1 mutations in Italian FALS and ALS patients is similar to the frequencies reported in other European countries. Because of the high percentage of new mutations, and the presence of mutations in apparently sporadic patients, a systematic molecular analysis of the SOD1 gene should be considered in the diagnostic procedure of ALS.

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CENTROMERIC DELETIONS OF THE SMN GENE: A SUSCEPTIBILITY FACTOR AFFECTING PROGNOSIS IN ALS. J. H. Veldink, L. H. van den Berg, J. H. J. Wokke, J. M. B. V. de Jong, O. J. Vogels, M. de Visser, F. Baas, J. M. Cobben, H. Scheffer, UMCU, AMC, AZN, AZVU, University Groningen (Utrecht, Amsterdam, Nijmegen, Groningen, NL)

Spinal muscular atrophy (SMA) is a relatively common childhood disorder resulting from the loss of spinal motor neurons. More than 98 % of childhood SMA-patients show a homozygous deletion or interruption in the telomeric copy of the survival motor neuron gene (telSMN). Estimations of heterozygous deletions of telSMN in the general population, which represent the carriers for SMA, range from 1 in 10 to 1 in 80. It is suggested that the centromeric copy of SMN (cenSMN) is responsible for a partially functional protein that compensates for an absent product of telSMN in SMA. As the putative genetic basis for sporadic amyotrophic lateral sclerosis (SALS) remains obscure, we investigated whether SMN has a role in the development and phenotype of SALS. We determined the presence of deletions of telSMN and cenSMN in 110 SALS patients compared to 100 healthy controls, using PCR-based DNA tests. We found no homozygous deletions in telSMN. Carriership for SMA appeared to be equally present in patients and in controls (1 in 20). SALS patient were at increased odds for homozygous cenSMN deletions (OR 4.4, 95 %CI 1.4–13.5). Multivariate regression analysis showed that the presence of a homozygous cenSMN deletion was an independent prognostic factor, like age at onset.

We conclude that cenSMN has a role as a susceptibility factor affecting prognosis and may thus be involved in the multifactorial cascade leading to the death of motor neurons in SALS.

Oral session 10

Motor neuron disease and motor neuropathy – 2

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NEURONAL NITRIC OXIDE SYNTHASE (NNOS) IMMUNOREACTIVITY IN THE SPINAL CORDS OF TRANSGENIC MICE WITH A G93A MUTANT SOD1 GENE. S. Sasaki, H. Warita, K. Abe, M. Iwata, Tokyo Women's Medical University, Okayama University (Tokyo, Okayama, J)

We immunohistochemically performed a prospective longitudinal study of the spinal cords of transgenic mice with a G93A mutant SOD1 gene (n=7) at four distinct time points, using anti-human neuronal nitric oxide synthase (nNOS) antibody to assess whether there is an evidence of the oxidative involvement of motor neurons. Specimens from age-matched non-transgenic littermate mice served as controls (n=7). In the non-transgenic littermate mice, the posterior horn (Rexed's laminae I and II) was immunostained for nNOS, whereas the anterior horns including the anterior horn neurons were spared. In transgenic mice, at age 6 months with no pathological change, the anterior horns were not immunostained for nNOS. At age 7 months (presymptomatic stage), degenerated anterior horn neurons and their neuronal processes were occasionally immunostained for nNOS, and at age of 8 months (early symptomatic stage) and late 8 months (end-stage), the somata of degenerated anterior horn cells and cord-like swollen proximal axons frequently showed positive nNOS immunoreactivity. Normal-looking neurons almost always remained negatively immunostained for nNOS. These findings suggest that nitric oxide may be involved in the pathomechanism of degeneration of motor neurons in these transgenic mice, although further studies are needed to show nitric oxide production in the anterior horn neurons of the mice.

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AN OPEN TRIAL OF CREATINE ON THE PULMONARY FUNCTION OF PATIENTS WITH ADVANCED AMYOTROPHIC LATERAL SCLEROSIS. D. Gross, V. E. Drory. Department of Neurology, Tel-Aviv Sourasky Medical Center, 6 Weizman St., Tel-Aviv, Israel

OBJECTIVE: To evaluate the possible role of dietary creatine supplementation on the pulmonary function of patients with advanced amyotrophic lateral sclerosis (ALS).

BACKGROUND: Dietary creatine supplementation was shown recently to have a positive effect on the muscle contraction and strength of patients with different neuromuscular disorders, including ALS, and also to improve the motor functioning of SOD-deficient mice.

DESIGN/METHODS: Five grams creatine daily were administered orally in an open-label trial design to eight patients with definite ALS in their advanced stage, as their pulmonary function became borderline. All patients reported shortness of breath with minimal exertion and most of them also had disturbed sleep. Patients performed pulmonary function testing including forced vital capacity (FVC), forced expiratory volume (FEV1), peak expiratory flow rate (PEF) and maximum voluntary ventilation (MVV) – all expressed as % of the predicted value for age, height, weight and gender. Pulmonary function tests were performed before treatment begin and two weeks after.

RESULTS: All pulmonary functions, measured at baseline, were in the 12–73 % range. There was a slight non-significant trend toward improvement of FVC and FEV1 values after creatine treatment, with no clinical correlate.

CONCLUSIONS: Creatine did not show any clinically significant effect on the pulmonary function in a selected group of ALS patients with respiratory distress symptoms.

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POSITIVE EFFECT OF SPECIALIZED CENTERS IN THE PROGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS PATIENTS. A. Chiò, L. Mazzini, G. Mora, C. Balzarini, A. A. Terreni, Univ. of Torino, Fondazione Salvatore Maugeri, and the PARALS (Torino, Veruno, I)

It is discussed whether the referral to a tertiary care, specialized center has a positive effect on survival and quality of life of patients affected by ALS. This issue is relevant, considering the costs related to specialized ALS centers and the aspects associated to geographical distributions of ALS centers. We have assessed the difference of clinico-prognostic characteristics of referral and population-based series in 3 cohorts of patients diagnosed in 1995–96. These included the patients followed-up in two ALS referral centers, the Veruno ALS clinic (235 cases), and the Torino ALS clinic (68 cases), and the patients from the Piemonte and Valle d'Aosta Register for ALS (PARALS) (124 cases). A significant difference in the age of onset (Veruno 56.3 yrs; Torino, 59.4 yrs; PARALS 64.6 yrs) and site of onset (bulbar onset, Veruno, 25 %; Torino, 27 %; PARALS, 38 %) was found. PEG and non-invasive ventilation were performed more frequently in cases followed-up in Veruno (27 % and 19 % respectively), and Torino (29 % and 10 %) than in the PARALS cohort (14 % and 5 %). Three-year survival time was significantly higher in cases followed-up in Veruno (57.2 %) and Torino (56.9 %) than in the PARALS cohort (36.4 %). Using a multivariate model (Cox proportional hazard model) factors significantly related to a survival were age, type of onset and center effect. In conclusion, although ALS patients referring to tertiary care center are younger, a significant better survival has been found in specialized ALS center, even after correction for other prognostic factors. This finding strongly support the institution of ALS specialized centers for a better care of these patients.

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REGION-SPECIFIC RNA SPLICING OF THE GLUTAMATE TRANSPORTER EAAT2. B. Schwalenstocker, C. Munch, A. Mink, A. Felbecker, U. Seefried, B-D. Zhu, A. Ludolph, T. Meyer, University of Ulm (Ulm, D)

The excitatory amino acid transporter 2 (EAAT2) is the major protein of glutamate uptake from the synaptic cleft and is of significant importance for the termination of glutamatergic neurotransmission and the prevention of excitotoxic damage of postsynaptic neurons. A reduced glutamate reuptake and a diminished expression of the EAAT2 protein have been reported in patients with amyotrophic lateral sclerosis (ALS), and the transgenic mouse model of autosomal-dominant ALS (SOD1G93A, G85R). The EAAT2 protein loss has been reportedly linked to aberrant splicing of the EAAT2 RNA. In contrast, we cloned several alternatively spliced EAAT2 RNA from both, ALS and control brain, showing that the EAAT2 RNA regulation is more complex than previously recognized. To study the functional meaning of alternative EAAT2 splicing we performed a quantitative PCR study in the hippocampus (HIPP), the frontal cortex (CX), thalamus (THA), and cerebellum (CB) (GeneAmp rTh Reverse Transcriptase RNA PCR, Perkin Elmer). We investigated the expression of eight 5'-splice variants (EAAT2/Ex12, /Ex6, /Ex1, /Ex9, /H2, /Ex11, /Ex3, /Ex2) and two alternative cleavage forms (EAA2/3U1, /3U3) of the EAAT2 RNA leading to variable untranslated and N-terminal protein coding sequences. The study revealed a distinct expression pattern of individual EAAT2 splice forms: EAAT2/Ex12, and /Ex6 were expressed in HIPP > CX > > CB = THA, whereas /H2 and /EX11 were detected in the CX > HIPP, but not in the CB and the THA. The Northern blot analysis of EAAT2/3U1 and /3U3 using multiple tissue blots of the human brain (Clontech, Palo Alto), and a human multiple tissue expression array (Clontech, Palo Alto) demonstrated an abundant expression of a 11 kb transcript (EAAT2/3U3) in the HIPP, CX, CB etc. whereas in the thalamus, putamen, caudate nucleus, and other regions a short cleavage product of 1,8 kb (EAAT2/3U1) was expressed. The sequence analysis of N-terminal isoforms of the EAAT2 polypeptide (PSORT II) showed different scores for the recognition of signal sequences for EAAT2/H2 (–12), /Ex12 (–4), and /Ex2 (+4) predicting a differential cellular sorting and localization of distinct EAAT2 splice forms. For functional and pathogenetic studies of EAAT2 splicing in ALS mouse models we cloned eight murine EAAT2 RNA resulting from alternative splicing and cleavage/polyadenylation. For the mouse EAAT2 we observed analogous mechanisms of RNA regulation and differential expression. We conclude that RNA splicing serves as a mechanism of region-specific EAAT2 regulation in the human and mouse brain. Based on the topographical and functional data on individual splice forms we are now able to study the pathogenetic involvement of EAAT2 splicing in ALS patients and transgenic models of familial ALS.

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MAXIMUM VOLUNTARY ISOMETRIC CONTRACTION (MVIC): INVESTIGATION OF INTRA-RATER RELIABILITY AND LEARNING EFFECT. D.M Dara Meldrum, N.A Atkins, O.H Hardiman, Beaumont Hospital (Dublin, IRL)

Maximum Voluntary Isometric Contraction (MVIC) objectively measures muscle strength, and has been the method of choice in recent clinical trials of new drugs in neuromuscular disease. MVIC is measured using a strain gauge attached to orthopedic bars, which in turn are attached via straps to the patient on a standard plinth. The force applied through the strain gauge for different muscle groups is analysed by computer. The purpose of this study was to test the intra-rater reliability of MVIC in our centre with a view to establishing a data base of normal adults. Methods: 10 subjects with no medical conditions (7F:3M; average age 29.7 ± 10) underwent MVIC of 11 muscle groups bilaterally (neck flexors, shoulder adductors and abductors, elbow, knee and hip flexors and extensors, ankle dorsiflexors and hand grip). Subject position,

strap position and verbal instructions were standardised. Subjects were retested by the same examiner within 4 days (mean 2 days ± 0.9). Each muscle group was tested twice and both the average and maximum of two values were taken for statistical analysis. Results: The intra-class correlation co-efficient (ICC) was high for all movements (0.7–0.8 for neck flexors, hip flexors, and ankle dorsiflexors; 0.9–0.99 for the remaining muscle groups). The ICC was similar regardless of whether the maximum or average of the two measurements was taken. Conclusion: MVIC testing yields highly reliable results when tested on normal subjects. There appears to be no significant learning effect in subjects performing MVIC from the first to the second time. The maximum or average of two values can be utilised when analysing results. A study of the range of values for a normal adult caucasian population is currently underway.

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PERIPHERAL BLOOD T-CELL TUMOR NECROSIS FACTOR-ALPHA BINDING IS INCREASED IN AMYOTROPHIC LATERAL SCLEROSIS. P. Bongioanni, M. Romano, M. Carboncini, M. Bresci, C. Chisari, G. Stampacchia, B. Rossi, University of Pisa (Pisa, I)

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease in which motor system is primarily involved with spinal and/or bulbar palsies. Up to date, many pathogenetic hypotheses have been done, including that of a derangement in the immune system. Tumor necrosis factor(TNF)-alpha, a cytokine playing a role in both the immune system network and apoptotic events leading to neurodegeneration, may represent a useful marker to address such an issue. In the present study, we assayed TNF-alpha binding on T cells from 19 definite (according to the El Escorial criteria) ALS patients with spinal or bulbar onset. Biochemical assays were performed before initiating riluzole treatment, and after 1, 3 and 6 months. We found that T cells of ALS patients had significantly ($p< 0.001$) more TNF-alpha receptors than those of age- and sex-matched controls (Bmax: 689 ± 36 vs 134 ± 8 (mean ± SEM) receptors/cell). TNF-alpha binding sites are of the same type in patients and healthy subjects (Kd: 67.1 ± 4.9 and 70.2 ± 5.4 (mean ± SEM) pM, respectively). Bmax values did not vary with therapy, but showed a trend for a further increase in 3 patients who remained untreated with riluzole for one or two months. Data are discussed in terms of MND immunopathogenesis, given that enhanced binding for TNF-alpha has been reported in activated T cells and taking into account any effects of riluzole treatment.

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SPINAL CORD GLIAL CELLS UP-REGULATE NEURONAL NITRIC OXIDE SYNTHASE IN SPORADIC AMYOTROPHIC LATERAL SCLEROSIS. J. M. H. Anneser, C. J. Eggett, P. G. Ince, P. J. Shaw, G. D. Borasio, Klinikum Grosshadern, University of Newcastle (München, D; Newcastle, UK)

Amyotrophic lateral sclerosis (ALS) is characterised by progressive degeneration of upper and lower motoneurons leading to spasticity, pareses and muscular atrophy. Several studies indicate that an excessive generation of nitric oxide (NO) may contribute to the pathogenesis of ALS. The enzyme NO synthase exists at least in three isoforms: neuronal NO synthase (nNOS), inducible NO synthase (iNOS), and epithelial NO synthase (eNOS). Recently, an induction of nNOS in astrocytes has been described in an animal model of familial ALS expressing a human Cu/Zn SOD mutation. We therefore examined the expression of nNOS in post mortem spinal cords of patients affected from sporadic ALS (n=5) and control patients without any history of neurologic disease (n=5). Using immunohistochemistry, we found an up-regulation of nNOS in spinal cord glial cells: A pronounced nNOS expression was observed selectively in ventral horn glial cells and in the corticospinal tracts of ALS patients, while controls showed only little signal in these regions. The enhanced nNOS expression in glial cells may be simply part of a reactive activation process; however, it may also contribute to motoneuronal degeneration via NO-mediated cytotoxic effects. (JMHA was supported by an ENS fellowship)

Oral session 11

Neurophysiology – 1

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FATIGUE IN MULTIPLE SCLEROSIS IS PARALLELED BY IMPAIRED NEURONAL CONDUCTION AS ASSESSED WITH TRANSCRANIAL MAGNETIC STIMULATION. M. R. Haupts, S. Daum, T. Lauter, G. Ahle, W. Gehlen, Ruhr University Knappschaftskrankenhaus (Bochum, D)

Abnormal fatiguability seriously affects everyday life of patients with multiple sclerosis (MS). Definition of pathogenesis and quantification of this fatigue are difficult to date. We assessed the degree of experienced daily fatigue and dependency from help as scored with the "Minimal Record of Disability", demographic data and neurological status (scored in the "Expanded Disability Status Scale", EDSS), magnetic resonance imaging (MRI) lesion patterns and transcranial magnetic evoked potentials in 46 patients (33 fem., 13 male) with confirmed MS (according to Poser-Criteria). Mean duration of disease was 7 (± 7) years, median EDSS 4.0. About 50 % of patients reported relevant handicaps due to fatigue, already some with first manifestations. There were no indications of underlying causal depressive disorders. Higher degrees of fatigue were more common in cases with more than 10 years duration of MS and dependency of help from others in daily life. Correlations of fatigue to MRI were poor (rho= 0.17). While EDSS scores showed a moderate correlation (rho=0.4), central conduction times to the upper extremities were significantly correlated with fatiguability (rho=0.5). This finding points to an important role of impaired central conduction for fatigue in MS patients.

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VALUE OF ELECTROPHYSIOLOGIC STUDIES OF THE DIAPHRAGM IN ALS. H. Lahrmann, G. Albrecht, P. Hitzenberger, M. Wild, U. Zifko, W. Grisold, Neurological Dept., Kaiser Franz Josef Hospital, LBI for Environmental Pneumology, Rehabilitation Clinic (Vienna, Bad Pirawarth, A)

In ALS patients nocturnal oxygen desaturations and hypercapnia may occur even in the absence of dyspnea. Determination of the optimal point of time to start non-invasive home ventilation (NIPPV) is sometimes difficult and requires early diagnosis of respiratory muscle involvement. We investigated the value of electrophysiologic studies of the diaphragm and inspiratory muscle function. Methods: In 11 successive ALS patients (6 female, 5 male, age 47–81 yrs) we assessed Karnofsky scale, dyspnea score, diaphragmatic needle electromyography (EMG), phrenic nerve conduction studies (onset latency and amplitude of compound muscle action potentials, CMAP), lung function (vital capacity, VC, and oxygen saturation, SpO2) and inspiratory muscle strength (maximal inspiratory pressure). Results: Karnofsky index was above 60 % in 6 patients, between 40 and 60 % in 4 patients and below 40 % in 1 patient. Diaphragmatic needle EMG showed fasciculations in 5 patients and fibrillations and positive sharp waves in 6; phrenic nerve onset latencies were increased in 6 patients (9.24 ± 1.99ms), CMAP amplitudes were reduced in 7 (240 ± 130uV); VC-values were below 80 % of normal in 8 patients and a significant reduction in maximal inspiratory pressure was found in 9 patients. In 4 patients, with spontaneous activity in diaphragmatic needle EMG, low respiratory muscle strength and significant nocturnal SpO2 decreases, treatment with nocturnal NIPPV was started. Conclusion: Our results indicate the value of electrophysiologic studies as an additional parameter for the diagnosis of inspiratory muscle involvement in ALS and may be helpful in further palliative management of these patients.

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HEMIFIELD VISUAL MOTION STIMULATION: CROSS TALK BETWEEN HEMISPHERES. Th. Brandt, S. Bense, Th. Stephan, T. A. Yousry, M. Dieterich, Ludwig-Maximilians-University (Munich, D)

In a previous fMRI study, we stimulated patients with complete homonymous hemianopia due to acute infarctions of the posterior cerebral artery with coherent visual pattern motion and observed a bilateral activation of occipito-temporal areas, the human homologue of the motion-sensitive middle temporal (MT) and middle superior temporal (MST) areas in the monkey. This finding indicated activation of MT/MST on the infarcted hemisphere in the absence of input from the ipsilateral primary visual cortex. Aim of this study was to analyze the activation pattern during hemifield motion stimulation in nine healthy volunteers.

Visual motion stimulation was presented using MRI-compatible video glasses, in which the right or left visual field could be darkened from the periphery to 8° beyond the vertical meridian (which is represented retinotopically in both hemispheres). Subjects had to fixate a blue dot presented directly

in front of them in the dark part of the field during all scanning periods. Pattern motion – restricted to one hemifield – consisted of random black-and-white dots that rotated clockwise or counterclockwise at a constant angular velocity of 30°/s. Functional images were acquired at 1.5 T using an EPI sequence (TE = 60ms, TR = 2500ms, voxel size 3.75 x 3.75 x 5 mm3), and realigned, spatially normalized, and smoothed prior to statistical group analysis (SPM99b).

Visual motion stimulation within the right or left hemifield caused similar activation patterns in the striate and extrastriate visual cortex V1 (BA 18/17) and in a parieto-occipital area of the medial occipital gyrus covering V5 (BA 19/37, MT/MST) on the hemisphere contralateral to the stimulated hemifield. On the hemisphere ipsilateral to stimulation, there was no activation in the primary visual cortex but activation was seen in a parieto-occipital region covering V5, which was significantly weaker than that on the contralateral hemisphere (t-test, $p < 0.05$).

In our stimulus configuration, the vertical edge of the motion pattern field was 8° distant from the fixation point. Therefore, it is unlikely that the activations of MT/MST found contralateral to the stimulated hemisphere were mediated by vertical meridian connections. Most likely callosal fibres provide for interhemispheric visuovisual transmissions that extend those described for the vertical meridian. In fact, neurons in the parietal and temporal lobes which have receptive fields that receive input from both visual hemispheres and callosal connections between occipito-temporal areas MT/MST (V5) have been described in monkeys. Since you cannot perceive two different states of body motion at the same time, both hemispheres have to interact in stimulus situations in which both visual hemifields have contradictory information about motion, e. g., when sitting in a train reading.

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DIFFERENTIAL EFFECTS OF GALVANIC VESTIBULAR STIMULATION ON GAIT DEVIATION DURING WALKING AND RUNNING. K. Jahn, E. Schneider, E. Schneider, M. Dieterich, T. Brandt, Ludwig-Maximilians University Klinikum Grosshadern (Munich, D)

Human locomotion depends on automatic spinal and supraspinal motor generators and is modulated by the input from different sensory sources. Prompted by our recent observation that an acute vestibular tone imbalance causes less deviation from the intended path when running than when slowly walking, we examined ten healthy subjects when walking or running at different step frequencies during galvanic vestibular stimulation.

A transient vestibular tone imbalance was induced by rectangular, binaural galvanic stimuli (1 mA) applied for 10 seconds. Blindfolded subjects were asked to walk (1 Hz step frequency) or run (3 Hz step frequency) toward a previously seen target. Mean gait deviation after 10 seconds of locomotion was 6.0±2.4° at 1 Hz and 2.8±1.8° at 3 Hz step frequency (mean±s. d., $p< 0.001$, paired t-test). After 5 m distance had been covered, the difference between walking and running was even larger (5.9±2.1° for 1 Hz walking versus 0.7±0.5° for 3 Hz running, $p< 0.0005$). Under control conditions without galvanic stimulation the deviation was 0.02±1.2° for walking and 0.08±0.9° for running. In a second experiment we investigated walking and running in place (no locomotion) by measuring body rotation after 10 steps at 1 Hz and 3 Hz step frequency. There was no significant difference in body displacement between the walking or running conditions.

Vestibular tone imbalance during galvanic stimulation has a stronger deviating influence when walking slowly than when running. We conclude that vestibular input is differentially regulated depending on the locomotion speed and pattern used. In contrast to goal-directed locomotion, there was no motor pattern-specific difference in vestibular control of walking and running in place.

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REPETITIVE MASSETERIC NERVE STIMULATION: AN ELECTRODIAGNOSTIC TEST FOR CRANIAL MUSCLES IN NEUROMUSCULAR TRANSMISSION DISORDERS. G. Pavesi, L. Cattaneo, S. Tinchelli, D. Mancia, Istituto di Neurologia Università di Parma (Parma, I)

Repetitive nerve stimulation is the most commonly used electrodiagnostic test for neuromuscular transmission. The most commonly tested nerves in the cranial district are the facial and the accessory nerves. The objectives of the current study were to: 1) develop a method for repetitive stimulation of the masseteric nerve; 2) obtain normative data for amplitude and area decrement of the motor (M) response. Subjects – 9 healthy subjects, aged 28–86 years (mean age 57,0 ± 22,1 years). Methods – Tests were performed with subjects lying supine. The masseteric nerve was selectively stimulated percutaneously by a coated monopolar needle inserted between the condyle and the coronoid process of the mandible immediately below the zygomatic process, which acted as the cathode. A surface plate electrode placed on the contralateral cheek acted as the anode. Masseteric M response was recorded using surface electrodes, the active electrode being placed on the muscle belly and the reference electrode on the neck, 2 cm below the mandibular angle. Stimuli were delivered in trains of 9, at a frequency of 3 Hertz. Stimulus intensity was set at 120% of the one needed to obtain a maximal M response. To avoid movement artifacts the subject's jaw was held passively closed by the operator's hand. The following protocol was used: 1) two trains of stimuli were given at rest. 2) The subject performed a maximal isometric contraction of the masseter muscle for 30 seconds followed by trains of stimuli every 15 seconds for two minutes and every 30 seconds for the following three minutes. Data analysis – the decrements in both amplitude and area were calculated between the first and the fifth stimulus of each train. Amplitude was taken from baseline to negative peak and area was taken under the negative phase. The maximal values of decrement in amplitude and area for each subject were then averaged. Results – M responses of all subjects showed simple biphasic waveforms. Mean decrements were of 2.6 % ± 2.2 in amplitude and 6 % ± 2.0 in area. None of the subjects reported local side effects. The test was never perceived as painful. Conclusions – Repetitive masseteric nerve stimulation (RMNS) is a well-tolerated procedure, which causes minimal discomfort to the patient. The results showed a very low variability. In conclusion, RMNS adds a possibility in testing the cranial muscles in disorders of neuromuscular transmission.

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TRANSCRANIAL MAGNETIC STIMULATION IN WILSON'S DISEASE BEYOND CENTRAL MOTOR LATENCIES. P. Grosse, K. Irlbacher, S. Röricht, B.-U. Meyer, Charite, Campus Virchow-Klinikum (Berlin, D)

Transcranial magnetic stimulation (TMS) so far has revealed subclinical changes in central motor latency (CML) in patients with Wilson's disease (WD). We present five patients with Wilson's disease with normal CML but pathological transcallosal inhibition and cortico-cortical inhibition. Methods: Measurement of CML was performed with a round coil (Magstim 200, 1.3fold above motor threshold) while transcallosal inhibition of tonic EMG-activity was elicited using a focal 8-shaped coil (Magstim 200, 80 % output). In two patients with normal motor thresholds we additionally examined corticocortical inhibition and facilitation according to the method described by Kujirai et al. (J Phys 1993) with a focal 8-shaped coil connected to two Magstim 200-units. The intensity of the conditioning stimulus was kept 5 % below active threshold, while the test shock was set to evoke a muscle response of 1 mV peak-to-peak amplitude. Interstimulus intervals between 1 and 15 ms administered randomly were investigated for relaxed muscles. All EMG-responses were recorded bilaterally from the first dorsal interosseus muscle. Four of the five patients had longstanding WD with and without neurological symptoms. Two patients were treated with penicillamin, one with trientine. Only one younger patient had recently diagnosed non-neurological WD and had not yet received treatment. Results: All five patients had normal central and peripheral motor latencies. However, all patients showed a pathologically prolonged duration of transcallosal inhibition irrespective of neurological involvement or treatment. In the two patients we investigated corticocortical inhibition and facilitation we found both disturbed inhibition in at least one hemisphere of an individual patient. Conclusions: Our findings add to the previously described abnormalities found in TMS in Wilson's disease. They point to both a disturbance of interhemispheric transfer between motor cortices and to impaired motor cortex excitability cortical dysfunction, even when clinical neurological examination is normal. As in other studies on evoked potentials in WD there was no strict correlation between morphological changes in MRI and findings in TMS. As abnormalities could be demonstrated in treated as well as in untreated patients it is unlikely that these abnormalities are related to medication alone. However, as all patients had significant liver dysfunction metabolic derangement may add to the neurophysiological abnormalities shown in TMS.

Oral session 12

Neurophysiology – 2

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ANATOMIC LOCATION OF THE FRONTAL EYE FIELD (FEF): COMPARISON OF FMRI AND INTRAOPERATIVE MAPPING. S. Mueller-Schunk, T. Stephan, S. Bense, J. Ilmberger, C. Gall, M. Dieterich, H. Reulen, T. A. Yousry, Neuroradiology, Klinikum Grosshadern Ludwig Maximilian University, Munich, Neurology, Klinikum Grosshadern, Physical Med., Klinikum Grosshadern, Neurosurgery, Klinikum Grosshadern (Munich, D)

In humans the functional anatomy of the FEF has been investigated using either fMRI, or subdural grid electrodes and VEPs (1). To our knowledge, no study has yet mapped the FEF intraoperatively.

The aim of our study was to evaluate the FEF by cortical mapping during open surgery and to compare this location with the one defined by fMRI.

Methods: A 38-year-old woman presented with history of epileptic convulsions. MRI detected a tumor in the left frontal lobe. She underwent fMRI and surgery one day later. fMRI: 60 scans containing 5 active and 6 baseline phases were acquired with a 1.5 Tesla scanner, using T2* weighted EPI sequences (TR/TE = 96/66 ms, matrix = 128x128, 20 axial slices, 5 mm thickness). The stimuli were presented through goggels. In the active phase the patient performed visually guided saccades with a dot popping up in the left or right periphery of the screen (angle=24°). In the baseline phase she had to fixate a stationary dot in the center of the screen. The data were analyzed with SPM'99 and transferred to an individual 3D surface of the patient's brain. Due to an anatomical hypothesis (2) activation was defined by an uncorrected $p < 0.001$. Intraoperative mapping: During surgery direct electrical stimulation of various cortical areas was performed including the FEF as defined by previous fMRI. The visual stimuli presented to the patient were identical to those used for fMRI. Cortical stimulation was performed during the active phase (guided saccade) and during the baseline condition (fixation). Eye movements were recorded by electronystagmography.

Results: The fMRI analysis showed one area of significant activation in the precentral sulcus adjacent to the precentral gyrus. A smaller area was identified in the middle frontal gyrus. Stimulation of the FEF during the saccade task led to an interruption of the saccades. One second after stimulation a contraversive ocular deviation of about 5–10 degrees was registered during the saccade task as well as during fixation. The stimulation produced no eye movements in any other location.

Conclusions: The location of the FEF as determined by fMRI is consistent with that reported in the literature (2). Cortical mapping shows, that this area is indeed associated with the processing of oculomotor tasks, especially saccades. Stimulation causes an interruption of the saccades, as well as an ocular deviation to the contralateral side during both, saccadic eye movement and fixation. In humans these effects have been previously described using grid electrodes (1) and were now also veryfied using direct cortical stimulation. The comparison of the cortical surface during surgery with the 3D MRI/fMRI surface revealed that the anatomic location of the FEF was identical in both.

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PARIETAL CORTEX ACTIVATION IS ESSENTIAL FOR SUCCESSFUL EXECUTION OF VISUOSPATIAL TASKS: COMBINED EVIDENCE FROM FMRI AND RTMS. D. E. J. Linden, D. Hubl, A. Sack, D. Prvulovic, M. Jandl, T. Dierks, F. E. Zanella, R. Goebel, H. Steinmetz, Johann Wolfgang Goethe-Universitaet, Maastricht University (Frankfurt, D; Maastricht, NL)

Functional magnetic resonance imaging (fMRI) provides information about transient local changes in neuronal activation. Information on the functional relevance of the activation of brain areas can be obtained by inducing temporary regional deactivations using repetitive transcranial magnetic stimulation (rTMS). We applied the combination of these two techniques to the question of the functional relevance of parietal cortex activation during the performance of visuospatial tasks.

GOAL: To test the hypothesis that the activation of parietal cortex that is observed during the performance of spatial tasks on visual material is functionally relevant rather than epiphenomenal.

METHODS: We tested the hypothesis using a block-design fMRI methodology that can identify parietal areas activated during visuospatial tasks and a multivariate two-factorial design for rTMS in twenty healthy volunteers. Subjects saw sequences of coloured clocks and performed a task that required them to discriminate angles, colours, or conjunctions of both during fMRI and before and after 10 minutes of real or sham rTMS at 1 Hz to the posterior parietal cortex (PPC). A differential effect of real rTMS on reaction times or error rates of the angle discrimination and conjunctions task conditions was assumed to confirm our hypothesis that PPC activation is essential for successful execution of visuospatial cognitive tasks. A general linear model for task-related fMRI signal changes was used to assess the modulation of neural activity during task conditions. Reaction time data before and after real and sham rTMS were analyzed using a two-way ANOVA.

RESULTS: For the visuospatial tasks (angle discrimination and conjunction) we found a selective enhancement of BOLD (blood oxygen level-dependent) fMRI signal in PPC (Brodmann's area 7) and a selective impairment of performance after rTMS to the parietal lobes, which was not observed for the non-spatial task condition (colour discrimination).

CONCLUSIONS: These findings suggest that neuronal activity in the posterior parietal cortex of humans is essential for the execution of spatial judgements on visually presented material.

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HYPEREXCITABILITY OF THE MOTOR CORTEX IN SYMPTOMATIC FOCAL EPILEPSY DEMONSTRATED BY TRANSCRANIAL MAGNETIC STIMULATION. K. Schmierer, K. Irlbacher, H.-J. Meencke, B.-U. Meyer, Charite, Epilepsiezentrum Berlin (Berlin, D)

Objective: To determine the excitability of the motor cortex in patients with pharmacoresistent symptomatic focal epilepsy using transcranial magnetic stimulation (TMS). Hyperexcitability was assumed when significant asymmetry could be demonstrated for motor thresholds, number of excitable scalp positions, and maximum response amplitudes.

Methods: Six patients with symptomatic focal epilepsy of different etiologies (trauma, ischemic stroke, arterio-venous malformation, cerebral lupus erythematosus) having simple and/or complex partial seizures with and without secondary generalisation were investigated. Five patients had a mild to moderate hemiparesis contralateral to the hemisphere with the epileptic focus. The epileptic focus in every individual patient had previously been determined by ictal EEG recordings. All patients were on antiepileptic medication comprising exclusively channel blocking agents (LTG, CBZ).

Using a Magstim 200 – stimulator (2-Tesla-version), single pulse focal TMS (eight-shaped coil) was performed at different positions over a 1x1 cm scalp grid. Successive positions were stimulated until the area where motor responses were produced was surrounded by inactive positions. Three stimuli were applied at every position with an intensity of 1.3 times the resting motor threshold and averaged. Motor evoked potentials (MEPs) were recorded bilaterally from the first dorsal interosseus muscle. Motor cortical output maps showing the size of the elicited MEPs and the number of excitable scalp positions were generated. The amplitude-weighted center of gravity for each map was measured. Data were compared with a group of healthy volunteers which were subjected to the same experimental procedures.

Results: In five of the six patients the resting motor threshold was significantly lower and the number of excitable scalp positions was higher in the hemisphere ipsilateral to the epileptic focus compared to the contralateral hemisphere. In four patients the maximum response amplitudes elicited by the stimulation of the affected hemisphere were larger than those evoked contralaterally. Hemispheric asymmetries of the center of gravity were detected in two patients only.

Conclusion: Hyperexcitability of the motor cortex ipsilateral to the epileptic focus can be demonstrated using TMS. Our findings point to a disinhibition of the primary motor cortex in the hemisphere with both the structural brain lesion and the epileptic focus in most of the cases. Thus, there is a discrepancy between impaired motor function and high motor cortex excitability in this group of patients.

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REVERSIBLE PROLONGATION OF MOTOR CONDUCTION TIME FOLLOWING SPINAL NEUROGENIC CLAUDICATION. E. Lang, M. J. Hilz, H. Erxleben, M. Ernst, K. Liebig, B. Neundörfer, University Clinic Erlangen-Nuremberg (Erlangen, D)

Irradiation of pain from the lower back into the legs during walking may result from intermittent spinal neurogenic claudication or referred pain phaenomena follwing irritation of musculoskeletal structures of the spine. Differentiation of both aetiologies may be difficult in older people with radiological signs of a narrow spinal canal. Therefore we developed an electrophysiological test procedure to demonstrate the pain associated motor deficit during spinal neurogenic claudication. Objective measures of intermittent claudication of the cauda equina may improve diagnosis and thereby the outcome of therapy.

Methods: 15 patients (5 women, 10 men, age 66 ± 9y) with a history of back pain that irradiates into the legs during walking (reports of accompanying weakness and/or numbness in the legs in 11 patients) were selected in the

orthopedic department. Neurological examination disclosed cerebral and medullar causes for the complaints. Motor conduction time (MCT) following cortical magnetic stimulation (Magstim) was measured (Viking IV, Nicolet) to the tibial anterior and/or gastrocnemial muscle (depending on distribution of pain and/or neurological deficit during walking) before and after treadmill test. Walking was stopped if pain/neurological deficit was maximal.

Results: At the end of the walking test (mean maximal distance 188 ± 138 m) all patients complained about the typical pain and 9 patients about weakness and/or numbness in their legs. In 8 of the latter patients we observed immediately after walking an increase of MCT by 2,3 ± 1,1 ms ($p< 0,001$, Wilcoxon matched pairs sign rank test) that decreased after different times parallel to the complaints of the patients to baseline value. Retest comparisons in 3 patients demonstrated a good reproducibility of the results of the first run. In the other patient and the 6 patients without neurological deficit during walking the MCT did not change significantly after walking (0,03 ± 0,9 ms).

Conclusions: In patients with leg pain that depends on walking the comparison of symptoms and changes of MCT following standardized treadmill stress can demonstrate a pain associated motor conduction deficit. Reversible prolongation of MCT indicates spinal neurogenic claudication and confirms the diagnosis.

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CORTICAL "DEACTIVATION" DURING VESTIBULAR GALVANIC STIMULATION (FMRI). S. Bense, Th. Stephan, T. A. Yousry, Th. Brandt, M. Dieterich, Ludwig-Maximilians-University (Munich, D)

Galvanic vestibular stimulation at mastoid level acts on the eighth nerve and significantly activated the multisensory vestibular cortex, especially of the parieto-insular vestibular cortex (PIVC), in a previous FLASH-fMRI study [1]. Aim of this study was to analyze not only BOLD signal increases (activations) but also simultaneous BOLD signal decreases ("deactivations") for galvanic vestibular (GVS) and galvanic (nonvestibular) cutaneous stimulation (GPS). Deactivation is of particular interest, since in an earlier PET study on vestibular caloric irrigation, we found bilateral decreases in rCBF of the visual cortex (Brodmann areas, BA 17, 18, and 19).

Adhesive carbon electrodes were placed over both mastoid processes (cathode left, anode right) and additionally – for control – paravertebrally at neck C5/6 level (GVS). A battery-powered generator outside the Faraday cage applied rectangular direct electric currents. Functional images were acquired at 1.5 T using an EPI-sequence (24 slices, TE = 66 ms, TR = 5500 ms, 1.88 x 1.88 x 5 mm3, 128 x 128 matrix). All volumes were realigned, spatially normalized, and smoothed prior to statistical group analysis (SPM96). For the contrasts rest – GVS, and rest – GPS, p-values < 0.001 corrected for multiple comparisons, were considered significant.

Anodal stimulation at right mastoid level in all six subjects led to an apparent counterclockwise self-rotation of 90° to 360° around the nasal-occipital axis and mild to moderate cutaneous pain sensations. Both contrasts, rest – GVS and rest – GPS, showed significant signal decreases in the central sulcus region, predominantly in the postcentral gyrus analogously to the primary somatosensory cortex (BA 2/3/4 left, BA 3/4/6 right). During GVS, further significant signal decreases were found in the visual cortex bilaterally (fusiform/inferior occipital gyrus, BA 18/19, sparing BA 17), and in the right precuneus near the interhemispheric fissure (BA 7), whereas GPS led to an additional signal decrease in the middle temporal/occipital gyrus (BA 19/39/18).

Thus, GVS not only elicits a complex pattern of activations which can be related to ocular motor and vestibular function, but it also interacts with other sensory systems by means of circumscribed "deactivations" within the visual or somatosensory cortex. Intersensory inhibitions may provide a basic mechanism for spatial orientation and self-motion perception. In case of inappropriate or misleading input from two afferent sensory systems, visual-vestibular or nociceptive-somatosensory, a perceptual mismatch can be avoided by suppressing the input from one of the sensory systems.

(1) S. F. Bucher et al., Ann Neurol 44:120–125, 1998

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FUNCTIONAL REORGANISATION OF THE MOTOR CORTEX AFTER ISCHAEMIC STROKE IN MAN. R. Piniero, S. Pendlebury, H. Johanssen-Berg, P. M. Matthews, University of Oxford (Oxford, UK)

Recruitment of unimpaired, functionally redundant pathways (either distant or local) may minimise eventual disability after brain injury. To further test this concept, we studied 18 patients who recovered from ischaemic stroke leading to hemiparesis, as well as 10 aged (57–83 y. o.) and 10 younger (22–38 y. o.) normal controls using FMRI with a sequential finger tapping protocol. All showed similar numbers of significantly ($p< 0.01$) activated voxels in primary sensorimotor (SMC) and supplementary motor (SMA) cortex, but patients showed a reduced SMC lateralisation index (LI) with movement of the affected dominant hand (LI= −18±72 vs. 43±38 for aged [$p< 0.04$] and 74±29 for young [$p< 0.005$] controls). 9/36 hand movements in patients (cf. only 3/40 controls) showed greater activation of the ipsilateral than contralateral SMC. The centre of left SMC activation was shifted posteriorly by a mean of 1.2 cm for patients with movement of the affected, dominant right hand ($p< 0.01$). These results suggest that previous stroke injury "unmasks" ipsilateral SMC and perhaps also leads to local cortical functional reorganisation in the affected hemisphere. Both changes may contribute to recovery. (Supported by MRC and EC BIOMED II)

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ALTERED PATTERNS OF CORTICAL MOTOR ACTIVATION DURING HAND MOVEMENTS IN PATIENTS WITH PURE MOTOR OR SENSORY NEUROPATHIES. H. Reddy, M.A Lee, H. Johansen-Berg, M. Donaghy, P. M. Matthews, FMRIB Centre University of Oxford (Headington, Oxford, UK)

Previous studies with animal models have suggested that peripheral deafferentation can change patterns of brain activation during both motor tasks and sensory stimulation. To investigate these phenomena in man we used functional magnetic resonance imaging to study patterns of motor activation during a finger flexion-extension task in 6 patients with pure motor and 4 patients with pure sensory neuropathies and in 7 normal controls. The numbers of significantly activated pixels in the sensorimotor cortex of patients with pure motor neuropathies (117± 41. $p< 0.005$) were substantially greater than in either normal controls (15± 9) or in patients with pure sensory neuropathies (28± 17) during slow (10% maximum rate) finger tapping. A similar trend, but a smaller relative difference was found during fast (75% maximum rate) finger tapping, which increased the numbers of pixels significantly activated in all groups ($p< 0.05$). Particularly striking was an increase in the relative activation of the ipsilateral sensorimotor cortex in the motor neuropathy patients (motor neuropathy, 70± 22 pixels;controls 2± 3 pixels, $p< 0.003$). Because of this, the relative lateralization (where 1 implies activation of the contralateral hemisphere only and 0 is symmetrically bilateral) of cortical activation during the finger tapping was lower for the motor neuropathy group (0.2 ± 0.1, $p< 0.003$ to controls) than for either of the other two groups (sensory neuropathy, 0.5± 0.2; controls, 0.7± 0.2). The motor neuropathy patients also showed a mean posterior shift of 1.2 cm in the localisation of the centre of activation of the sensorimotor cortex relative to the normal controls ($p< 0.05$). In contrast, the pure sensory neuropathy group did not differ significantly in either extent or location of activation from the normal controls group, but showed a trend toward an anterior shift in centre of sensorimotor activation ($p< 0.06$). We conclude that peripheral motor nerve deafferentation leads to altered cortical recruitment during finger movements. This particularly involves increased activation of ipsilateral cortical motor pathways. In order to move their fingers in a similar way, patients with weakness from a motor neuropathy must activate motor units of larger size than normal controls. Our results suggest that recruitment of motor units of different sizes may show differences in cortical representation, even for the same movement. Studies with the pure sensory neuropathy patients suggest that sensory afferents contribute only modestly to the normal sensorimotor cortical activation response with hand movements.

WEDNESDAY, JUNE 21st

Oral session 13

Cerebrovascular disorders – 3

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A PROSPECTIVE STUDY OF HEADACHE ASSOCIATED WITH ACUTE STROKE. A. Verdelho, J. Ferro, T. Pinho, E. Melo, P. Canhão, F. Falcão, Hospital Santa Maria (Lisboa, P)

Objective. To describe and classify headaches associated with acute (first week) cerebrovascular diseases (CVD) using International Headache Society (IHS) fourth digit classification. Method. We interviewed consecutive patients admitted to a stroke unit, with ischaemic or intracerebral haemorrhagic stroke, using a validated headache questionnaire. The interview was carried out daily from the day of stroke onset to the 8th day. A lifetime history of headache was also obtained. Results. During the first 8 days, 123 patients re-

ported headache during at least one day. Most headaches (85,4 %) started on the day of stroke and 26 % before focal symptoms. Headache lasted for mean of 3,8 days (SD 2,1). While in the first day 38 % headaches were migraine-type, 38 % were severe and 37 % unilateral, by the 2nd day the majority were tension-type (48 %), only 18 % were severe and 27 % unilateral. On day 1 and on day 2, 11 % of the headaches could not be classified using 4th digit. Stroke types were ischaemic in 60 % of the patients and haemorrhagic in 40 % of the patients. Patients with haemorrhagic stroke had slightly more migraine-type headaches (40 %) than ischaemic strokes (37 %), but the difference did not reach statistical significance. Nausea or vomiting were present in 34 %, 15 % and 2 % of patients respectively at day 1, 2 and 8. The intensity of headache increased with movement (18 %, 12 %, 5 % of the patients at day 1, 2 and 8) and cough (32 %, 23 % and 5 % of the patients at day 1, 2 and 8, respectively). These percentages were similar both in ischaemic and haemorrhagic strokes. Previous primary headache was documented in 71 patients (45 patients with tension-type and 28 with migraine). There was an association between headache type before and after stroke: on the first day after stroke 30 (24 %) headaches could be considered a reactivation of previous ones. Conclusion. Headache characteristics associated with acute CVD change in the first days after stroke onset, often from a migraine to tension type headache. Headache is increased by movement and by cough. The presence of nausea/vomiting due to acute stroke can confound headache classification using the fourth digit. In 1/4 of the patients headache seems to be a reactivity of previous headache type.

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LEUKOARAIOSIS IN STROKE PATIENTS: INFLUENCE ON LONG TERM OUTCOME. P. Meynieu, . Henon, J. Froget, P. Vroylandt, F. Pasquier, JP. Pruvo, D. Leys, University Of Lille Hopital Roger Salengro (Lille, F)

Although leukoaraiosis (LA) is frequent in stroke patients, its clinical significance and its influence on outcome remains unsettled. The aim of this study was to evaluate in consecutive stroke patients, the influence of LA on vital, functional, and cognitive outcomes and the risk of recurrence within 3 years. Methods: The study population consisted of 202 patients (105 women) with a median age of 75 years (range: 42–100), consecutively admitted for an acute ischemic or hemorrhagic stroke with a clinical deficit lasting more than 24 hours. Survivors underwent neurological, neuropsychological and functional examinations at months 6, 12, 24 and 36. The diagnosis of dementia was based on ICD–10 criteria. In survivors who did not undergo the visits, the diagnosis of dementia was based on the IQCODE score obtained by telephone contact with the family or the general practitioner, with a cut-off 104. Patients with Rankin scores £2 were considered as independent. New vascular events were also recorded. Results: LA was present in 59,9 % of patients (95CI: 53–67 %). LA was an independent predictor of short and long-term mortality, and of stroke recurrence. Although LA was more severe in demented patients, it was not an independent predictor of post-stoke dementia. In survivors at months 6 and 36, the functional outcome was not independently influenced by the presence of LA. However, loss of autonomy was more frequent in patients with severe LA. Conclusion: Our results confirm that LA is a predictor of poor long-term outcome in stroke patients.

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THE ROMAN STROKE SATELLITE NETWORK. V. Gallo, E. Di Angelantonio, D. Toni, M. Fiorelli, A. Falcou, C. Argentino, C. Fieschi, G. La Gioia, Telespazio S. p.a (Rome, I)

Time is a crucial point for effective treatments in acute ischemic stroke. Evidences of the potential benefit of thrombolysis in highly selected cases, the high costs of expert stroke teams and stroke units, together with the need of optimizing the cost/effectiveness ratio of health care systems, induce to explore methods aimed at reducing the time interval from stroke onset to emergency treatment, and at improving the quality of the medical assistance by rationally exploiting existent resources. Emerging techniques such as satellite video telecommunications might turn out to be an excellent tool for acute stroke referral, integrated health services in the management of stroke, data collection, as well as training physicians and non stroke specialists, although standards must still be addressed. In order to evaluate whether tele-counseling is able to: 1. optimize the stroke referral pathway 2. reduce the number of inappropriate hospitalization 3. contribute in transferring into the clinical practice the guidelines for stroke management 4. institute a data bank useful for administrative evaluations, research and training in the field of cerebrovascular diseases, 3 out of the 6 Emergency Departments in the urban area of Rome, serving nearly 3.000.000 people, have recently been connected via a satellite network. Furthermore, 3 local hospitals, having head CT scanning, participate in the network in order to benefit of tele-counseling from the remote specialists. Costs, methods for accounting, concerted pathways, methods for protection of privacy and confidentiality of collected clinical data, will be reported together with technical information on the Roman Stroke Satellite Network.

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APOLIPOPROTEIN E AND THE RISK OF STROKE: THE ROTTERDAM STUDY. A. J. C. Slooter, P. J. Koudstaal, M. Hollander, M. L. Bots, A. Hofman, C. Van Broeckhoven, M. M. B. Breteler, C. M. van Duijn, Depart Epidemiol & Biostat, Department of Neurology, Julius Centre, Neurogenetics Laboratory (Rotterdam, Utrecht, NL; Antwerpen, B)

Genetic factors are involved in stroke, but few have been identified. A possible genetic risk factor is the apolipoprotein E polymorphism (APOE; alleles: APOE*2, APOE*3 and APOE*4). The gene product plays a crucial role in lipid metabolism. Carriers of APOE*2 have less atherosclerosis compared to APOE3E3, while APOE*4 was found to predispose to atherosclerosis. It is controversial whether APOE is involved in stroke.

METHODS – Preliminary data were used from a population-based cohort study on 6645 subjects aged 55 years or over without a previous stroke in whom blood was collected for APOE typing. Classification of strokes was done by a neurologist, specialised in stroke, using CT scan information in 62 % of cases. We used Cox' proportional hazards models to assess the relative risk of stroke, adjusted for age, sex and smoking, with APOE3E# as a reference.

RESULTS – In this sample, 256 strokes were identified during 5.3 follow-up years (mean; SD=1.6). The relative risk associated with APOE2E2 was 0.4 (95 % confidence interval (CI) 0.1 to 3.0), with APOE2E3 1.1 (95 % CI 0.7 to 1.5), with APOE2E4 1.2 (95 % CI 0.6 to 2.4), with APOE3E4 0.9 (95 % CI 0.6 to 1.2) and with APOE4E4 1.0 (95 % CI 0.4 to 2.4). Restriction of the analyses to ischaemic or haemorrhagic strokes did not alter our findings.

CONCLUSION – Our preliminary data suggest that the APOE genotype is not involved in the risk of stroke. Complete data will be presented at the ENS meeting.

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PROGNOSTIC FACTORS OF OUTCOME IN CEREBRAL SINUS THROMBOSIS: A PROSPECTIVE STUDY. S. de Bruijn, R.J de Haan, the CVST study group, J. Stam, Academic Medical Centre (Amsterdam, NL)

The prognosis of cerebral venous sinus thrombosis (CVST) is variable and the outcome may range from complete recovery to death. Prognostic factors to predict outcome in the acute phase of CVST have not been analysed in a prospective study. Methods: We prospectively investigated prognostic factors of patients enrolled in a clinical trial (full dose fractionated heparin versus placebo 1). The principal outcome measure was death or dependency after 12 weeks, defined as a modified Rankin score of 3 or worse. Univariate relations between possible prognostic factors and outcome were analysed with X2 tests. All factors associated with outcome ($P < 0.25$) were forced into a logistic regression model with a forward selection procedure. Results: 59 patients (50 women, 9 men) were studied, with a mean age of 37 years (range 18 to 80). After 12 weeks 10 patients (17 %) had a poor outcome. The univariately identified factors related to poor outcome were papilloedema, altered consciousness, coma, age > 33 years, duration of symptoms < 10 days, intra-cerebral haemorrhage before treatment, and involvement of the straight sinus. Isolated intra-cranial hypertension and a delta sign on CT scan were associated with a good outcome. In the multivariate analysis coma and cerebral haemorrhage were significantly associated with a poor outcome (odds ratio for coma 8.2 (95 % confidence interval 1.4–46.5); for haemorrhage 10.0 (CI 1.1–91.8). Involvement of the straight sinus was also related to poor outcome, but the association did not reach statistical significance ($P = 0.07$). Conclusion: Coma and intra-cerebral haemorrhage (before treatment) are independent predictors of a poor outcome in sinus thrombosis. De Bruijn SFTM, Stam J, for the CVST study group. Randomized, Placebo-Controlled Trial of Anticoagulant Treatment With Low-Molecular-Weight Heparin for Cerebral Sinus Thrombosis. Stroke 30; 1999: 484–488.

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EVALUATION OF COLLATERAL FLOW IN PATIENTS WITH CRITICAL INTERNAL CAROTID ARTERY DISEASE AND LIMITED ACOUSTIC BONE WINDOWS WITH ECHO-ENHANCED TRANSCRANIAL COLOR CODED DUPLEX SONOGRAPHY. G. Gahn, G. Hahn, S. Hallmeyer-Elgner, H. Bourquain, R. von Kummer, H. Reichmann (Dresden, D)

Background and Purpose: To assess the diagnostic efficacy of echo-enhanced transcranial color coded duplex sonography (TCCD) for noninvasive evalua-

tion of collateral pathways through the circle of Willis in patients with limited acoustic bone windows and critical symptomatic carotid disease.

Methods: We prospectively evaluated 30 consecutive patients (7 women, 23 men, mean age 63,8 ± 12,1) with echo-enhanced TCCD (echo-enhancing agent: Levovist®; Schering, Germany) and correlative transfemoral digital substraction angiography (DSA). We only included patients with critical symptomatic carotid stenosis (> 90% lumen diameter reduction) or carotid occlusion and no detectable colorflow signals of the circle of Willis by unenhanced TCCD due to limited acoustic bone windows. 28 patients had unilateral disease (16 stenoses, 12 occlusions), 2 patients had bilateral disease (1 bilateral occlusion, 1 occlusion on one side and stenosis on the other).

Results: Echo-enhanced TCCD visualized the circle of Willis bilaterally in all patients. Echo-enhanced TCCD detected collateral blood flow through the anterior communicating artery in 16 of 18 patients (sensitivity 89%, 95% CI 65–99%) and was false positive in one out of 11 patients without collateral flow (specificity 91%, 95% CI 59–100%). For the posterior communicating artery, sensitivity was 11/14 (79%, 95% CI 49–95%) and specificity was 15/16 (94%, 95% CI 70–100%).

Conclusion: Echo-enhanced TCCD provides non-invasive evaluation of collateral flow through the communicating arteries of the circle of Willis with high sensitivity and specificity in patients with critical obstructions of the internal carotid artery and limited acoustic bone windows.

Oral session 14

Cerebrovascular disorders – 4

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THE CALCIUM ANTAGONIST NIMODIPINE INCREASES FIBRINOLYTIC ACTIVITY IN PATIENTS WITH SUBARACHNOID HEMORRHAGE. Y. B. W. E.M. Roos, M. Levi, T. A. Carroll, L. F. M. Beenen, D. S. M. Molenaar, Academic Medical Center, Royal Hallamshire Hospital, Acad. Hosp. of the Free University (Amsterdam, NL; Sheffield, GB)

Calcium antagonists have been associated with an increased risk of gastro-intestinal hemorrhages and surgical bleedings (1, 2). Inhibition of platelet aggregation was suggested as the explanation, although this has never been demonstrated. However, these pro-hemorrhagic effects might also be caused by inhibition of the release from activated platelets of plasminogen activator inhibitor (PAI–1), the main regulator of endogenous fibrinolysis. To investigate whether the calcium antagonist nimodipine, which is widely used in patients with aneurysmal subarachnoid hemorrhage, has an effect on fibrinolysis, we measured parameters of fibrinolysis in patients with subarachnoid hemorrhage treated with and without nimodipine.

Methods – Plasminogen activator activity (PA) was measured by an amidolytical assay. Briefly, 25 ml of plasma was mixed to a final volume of 250 ml with 0.1 M TrisHCl, pH 7.5, 0.1% (v/v) Tween–80, 0.3 mM S–2251 (Chromogenix, Mölndal, Sweden), 0.13 M plasminogen and 0.12 mg/ml CNBr fragments of fibrinogen (Chromogenix, Mölndal, Sweden). The results were expressed as IU/ml. Tissue plasminogen activity (t-PA) antigen (Asserachrom t-PA, Diagnostica Stago, Asnieres-sur-Seine, France) and PAI–1 antigen (TintElize PAI–1, Biopool, Umea, Sweden) were measured by ELISA tests. Individual patient results were grouped and averaged into six time windows (day 1–3, day 4–7, week 2, 3 and 4, and results obtained after 6 weeks). The samples were tested without knowledge of treatment or the timing of withdrawal of treatment. Statistical significance was tested with paired sample t-tests and unpaired sample t-tests where appropriate.

Results – The results show that in patients with subarachnoid hemorrhage treated with nimodipine plasma fibrinolytic activity significantly increases in contrast to patients that are treated without nimodipine. This increase in fibrinolytic activity appears to be due to a 1.6-fold decrease in plasma levels of PAI–1. Both plasminogen activity and PAI–1 returned to baseline after treatment with nimodipine was discontinued.

Conclusions – Our results not only explain the observed pro-hemorrhagic effects of calcium-antagonists but also offer a completely new explanation for the up till now unsolved mechanism by which nimodipine brings about its beneficial effect on cerebral ischemia in patients with subarachnoid hemorrhage. References: 1. BMJ 1995; 310:776–777. 2. Lancet 1996; 347:1061–1065. 3. Thromb Haemost 1982; 48:266–269.

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COLOR CODED DUPLEX SONOGRAPHY AND GADOLINIUM-ENHANCED BOLUS MR-ANGIOGRAPHY IN HIGH-GRADE SYMPTOMATIC ICA-STENOSIS: IS DIGITAL SUBTRACTION ANGIOGRAPHY OBSOLETE? S. Friese, H. Krapf, M. Fetter, U. Klose, M. Skalej, W. Küker (Tübingen, D)

The established technique for screening and staging of stenoses of the internal carotid artery (ICA) is doppler and duplex sonography. For the imaging of ICA occlusive disease, magnetic resonance angiography (MRA) is replacing digital subtraction angiography (DSA) because it is non-invasive and cheaper. However, even in contrast-enhanced MRA (CE-MRA), the sensitivity and specificity are lower than in DSA. The purpose of this study was to evaluate if a non-invasive approach with Duplex sonography and CE-MRA is adequate for the diagnostic evaluation of carotid artery stenosis and in which cases additional DSA may be required. Material and Methods: CE-MRA was performed in 193 symptomatic patients (119 male, 74 female; mean age 67.5 yrs.) with sonographic findings of severe ICA stenoses. The MRA examination protocol (1.5 tesla unit) contained a heavily T1-weighted contrast bolus enhanced 3D – gradient echo sequence. Using a time-resolved technique, the measurement was divided into 4 x 10 sec repetitions with 0.5 s interval. MIP-reconstruction was performed after subtraction of the first non-contrasted sequence. The degree of stenosis was estimated retrospectively by two experienced radiologists blinded to the colour coded duplex sonography (CCDS) results. Results: The consistency of MRA and ultrasound was sufficient to plan thrombendarterectomy in 182/193 cases. In 11 cases MRA had to be supplemented by DSA. In 3 of these cases ultrasound examination diagnosed a filiforme stenosis of the ICA which was not visible with MRA. In all of these cases, DSA revealed a very short (1–2 mm), high-grade, excentric stenosis. This was in line with the intraoperative findings. CE-MRA detected patency in 5 patients with high-grade and low-flow carotid artery stenoses, which had been regarded as occlusion by CCDS. Conclusion: The combination of Doppler-ultrasound and contrast-enhanced MRA is a powerful tool for the non-invasive presurgical evaluation of the carotid arteries. Only in selected cases, DSA has still to be performed.

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THE SYNTHETIC OCTAPEPTIDE NAP EXERTS NEUROPROTECTION IN A MODEL OF FOCAL CEREBRAL ISCHEMIA BY REDUCING APOPTOSIS. R. R. Leker, A. Teichner, N. Grigoriadis, R. Nussen, Y. Cohen, I. Gozes, Hadassah University Hospital (Jerusalem, IL)

Vasoactive intestinal peptide (VIP) is cerebroprotective in several experimental models including focal cerebral ischemia. A new family of glial peptides, which includes activity dependent neuroprotective protein (ADNP), mediates at least part of the neuroprotective effects of VIP. NAP, a synthetic octapeptide related to ADNP was previously found to reduce ischemic cerebral damage in rats. Goals: To explore whether NAP reduces apoptotic cell death under ischemic conditions. Methods: Spontaneous hypertensive rats underwent permanent middle cerebral artery occlusion (PMCAO) by craniotomy and electrocoagulation. Rats were injected with either NAP (3 g/kg) or vehicle IV, I hour after PMCAO and were sacrificed 24, 48 and 72 hours later (n=5 animals per group, per time point). The maximal infarct diameters were identified on H&E slices and the infarcted tissue was systematically divided into core and penumbral zones. Apoptotic cells were identified on consecutive slices by the terminal deoxynucleotidyl-transferase end nick labeling (TUNEL) method, and immunohistochemical staining with a monoclonal antibody to caspase 3. Apotptotic cells were counted in predetermined zones of ischemic core and penumbra (n=10 high power fields per animal). Results: The numbers of both TUNEL and caspase 3 positive cells were significantly reduced in the ischemic core and penumbral zones of treated rats as compared with vehicle treated rats at all time points examined ($P < 0.05$ at all time points). The maximal relative reductions in the number of both TUNEL-positive and caspase 3 positive cells in core and penumbral zones were observed at 24 hours post PMCAO. Absolute reductions in the number of positive cells were maximal at 72 hours post PMCAO for TUNEL staining, and at 24 hours after the stroke for caspase 3 immunohistochemistry. Conclusions: At least part of the cerebroprotective effects exerted by NAP in this model of focal irreversible ischemia are mediated by a reduction in the number of cells undergoing apoptotic death.

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NO ASSOCIATION BETWEEN LACUNAR INFARCTION, HYPERTENSION OR DIABETES: TRUTH OR HERESY? I. Henriques, L. Rebocho, C. Barata, A. Leitão, Hospital Espírito Santo (Évora, P)

High blood pressure (HBP) and diabetes are traditionally considered associated with small vessel disease and with the occurrence of lacunar infarction (LI). We studied the hypothesis that HBP and diabetes are not particularly associated with lacunar type of stroke. Methods: We prospectively studied 125 consecutive first ever ischemic stroke patients with a protocol that includes at

least one CT-scan or MRI. We considered the classic lacunar syndromes. HBP was defined according to the V Joint National Committee criteria, and diabetes considered in the presence of known disease or according to the American Diabetes Association and WHO criteria. We used a statistical package that includes logistic regression analysis. Median age was 60 years and 77 patients were male (61%). Results: From 125 patients, 67% presented with HBP (n=84) and 25% were diabetic. Lacunar infarction was present in 65 patients (52%). Logistic regression analysis showed no association between LI and HBP (p= 0.3748; Odds Ratio: 1.42; 95% Confidence Interval 0.66–3.06), or between LI and diabetes (p= 0.6169; Odds Ratio: 1.25; 95% Confidence Interval 0.53–2.95). Conclusion: In this group of ischemic stroke patients, with a high prevalence of HBP and diabetes, no association was found between lacunar infarction and HBP or Diabetes. A recent population-based study showed similar results. Comparison with similar hospital-based studies would be of great help in the comprehension of this promising subject.

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THE PREVALENCE OF ADULTS WITH SYMPTOMATIC ARTERIOVENOUS MALFORMATIONS OF THE BRAIN. Rustam Al-Shahi, Jason Fang, Stephanie Lewis, David Watson, Anne Leigh Brown, Charles P Warlow, University of Edinburgh Bramwell Dott Building (Edinburgh, UK)

Background: Arteriovenous malformations of the brain (AVMs) account for approximately 30% of non-traumatic intracerebral haemorrhages in young people and may also cause epileptic seizures, headache and progressive neurological deficit in otherwise healthy young adults. Their relatively low early case fatality means that the majority of patients survive haemorrhage, with a significant risk of recurrence and long-term disability. Despite the importance of AVMs, there is considerable uncertainty about their prevalence.

Methods: We used multiple, overlapping sources of case ascertainment to establish the point prevalence of symptomatic AVMs in the adult population of the Lothian Health Board area of Scotland. Cases were sought from all general practitioners, hospital neurologists and neurosurgeons in this geographical area, the specialist AVM clinic at our hospital and routine coding of hospital discharge data. Case notes and brain imaging were reviewed to validate each patient's AVM diagnosis, and ensure they were alive, over the age of 16 years and resident in the geographical area of the study on the prevalence date of 30th June 1998. We obtained full ethical approval for this study from the relevant research ethics committees.

Results: 55 of 80 potential cases met our inclusion criteria. The population of the Lothian Health Board area over the age of 16 years on 30th June 1998 was 637,144, giving a minimum symptomatic AVM prevalence of 8.6/100,000 (95% CI 6.4–10.9). Using capture-recapture analysis to adjust for incomplete ascertainment, log-linear modelling with the best-fitting three source model gave a minimum estimate of symptomatic AVM prevalence of 10/100,000 (95% CI 9.3–11.8). 66 other potential cases remain to be validated and complete data will be presented at the meeting.

Conclusions: These preliminary results imply that symptomatic AVMs are more common than originally proposed by a retrospective study based at the Mayo Clinic (conducted before the modern era of neuro-imaging). These data help assess the comparative epidemiology of AVMs, and stress their importance as a cause of long-term disability in adults.

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THE RELATION OF WHITE MATTER HYPERINTENSITIES TO REGIONAL CEREBRAL BLOOD FLOW IN ELDERLY NORMALS. F. Payer, R. Schmidt, K. Brodtrager, P. Kapeller, H.-P. Hartung, F. Fazekas, Karl-Franzens University (Graz, A)

Objective: To investigate the effect of white matter hyperintensities (WMH) on cortical and subcortical blood flow in normal elderly individuals.

Method: We studied 317 randomly selected clinically normal volunteers of a population based stroke prevention study. All participants (mean age: 60.5 years; range: 50–75) underwent extensive clinical, laboratory, and neuropsychological testing. The extent of the total white matter hyperintensity area and the size of ventricles and cortical sulci were determined with morphometric measurements on a 1.5 T MRI. Regional cerebral blood flow (rCBF) was studied at rest with SPECT and 99mTc-HMPAO. A set of predefined regions of interest (ROI) was overlaid on cortical regions and subcortical nuclei. The ratio of the mean count in each ROI to the cerebellar activity was computed and compared to MRI abnormalities.

Results: WMH occurred in 150 (47.3%) individuals (mean extent of WMH area: 2.58 ± 5.7 cm^2). Subjects with WMH had significantly lower rCBF ($p < .05$) in all cortical brain regions (frontal, sensorimotor, parietal, temporal, and occipital) and subcortical nuclei relative to the cerebellum as those without WMH. In a forward stepwise regression analysis including age, morphometric atrophy variables, cerebrovascular risk factors, gender, and neuropsychological performance the extent of WMH remained a significant independent predictor for reduced rCBF in the frontal and occipital region, and the subcortical nuclei. Partial correlations between reduction of rCBF and WMH area found weak but statistically significant correlations in the frontal ($r = -.13$; $p < .04$) and occipital ($r = -.12$; $p < .04$) regions.

Conclusion: Our data indicate that clinically silent white matter changes may affect cerebral blood flow. The reduction of rCBF in subjects with higher extent of white matter lesion area may reflect neuronal deactivation due to disturbance of cerebral pathways.

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MID-TERM RESULTS AFTER ENDOVASCULAR THERAPY OR SURGICAL CLIPPING – IS OUTCOME DIFFERENT? C. Kremer, G. Lammers, C. Groden, G. Weineck, H. C. Hansen, University Hospital Eppendorf (Hamburg, D)

Background: Endovascular aneurysm occlusion is an accepted alternative therapy in the treatment of patients suffering subarachnoid hemorrhage (SAH). Early outcome results according to the Glasgow outcome scale (GOS) are comparable. Is there any difference concerning mid-term morbidity and the incidence of neuropsychological deficits?

Methods: Out of a total of 183 patients (pat.) admitted for SAH to our hospital between 1993–1997, 128 could be evaluated for the present study. 73 were treated by endovascular therapy (ET) and 55 by surgical clipping. 51 pat. (70%) treated by ET (ET-group) and 46 pat. (84%) treated by surgical clipping (S-group) were graded 1–3 according to Hunt and Hess (H. H.) on admission. The outcome of 101 pat. could be evaluated by answering a questionnaire, 27 were in a vegetative state or had died. Outcome was scored by GOS and Rankin-Scale. All 101 pat. were asked for neuropsychological deficits. Mean interval to evaluation was 4 (2–6) years.

Results: Mortality (GOS 1) was lower in the S-group with 4 pat. (7%) compared to 19 pat. (26%) in the ET group, leaving 49 surgical and 47 ET treated patients for morbidity comparison (excluding pat. in vegetative state and 3 ET and 2 S-group pat.,who could not be scored by Rankin). Good recovery (GOS 4 and 5) was reached by 49 pat. (67%) in the ET and 46 pat. (83%) in the S-group. Morbidity according to Rankin-scale (Rankin 5–2) was 41% (20 pat.) in the S-group and 29% (14 pat.) in the ET-group. 25 pat. (51%/45% of total number) in the S and 18 pat. (38%/25% of total) in the ET group complained about neuropsychological deficits.

Conclusion: Mortality and morbidity are different in patients treated by ET and surgical clipping. Mortality was higher in the ET-group, presumably because of worse entry conditions according to H. H. Surprisingly morbidity was lower in the ET group as shown in a smaller proportion of pat. with Rankin 2–5 as well as neuropsychological complaints.

Oral session 15

Dementia and higher function disorders – 3

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A HIERARCHICAL SCALE TO ASSESS BRAIN VASCULARITY ON CT FILMS IN DEMENTING AND NON-DEMENTING COGNITIVE IMPAIRMENT. C. Geroldi, S. Galluzzi, L. Bresciani, C. Testa, G. Binetti, O. Zanetti, A. Bianchetti, M. Trabucchi, GB. Frisoni, IRCCS S. Giovanni di Dio – Fatebenefratelli (Brescia, I)

Objective: To test the validity of a newly developed rating scale to assess cerebrovascular disease on CT films. The scale assumes that different types of lesions have different power to cause cognitive impairment: leukoaraiosis is assumed to be the less efficient, subcortical lesions are intermediate, and cortical lesions are the most efficient. Within these 3 domains, severity is weighed in order to reflect this hierarchy.

Background: In 1998, the European Task Force on Age-Related White Matter Changes reviewed the available scales to visually rate cerebral vascularity concluding that "the ideal rating scale does not yet exist". These have generally been developed to assess vascularity by weighing site and size according to descriptive criteria. A pathogenetic model linking lesions to cognitive deterioration was generally not assumed.

Design/Methods: The developed scale rates presence and severity (number and size, i. e. > or < than 2 cm) of cortical and white matter hemispherical (frontal, temporal, parietal, occipital) and deep subcortical lesions, and of leukoaraiosis (score of 0 to 18) as assessed on CT films. Vascularity scores are: 0, no vascular lesions; 1, isolated mild leukoaraiosis; 2, moderate

leukoaraiosis or 1 large or max. 2 small lacunes; 3, severe leukoaraiosis or more/larger lacunes; and 4, severe leukoaraiosis with more/larger lacunes or cortical lesions. Known-group validity was tested across the diagnostic categories of NINDS-AIREN vascular dementia (VaD), vascular cognitive impairment – no dementia (CIND), mild cognitive impairment (MCI), and NINCDS-ADRDA Alzheimer's disease (AD) with and without cerebrovascular disease (CVD). Convergent validity was tested within the AD group versus other indicators of vascularity: motor functions with extrapyramidal symptoms (Richards' Extrapyramidal Symptoms scale, EPS), time to walk 15 meters (in sec.), and balance (Tinetti scale). All patients had MMSE of 18 and higher. VaD were 17 patients with MMSE 21±2, age 80±7 years. Vascular CIND were 28 patients with MMSE 24±3, age 80±5 years. MCI were 16 patients with MMSE 24±3, age 73±8 years. AD were 63 patients with MMSE 21±2, age 76±8 years. Inter-rater (IR) and test-retest (TRT) reliability were tested in a sample of 20 patients.

Results: Intraclass correlation coefficients for IR and TRT reliability were between 0.85 and 0.92. Vascularity as graded with the hierarchical scale was significantly lower in MCI and AD than both vascular CIND and VaD (1.5±0.9, 1.7±1.3, 2.8±1.0, and 3.0±1.1; p< 0.0005). In a discriminant analysis, the vascular score alone allowed to discriminate AD from VaD individuals with 74% accuracy, and MCI from vascular CIND with 70% accuracy. AD patients were divided into 3 groups according to the vascular score: 13 scored 0, 34 scored 1 or 2, and 16 scored 3 or 4. Extrapyramidal symptoms were increasingly severe (EPS score: 0.5±1.0, 1.7±1.7, and 3.0±3.1, p for trend=0.0003), gait increasingly slow (15.3±3.5, 17.6±5.4, and 19.9±4.0 seconds, p=0.03), and balance increasingly poor (Tinetti score: 14.2±1.1, 13.5±2.9, and 11.7±1.3, p=0.05) across groups.

Conclusion: The hierarchical scale for cerebral vascularity is a valid tool to estimate the vascular component in patients with cognitive impairment. Its practical usefulness to differential diagnosis in the routine clinical setting still needs to be explored.

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NON-DEMENTING COGNITIVE IMPAIRMENT IN A MEMORY CLINIC: RECOGNITION OF THE DEGENERATIVE AND VASCULAR ETIOLOGY. S. Galluzzi, C. Geroldi, L. Bresciani, C. Testa, G. Binetti, O. Zanetti, M. Trabucchi, GB. Frisoni, IRCCS S. Giovanni di Dio – Fatebenefratelli (Brescia, I)

Background: Recognizing individuals with very early cognitive deterioration is presently matter of great interest. Criteria for the degenerative form of non-dementing cognitive impairment (Mild Cognitive Impairment – MCI) have been developed by the Mayo Clinic group, but its relationship to non-dementing cognitive impairment due to a vascular etiology (vascular cognitive impairment no – dementia or vascular CIND) is unclear. In particular, the possibility of separating the two conditions in a clinical setting and their prevalence are unclear. The aim of this study is to describe the clinical features of individuals with MCI and vascular CIND seen in a memory clinic.

Subjects and methods: A prospective study of early cognitive impairment (Mini Mental State Examination – MMSE – of 19 and higher) was started at the Alzheimer's Unit, IRCCS San Giovanni di Dio – FBF, Brescia, on January 1st, 1996. As of December 31st, 1996, 16 consecutive individuals with MCI, 28 with vascular CIND, 63 with NINCDS-ADRDA probable and possible Alzheimer's disease (AD) and 17 with probable and possible NINDS-AIREN vascular dementia (VaD) were enrolled in the study. Vascular CIND was defined as the presence of: (i) cognitive impairment, (ii) vascular risk factors, and (iii) vascular lesions on computed tomography (CT) of site, size, and severity sufficient to cause the cognitive impairment as judged by 2 expert clinicians (GBF and CG). In addition to CT, all patients underwent complete medical and neuropsychological evaluation (including memory testing with the Babcock test), as well as measures of basic activities of daily living (Barthel index), and motor status (Tinetti balance and gait scale, ExtraPyramidal Symptoms – EPS – scale, and time required to walk 15 meters). A measure of medial temporal lobe atrophy was taken from CT (radial width of the temporal horn).

Results: Mean ages were 73, 80, 76, and 80 years in MCI, vascular CIND, AD, and VaD patients, while education was of 7, 6, 6, and 5 years. The mean MMSE was 25, 24, 21, and 21 points. As expected, the functional and neuropsychological performance of MCI and vascular CIND individuals was better than that of both demented groups although the variability of the performance in the latter was generally higher. Moreover, MCI and vascular CIND differed from AD and VaD patients for characteristics that had not been used for diagnosis. In particular, MCI were similar to AD patients for medial temporal lobe atrophy, extrapyramidal symptoms, motor function, and disability, while vascular CIND had more extrapyramidal symptoms, poorer motor function, greater disability, and relatively preserved memory performance, which were similar to those found in VaD patients. For example, the values of the EPS scale were 1.2±1.8 in AD, 1.2±1.6 in MCI, 4.3±3.5 in vascular CIND, and 3.2+2.3 (p< 0.0001) in VaD patients, while Tinetti balance scores were 13.6±2.1, 13.9±1.1, 11.9±2.8, and 10.9±3.7 (p< 0.0001) respectively.

Discussion: MCI and vascular CIND can be differentiated from AD and VaD and from each other. These data indicate that conditions of preclinical dementia can be recognized with simple diagnostic tools.

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A POLYMORPHISM OF THE PRION PROTEIN IS MODERATELY ASSOCIATED WITH AGE AT ONSET AND RATE OF COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE. V. M. Casadei, M. Franceschi, E. Brambilla, F. Veglia, A. Gavazzi, E. Calabrese, N. Canal, F. Licastro, S. Sorbi, C. Mariani, L. M. E. Grimaldi, IRCCS San Raffaele Hospital, Clinica Santa Maria, IRCCS Santa Maria Nascente, University of Bologna, University of Florence (Milan, Castellanza (VA), Bologna, Florence, I)

The PRNP gene, coding for the Prion Protein (Prp), has been implicated in spongiform encephalopathies. The biologic role of Prp is still unknown, although it may play a role in normal synaptic function. Recently, a large community based French study suggested that the codon 129 M/V polymorphism of the PRNP gene is associated with cognitive performance in aged non-demented individuals, as evaluated by the Mini Mental State Examination (MMSE). To investigate the role of this PRNP polymorphism in Alzheimer's disease (AD), we performed a case/control study on 212 Italian subjects (130 females, 82 males; mean age at disease onset 68.27 years) affected by probable sporadic AD and 201 age- and ethnicity-matched non demented individuals (80 females, 121 males; mean age 67.23 years). Their cognitive status was assessed by MMSE (normal score > 24/30). The patients were divided into those with an early onset (EO AD = onset before or at 65 years; n = 70), and those with a late onset (LO AD = onset after 65 years; n = 142) of disease. PRNP codon 129 M/V polymorphism was analysed by PCR followed by BsaA1 restriction endonuclease digestion. APOE 2–4 polymorphism was also determined. Chi-square test was used to compare genotype frequencies (GF) in case-control and case-case (EO AD vs LO AD patients) analyses. Due to the low representation of the VV genotype both in controls (0.09) and in AD (0.06), MV and VV genotypes were pooled together (V+). MMSE scores and years of education were also included in the analysis. In our control group, PRNP GF did not vary with age, gender, education or APOE4 carriage. No difference in genotype distribution between AD and control individuals was found (2X2 contingency table chi-square 2.6, p=0.1). However, a slight increase in MM genotype distribution was found in LO AD patients when compared to total controls (chi-square 4.4, p=0.036) and to controls > 65 years of age (chi-square 4.06, p=0.044). AD patients and controls had a similar education (mean value of 7.47 years of schooling for AD and 8.87 for controls). The same was observed after stratification of AD patients by their PRNP genotypes (7.52 years for MM; 7.41 for V+). When mean MMSE scores and disease duration were calculated in AD patients grouped according to their PRNP genotypes, we found that MM and V+ patients had a comparable mean MMSE score (15.28 in MM and 15.11 in V+), while MM patients showed a duration of the disease a mean of 9 months longer (47 months in MM and 38 months in V+ patients). We conclude that PRNP 129 M/V polymorphism is not a risk factor for AD, but it might have a role in influencing age at clinical onset, possibly by affecting the rate of cognitive decline over time.

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SEMANTIC MEMORY IN MILD FRONTOTEMPORAL DEMENTIA. V. Golfier, M. Didic, V. Leblay, E. Sartori, S. Belliard, M. Poncet, G. Edan, University Hospital Pontchaillou, University Hospital Marseille (Rennes, Marseille, F)

OBJECTIVE: To investigate semantic memory in mild frontotemporal dementia (FTD).

BACKGROUND: In the past few years, FTD has been studied extensively, but neuropsychological studies have not focused on semantic memory. However, clinical and PET studies have shown that left inferolateral temporal region plays a critical role in semantic knowledge, and that left inferior frontal cortex may be also involved in semantic processes. These two areas are affected in FTD.

DESIGN/METHODS: We included 9 patients meeting the criteria of FTD (Neary et al., 1998), in the early stage of the disease: mean duration of illness was 2,11 years (SD: 1,27) and mean score on the Mattis Dementia Rating Scale (DRS) was 113,8/144 (SD: 9,68). Control subjects were matched for age and educational level to the patients group. All the patients underwent a french executive battery and the digit span. Semantic memory was assessed with four subtests: (1) naming of 80 black and white line drawings (2) three-picture version of the Pyramids and Palm Trees Test (PPTT) (3) generation of verbal definition of 48 words, representing 4 categories (animals, fruits, clothes, vehicles) and semantic features questionnaire about the same 48 items.

RESULTS: Picture naming test was normal in all patients. PPTT score

was impaired in 8 patients. Patients were significantly worse than controls on definition of the 48 words ($p< 0,001$) and questionnaire ($p< 0,001$). There was no correlation between performances on semantic tests and score on the DRS, executive function, or attentional task. Only one patient had normal performances on semantic tasks. This patient presented with an apathetic type of FTD. All other patients were of the disinhibited type, and had abnormal results on semantic tests.

CONCLUSION: Semantic memory is not preserved in FTD, even at the early stage of the disease. These results cannot be only attributed to the rate of cognitive deterioration, executive dysfunction and attention disorders, and suggest that critical regions for semantic knowledge are not preserved in our population, especially in patients with clinical signs of orbitofrontal dysfunction. This subtype of FTD seems to be very different to the apathetic type, and close to semantic dementia, with degeneration of a frontotemporal system.

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COMPREHENSION OF HUMORISTIC AND FIGURATIVE DISCOURSE FOLLOWING RIGHT AND LEFT SELECTIVE CORTECTOMY IN EPILEPTIC PATIENTS. E. Sartori, H. Guyard, S. Belliard, V. Leblay, V. Golfier, J. Chapron, A. Biraben, G. Edan, University Hospital Pontchaillou, Department of Public Health Rennes (Rennes, F)

Previous studies investigating humoristic and figurative discourse deficits showed an important role of frontal and temporal right cortices. However, the function of these structures is still debated, especially in the use of contextual informations (inferences) and semantic knowledge by right-brain damaged patients to comprehend complex linguistic material.

OBJECTIVES: The aim of the present study was to look for a discourse deficit in patients with right cortectomy for intractable epilepsy and to evaluate their analysis of inferences and semantic knowledge in comprehension of the discourse.

DESIGN/METHOD: We compared two groups of patients with a right- (n=16) and left- (n=10) temporal or frontal cortectomy with a sex-, age- and education-matched normal control group (n=25). A set of tasks was designed exploring, in a first step, inferences (stories completion, anaphoric resolution) and semantic knowledge (real/chimeric objects decision, knowing proverbs comprehension), and, in a second step, comprehension of humoristic material (jokes and chimeric objects with caption completion) and figurative aspects of language (unknowing proverbs and metaphoric comprehension).

RESULTS: Patients with right cortectomy had significantly poor performances in tests exploring humour and figurative language ($p< 0.01$), whereas they did not differ from control group in tests exploring inferences and semantic knowledge without humour or figurative language. These differences were not correlated with age, intellectual level (WAIS) or duration of the disease. Patients with left cortectomy did not differ from controls in overall tasks. In the group of patients with right cortectomy, the principal components analysis generated a one-factor solution which had high loading (correlation coefficient > 0.5) from the scores of sub-tests exploring humour and figurative language, independently of the site of right cortectomy (frontal or temporal).

CONCLUSION: Patients with a right frontal or temporal cortectomy have difficulties to comprehend discourse (with a homogenous deficit involving humour and figurative language); this is not sufficiently explained by a deficit of inference or semantic knowledge, intellectual level or duration of disease; it could be the consequence of the disorganisation of a neuronal network including right frontal and temporal neocortices.

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FUNCTIONAL SEGREGATION OF MEMORY FOR OBJECTS AND LOCATIONS. WCM Machielsen, SARB Rombouts, F. Barkhof, MP. Witter, Ph. Scheltens, Vrije Universiteit (Amsterdam, NL)

Introduction: Animal studies have suggested the presence of two structurally and functionally distinct pathways within the hippocampal memory system 1,2. One pathway that is situated more anteriorly, including the perirhinal cortex, is involved in memory for objects. The other pathway, situated more posteriorly, includes the parahippocampal cortex and is more strongly involved in spatial memory. This putative functional segregation in the hippocampal system has not been extensively studied in humans yet. To assess the validity of this proposal, we used functional MRI (fMRI) during recognition of objects and recognition of spatial locations.

Methods: Ten normal healthy subjects (age 21–30 years) performed a recognition task. Before scanning, subjects were presented 8 pictures of single objects and 8 pictures of different spatial configurations of a table and/or chairs including a spatially positioned marker. During fMRI scanning, subjects were presented an object recognition (OR) and a location recognition (LR) condition. In both conditions, both a familiar picture and a novel alternative were presented in a block design (10 blocks with 8 items each, 3.5 sec per item with 1.5 sec interval). Subjects had to indicate the familiar picture by pressing a right or left-hand button.

We applied whole brain echo planar imaging (80 volumes, voxel size = 1.56 x 3.12 x 5 mm, 32 slices). Data were analysed with SPM99 3 and included realignment, normalisation and spatial smoothing (8 mm FWHM). Relative signal change was compared between OR and LR ($P = 0.000001$, uncorrected).

Results: Mean recognition scores were 99 % (range 98–100 %) for OR and 93 % (range 78–100 %) for LR. Group analysis revealed increased activation during OR relative to LR in the parahippocampal gyrus, predominantly anteriorly, with less activation posteriorly. Other areas of signal increase were fronto-polar (Left), middle frontal (L), superior frontal, cingulate, middle temporal, inferior parietal (L), and lingual gyrus, amygdala ®, insula, and lateral fissure. LR compared to OR revealed no regions of significant activation increases in the parahippocampal gyrus. Areas that did show this signal change were middle frontal ®, orbital and fusiform ® gyrus, and occipital and parietal lobe.

Conclusions: We found increased activation in the anterior parahippocampal gyrus during memory for objects, relative to spatial memory. In line with observations in animal studies 1,2, this activation might be attributed to the perirhinal cortex. The hypothesis that the parahippocampal cortex is more involved in spatial memory than object memory could not be confirmed in this study. In future work, our paradigm will be refined to further study the functional differences in memory for objects and spatial locations in humans. References: 1. Naber PA, et al. (1997) Neuroreport, 8:2617–2621. 2. Zhu XO, et al. (1996) Neuroreport, 7:1871–1875. 3. Friston KJ, et al. (1995) Hum. Brain Mapp., 2:165–189

Oral session 16

Extrapyramidal disorders – 1

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UNILATERAL DEEP BRAIN STIMULATION OF THE VENTRAL INTERMEDIATE (VIM) THALAMIC NUCLEUS CHANGES TREMOR CHARACTERISTICS IN PARKINSON'S DISEASE. E. S. Simon, D. Eidelberg, R. Thorne, N. Giladi, Tel-Aviv Medical Center Movement Disorders Unit, North Shore University Hospital (Tel-Aviv, IL; New York, USA)

Objective: To characterize effects of VIM stimulation therapy on tremor bilaterally. Background: Functional neuroimaging data point to involvement of network including the thalamus, pons, and premotor cortex in Parkinsonian tremor. The recent emergence of deep brain stimulation (DBS) treatment for refractory tremor offers excellent suppression of symptomatic tremor, with little or no side effects in properly chosen patients. We studied patients with tremor-predominant PD who underwent successful implantation of DBS electrodes to the VIM thalamic nucleus. Here we present preliminary results of a collaborative study involving electrophysiological tremor characterization and PET neuroimaging in these patients. Methods: Patients with tremor-predominant PD who obtained significant relief with VIM stimulation were studied (n=3). Arm motion was measured bilaterally using triaxial accelerometers (TRIAXs) placed on the dorsum of the hands, with the arm at rest. Data were collected for 90 seconds with the simulator turned ON and OFF, each condition repeated twice. TRIAX signals were filtered and digitized, and were analyzed in segments of 4 seconds. The parameters measured for each TRIAX were amplitude, peak frequency, coherence, and inter-axis phase relationships. Results: Although there was negligible visible tremor with the stimulator ON, the TRIAXs detected low-amplitude tremor (peak frequency 5–7 Hz). In contrast, with VIM stimulator turned OFF there was tremor of high magnitude (peak frequency 3–4 Hz). A similar jump in frequency was seen in the hand homolateral to the DBS electrode, where there was little change in amplitude attributable to the stimulation. Further coherence between the Y- and Z-axis of the TRIAX on the symptomatic hand was higher with the stimulator turned ON. Interestingly, there were differential phase difference profiles between the Y- and Z-axis in the symptomatic hand related to stimulator activation. Conclusions: These data, indicating that the structure of the rest tremor as shifted in response to the thalamic stimulation, offer insight into the effects of thalamic DBS in Parkinson's disease, and also may advance our understanding of neural mechanisms responsible for tremor.

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OLANZAPINE IN HUNTINGTON'S DISEASE. D. Paleacu, M. Anca, N. Giladi, Neurological Service, Abarbanel MHC, Movement Disorders Unit (Bat Yam, Tel Aviv, IL)

Objective: To study the effect of olanzapine (OL) on the motor and behavioral symptoms of Huntington's Disease (HD) patients. Background: HD is a genetic neurodegenerative disease which manifests a triad of symptoms including a movement disorder, dementia and psychiatric symptoms. This combination limits the drug treatment options in HD. OL is a novel antipsychotic drug with a high affinity for a number of receptors and a low profile of side effects compared to conventional neuroleptics, traditionally used in HD. Methods: Five HD patients (3 males, 2 females) with a mean age of 46.6 years and longstanding disease (mean duration:10.4 years) received OL when other medication failed to improve their motor or psychiatric symptoms. Indications included: psychomotor agitation (2), depression with psychotic features (1), disruptive behaviour (1) and excessive drooling following tetrabenazine treatment (1). Patients were assessed using the Clinical Global Impression of Change Scale where 1=marked improvement, 2=good, 3=mild, 4=no change and 5=worsening and the motor and behavioral subsets of the Unified Huntington Disease Rating Scale. Evaluations were done before and after one year on OL.

Results: Mean treatment length was 12.6 months and the mean dose of OL was 16 mg/day. All patients improved with a mean CGIC score of 2 (two patients scored 1). The behavioral UHDRS markedly improved from 26.6 before OL to 12 after OL, mainly by decreased anxiety, irritability and aggression scores; whereas the motor UHDRS remained practically unchanged: from 38.8 before OL to 37.7 after OL treatment. One patient enjoyed a marked improvement of her chorea and this might be due to OL.

Conclusions: OL is a useful and good alternative treatment in HD symptoms after other medical options have failed. It is mainly effective for the psychiatric features of the disease and has a minor effect on the motor features with a possible anti-chorea effect.

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CHILDHOOD-ONSET DYSTONIA: CLINICAL AND RADIOLOGICAL FINDINGS IN 31 CHILDREN. M.E Eraksoy, M.B Barlas, Z.Y Yapici, F.E Erdogan, E.D Deniz, H.O Ozcan, Ist Fac Med, Neurology, The Spastic Children Foundation of Turkey (Istanbul, TR)

The differential diagnosis of childhood-onset dystonia is important because dopa responsive dystonia (DRD) and Wilson disease (WD) respond well to treatment, particularly WD is universally fatal if overlooked.

The objective of this study was to reveal final diagnosis, clinical course, and therapeutic response in children presented with dystonia between 1993 and 1998. Charts were reviewed and all patients with dystonia were recorded. Suspected patients were re-examined and the data were updated. Cranial MRI, metabolic screening tests, ophthalmologic examination were performed in all patients. In child neurology unit, 22.000 children with neurological problem were evaluated over 5 yrs. Of 22.000, 350 (1.6 %) and 30 (0.1 %) children presented with dystonic-dyskinetic cerebral palsy and other dystonic syndromes, respectively. The second group was studied. Mean age at onset was 9 yrs (ranged from 3 to 15 yrs). There were 18 females and 13 males (F / M: 1.3 / 1). In most of the patients (41.9 %), dystonia firstly appeared in the lower limbs. Final diagnoses were Hallervorden-Spatz Disease (n=7), DRD (n=5), primary dystonia (n=5), dystonia with striatal lucency (n=4), WD (N=3), Leigh disease (n=2), delayed onset dystonia (n=2), infantile Huntington's disease (n=1) and acute bilateral striatal necrosis (n=1). Cranial MRI findings in these patients were compatible with their clinical diagnosis. Dramatic and sustained improvement was seen in a patient with DRD at follow-up. The dystonic symptoms seen in other DRD and WD patients incompletely improved with medical therapy. The remaining of the patients progressed to more generalized dystonia and failed to respond to therapy. Two patients died and stereotaxic neurosurgery had to be performed in seven patients at follow-up.

In conclusion, younger patients with a shorter duration of symptoms tend to respond to therapy best. This indicates the need for correct diagnosis and initiation of therapy early in the course of childhood-onset dystonia.

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PRAMIPEXOLE INDUCED EPISODES OF IRRESISTIBLE DAYTIME SLEEPINESS. I. Schlesinger, P. D. Ravin, U Mass Memorial Medical Center (Worcester, MA, USA)

Recent publications regarding pramipexole's role in causing sleep attacks raise questions regarding the safety of the new selective D2 agonists in Parkinson's disease therapy. We have interviewed forty consecutive Parkinson's patients (pts) on pramipexole therapy seen at our tertiary Movement Disorders clinic to try to establish whether there is a relationship between pramipexole use and irresistible daytime sleepiness. We questioned pts and partners regarding incidence of sleep initiation difficulties, sleep fragmentation, early morning arousals, daytime somnolence and napping, apnea and snoring, parasomnias (hallucinations, vivid dreams and nightmares) and sudden overwhelming need to sleep episodes. Data relating to cognitive status, mood disorders, stage of disease, length of disease, dose of pramipexole and other medications were determined by chart review. Twenty five men and fifteen women between the ages of 35 and 77 years (mean 50.5 ± 2.1 years) with Parkinson's disease for 1–22 years (mean 10.0 ± 2.8 years) in stages I to IV Hoehn and Yahr (mean stage 3) established our cohort of pramipexole treated pts. Total dose of pramipexole varied between 0.5–9 mg a day (mean 1.8 ± 0.4 mg). Eighteen pts reported irresistible episodes of a need to sleep during the day while engaged in activities where falling asleep was inappropriate, thirteen while driving long distances (typically on highways). One sustained an MVA and had a mild concussion after driving off the road. Six of thirteen pts with episodes while driving pulled over to the side of the road and had complete resolution of sleepiness with a 5 to 10 minute nap. Most pts experienced these episodes at a predictable time of day, 30 to 120 minutes after a dose of pramipexole. All reported premonitory sleepiness with many resorting to strategies to arouse themselves. Risk factors for these episodes were monotonous activities at a set time each day relative to their dosing schedule in pts with parasomnias ($p < 0.05$) and sleep fragmentation ($p < 0.05$). Incidence of other sleep disturbances in our cohort did not differ significantly between pts with or without episodes of sleepiness. Improvement in affected pts was achieved by either changing the schedule of pramipexole dosing (one patient) or amount per dose (five pts) to accomplish less peak-dose effects during the problematic time of day. Pramipexole was discontinued in three pts without attempting dose changes first. Others accommodated the sleepiness by taking naps routinely. One patient had spontaneous resolution of the sleepiness after a month on pramipexole. We conclude that pramipexole is commonly implicated in episodic irresistible sleepiness during the day. Dose and timing adjustments of pramipexole or napping were effective in mitigating this problem. Physicians need to question patients directly about daytime sleepiness in order to avoid drug induced episodes. Other dopamine agonists should be investigated further with regards to irresistible daytime sleepiness.

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THE INFLUENCE OF VISUAL FEEDBACK ON POSTURAL RESPONSES IN PARKINSON'S DISEASE (PD). S. Ashkenazi, M. Himerlfarb, A. D. Korczyn, Tel Aviv University Medical School (Ramat Aviv, IL)

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DOPAMINE AGONISTS AND COMT INHIBITORS IN PARKINSON'S DISEASE: A COMPARISON OF THEIR EFFICACY AND TOLERABILITY. R Inzelberg, P.F Nisipeanu, E Schechtman, S.C Blumen, R.L Carasso, Hillel Yaffe Medical Center, Ben Gurion University (Hadera, Beer Sheva, IL)

Dopamine agonists (DA) and COMT inhibitors were found to be effective in PD patients uncontrolled by levodopa (LD). Since they have not been evaluated against each other, we aimed at comparing three DA [Pergolide (PRG), Pramipexole (PRX), Ropinirole (ROP)] and two COMT inhibitors [Tolcapone (TOL) and Entacapone (ENT)] as add-on to LD, by analyzing recent randomized double-blind placebo (PBO) controlled studies* (1756 patients). The statistical analysis used the odds ratio, number needed to harm and combine p-value by chi-square. The efficacy measures common to all studies were the reduction in daily LD dose versus baseline and "off" duration, which were not comparable from the reported data. The reported reduction in LD dose was significant for all drugs versus PBO, but most significant for PRX and ENT ($p < 0.0001$). The most significant reduction in "off" hours was reported with PRX, PRG and ENT ($p < 0.001$). The common tolerability measures were the percentage of patients withdrawn due to side effects and those who developed dyskinesias. For withdrawals due to side effects, odds ratios and confidence intervals showed that PRX, ROP and ENT were similar to PBO, while TOL and PRG (marginally) caused more withdrawals due to side effects. All drugs caused more dyskinesia than PBO ($p < 0.0001$). The odds ratios and confidence intervals for dyskinesia overlapped for all drugs except for TOL (one study, 600 mg daily) whose intervals were much higher [5.89 (15.85–204.26)]. PRX and ENT enabled the greatest reduction in LD dose, PRX, PRG and ENT in "off" duration. PRX, ROP and ENT had better tolerability than other DA and TOL. TOL (600 mg) cause more dyskinesia than ENT and DA. When all efficacy and tolerability measures were considered, PRX and ENT were the most acceptable choices in this meta-analysis. * Ann Neurol 1997, 42:747–755; Neurology 1996, 46:1062–1065; 1997, 49:162–168; 1066–1071; 1998, 51:1057–1062; 1309–1314; Mov Disord 1994, 9:40–47; J Neurol Neurosurg Psychiatry 1997, 63:421–428.

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SPECIFIC CLINICAL PHENOTYPE ASSOCIATED WITH THE ALPHA-SYNUCLEIN PARKINSON'S DISEASE IN COMPARISON TO FAMILIAL PARKINSON'S DISEASE. S Papapetropoulos, C Paschalis, A Athanassiadou, A Papadimitriou, J Ellul, MH Polymeropoulos, Th Papapetropoulos, University Hospital of Patras, Medical School of Larissa, Novartis (Rion – Patras, Larissa, GR; USA)

An Ala53Pro mutation of the alpha-synuclein in exon 4 has been recently identified as a rare cause of autosomal Parkinson's Disease (PD). We set out to study the clinical characteristics of patients with chromosome 4 linked PD (alpha-synPD) and compare them with familial PD (fPD) patients, who had not the alpha-synuclein mutation. Methods: An investigator blinded to the results of the genetic analysis examined 15 alpha-synPD and 43 consecutive fPD patients. Together with demographic data, information on age at onset of the illness, duration of PD and modality of presentation were collected. The Unified Parkinson's Disease Rating Scale, the Hoehn & Yahr and Schwab-England scales have also been completed. Results: alpha-synPD patients were significantly younger (average 11.8 years, p=0.003) and showed the first sign of the disease significantly earlier in life (average 12.7 years, p=0.002) compared to fPD patients. Tremor was almost absent at onset of the disease in alpha-synPD patients compared to the fPD patients (presence of tremor in 6.7 % and 41.8 % of patients respectively, p=0.01). During the course of the disease only one of the 15 alpha-synPD patients went on to develop tremor, thus tremor at the time of examination was still predominant in fPD patients (p=0.01). Although the duration of the disease did not differ significantly between these two groups of patients (mean difference 1.7 years, p=0.24), at the time of examination rigidity, bradykinesia, postural instability, orthostatic hypotension and the mean scores of the above mentioned scales measuring severity of the disease did not differ significantly. Conclusion: The younger age at onset and the almost absence of tremor distinguished alpha-synPD from other fPD patients. The rate of progression of the disease did not differ significantly between alpha-synPD and fPD patients.

Oral session 17

Epilepsy – 1

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MAGNETIZATION TRANSFER AND DIFFUSION-WEIGHTED IMAGING IN NOCTURNAL FRONTAL LOBE EPILEPSY. Marco Bozzali, Mara Cercignani, Luigi Ferini-Strambi, Massimo Filippi.

Nocturnal frontal lobe epilepsy (NFLE) is a distinct, autosomal dominant epileptic syndrome characterized by clusters of brief nocturnal motor seizures, normal interictal electroencephalogram and partial seizures. No abnormalities are shown by conventional magnetic resonance imaging in NFLE patients. We used MTI and DWI to assess in-vivo whether subtle tissue abnormalities could be detected in the brain from patients with NFLE compared to patients with idiopathic generalized epilepsy (IGE) and healthy controls.

We studied 29 patients with NFLE, 9 patients with IGE and 17 sex- and age-matched healthy controls. Dual echo turbo spin echo (TSE), 2D gradient echo (GE) with and without an off resonance saturation pulse, spin-echo echo-planar pulse sequence, which collects one T2-weighted and three identical isotropically diffusion-weighted images per slice were collected from each subject. From the two GE images, with and without the saturation pulse, MTR maps were derived. After correction for misregistration, an image of the mean diffusivity ($\bar{D}$) was calculated. Histograms of the average MTR and $\bar{D}$ maps were produced after removal of the extra-cerebral tissue and of cerebrospinal fluid. For each histogram (normalized by the total number of pixels contributing to the histogram), the following measures were then derived: the relative peak height (i.e., the proportion of pixels at the most common MTR and $\bar{D}$ value), the peak position (i.e., the most common MTR and $\bar{D}$) and the mean brain MTR and. No abnormalities were seen on the dual-echo TSE images of any of the controls and patients. The peak height of the MTR histogram from NFLE patients was significantly lower than those from controls (p=0.004) and IGE patients (p=0.01). A significant decrease was also found for the peak height of the $\bar{D}$ histogram between NFLE patients and controls (p = 0.001). No significant difference was found for any of the MTR and $\bar{D}$ metrics between controls and IGE patients. Subtle and widespread abnormalities related to water intra/extra-cellular distribution and motion are detectable in the brain of patients with NFLE.

Our results suggest that the amount of 'truly' normal brain tissue is reduced in patients with NFLE.

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ANTIEPILEPTIC DRUG TREATMENT IN SURGICAL AND NON-SURGICAL TEMPORAL LOBE EPILEPSY PATIENTS: A LONG-TERM FOLLOW-UP STUDY. C. G. Bien, M. Kurthen, K. Johanson, C. Helmstaedter, C. E. Elger, University of Bonn (Bonn, D)

Purpose: The principal goal of epilepsy surgery is to achieve seizure freedom. Next to that, it is intended to improve health related quality of life which in part depends on the amount of antiepileptic drugs (AEDs) which are administered for chronic treatment. The present study was performed to evaluate the long-term impact of surgical treatment in temporal lobe epilepsy (TLE) on antiepileptic drug usage.

Methods: The study compared seizure status (completely seizure free or not seizure free) and AED treatment (no AEDs, monotherapy or polytherapy) of surgical patients (group S, n=154) and non-surgical patients (group NS, n=96) with TLE. Relevant data were collected at two visits, the first one (visit 1) immediately prior to surgery or refusal of surgery and continued mere medical treatment, respectively, and a second one (visit 2) after a mean interval of 55 ±25 months.

Results: At visit 2, 97 (63 %) of the operated and 15 (16 %) of the non-operated patients were seizure free. The operated patients took significantly less AEDs than non-operated patients: no AEDs: 9 % vs. 1 %; monotherapy: 54 % vs. 27 %; polytherapy 37 % vs. 72 %. Among the patients with monotherapy, 20 % of group S but only 4 % of group NS took a standard AED at a subtherapeutic blood level. If the subgroups of seizure free patients from both groups were compared, there was again a significant difference in AED usage in favor of the operated patients: no AEDs: 13 % of group S vs. 0 % of group NS; monotherapy: 65 % vs. 53 %; polytherapy: 22 % vs. 47 %. No significant difference was found between the patients of the two groups who continued to have seizures.

Conclusions: This long-term study indicates that surgical TLE patients need significantly less AEDs than non-surgical patients. This difference is due to the operated seizure free patients which take less AEDs than any other subgroup. Surgically treated but not seizure free TLE patients do not do better than non surgical patients with continuing seizures.

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EPILEPTIC NYSTAGMUS AND OCCIPITAL LOBE EPILEPSY: THREE CASES. M. Coustans, D. Taussig, V. Golfier, C. Allaire, A. Biraben, G. Edan, University Hospital Pontchaillou (Rennes, F)

We report three cases of children with epileptic nystagmus (EN) characterised by oculoclonic movements. These epileptic manifestations were the principal or unique epileptic manifestation. Patients: Three patients (from 9 to 17 years old) were admitted in our hospital for epilepsy. Two of them had refractory epilepsy and came for surgical investigations and one girl (who had a sporadic Bourneville tuberoses sclerosis) came for diagnostic investigations. We noted clinical characteristic seizures consisting in isolated oculoclonic movements for all the children. The seizures were prolonged and sometimes oculoclonic status occurred. Ictal EEG registrations showed localised occipital discharges with poor propagation in other lobes. Ictal single photon emission computed tomography (SPECT) showed hyperperfusion restricted to the polar occipital lobe for the three cases. There were other types of seizures associated for two of them. Magnetic resonance imaging (MRI) revealed for all these cases a possible focal cortical dysplasia of occipital lobe. For the young boy who had an occipital cortectomy, the anatomo-pathologic evaluation confirmed the focal cortical dysplasia. DISCUSSION: EN is rarely an isolated ictal phenomenon. In these observations ictal EEG and ictal SPECT confirmed partial occipital seizures. These types of seizures prolonged with focal ictal abnormalities of EEG and SPECT might be explained by occipital pole origin or by the lesion which may be cortical dysplasia. The mechanisms underlying the phenomenon of EN are not fully understood, but dysfunction of cortical pathways controlling saccades is suspected. CONCLUSION: These three cases show occipital partial seizures with nystagmus epileptic as the only epileptic manifestation. This diagnosis can be difficult and may need exploration by video-EEG for the diagnosis.

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ANTICIPATION OF EPILEPTIC SEIZURES BY NON-LINEAR ANALYSIS OF SCALP EEG. V Navarro, M Le Van Quyen, J Martinerie, P Boon, M D'Havé, C Adam, F Varela, M Baulac, LENA, CNRS UPR 640, Department of Neurology (Paris, F; Gent, B)

Non-linear mathematical methods, based on time series analyses of intracerebral EEG recordings, have shown their ability to anticipate seizure onset

(Nature Medicine, 1998; 4, 1173–1176, Martinerie et al.). Dynamical changes occur several minutes prior to seizure, allowing to define a pre-ictal state. We have now extended our work to the study of scalp EEG recordings, an easy and non-invasive way to allow non-linear analyzes in a wider population of epileptic patients. Methods. Scalp EEG recordings, including 40 minutes before a seizure, were obtained from 18 patients with refractory temporal lobe epilepsy. Simultaneous intracranial and scalp EEG recordings were performed for 5 other patients. The beginning of the seizures was defined by the onset of the first clinical symptoms or significant EEG changes. We used a new non-linear method based on the quantification of the dynamical similarity between two distant segments in time. This method, we previously developed, is less sensitive to the numerous artifacts present in scalp EEG than the current nonlinear methods, with higher computational speed (NeuroReport, 1999; 10, 2149–2155, Le Van Quyen et al.). Results. In 95 % of the patients, statistically significant pre-ictal changes were discernible several minutes in advance. The topographical distribution on the scalp electrodes of these pre-ictal dynamical changes was variable. The temporal lobe ipsilateral to the focus was generally involved. The contralateral temporal lobe was often the site of changes, although less precocious and pronounced. These dynamical changes detected on the scalp were closely correlated with those detected intracranially. Conclusion. Pre-ictal dynamical changes are detectable on scalp EEG recordings from patients with temporal lobe epilepsy. Our method had considerable clinical implications for the development of warning system or therapeutic interventions before the seizure.

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MR SPECTROSCOPY OF THE HIPPOCAMPAL FORMATION AND LATERALIZED MEMORY DEFICITS WITH RESPECT TO POSTOPERATIVE SEIZURE- AND NEUROPSYCHOLOGICAL OUTCOME. E. Pauli, I. Schäfer, K. Eberhard, H. Stefan, Dept. of Neurology, Center Epilepsy University of Erlangen-Nuremberg, Dept. of Neurosurgery (Erlangen, D)

Neuronal loss of hippocampal structures and associated memory deficits are common features in mesial temporal lobe epilepsy (TLE). We compared the preoperative CSI spectroscopy of the hippocampal structures with specific memory functions in patients with TLE, and we evaluated these results regarding the postoperative seizure outcome and neuropsychological deficits. Methods: 26 patients with cryptogenic TLE scheduled for surgical treatment were investigated by high-spatial-resolution CSI, performed with a two-dimensional phase-encoding spin-echo sequence using a 1.5-Tesla system and neuropsychological assessment including intracarotid sodium amytal test (IAT) preoperatively. Seizure outcome and memory outcome was examined one year postoperatively. Verbal memory and figural memory were measured by the Berliner Amnesia Test (BAT). The results were classified in "no deficit", "verbal memory deficit", "figural memory deficit" and "bilateral memory deficit" according to a z-value > = 1 SD below 0. The laterality ratio [ratio=(left-right)/(left+right)] was computed for the CSI as well as for memory functions [(verbal – figural) / (verbal + figural)]. Results: A significant linear correlation was found between CSI spectroscopy values for the dominant hippocampal formation and verbal memory scores. Pathological NAA/Cho ratios for the dominant hemisphere were associated with low verbal memory performance. Beyond that, the correlation between the laterality ratios for CSI and memory was found to be statistically significant. For those patients who became seizure free postoperatively verbal memory deficits were accompanied by pathological increased CSI values for the left hippocampal structures and by normal values for the right hemisphere. Figural memory deficit showed the diametrical proportions. In those patients who did not become seizure free, verbal deficits and bilateral memory deficits were related to bilateral enhanced CSI values. Conclusion: Our results demonstrate that CSI spectroscopy findings of hippocampal pathology are related to lateralized memory deficits in patients with TLE. In these patients who are scheduled for epilepsy surgery CSI investigation may provide a promising tool for prediction of memory function and postoperative outcome.

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LONG-TERM RESULTS AND COST-EFFICACY ANALYSIS OF VAGUS NERVE STIMULATION IN PATIENTS WITH REFRACTORY EPILEPSY, THE EXPERIENCE IN BELGIUM. K. Vonck, P. Boon, M. D'Havé, S. O'-Connor, T. Vandekerckhove, J. De Reuck, Ghent University Hospital, Cyberonics, Europe (GENT, Zaventem, Gent, B)

Rationale: Vagus nerve stimulation (VNS) is an efficacious treatment for patients with refractory epilepsy who are unsuitable candidates for resective or disconnective epilepsy surgery or who have had insufficient benefit from such a treatment. A few studies have suggested that VNS remains efficacious on a long term basis. VNS requires a substantial financial investment. We studied clinical efficacy of VNS in a group of 25 patients with follow-up of up to 4,5 years. We also compared the cost of ongoing and daily routine treatment of refractory epilepsy before and after treatment with VNS. Patients and methods: Twenty-five patients (12 M, 13 F) with mean age of 31 years (range:12–49; SD=9.2) and mean duration of complex partial epilepsy of 18 years (range:4–35; SD=8.5) underwent VNS at Ghent University Hospital. Mean post-implantation follow-up was 29 months (range:9–57; SD=15.4). We prospectively assessed seizure frequency and type, prescribed AEDs, number of hospital admission days and clinic visits and calculated the epilepsy-related direct medical costs and compared this with pre-implantation data. Specific costs due to presurgical evaluation were not taken into account. Results: Mean complex partial seizure frequency decreased from 21 seizures/month (range:2–180; SD=36.0) to 9 seizures/month (range: 0–60; SD=13.3) (p=0.00002). The mean yearly epilepsy-related direct medical costs per patient dropped from 5469 US$ (range: 715–18879 US$; SD=4715.2) to 2828 US$ (range: 922–6155 US$; SD=1425.7) (p=0.0028). The mean number of hospital admission days was reduced from 13 days/year (range:0–60; SD=17.5) to 3 days/year (range: 0–13; SD=4.2)) (p=0.004). Conclusion: VNS remains an efficacious treatment on the long-term for patients with refractory partial seizures. VNS also has a promising cost-efficacy profile.

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Oral session 18

Epilepsy – 2

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SOURCE LOCALIZATION CAN REPLACE INVASIVE EEG RECORDING IN THE PRESURGICAL EVALUATION OF REFRACTORY EPILEPSY. P. Boon, M. D'Havé, G. Van Hoey, B. Vanrumste, K. Vonck, P. Van Walleghem, T. Vandekerckhove, J. De Reuck, Ghent University Hospital (GENT, Gent, B)

Rationale: Source localization of epileptic foci using ictal spatiotemporal dipole modeling (ISDM) yields reliable anatomical information in presurgical candidates. The methodology and results have been validated but ISDM requires substantial resources from EEG and neuroimaging laboratories. The number and profile of patients who may benefit from it is presently unknown. The purpose of this study is to demonstrate the clinical applicability in a prospectively analyzed series. Patients and methods: The study includes 100 patients (51 males, 49 females) with mean age of 31 years (range: 2–63 years), mean duration of epilepsy of 20 years (range: 1–49 years) and refractory partial seizures. All patients were prospectively enrolled in a comprehensive presurgical evaluation protocol including video-EEG-monitoring (with prolonged interictal and ictal recording), optimum-MRI, interictal FDG-PET and neuropsychological assessment. Ictal EEG could be recorded in 93 patients. ISDM was performed in those patients in whom suitable ictal EEG files were available. The clinical applicability of ISDM was compared in three groups of patients; 41 patients in whom ictal EEG recording and MR were congruent (group I); 26 patients in whom results were not incongruent (group II) and 26 patients in whom the results were incongruent (group III). Results: ISDM could be performed in 31 patients: 15 in group I; 3 in group II and 13 in group III. ISDM influenced decision-making in none of the patients in group I; in 1/3 in group II and in 8/13 in group III. Typically, results of ISDM helped to avoid intracranial EEG recordings in what appeared to be unsuitable candidates for resection by clearly confirming the discongruency between ictal EEG and MRI findings. Conclusions: In this series of 100 presurgical candidates, source localization with ISDM could be performed in 33 % of patients. In 10 % of patients, it proved to be a key element in the surgical decision process by avoiding intracranial recording. (Supported by grants BOZF–01 104495 and 011A0996 from the University of Gent, by a grant from the Fund for Scientific Research – Flanders (F. W. O.) and by the Clinical Epilepsy Grant 1999–2001.)

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HYPERMOTOR SEIZURES IN CHILDREN. A. Weinstock, P. Giglio, S. L. Kerr, M. E. Cohen, SUNY Buffalo (BUFFALO, USA)

Objectives: To delineate the clinical and video-EEG manifestations of children with hypermotor seizures (HS). Background: Some types of seizures in

children may be difficult to recognize. In the semiological seizure classification (SSC) proposed by Luders et al., seizures are classified solely on the basis of the clinical manifestations of the ictus, while no EEG findings or other test results influence the seizure classification (1). HS are complex motor seizures ("complex" refers to the complex characteristics of the movements), usually arising from mesial or orbital frontal regions. They are characterized by marked behavioral movements and are therefore often misdiagnosed as pseudoseizures. Methods: We report three children who were diagnosed with HS with continuous video EEG monitoring. All patients were referred because of clinical suspicion of pseudoseizures. Manipulation of the digital EEG included review of the EEG in a transverse montage, application of high frequency filters, change in sensitivities, and attention to the emergence of postictal slow activity. Presented in this study is a retrospective review of the patient's clinical information, video-EEG data and outcome. Results: The mean age of the patients was 10 years. There were two boys, and one girl. In all three patients there was a history of behavioral disorder, with two carrying a diagnosis of Attention Deficit Hyperactivity Disorder. The admission examination was significant for inappropriate behavior in all three patients. Neurological examination was normal. MRI of the brain was normal in two patients, and revealed an unrelated Chiari malformation in one patient. Clinical seizure activity in all three patients consisted of marked motor activity, with upper extremity flapping or shaking and kicking. In two patients there was screaming, and shouting. Intense fear was present in one patient. The hypermotor activity progressed in two patients to tonic-clonic activity. In one patient seizures occurred out of sleep or upon awakening. The interictal EEG data was normal in one patient, and revealed a continuous generalized slowing and slowing of the posterior dominant rhythm in the 2 other patients. One of the latter patients had interictal epileptiform activity in the frontal and midline regions. The ictal EEG revealed profuse superimposed EMG activity in all patients. The ictal activity revealed midline theta activity progressing to a generalized clonic EMG artifact like activity in one case, bi-frontal slow rhythmic delta activity in 1 case progressing to generalized rhythmic theta pattern, and in the third case a diffuse EMG artifact followed by post-ictal slowing. On further follow up good seizure control was achieved in two patients with polytherapy. In the patient with nocturnal seizures, control proved more difficult despite maximization of anti-epileptic treatment. This patient is currently being evaluated for epilepsy surgery. Conclusions: Diagnosis of HS may be challenging, especially because of confusion with pseudoseizures. Video-EEG may is the most effective way for diagnosing this type of seizures. The SSC has helped improve recognition and description of these events as seizures. References: H. Lüders et al.; Semiological Seizure Classification. Epilepsia: 39 (9):1006–1013, 1998

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THE IMPACT OF COMPREHENSIVE EPILEPSY CARE IN PEOPLE WITH MENTAL DISABILITY. A. Gil-Nagel, N. Camarero, J. de la Cruz, P. López de Armentia, M. D. Jiménez-Hernández, P. Martínez-Martín, Hospital Ruber Internacional, Comunidad de Madrid, Hospital 12 de Octubre, Hospital Nuestra Señora de Valme (Madrid, Sevilla, E)

Medical care of patients with epilepsy and mental disability is complicated by their communication impairment, high rate of resistance to antiepileptic drugs, frequent use of polypharmacy, lower level of supervision and communication difficulties between the neurologist and the primary care physician. Objective: In this study we analyzed if comprehensive epilepsy care changes the utilization of medical resources and reduces the cost of the disease in people with mental disabilities. Methods: This is an evaluative study performed on 120 patients from a developmental center. The intervention, performed during 1999, included: (1) opening an epilepsy clinic at the center, (2) discussing each patient directly between the epilepsy specialist, the primary care physician and the nurses, (3) providing epilepsy education to the staff, families and legal guardians, and (4) assessing the risk for injuries and providing adequate protection. The main outcomes were: number of clinic visits, evaluations in the emergency room, days of hospitalization, number of antiepileptic drugs prescribed and cost of epilepsy care. The same patients were used as historical reference group. Data collection was retrospective for 1997–98 and prospective for 1999. The occurrence of events per patient per year (PY) are presented and compared before and after the intervention. Results: A total of 58 patients (48 %) had epilepsy and were included in this analysis. During the period of 1997–98 there were 1.5 clinic visits PY, 0.62 emergency room visits PY, 0.41 days of hospitalization PY, and 2.1 antiepileptic drugs prescribed PY. After the intervention there was a three fold increase in clinic visits (4.5 PY), more than 90 % reduction in emergency room visits (0.06 PY) and days of hospitalization (0.03 PY) and nearly a 25 % decrease in prescriptions filled (1.6 PY). The cost was calculated based on prices of 36 Euros for a clinic visit, 427 for an emergency room evaluation, 228 for each day of hospitalization and 96 for one year of treatment with an antiepileptic drug. After the intervention there was an increase of 108 Euros PY due to clinic visits (the cost of the intervention), and a reduction of 239 Euros PY in emergency care, 86 Euros PY in hospitalization and 48 Euros PY in antiepileptic drug treatment. This results in a saving of 265 Euros PY after the intervention. Conclusion: In a sample of patients with developmental disabilities, comprehensive epilepsy care reduced the number of visits to the emergency room, days of hospitalization and antiepileptic drugs used. As a result of these, the cost was reduced.

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ANTIDEPRESSANTS AND SEIZURES: A PROSPECTIVE STUDY IN AN EMERGENCY ROOM. G. Besson, M. Mallaret, C. Louis, G. Milin, J. Mingat, Service de Neurologie, Service de Pharmacologie, Service d'Accueil et d'Urgences (Grenoble Cedex 9, F)

The prevalence of depression is about 16 % in France. Since few years, a lot of new antidepressants has been commercialized. We have only few data on the adverse events of these new antidepressants and especially on the occurrence of seizures. The aim of this study was to evaluate the frequency of antidepressant therapy in patients admitted for an epileptic seizure in an emergency room. Methods. All patients consecutively admitted in the medical emergency room of the CHU of Grenoble between October 1998 and April 1999 were included. The history of epilepsy and the current medical therapy were recorded. Standard blood tests including Na and glucose levels were performed in all patients. The level of antiepileptic drugs was recorded for the known epileptic patients. An EEG or a CT scan were performed for selected patients. Results. 8813 patients were included. Among 296 patients with antidepressants (3.4 %), 31 were admitted for a seizure. Among 8517 patients without antidepressants, 83 were admitted for an seizure. Thus the relative risk to have a seizure when treated with antidepressants was 10.7 and the odds ratio was 11.9 (95 % CI: 7.75–18.25). The most common antidepressant therapies were serotonin re-uptake inhibitors (49.7 %) and tricyclic drugs (19.6 %). Among 114 patients admitted for an epileptic seizure (1.3 %), 72 had a history of epilepsy and 31 were treated by antidepressants (27.2 %). The seizure may be explained by alcohol consumption in 13 %, by a history of stroke in 8 %, by a brain tumor in 7 %, a metabolism disorder in 2 % (hyperglycemia, renal insufficiency), a benzodiazepin treatment arrest in 1 %. Among the 72 epileptic patients admitted for a seizure, 24 had a poor compliance and 21 had no risk factor. Conclusions: While many causes may explain epileptic seizures in patients admitted in a medical emergency room, antidepressants are an important risk factor. If antidepressants are probably not the sole risk factor for epileptic seizures, they probably strongly increase the risk of the occurrence.

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USEFULNESS OF EEG IN THE DIAGNOSIS OF ADULT-ONSET PARTIAL EPILEPSY: DISTANCE FROM THE LAST SEIZURE. U. Aguglia, R. L. Oliveri, A. Gambardella, E. Le Piane, D. Messina, A. Labate, G. Turano, Centro Regionale Epilessie Ospedali Riuniti Reggio Cal., Università di Catanzaro (Reggio Cal., Catanzaro, I)

Objective: to determine whether interictal EEG recording is helpful for the diagnosis of adulthood onset epilepsy according to the time interval from the last seizure. Background: it is well known that 40/70 % of adults suffering from seizure disorders have normal interictal EEG recordings. These patients often constitute a major diagnostic problem in clinical practice and activation of EEG is often unsuccessful also after sleep deprivation. Recently King et al. (Lancet 352:1007–1011, 1998) showed that an epilepsy syndrome can be diagnosed in most first-seizure patients if the EEG recording could be obtained within 24 h of the seizure. Design/Methods: we recruited patients over 18 years of age, consecutively presenting to our department with a clinical suspect of cryptogenetic or lesional partial epilepsy with onset in adulthood, and without prior antiepileptic treatment. Patients with non-epileptic episodes such as psychogenic seizures, or convulsive syncopes were not enrolled. In the period September 1997–September 1998 a total of 90 patients were considered eligible for the study: after the interview 52 patients were enrolled and underwent EEG recording. We used 21 channel digital recordings, with standard 10–20 electrode placement. EEG lasted for 30 minutes, including hyperventilation for 5 min, and ILS at 1–30 Hz. All EEG recordings were routinely videotaped. EEG readings were done in conference by two experienced neurologists (U. A. and A. G.). EEG recordings were coded as abnormal if records showed focal spikes, or sharp waves followed by slow waves. Results: twenty-five patients out of 52 (48 %) showed an abnormal EEG. Among these patients 17 performed the EEG within 48 hours from the last seizure, and 8 at an interval greater than 48 h. Twenty-seven patients showed a normal EEG. Twenty-six subjects with normal EEG findings performed the recordings af-

ter 48 h from the last seizure, and only one underwent the EEG recordings within 48 hours from the last seizure. A two-by-two table in whom the patients were classified according to the distance from the last seizure (less or greater than 48 h) and EEG findings (abnormal or normal EEG) yielded a significant p-value of 0.001 (chi-square value = 10.2; 52 d.f). Conclusions: in patients with partial epilepsy with onset in adulthood that underwent standard EEG recording the discovery of epileptiform activity is closely linked to the timing of the last seizure.

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EFFICACY OF GABAPENTIN IN ADULT PATIENTS WITH SEVERE LEARNING DISABILITIES: AN OPEN-LABEL COMPARATIVE STUDY. P. Crawford, S. Brown, M. Kerr, Parke-Davis Clinical Trials Group, Dept of Neurosciences York District Hospital, Little Plumstead Hospital, Welsh Centre for Learning Disabilities, Parke-Davis (York, Norwich, Cardiff, Eastleigh, UK)

Purpose: 1. To evaluate the efficacy and safety of gabapentin in patients with learning disabilities, who are uncontrolled on their current therapy. 2. To evaluate the effects of gabapentin on the behaviour and mood of patients with learning disabilities. 3. To compare the effects of gabapentin with those of lamotrigine. Methods: This was an open label, randomised, parallel group, multicentre add-on study of gabapentin in patients with learning disabilities. Lamotrigine was chosen as the active comparator drug. A total of 109 patients, aged 12 years and older, with drug-resistant localisation related epilepsy and learning disabilities were screened for the study, 83 patients were randomised, 39 to gabapentin treatment (1200–3600 mg per day) and 44 to lamotrigine (100–400 mg per day). 34 and 35 patients completed 6 months of treatment in the gabapentin and lamotrigine treatment groups, respectively. The population who entered the study had a complex range of learning disabilities characterised by, 30% being unable to talk and 39% either unable to walk or only capable of walking with supervision. When considering aspects of dressing and feeding, 72% were unable to dress adequately without a degree of supervision and 59% required a degree of supervision for adequate feeding. At baseline the median number of seizures in an average 28 day period for the randomised trial patients was 13. Results: The percentage of patients achieving a greater than or equal to 50% reduction in seizure frequency, on gabapentin was 50%, with a mean reduction in seizures over the course of the study of 51%. Compared to lamotrigine, no statistically significant treatment differences could be identified (48.6% of patients on lamotrigine achieved a greater than 50% reduction in seizure frequency and the mean reduction in seizures was identical). The safety profile of gabapentin was consistent with that seen in previous clinical trials. Adverse events leading to the withdrawal of patients from the study occurred with 3 patients on gabapentin (all in the titration phase), while for lamotrigine this figure was 5 (3 during titration and 2 during the evaluation phase). Carer rated visual analogue scales detected significant improvements ($P< 0.05$) for the gabapentin treated patients in seizure severity, attention, general health and sleeping pattern, while for lamotrigine only seizure severity improved significantly. Individual significance levels from several other rating scales should be interpreted cautiously due to the number of scales assessed, however, they support improvements in cooperation, communication and restlessness for gabapentin when compared to lamotrigine. Conclusion: Gabapentin is a safe and effective antiepileptic drug for learning disabled patients and has been shown to be as effective as lamotrigine in treating partial seizures. In addition, gabapentin would appear to have greater positive benefits on behaviour.

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LONG-TERM RETENTION RATES OF GABAPENTIN, LAMOTRIGINE AND TOPIRAMATE IN CHRONIC EPILEPSY. S.D Lhatoo, I. C. K. Wong, J. W. A. S. Sander, Epilepsy Research Group (London, UK)

Objectives: To determine the long-term retention rates of lamotrigine (LTG), gabapentin (GBP) and topiramate (TPM) therapy in a tertiary referral clinic for chronic epilepsy. Methods: 424 consecutive patients with chronic epilepsy started on LTG, 158 on GBP and 393 on TPM were analysed. The percentages of patients who continued therapy on LTG, GBP and TPM respectively were estimated using Kaplan Meier survival analysis. Factors influencing retention were analysed using Cox regression analysis. Results: Kaplan Meier survival analysis showed that at three years, 30% continued therapy on TPM compared to 29% on LTG and < 10% on GBP. Adverse events resulted in therapy withdrawal in 40% of patients on TPM compared to GBP (37%) and LTG (22%). Perceived lack of efficacy led to treatment withdrawal in 39% of patients on GBP compared to LTG(34%) and TPM (19%). Cox regression estimated that a quarter or less of patients with chronic partial epilepsy are likely to continue therapy with a new AED beyond 5 years. Conclusion: The impact of these new AEDs on the long-term course of chronic partial epilepsy is likely to be small as approximately three out of four patients will discontinue therapy. More patients appear to continue on TPM than LTG or GBP, a possible reason being better perceived efficacy of TPM, despite having the highest incidence of adverse events. As the most recent of the 3 drugs however, patients may also have been more likely to stay on TPM for want of a newer drug. These low retention rates may help to reinforce the belief that where the seizure disorder is due to a surgically remediable cause (such as hippocampal sclerosis), surgery should be offered at an earlier stage rather than trying each new AED in turn. In the meantime, the quest for better drugs must continue.

Oral Session 19

Multiple Sclerosis – 3

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METABOLITE CHANGES IN NORMAL APPEARING WHITE MATTER AND CORTICAL GREY - PRELIMINARY DATA FROM EARLY RELAPSING REMITTING MULTIPLE SCLEROSIS PATIENTS. P. Kapeller, M. A. McLean, C. Griffin, D. Chard, G. J. M. Parker, A. J. Thompson, D. H. Miller (Graz, A; Bucks/St.Peter, London, GB)

Normal appearing white matter (NAWM) and cortical grey matter (CGM) are neuropathologically shown to be affected in multiple sclerosis (MS). CGM and NAWM involvement may contribute extensively to the patients' clinical status and their demonstration may close the gap between MRI findings and disability. Furthermore it is unknown how early in disease such involvement occurs although such knowledge will be important in understanding disease pathogenesis. Therefore we employed 1H magnetic resonance spectroscopic imaging (1 HMRSI) to study the metabolite changes in patients with early relapsing remitting MS and focused in this preliminary analysis on NAWM and CGM.

Subject and methods: 15 early relapsing remitting MS patients (mean age 36, range 25–49; 9 females, 6 males; mean disease duration 1.8 years, range 0.6–2.8; median EDSS 1, range 0–2,5) and 12 age matched controls (mean age 32; 3 females, 9 males) were studied using quantitative 1HMRSI (TE: 30ms, TR: 3000ms), conventional T1 and T2 weighted MRI with and without Gadolinium and a 1.5mm 3D fast spoiled gradient recall (FSPGR). The 1.5mm FSPGR images were segmented using SPM96. This enabled to determine the percentage of grey matter, white matter and cerebrospinal fluid (CSF) for each voxel respectively. Fourier transformation was performed without zerofilling or apodization using General Electric's Sage/IDL. LCModel was used for quantifying the metabolite concentrations for myo-inositol (Ins), choline containing compounds (Cho), creatine/phosphocreatine (Cr), glutamate/glutamine (Glx) and N-acetyl-aspartate (t-NAA) (the sum of N-acetyl-aspartate and N-acetyl-aspartyl-glutamate). To avoid unreliable CSF partial volume effects we omitted voxels containing more than 20% CSF.

Results: NAWM: Compared to control subjects early relapsing remitting MS patients revealed reduced t-NAA concentrations (controls: mean 8.4; MS: mean 7.8; $p=0.018$) and increased Ins concentrations (controls: mean 3.5; MS: mean 4.2; $p=0.03$). CGM: MS patients showed slightly reduced t-NAA concentrations (MS: mean 7.4; Controls: mean 8.3; $p=0.012$), and reduced Ins (MS: mean 4.0; Controls: mean 4.5; $p=0.035$).

Conclusion: NAWM and CGM are both affected early in the course of relapsing remitting MS. The reduction in t-NAA in both sites indicates neuronal damage or dysfunction in otherwise normal appearing tissue. The changes Ins are more difficult to interpret. The increased Ins concentration in NAWM may indicate gliosis. Possible explanations for its decrease in CGM are an overall reduction in cellular density or neuronal loss in the absence of proliferating glial cells.

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11C-PK 11195 (PK)-POSITRON EMISSION TOMOGRAPHY (PET): AN IN VIVO INDICATOR FOR ACTIVATED MICROGLIA IN MULTIPLE SCLEROSIS (MS) LESIONS. E. Elitok, M. Schmid, A. Claus, J. Karitzky, B. Neumaier, R. Tomczak, J. Kotzerke, A. Gerhard, B. Landwehrmeyer, A.C. Ludolph, S.N. Reske, J. Schwarz, H. Tumani, University of Ulm, Nuclear Medicine, University of Ulm, Neurology, University of Ulm, Radiology (Ulm, D)

Objective: To investigate whether PK-PET which detects activated microglia is a more useful diagnostic tool than gadolinium contrasted magnetic resonance imaging (Gd-MRI) for showing active brain lesions in patients with MS. Background: MS is a chronic inflammatory disease of the central nervous system with a broad clinical spectrum and heterogeneous lesion pathology. In vivo, active MS lesions are characterized by disturbed blood-brain-barrier as visualized by Gd-MRI. Histopathologically, microglial activity defines stage of lesions. Activated microglia is known to express peripheral benzodiazepine binding sites (PBBS). The radio tracer PK binds specifically to PBBS and can be visualized by PET. Methods: 8 patients (4 male, 4 female, 25–43 years old, Median 31,5 and SD 5,94) with definite MS according to Poser criteria were examined. The clinical course was relapsing remitting (RR-MS, 4 patients) and secondary progressive (SP-MS, 4 patients). All patients except one received steroid pulse therapy 1–41 days prior to MRI and PET examinations. None of the patients were under long-term immunomodulatory treatment. PET and MRI (T1+Gd) examinations were obtained within 24 hours. The injected dose of PK was between 229 and 896 MBq (specific activity at time of injection was 23,0–113,9 GBq/μmol, Median 52,8 GBq/μmol, SD 22,7). Visual inspection of summation images disclosed areas of increased signals ("lesion"). The number of lesions in different brain regions including cerebellum, brain stem, white matter surrounding the lateral ventricles, corpus callosum and optic nerves were evaluated by two physicians independently. A lesion was accepted if detectable on two adjacent planes. Results: The quality of the PET images correlated positively with the specific activity of PK. The discrepancy of lesion counts per patient between both examiners was lower for the Gd-MRI than for the PET images. In all PK-PET examinations lesions were observed (3–9 lesions per patient). In contrast, only in 4 of the 8 MRI scans Gd-enhanced lesions (1, 3, 4 and 4 lesions per patient) were detected. In 6 patients PK-uptake was seen in both optic nerves while Gd-MRI signals were not present. Lesions with PK-uptake were also detected in brainstem and cerebellum. In patients with SP-MS more lesions with PK-uptake were present (6, 6, 8 and 9 lesions) than in patients with RR-MS (4, 5, 7 and 8 lesions). Conclusions: The data suggest that PK-PET may be a useful tool to detect MS-lesions with activated microglia in vivo. PK-PET may be superior to Gd-MRI since more lesions were detected by PK-PET. These results await confirmation by quantitative analysis of PK-signals currently under way. Obviously, activated microglia indicated by PK-uptake occurs independent of blood-brain-barrier disturbance as shown by Gd-enhancement. Patients with SP-MS tend to show more lesions with PK-uptake than patients with RR-MS.

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WHOLE BRAIN HISTOGRAMS OF QUANTITATIVE DIFFUSION WEIGHTED MRI IN MULTIPLE SCLEROSIS CORRELATE WITH DISABILITY AND CEREBRAL ATROPHY. M. Wilson, X. Lin, P.S Morgan, L.D Blumhardt, University of Nottingham Medical school (Nottingham, UK)

Diffusion weighted imaging (DWI) using magnetic resonance (MR) allows quantitative assessment of the integrity of cerebral tissue. Previous DWI studies in multiple sclerosis (MS) have shown abnormal apparent diffusion coefficient (ADC) in both lesions and normal appearing white matter (NAWM). In a diffuse disease process such as MS, methods which quantify total tissue integrity may prove more useful than measurement of discrete lesions or apparently NAWM. Methods: Twenty-two patients with clinically definite MS (15 relapsing-remitting, 7 secondary progressive) were studied. All patients underwent standard dual echoT2-weighted sequences, DWI and 3D-magnetisation prepared rapid acquisition gradient echo (MPRAGE) imaging and neurological assessments, including rating on the expanded disability status scale (EDSS). ADC maps were processed from the DWI data and the brain segmented by a semi-automated thresholding technique. An ADC histogram was generated for each patient from which mean ADC, quartiles, peak ADC and peak height of the curve on the y axis (pixel count normalised to total brain volume) were determined. Lesions on T2 scans were measured using a semi-automated thresholding technique. Supratentorial brain volume was measured from MPRAGE scans using stereology and corrected for total intracranial volume. All assessments were performed blind to clinical details. Results: Peak height of the ADC curve correlated with both EDSS ($r = -0.53$, $p = 0.01$) and disease duration ($r = -0.54$, $p = 0.01$), but not with age. Brain volume correlated with peak height ($r = 0.55$, $p = 0.01$), but not with disability. Total T2 lesion volume was also correlated with disability ($r = 0.46$, $p = 0.03$), although less strongly than with peak height of the ADC curve. Conclusions: This is the first study to demonstrate that quantitative diffusion weighted MRI histograms in multiple sclerosis correlate with clinical parameters (disability, disease duration) and cerebral atrophy on MRI. Cerebral atrophy and fixed neurological disability can probably be attributed mainly to axonal loss, which would be expected to have a significant effect upon ADC. Extension of this method to larger numbers of patients and longitudinal studies will further elucidate its sensitivity, reproducibility and potential role in clinical practice and treatment trials.

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DISTRIBUTION OF MYELIN ASSOCIATED GLYCOPROTEIN (MAG) AND OLIGODENDROCYTE PATHOLOGY IN VIRAL AND NON-VIRAL DISEASES OF THE CENTRAL NERVOUS SYSTEM. H. Rauschka, M. Schmidbauer, K. Jellinger, H. Lassmann, Brain Research Institute, Dep. of Neurology / Hospital Lainz, LBI of Clinical Neurobiology (Vienna, A)

Preferential loss of myelin associated glycoprotein (MAG) in comparison to other myelin proteins has been suggested to reflect primary oligodendrocyte injury in demyelinating conditions. It has been observed in active lesions of progressive multifocal leukoencephalopathy (PML) and in a portion of multiple sclerosis (MS) cases. OBJECTIVE: To investigate if preferential loss of MAG is a feature of oligodendrocyte injury in viral diseases of the central nervous system. METHODS: On formalin-fixed and paraffin-embedded brain specimens of herpes simplex virus (HSV) encephalitis (6 cases), PML (10 cases), cytomegalovirus (CMV) encephalitis (8 cases), acute disseminated encephalomyelitis (ADEM) (2 cases), MS (73 cases), subcortical vascular encephalopathy (SVEP) (2 cases) and stroke (1 case) we performed routine staining and immunohistochemistry (single and double staining) with antibodies against different myelin proteins (MAG, myelin oligodendrocyte glycoprotein (MOG) and CNPase), the apoptotic marker caspase 3, JC-virus, HSV 1 and 2 and CMV. In regions of demyelination we compared the distribution of the myelin-proteins mentioned above and investigated oligodendrocyte alterations qualitatively and quantitatively.

RESULTS: We found actively demyelinating areas in lesions of 4/10 PML cases and also at the border of lesions in 5/6 cases of HSV-encephalitis and 2/8 cases of CMV- encephalitis. Preferential MAG-loss associated with oligodendrocyte apoptosis was evident in all active demyelinating areas. In 73 cases of MS with actively demyelinating lesions, MAG-loss and concomitant oligodendrocyte apoptosis were found in 22 preferentially malignant cases. In contrast, there were no indications of oligodendrocyte apoptosis and preferential MAG-loss in more chronic lesions of MS, PML, HSV-encephalitis and CMV-encephalitis. No preferential MAG-loss was observed in active lesions of ADEM, SVEP and stroke.

CONCLUSION: Preferential MAG-loss and oligodendrocyte apoptosis are features of actively demyelinating lesions in several viral diseases of the central nervous system, whereby this pattern cannot be seen in autoimmune-mediated diseases. The occurrence of MAG-loss in some cases of (preferentially malignant) multiple sclerosis opts for the role of a so far unknown virus in at least a subgroup of MS.

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VENTRICULAR ENLARGEMENT AND BRAIN ATROPHY IN MULTIPLE SCLEROSIS: A SERIAL MRI STUDY. X. Lin, B.P Turner, L.D Blumhardt, University Of Nottingham (Nottingham, UK)

Recent studies have suggested that atrophy is a useful marker of tissue destruction and axonal loss in multiple sclerosis (MS). Further, the rate of atrophy appears to be related to disease activity as reflected by T1-gadolinium (T1-GD) enhancing lesions and relapse rate. The present study was designed to quantify the volume of different structures using 3-dimensional (3D) MRI over a period of 18 months. Methods: Forty patients, 20 with relapsing-remitting (RR) and 20 with secondary progressive (SP) MS were imaged (3D T1-weighted MRI post-GD) at baseline, months 6, 12 and 18 during a trial of interferon beta–1a. Expanded Disability Status Scale and Scripps Neurologic Rating Scale (SNRS) scores were acquired within 24 hours of each MRI. The volumes of supratentorial and infratentorial structures and the lateral ventricles were estimated using modern design stereology and point counting on 3D MR images. Results: The baseline analysis showed significantly lower supra- and infratentorial volumes ($p < 0.001$) and significantly higher volumes of lateral ventricles ($p < 0.01$) in all patients compared with healthy subjects. Lateral ventricular volumes were significantly correlated with supratentorial ($r = -0.55$, $p = 0.0003$) and T2-lesion ($r = -0.60$, $p = 0.0001$) volumes.

MRI analysis for the total patient cohort showed increases in the lateral ventricular volumes at months 6, 12 and 18 ($p < 0.05$), without a significant reduction of supra- or infratentorial volumes. The mean change of lateral ven-

tricular volume was 15% for all patients, 18.9% for RR and 11.2% for SP MS, but the differences were not significant (p=0.08). Enlargement of the lateral ventricles at month 18 was greater in patients with T1-GD lesions at baseline than in those without (median 3.94 ml vs 1.3 ml; p=0.0018). The SNRS change was significantly (p=0.02) higher in SP than RR MS. There was no correlation between the change of disability and lateral ventricular volume.

Conclusion: The rate of cerebral atrophy in MS is related to disease activity on MRI, confirming the relationship between atrophy and active inflammatory disease processes. Further, the volume change of the lateral ventricles is a more sensitive measure than either supra- or infratentorial brain structural volumes for the quantification of atrophy in short duration treatment trials.

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INTRAVENTRICULAR TRANSPLANTATION OF NEUROSPHERES IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS: MIGRATION OF CELLS INTO INFLAMED WHITE MATTER AND ATTENUATION OF CLINICAL DISEASE. T. Ben-Hur, D. Karusis, R. Mizrachi-Kol, E. Reinhartz, O. Abramsky, Hadassah – Hebrew University Hospital (Jerusalem, IL)

Objectives: To study the survival, migration and clinical value of precursor-cell transplantation in an animal model of multiple sclerosis (MS). Background: MS is a chronic, multifocal, immune-mediated demyelinating disease. Current therapies have only mild efficacy in preventing long-term disability and there is no effective treatment to enhance myelin regeneration. Transplanted oligodendrocyte precursor cells can remyelinate focal lesions efficiently. Clinical application of cell transplantation will require the enhancement of their long-term survival in normal and hostile brain environments and promoting their migration into the multiple foci of disease. The clinical value of this approach is still unknown.

Methods: Newborn rat neural stem cells were grown in spheres in defined medium, supplemented with fibroblast growth factor 2 (FGF2) and directed to a glial fate by addition of thyroid hormone. Neurospheres were stained with the fluorescent nuclear dye Hoechst and stereotaxically injected into the ventricles of adult rat brains. Acute experimental autoimmune encephalomyelitis (EAE), the animal model of MS, was induced by immunization with spinal cord homogenate. Animals' brains were sectioned for fluorescence microscopy to detect transplanted cells, hematoxylin and eosin histochemistry and immunohistochemistry for intercellular adhesion molecule-1 (ICAM-1).

Results: Transplanted spheres survived in the ventricles over 2 months, without significant invasion into brain parenchyma. Neurosphere cells expressed mRNA transcripts of FGF2 and platelet derived growth factor, which may have maintained their survival in the growth factor poor environment of the intact brain. Following induction of EAE, transplanted cells migrated into the inflamed white matter tissue (but not into gray matter) and differentiated into oligodendrocytes. In rats that were transplanted with the neurospheres a month prior to induction of EAE, a significantly milder clinical disease developed, as compared to medium-injected, control rats. Histopathological quantification of EAE severity showed a non-significant reduction in perivascular inflammatory infiltrates in transplanted animals. Computer-assisted image analyses of ICAM-1 expression in the brain showed a significant decrease in staining intensity in the transplanted rat brains.

Conclusions: Intraventricular transplantation of neurospheres may supply the brain with a stable reservoir of cells that react to inflammatory stimuli by migration into the brain and differentiation into oligodendrocytes. These neurospheres can attenuate the clinical course of disease, possibly by an immunomodulatory effect.

Oral session 20

Multiple Sclerosis – 4

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DIFFERENT PROGNOSIS AND RESPONSE TO INTERFERON BETA-1A (REBIF) THERAPY IN "RELAPSING" AND "NON-RELAPSING" SECONDARY PROGRESSIVE MS. J. Palace, The SPECTRIMS Study Group, Radcliffe Infirmary (Oxford, Oxford, UK)

The SPECTRIMS study1 investigated two doses of IFN beta-1a (Rebif) in SPMS, and reported significant benefits in relapse rate, MRI activity and MRI burden of disease (BOD). However, only a trend was apparent for disability progression. Aim: To determine whether relapses in the 2 years prior to study entry affected the prognosis or response to treatment with IFN beta-1a. Study design: In the double-blind, multinational SPECTRIMS study, 618 patients with SPMS were randomised to treatment with either 22 mcg or 44 mcg IFN beta-1a (Rebif), or placebo, three times weekly (tiw) for 3 years. The primary endpoint was slowing in progression of disability. Clinical evaluations were at 3-monthly intervals, with magnetic resonance imaging (MRI) scans (proton density/T2 every 6 months, and T1-gadolinium enhanced every month for the first 9 months in 40% of the patients). Results: Of the patients in the study, 293 (47%) reported relapses during the 2 years prior to entry. At baseline, these "relapsing" patients differed significantly from the "non-relapsing" group: they were younger, had shorter duration of MS and SPMS, had experienced greater deterioration in 2 years pre-study despite similar Expanded Disability Status Scale (EDSS) score at entry, had higher Ambulation Index, and more MRI activity. "Relapsing" patients in the on-study placebo group suffered a significantly higher relapse rate (1.08 vs. 0.39) compared to "non-relapsing" patients, greater MRI activity (1.17 vs 0.33 lesions/scan) and change in BOD (11.8% vs 8.4%). Patients in the "relapsing" subgroup were significantly less likely to progress than the "non-relapsing" group (odds ratio (OR) for proportion progressing compared to placebo = 0.52 (p = 0.03) for "relapsing" SPMS vs OR = 1.07 (p = 0.8) for "non-relapsing" SPMS). All secondary outcome measures (relapse rate, MRI T2 activity and change in BOD) were significantly benefited by therapy with both doses of IFN beta-1a in the "relapsing" group while only modestly affected in the "non-relapsing" group, and only with high dose.

Conclusions: The results show that patients with "relapsing" SPMS have more active disease prior to and during the study, are younger with shorter disease duration than the "non-relapsing" group, and have a better response to therapy with IFN beta-1a. In the study with IFN beta-1b in SPMS, it was found that patients with more advanced disease and greater disability responded less well to therapy than those with lower disability.

These data add weight to the suggestion that MS should be treated early, during the relapsing phase of the disease, in order to obtain maximum therapeutic benefit.

Paty DW. J. Neurol 1999; 246. 2. Betaseron Canadian Monograph, June 30, 1999.

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DETECTION OF IDENTICAL EXPANDED T CELL CLONES IN THE CSF AND PERIPHERAL BLOOD OF MULTIPLE SCLEROSIS PATIENTS DURING RELAPSE. N. Goebels, Ch. Skulina, H. Wekerle, R. Hohlfeld, Klinikum Grosshadern, MPI for Neurobiology (Munich, Martinsried, D)

Multiple sclerosis (MS) is assumed to be an inflammatory autoimmune disease of the central nervous system (CNS). The responsible components of the immune system and the precise molecular targets are still unidentified. Expanded lymphocyte populations have been suggested to be involved in autoimmune diseases. The goal of our study was to identify expanded T cell populations in cerebrospinal fluid (CSF) and peripheral blood lymphocytes (PBL) of MS patients.

Methods: We employed a PCR-based method to identify and characterize clonally expanded T cells. The method ("CDR3 spectratyping") relies on the natural length variation of the third hypervariable region (CDR3) of the rearranged T cell receptor gene: whereas a polyclonal T cell population shows a random, Gauss-distributed length variation of the CDR3, a clonally expanded population has a uniform CDR3 length, which can be identified as a single band on a sequencing gel. The identity of these expanded T cell clones can often be determined by subsequent cycle sequencing.

Results: We analysed matched pairs of cDNA from CSF cells and CD4+, CD8+, CD25+ and CD38+ PBL subpopulations of MS patients. We repeatedly detected identical clonally expanded T cell clones both in the CSF and in activated subpopulations of PBL of MS patients during relapses. In one patient, we recovered an expanded CSF T cell clone after 4 years in the activated PBL subpopulation during a relapse. We compared the CDR3-sequences of expanded CSF and PBL T cell clones with previously established T cell lines specific for myelin basic protein (MBP) of this extensively studied patient. Interestingly, we found no matching CDR3 sequence. This indicates, that these expanded T cell clones recognise antigens different from MBP.

Conclusion: It has been previously established in animal experiments, that activated T lymphocytes have the ability to cross the blood brain barrier and migrate through the CNS. We now have demonstrated by CDR3 spectratyping, that expanded, activated peripheral blood T cell clones can be recovered in the CSF compartment of MS patients during relapses. We postulate, that T lymphocytes activated in the peripheral blood compartment may be involved in the initiation of MS relapses. Current experiments aim to identify the antigen specificity of these T cell clones.

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A PHASE I/II STUDY IN RHESUS MONKEYS AFFECTED BY EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS USING A CYTOKINE GENE THERAPY APPROACH. P. Poliani, H. Brok, R. Furlan, F. Ruffini, A. Bergami, G. Desina, P. Marconi, M. Rovaris, L. Adorini, G. Comi, B. t'Hart, G. Martino, San Raffaele Scientific Institute, Biomedical Primate Research Centre, IRCCS Casa Sollievo della Sofferenza, University of Ferrara, Roche Milano Ricerche (Milano, RIJSWIJK, San Giovanni Rotondo (FG), Ferrara, I; Rijswijk, NL)

We have previously shown that intracisternal (i. c.) injection of a Herpes Simplex virus (HSV) type-1-derived vector containing the murine interleukin (IL)-4 gene, in mice affected by experimental autoimmune encephalomyelitis (EAE), induces heterologous cytokine gene expression in the central nervous system (CNS), local production of the cytokine and clinical and pathological amelioration of the disease. Here we describe a phase I/II study in non-human primates (Rhesus monkeys) affected by EAE using a HSV-1-derived vector expressing human IL-4 (TH:IL4). We first delivered by i. c. and lumbar injection (l. p.) a control HSV-1-derived vector carrying the LacZ reporter gene (THZ) into the CNS of 3 monkeys that have been sacrificed 3 days after the injection. The vector distributed throughout the cerebrospinal fluid (CSF) spaces, efficiently infected the ependymal cell layer and expressed the reporter gene with no signs of inflammatory response to the injection procedure and/or to the vector itself. We then performed a toxicity study injecting two additional monkeys (i. c. and l. p.) with the TH:IL4 vector. The monkeys showed neither systemic/neurological toxicity, absence of neuropathological signs, absence of serum and CSF HSV-1 copies and anti-HSV-1 antibodies. We then tested the therapeutic efficacy of the TH:IL-4 vector in 10 monkeys immunized with 5 mg of whole myelin homogenate. Five monkeys have been i. c. injected with the TH:IL-4 vector and 5 with the THZ control vector. Injections were performed 12 days post-immunization (p. i.). Serum samples for routine hematological examination and for immunological studies have been collected weekly and CSF withdrawal has been performed at the time of vector injection and at sacrifice. All five control monkeys showed clinical and/or magnetic resonance imaging (MRI) signs of EAE along with macroscopic and microscopic signs of CNS pathology (inflammatory infiltrates, demyelination, axonal damage). Only two of the IL-4-treated monkeys had clinical and histopathological signs of the disease while the remaining 3 did not show any clinical, MRI or pathological signs of disease. Our results indicate that i. c. delivery of HSV-1-derived vector engineered with the anti-inflammatory cytokine IL-4 gene is a feasible and non toxic therapeutic tool that exerts a significant protective effect on experimental immune-mediated demyelination in non-human primates.

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INTRACELLULAR CYTOKINE PROFILE OF PATIENTS WITH PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS. J. Killestein, B. F. Den Drijver, B. M. J. Uitdehaag, R. A. W. Van Lier, C. H. Polman, University Hospital 'Vrije Universiteit', CLB (AMSTERDAM, NL)

Objective: To combine immunofluorescent staining of intracellular cytokines with T-cell subset immunostaining to evaluate expression of pro- and anti-inflammatory cytokines in both CD4 T cells and CD8 T cells derived from peripheral blood of untreated multiple sclerosis (MS) patients with either primary progressive (PP), secondary progressive (SP) or relapsing-remitting (RR) MS.

Background: MS is a T cell-mediated chronic inflammatory disease and cytokines have been hypothesized to contribute significantly to disease progression in multiple sclerosis. The role of cytokines has been extensively studied. Surprisingly, the cytokine secretion pattern from intracellular staining of T cell subsets of MS patients has not been thoroughly examined by flow cytometry so far.

Methods: Sixty-five MS patients (21 PP, 22 SP, 22 RR) with clinically definite MS were studied. Peripheral blood-derived mononuclear cells were treated for 4 hours with PMA, ionomycin and monensin. The cells were immunostained with CD8-PerCP and CD4-APC and fixed in 4 % PFA. Fixation was followed by permeabilization with 0.1 % saponin. Cytoplasm was stained with Fitc-labeled (IFN-gamma, IL-2, TNF-alpha) and PE-labeled (IL-4, IL-13, IL-10) monoclonal antibodies. Cells were analyzed using a FacsScan and Cellquest software. Statistical analysis comparing the different MS subgroups was by one-way ANOVA and post-hoc Bonferroni test ($p < 0.01$ was considered significant).

Results: One-way ANOVA demonstrated significant differences between the MS subgroups in the mean percentage of CD4 T cells expressing IL-2 ($p < 0.001$), TNF-alpha ($p < 0.001$) and IL-13 ($p < 0.01$). A trend was observed for IFN-gamma ($p=0.063$). For CD8 T cells, the mean percentage of IL-4, IL-10 and IL-13 expressing cells showed a significant difference between the subgroups as well ($p < 0.001$, $p < 0.01$ and $p < 0.01$ respectively). The post-hoc Bonferroni test demonstrated that the differences between MS subgroups were based on a significant decrease in the IL-2, TNF-alpha and IL-13 producing CD4 T cells in PPMS compared to both RR and SPMS patients. For CD8 T cells, a significant increase in IL-4, IL-10 and IL-13 producing cells in PPMS patients was found. No significant differences in intracellular cytokine profiles between RR and SPMS could be detected.

Conclusions: The data presented suggest that patients with PPMS, who already have been demonstrated to display different clinical and pathological features, also show marked immunological differences, as measured by intracellular cytokine flow cytometry, compared with the other forms of the disease. In general, the T cells of PPMS patients express less pro- and more anti-inflammatory cytokines. However, the exact mechanism by which cytokines are involved in PPMS remains to be clarified.

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BRAIN ATROPHY IN MULTIPLE SCLEROSIS: RELATION TO DISEASE PHENOTYPE AND DISABILITY. N. Kalkers, E. Bergers, F. Barkhof, C. Polman, AZVU (Amsterdam, NL)

In multiple sclerosis (MS) clinical trials, there is a need to obtain more efficient and sensitive outcome parameters, correlating with the clinical stage of the disease. Although magnetic resonance imaging (MRI) is succesful in diagnosing MS, there is a poor correlation between MRI based measurements and disability. Several new MR measurements are being studied including measures of brain atrophy. Brain atrophy measurement can (probably) be used as a marker of demyelination and axonal loss, the histopathological correlates of progressive disability. The aim of this study is to determine whether there are differences in brain atrophy parameters between 3 major MS phenotypes, and to study the correlation between brain atrophy parameters and the expanded disability status scale (EDSS).

Methods: 104 MS patients (22 primary progressive [PP], 24 secondary progressive [SP] and 58 relapsing-remitting [RR]) underwent an MRI examination. Whole brain parenchyma and total ventricular volume were measured on T1-weighted scans, intracranial volume was measured on GE or T2-weighted scans. Two ratios were calculated: 1) ventricular fraction: ventricular volume/whole brain parenchyma (VF) and 2) parenchymal fraction: whole brain parenchyma/intracranial volume (PF). The EDSS was measured as a measure of impairment/disability.

Results: The mean EDSS was 3.1 in the total group; RR patients had the lowest score on disability measurement (1.9); higher scores were found for SP and PP patients (both 4.6). Median VF in the total group was 0.029; with values of 0.023, 0.037 and 0.036 for RR, PP and SP subgroups respectively. In the total group the PF was 0.81, this was 0.83 for the RR group, and 0.80 and 0.79 for the PP and SP groups, respectively. For the total group the correlation of the EDSS with the VF was 0.38 ($p < 0.001$) and with the PF -0.36 ($p < 0.001$). Significant correlations remained the same when the relapse-onset patients (RR and SP) only, were analyzed.

Conclusion: This study, involving a wide range of disability scores and three major phenotypes in MS, shows significant correlations between two brain atrophy parameters and disability. It thereby confirms observations found in previous studies with more selected patient samples. Future studies should address the longitudinal relationship with disability and cognition, the correlation with other MRI techniques as magnetization transfer ratio histogram analysis, as well as the sensitivity to change over time.

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DISPLACEMENT MRI: APPLICATION OF Q-SPACE DIFFUSION MAGNETIC RESONANCE IMAGING TO MULTIPLE SCLEROSIS. Y. A. Assaf, D. B. Ben-Bashat, J. C. Chapman, A. D.K Korczyn, S. P. Peled, T. H. Hendler, M. G. Graif, Y. C. Cohen, Tel Aviv University, Sourasky Medical Center (Tel Aviv, IL)

The detection of demyelination in multiple sclerosis (MS) by magnetic resonance imaging (MRI) may be limited, even in the chronic phase of the disease. Here we present a new MRI technique, q-space diffusion imaging, that measures the displacement of water molecules in the axonal milieu and therefore specific for axonal damages. This specificity was tested on models of demyelination in rats and on myelination in the developing rat spinal cord. The q-space analysis measures the displacement distribution profile of water molecules in several directions giving two parameters: the mean displacement (which correlates to mean axonal diameter) and the probability for zero displacement (which also correlates to axonal density).

The myelin membrane in MS is disrupted, therefore water molecules can diffuse more freely reaching larger distances. Consequently, broader displacement distribution profiles are observed. In severe MS patients, we were able to distinguish and grade between plaques in which the mean displacement reached values of CSF (10–12mm at diffusion time of 70ms) and plaques in

which the displacement was lower (5–9mm) but significantly different from displacement in normal white matter (3–4mm). All these plaques were detected as hyper-intense areas in fluid attenuation inversion recovery (FLAIR) images. In patients with severe disease, areas of normal appearing white matter (NAWM), as detected in FLAIR, were shown to be abnormal in the q-space images. This abnormality was best observed in the probability images of the q-space analysis (6–6.5 and 7.5–8 a. u. in MS and normal patient, respectively). The q-space images were compared and correlated with standard MRI protocols for MS patients that included FLAIR, magnetization transfer (MT), diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS). This technique was also tested on patients with mild disease. The abnormal areas seen in the q-space images were correlated with plaques shown in FLAIR images. In addition, the q-space images revealed other areas of abnormal displacement probability, which may indicate early detection of MS white matter pathology. Further studies will show the clinical value of this new technique.

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A POINT MUTATION IN PTPRC (CD45) IS ASSOCIATED WITH THE DEVELOPMENT OF MULTIPLE SCLEROSIS. M. Jacobsen, D. Schweer, M. Happel, A. Ziegler, W.-H. Oertel, N. Sommer, B. Hemmer (Marburg, D)

Multiple sclerosis (MS) is the most common demyelinating disease of the central nervous system (CNS), predominantly affecting young adults. It is widely accepted that a dysregulated immune response against brain resident antigens is central to the yet unknown pathogenesis of the disease. While there is evidence that the development of MS has a strong genetic component, specific genetic factors are largely unknown. Here we show that a point mutation in the protein-tyrosine phosphatase, receptor-type, C gene (PTPRC, coding for the CD45 receptor) in the heterozygous state is associated with the development of MS. A C to G nucleotide transition in exon 4 of the gene locus results in abnormal expression of high molecular weight CD45 isoforms on memory T cells and monocytes. A case-control study demonstrated the presence of the PTPRC mutation in 6.4 % of MS patients (95 % confidence interval: 3.6 %–10.6 %) but not in healthy donors (p=0.00013) or patients with other inflammatory CNS diseases (p=0.045). The PTPRC mutation was also found to segregate with the disease in three multiplex MS families ($p < 0.01$). This is the first report of the association of a point mutation in an immunologically relevant gene with MS.

130a
EFFECTS OF INTERFERON BETA-1A (REBIF) IN PATIENTS WITH ACUTE NEUROLOGICAL SYNDROMES AT HIGH RISK OF DEVELOPING CLINICALLY DEFINITE MULTIPLE SCLEROSIS (shortened title). G. Comi, M. Filippi, F. Barkhof, D. Durelli, G. Edan, O. Fernandez, H. P. Hartung, P. Seeldrayers, P. Soelberg-Sorensen, M. Rovaris, F. Martinelli, V. Martinelli, M. Rodegher, G. Francis, O. R. Hommes and the ETOMS study group (Milan, I; Amsterdam, NL; Turin, I; Rennes, F; Malaga, E; Graz, A; Charleroi, B; Copenhagen, DK; Geneva, CH; Nijmegen, NL)

(The complete abstract is on page 217, because it arrived after the editorial deadline).

Oral session 21

Muscle Disorders –1

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A DISTINCT PHENOTYPE OF DISTAL MYOPATHY IN A LARGE FINNISH FAMILY. I. Mahjneh, B. Udd, A. Paetau, H. Somer, Div. of Neurology, Kainuu Central Hospital, Neurology, Vaasa Central Hospital, Dept. of Pathology,Univ. of Helsinki, Dept. of Neurology, Univ. of Helsinki (Kajaani, Vaasa, Helsinki, FIN)

Distal myopathies are a heterogeneous group of inherited neuromuscular disorders characterized by involvement of the distal muscles in the extremities. We report a clinical, histopathological, immunocytochemical, electrophysiological, and radiological study of 7 patients (5 men and 2 women) with an age range from 36 to 82 years. All patients belonged to four generations of a Finnish family. The disease showed autosomal dominant inheritance. The age at onset ranged from 32 to 45 years. The first symptoms for referral were clumsiness on the hands in 3 patients and on the legs in 4 patients. The interval between the involvement of lower after upper/upper after lower extremities ranged from 2 to 3 years. Patients had a steppage gait. At onset they were unable to walk on heels, while walking tiptoes was possible. Asymmetry of muscle involvement was common. The pattern of muscle involvement studied both with manual muscle testing (MRC scale) and with muscle CT scans, was characterised on the upper limbs by early involvement of pollicis abductor and opponent, first interossei dorsales and abductor digiti minimi while on the lower limbs TA, EDL, gastrocnemius, gluteus medium and TFL were involved early in most patients. With the progression of the disease, other intrinsic muscles of the upper limbs became involved as well as long finger extensors, wrist extensors, triceps and infraspinatus. On the lower limbs, the disease spread to the proximal muscles also. The progression of the disease has been slow or moderate, but intrafamilial variability has been seen. EMG showed in all patients mostly myopathic features, in 2 patients MCS from n. peroneus showed reduced amplitudes. Serum CK was normal or slightly elevated. Muscle biopsy showed a severe dystrophy-level pathology. There was severe endomysial fibrosis, some areas with scant T-cells, pronounced fiber size variation (diameter 10–140u), abundant rimmed vacuoles and some cytoplasmic inclusion bodies. Also some group atrophy could be observed, COX-negative fibers were not observed. Some fibers and rimmed vacuolar material were SMI–31-immunopositive. The biopsy picture thus represents a rimmed vacuole-positive dystrophy with features also of the IBM-group. In all patients DNA-analysis showed that they do not share haplotypes with Welander nor with TMD. We conclude that our patients have a distinct phenotype of distal myopathy which has not been reported before in literature.

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ANALYSIS OF DYSTROPHIN EXPRESSION IN AMINOGLYCOSIDE TREATED MYOTUBES OF DUCHENNE MUSCULAR DYSTROPHY PATIENTS. S. Corti, A. Martinuzzi, G. P. Comi, F. Locatelli, S. Salani, F. Fortunato, C. Angelini, N. Bresolin, G. Scarlato, Università di Milano, IRCCS E. Medea, Università di Padova (Milano, Conegliano, Padova, Bosisio Parini, I)

Aminoglycoside antibiotics have been shown to suppress stop codon mutations and partially restore gene function both in vitro (Cystic Fibrosis and mdx cells) and in vivo (mdx mouse). Currently there is no treatment for Duchenne Muscular Dystrophy (DMD) that results from mutations in the dystrophin gene. Approximately 30 % of these mutations in undeleted DMD patients are accounted for by nucleotide changes creating premature stop codons. Given that long terms aminoglycoside treatment can cause hearing loss and nephrotoxicity, the effectiveness of this approach must be investigated in vitro before any clinical trial in DMD patients. We established primary differentiated muscle cultures from controls, six DMD (four without deletion and two with deletion of the dystrophin gene) and one patient with genetically defined beta-sarcoglycanopathy. The cells were kept for 10 days in the presence of different concentrations of gentamicin (from 100 to 500 mg/ml). Dystrophin expression was analyzed by immunocytochemistry and Western blot with NH2, rod-domain and COOH monoclonal antibodies with chemioluminescence detection. Western blot analysis failed to demonstrate dystrophin expression in any DMD patient. At the moment, our data do not provide support to aminoglycoside trials in DMD patients selected on the basis of the absence of major deletions of the dystrophin gene

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MOLECULAR BASIS OF GLYCOGEN STORAGE DISEASE TYPE IIIA. S. Lucchiari, G. P. Comi, A. Bordoni, I. Fogh, N. Bresolin, G. Scarlato, Università di Milano (Milano, I)

We studied 16 Glycogen Storage Disease (GSD) type IIIa patients, with amylo–1,6-glucosidase, 4-alfa-glucanotransferase (AGL) deficiency. These patients represent 28 independent alleles, since two of them are related (sisters of other investigated patients). The age range varies from 3 to 47 years; 10 of them being adults and 8 still younger than 18 years. The following clinical and laboratory data have been collected: sex (males: 7: females 9); actual age; age at onset of clinical signs; liver involvement (both as infantile hepatomegaly and liver function follow up); age at onset of muscle weakness; nature and segmental distribution of muscle involvement (muscle cramps, fatigue, fixed muscle weakness and hypotrophy; CPK levels during the follow up; lactate production during ischaemic exercise; electromyography); heart involvement; intercurrent diseases. We identified nine new mutations in the AGL gene of 13 independent GSD IIIa patients, as follows (i) a homozygous T-to-A transversion in the second nucleotide at the donor splice site of intron 4; (ii) a G-to-A transition in the first nucleotide of donor splice site of intron 21, in four independent patients, in two of them in homozygosity and in other two in heterozygosity; (iii) a homozygous G-to-C transversion in the first nucleotide of splice site of intron 26 in one patient; (iv) a homozygous G49T mutation in exon 4 leading to the creation of a stop codon; (v) a heterozygous G1538C mutation in exon 13 leading to the creation of a stop codon; (vi) a heterozygous C3148T mutation in exon 25, resulting in an aminoacid substitution Pro -> Ser; (vii) a homozygous G4142A mutation in exon 32, leading

to the creation of a stop codon; (viii) a heterozygous insertion AA at nt 4273 in exon 33, in two patients, leading to the creation of a stop codon; (ix) a heterozygous insertion T at nt 621 in exon 7 in one patient. The percentage of identified mutations is 68% (19 out of 28 investigated alleles). The G-to-A transition in the first nucleotide of donor splice site of intron 21 accounts for 21.4% of the investigated alleles; it may thus represent a common mutant allele at least in the Italian GSDIIIa population. The phenotypic presentation of 12 out of 13 genetically diagnosed patients is consistent with a definition of GSD type IIIa. The high genetic variability in a relatively low patients sample makes genotype-phenotype correlation difficult, although it seems that frameshift and stop codon mutations are associated with marked muscular involvement. At least in one family, we observed intrafamilial variability, suggesting the existence also of other factors modulating the GSDIII phenotype.

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VARIABLE CLINICAL SPECTRUM OF DYSFERLIN DEFICIENCY. J. J. Sevilla, T. Sevilla, F. Mayordomo, E. Gallard, C. Serrano, I. Illa, Hospital Universitari La Fe, Hospital Santa Creu i Sant Pau (Valencia & Barcelona, E)

Recently there have been reported mutations in the dysferlin gene associated either with limb girdle muscular dystrophy 2B (LGMD–2B) and "Miyoshi distal myopathy"; the latter is characterised by an initial affectation of gastrocnemious muscles and subsequent involvement of more proximal parts. However, there are some evidences of a broader clinical spectrum of "dysferlinipathies" that is not yet well defined. Objectives: To describe different clinical syndromes associated to dysferlin deficiency.

Patients and Methods: The study was carried out in patients with limb-girdle, distal or mixed muscle dystrophy, defined by high serum CK and conventional EMG and histology criteria. Any known ethiology of the myopathy had being excluded by means of histologic, immunostaining, molecular or biochemical investigation (e. g.: dystrophin, calpain, FSHD, myotonic dystrophy or mitochondrial diseases). The diagnosis of dysferlinopathy was established by muscle biopsy immunostaining with antidysferlin antibodies. The distribution of muscle involvement was established by clinical (manual muscle testing) or CT (serial axial slices in predetermined anatomical levels) procedures.

Results: There were 14 patients presenting dysferlin defiance; 9 of them were familiar (belonging to 4 pedigrees) and 5 sporadic. The age of onset was similar in all cases, but there were differences in the pattern of muscle involvement and severity. At least three well-defined clinical patterns were prominent: the classical Miyoshi, a distal form affecting preferentially the tibioperoneal group, and a limb-girdle and distal form with more irregular involvement.

Conclusions: Mutations in the dysferlin gene are expressed by different phenotypes that include limb-girdle, Miyoshi form and others. Any form of non-diagnosed muscular dystrophy must be tested for dysferlin deficiency.

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PRION GENE GENETICS AND SPORADIC INCLUSION-BODY MYOSITIS. J. B. Lampe, G. Gossrau, M. Walter, H. Kitzler, D. E. Pongratz, H. Lochmüller, H. Reichmann, Neurologische Klinik der TU, Friedrich-Baur-Institut (Dresden, Friedrich-Baur-Institut München, D)

Sporadic inclusion-body myositis (s-IBM) is a slowly worsening chronic muscle disorder most common in patients older than 55. The muscle biopsy reveals an inflammatory myopathy with intracellular amyloid deposits. The prion protein has been identified as one of several neurodegeneration-associated components of these inclusions (Askanas et al., 1993). Interestingly, transgenic mice overexpressing the PrP gene develop a necrotizing myopathy sharing some features with inclusion body myopathies (IBM) (Westaway et al., 1994). Homozygosity at the polymorphic prion gene codon 129 predisposes to sporadic and iatrogenic Creutzfeldt-Jakob disease (CJD) and new variant CJD (Collinge et al., 1991; Palmer et al., 1991; Hill et al., 1997). We determined the prion gene codon 129 in 22 sporadic inclusion body myositis (s-IBM) patients using PCR and restriction digest. Fourteen patients (64 percent) showed the methionine/methionine (M/M) genotype at prion gene codon 129, seven patients (32 percent) valine/methionine (V/M), and one patient (5 percent) valine/valine (V/V). In the control group only 23 individuals revealed M/M (40 percent), 29 (51 percent) V/M, and 5 (9 percent) V/V, which is comparable to those genotype frequencies reported from three different Western European (156 M/M, 39%; 44 V/V, 11%; 198 V/M, 50%). In the group with s-IBM excess methionine homozygosity was statistically significant (p=0.023). The odds ratio (OR) amounts to 2.71 (1.04–7.26) (Lampe et al., 1999). Additionally, we sequenced the PRNP gene of 22 s-IBM patients. We identified one patient with s-IBM who heterozygously harbours a novel missense prion-gene (PRNP) mutation which is expressed in skeletal muscle. This mutation was not identified in 63 healthy controls. Therefore, the mutation is not a frequent PRNP polymorphism. The resulting amino acid exchange involves a part of the protein which is highly conserved across different mammalian species (Schatzl et al., 1995).

Askanas et al., (1993). Neuroreport 5, 25–8; Collinge et al. (1991). Lancet 337, 1441–2; Hill et al. (1997). Nature 389, 448–50; Lampe et al., Lancet 353, 465–466; Palmer et al. (1991) Nature 352, 340–2; Schatzl et al. (1995) J. Mol. Biol. 245, 362–374; Westaway et al., (1994). Cell 76, 117–29.

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MITOCHONDRIAL IMPAIRMENT OF HUMAN MUSCLE IN FRIEDREICH ATAXIA IN VIVO. L. Schöls, C. Hardt, J. T. Epplen, J. Zange, M. Vorgerd, Department of Neurology, Department of Human Genetics, Human Molecular Genetics, Institute of Aerospace Medicine (Bochum, Essen, Cologne, D)

Friedreich ataxia (FRDA) is due to mutations in the gene encoding the mitochondrial protein frataxin. This 31P magnetic resonance spectroscopy (31P-MRS) study on the calf muscle of FRDA patients provides in vivo evidence of a severe impairment of mitochondrial function. Mitochondrial ATP resynthesis was studied by means of the post exercise recovery of phosphocreatine. After ischemic exercise in calf muscles of all patients phosphocreatine recovery was dramatically delayed. Time constants of recovery correlated with mutations of the frataxin gene, the age of the patients, and disease duration. 31P-MRS represents the first expedient tool for monitoring therapeutic trials in FRDA non-invasively.

Oral session 22

Muscle Disorders – 2

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TWO DYSTROPHIN PROTEINS AND TRANSCRIPTS IN A MILD BMD AS A RESULT OF A PUTATIVE ABERRANT SPLICING EVENT. M. Sironi, G. Felisari, A. Bardoni, R. Cagliani, F. Fortunato, A. Prelle, L. Tancredi, M. C. Bonaglia, U. Pozzoli, N. Bresolin, G. P. Comi, Irccs Eugenio Medea, Irccs Ospedale Maggiore Policlinico (Bosisio Parini Lc, Milano – Italy, I)

Duchenne Muscular Dystrophy (DMD) and the milder variant, Becker Muscular Dystrophy (BMD) are caused by mutations in the gene coding for dystrophin, a high-molecular weight cytoskeletal protein. Some 60% of DMD/BMD males have deletions involving one or more exons of the dystrophin gene. Duplications account for another 5% of cases. The 35% of affected individuals who have no detectable deletion or duplication have point mutations or more subtle alterations in the dystrophin gene. These mutations are spread throughout the gene with little evidence of mutational hot-spots. We report the case of a 17 year old boy with the clinical phenotype of a mild BMD and serum CK of 800–1000 U/L. No detectable deletion or duplication in the dystrophin gene was detected by the routine multiplex PCR method. His muscle was biopsied at the age of 11 and showed the morphological characteristics of BMD with a global dystrophin immunoreactivity reduction and a discontinuous labelling pattern in same fibers. Cytogenetic analysis at high resolution banding (no less than 550 bands) revealed a normal karyotype (46 XY). Western blot analysis was performed using three different dystrophin-specific monoclonal antibodies against the N-terminal, mid-rod and C-terminal domain of dystrophin. With the first two antibodies, in addition to the 427 kD dystrophin band, a faster migrating band of approximate weight of 300–350 Kda was detected while with a C-terminal directed antibody only the 427 KDa protein was evidenced. Total RNA was extracted from the muscle biopsy and retrotranscribed to perform RT-PCR analysis. Amplification with forward and reverse primers located in exons 60 and 66 respectively revealed the presence of two products, one of the expected molecular weight of 694 bp and one of a smaller molecular weight (293 bp). Sequence analysis of the lower molecular weight band indicated that the 13th nucleotide of exon 62 was joined directly to the 14th nucleotide of exon 66, while no abnormality was present in the 694 bp product. The same result was obtained using total RNA from the patient's lymphoblastoid cell line. The molecular data are in full accordance with the estimated molecular weight of the shorter protein detected at the western blot. Sequence analysis of exons 60 through 67, of single splice sites and branch points revealed no genomic mutation. We report a unique case of a mild BMD patient with simultaneous expression of a putative truncated dystrophin together with a full-length protein in all his muscle fibers. It is tempting to speculate that an aberrant splicing event might be responsible for our molecular findings.

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CYTOKINE AND CHEMOKINE EXPRESSION IN HUMAN MYOBLASTS. R. Mantegazza, M. De Rossi, P. Bernasconi, F. Baggi, R. de Waal Malefyt, F. Cornelio, "C.Besta" National Neurological Inst, DNAX Research Institute, "C.Besta" national Neurological Inst (Milan, I; Palo Alto, USA)

The idiopathic inflammatory myopathies are characterized by antibody- or cell-mediated immune response against unknown muscle tissue antigens. In these diseases a cellular infiltrate, composed of T and B lymphocytes, macrophages and natural killer cells, may invade muscle tissue with a gradient from the perivascular to the endomysial compartment. Muscle cells may be actively involved in the processes of mononuclear cell recruitment and activation from the blood stream to the areas of inflammation. In order to verify this hypothesis, cultured human myoblasts were tested for their capacity to express different pro-inflammatory cytokines and chemokines at mRNA level (by RT-PCR) and protein secretion (by ELISA), in the presence of interferon-gamma and tumor necrosis factor-alfa alone or in combination. The following cytokines and chemokines were evaluated: interleukin–1 (IL–1) alfa, IL–1beta, IL–6, IL–8, monocyte chemotectic protein–1 (MCP–1), Regulated upon Activation Normal T cell Express and Secreted (RANTES), and tumor necrosis factor-alfa (TNF-alfa). We confirmed the constitutive and the overinduced by pro-inflammatory cytokines, expression of IL–1 and IL–6 by human myoblasts; moreover, we discovered that TNF-alfa may be expressed on an autocrine fashion by myoblasts themselves and that Il–8 is expressed constitutively while MCP–1 and RANTES are expressed only after proper induction.

Our results underline the importance of human myoblasts in the recruitment of leukocytes from the blood stream and, most probably, in the cross talk between infiltrating inflammatory cells and myoblasts, creating the conditions for a chronic inflammation. The muscle cell capacity of being a good responder to the soluble mediators of inflammation has to be kept in mind also in the view of intramuscular vaccination and use of engineered myoblasts as vehicles in gene therapy.

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IMPAIRED PROBLEM-SOLVING STRATEGIES IN PROMM CORRELATE WITH FRONTAL CEREBRAL BLOOD FLOW REDUCTION. G. Meola, V. Sansone, M. Cotelli, S. Cappa, D. Perani, C. A. Thornton, R. T. Moxley, Istituto Policlinico San Donato Milanese, Milan, Universitiy Brescia, Universtiy Vita e Salute, University Rochester (San Donato Milanese, Milan, Brescia, I; Rochester, USA)

H2 15 0 PET studies have recently demonstrated a reduction in cerebral blood flow (rCBF) in the frontal, temporal and parietal lobes associated with visual-spatial impairment in proximal myotonic myopathy (PROMM) and in myotonic dystrophy type 1 (DM1).

AIM: To correlate rCBF frontal abnormalities and impaired visual-spatial responses with the behavioral and affective changes observed in patients with PROMM and DM1.

METHODS: 10 patients with PROMM, 10 patients with moderately-severe DM1 (E2 CTG expansion) and 10 age, sex and education-matched controls were subjected to a battery of frontal lobe tests (Computerized Attentional Assessment, TEA; Winsconsin Card Sorting Test, WCST; Stroop Test, ST; Trail Making Test A and B, TMT and Tower of London Test, TLT computerized version) and to a personality and behavioral assessment.

RESULTS: Basic attentional and alertness functions (TEA, TMT) were normal in both PROMM and DM1 patients. Cognitive strategies and visual-spatial decisions (WCST, ST and TLT) were significantly impaired in patients with PROMM: TLT, 102 % of error above optimal strategy, $p < 0{,}0001$ compared to 64 % of error above optimal strategy, $p < 0{,}001$ in patients with DM1 (controls: 12.6 % ± STD 8.3 of error above optimal strategy). Similar but less pronounced impairment was found in WCST and ST.

CONCLUSIONS: Although preliminary, our data suggest a selective impairment in cognitive strategies for sequential visual-spatial decisions in PROMM and DM1. This correlates with the previously described frontal cerebral blood flow reduction. More patients with PROMM and DM1 are currently being studied to better correlate these preliminary neuropsychological results with the personality patterns present in PROMM and DM1.

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HISTOCOMPATIBILITY ANTIGENS IN SPORADIC INCLUSION-BODY MYOSITIS. G. Gossrau, M. Füssel, M. C. Walter, D. E. Pongratz, H. Lochmüller, H. Reichmann, J. B. Lampe, University Hospital Dresden, University Hospital Munich (Dresden, Munich, D)

Sporadic inclusion body myositis (s-IBM) is an inflammatory muscle disorder most common in patients older than 55 years. Clinically, a slowly worsening weakness of affected skeletal muscles is present. Histologically, muscle fibres show intracellular amyloid deposits, which are accompanied by varying degrees of infiltrating CD8+ T-cells. The combination of neurodegeneration-associated proteins and marked inflammation is unique to s-IBM.

We analysed the HLA class I and II alleles in a series of 27 patients suffering from s-IBM using sequence specific primer pairs. The results obtained were compared to published controls (1). Analysing HLA class II, we detected the DRB1*0101,*0102,*0104 allele in 10 patients (antigen frequency 37 % in patients vs. 18,0 % in normal controls, allele frequency 20,3 % vs. 9,5 %), the DRB1*0301,*0304,*0305,*0306 allele in 11 patients (antigen frequency 40,7 % vs. 19,2 %, allele frequency 20,3 % vs. 10,1 %), and the DRB1*1301-*1327 allele in 10 patients (antigen frequency 37,0 % vs. 20,6 %, allele frequency 20,3 % vs. 10,9 %). The typing of HLA class I showed the A*0301-*0303N allele in 13 patients (antigen frequency 48,1 % vs. 26,2 %, allele frequency 31,4 % vs. 14,1 %).

The HLA-A* predisposition for s-IBM has not been described before. Most muscle fibres in IBM show an increased HLA class I molecule expression on the cell surface (2). Interestingly, T-cells infiltrating s-IBM muscle show a restricted T-cell receptor usage (3). In this way CD8+ cytotoxic T-cells may detect antigens bound to distinct HLA class I molecules. Hence, the aetiology of s-IBM may be triggered by so far unknown immune mechanisms.

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MYCOPHENOLATE MOFETIL FOR LONG-TERM IMMUNOTHERAPY OF SEVERE MYASTHENIA GRAVIS. C. Schneider, R. Gold, K. Reiners, K. V. Toyka, University of Würzburg (Würzburg, D)

Background: Long-term immunotherapeutics in myasthenia gravis include glucocorticosteroids, azathioprine, cyclosporine A, and cyclosphosphamide. Occasionally, these drugs are not sufficiently effective or may lead to untolerable side effects. Mycophenolate mofetil (MMF) is a new immunosuppressive drug already established in transplantation medicine. Recently, an anecdotal favourable report on a patient with myasthenia gravis has been published (Hauser et al., 1998). Methods: We initiated MMF treatment in four patients with severe refractory myasthenia gravis who did not tolerate or respond to combined treatment with azathioprine and cyclosporine A or even cyclophosphamide. Two men, 61 and 69 years old, and one young woman, 20 years old, had generalised myasthenia with bulbar involvement and a 49 year old woman had generalised myasthenia gravis and polymyositis. Results: In all these patients MMF in a daily dose of 1.5 to 2.0 g was well tolerated and resulted in considerable improvement of myasthenic symptoms within three to six months after the beginning of MMF therapy. In all patients anti-acetylcholine receptor antibodies decreased during the observation. Glucocorticosteroids could be discontinued six to nine months after MMF therapy had been started. Conclusion: Our observations indicate that treatment with MMF may have beneficial effects on myasthenia gravis. MMF may be considered as a further treatment option in severe myasthenia gravis when standard therapeutic regimens fail. Formal clinical trials are warranted to evaluate the efficacy and safety of this drug in myasthenia gravis.

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STIFFNESS ON EXERCISE IN A SWISS FAMILY: A NON PROGRESSIVE DISORDER OF MUSCLE FUNCTION WITH NORMAL EXPRESSION OF CA2+ ATPASE IN FAST-TWITCH MUSCLE FIBERS. T. Kuntzer, R. Janzer, J. Bogousslavsky, D. H. MacLennan, CHUV, Best Department of Medical Research (Lausanne, CH; Toronto, CDN)

We report 2 brothers with stiffness on exercise (Brody's syndrome) with a normal expression of Ca2+ ATPase of the fast-twitch skeletal muscle sarcoplasmic reticulum (SERCA1).

Clinical examination showed no weakness nor myotonia. Exercises such as opening and closing hands or eyes induced progressive stiffening, some pain in the exercised muscles, and increasing difficulty relaxing them. A molecular genetic study was made and demonstrated in the involved members of the family a Pro789 to Leu mutation in the ATP2A1 gene on chromosome 16p, encoding SERCA1.

The results of this family show that in Brody's syndrome Ca2+ ATPase in fast-twitch muscle can be present but inactive and that immunostaining of

skeletal muscle to detect loss of SERCA1a protein is not adequate for diagnosis of ATP2a1-linked Brody disease.

Oral session 23

Peripheral Neuropathy – 1

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COMPARISON OF ELECTRODIAGNOSTIC CRITERIA FOR DEMYELINATION IN PATIENTS WITH CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP). D. S. M. Molenaar, M. Vermeulen, R. de Haan, Academic Medical Center (Amsterdam, NL)

The study compared the diagnostic value of four previously published sets of electrodiagnostic criteria for demyelination in 64 patients whose history and physical examination indicated that CIDP was a possible diagnosis. We aimed to see whether the diagnostic value of the sets could be enhanced. We studied the sensitivity and specificity of the sets of criteria. Multivariate logistic regression analysis was used to identify superior individual criteria. Further improvement of the diagnostic properties of the most important criteria was investigated by using Receiver Operating Characteristic (ROC) curves. Sensitivity of the sets of criteria ranged from 56–70 %, and specificity ranged from 85–98 %. No single set of criteria demonstrated strong sensitivity and specificity. Multivariate logistic regression analysis showed that slowed motor nerve conduction velocity (MNCV) in at least two motor nerves (of which at least one should be an arm motor nerve), was the strongest independent predictor of CIDP (range Odds Ratio = 16.5–26.2). The optimum cut off value of the MNCV (sensitivity 78 %; specificity 90 %) was either 80 % of the lower limit of the normal range when the distal compound muscle action potential (CMAP) was at least 2 mV (peak to peak), or 70 % of the lower limit when CMAP was less than 2 mV. We conclude that this simple criterion of slowed MNCV significantly increases the confidence of CIDP diagnosis in patients with clinical signs consistent with CIDP.

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MALIGNANT CELL INFILTRATES AND SARCOID GRANULOMAS AS UNCOMMON CAUSES OF MULTIFOCAL NEUROPATHY WITH CONDUCTION BLOCKS. G. Said, J. Senant, P. Lozeron, C. Lacroix, D. Decaudin, O. Prelles, D. Adams, Service de Neurologie Hôpital de Bicêtre, Univ Paris-Sud (Le Kremlin Bicêtre, F)

Nerve conduction block is a key feature of acquired inflammatory demyelinating polyneuropathies. However this finding can be sometimes misleading and delay specific treatment. We recently investigated two patients with subacute multifocal neuropathy and multiple nerve conduction blocks related to malignant infiltrates of the nerve in one case, to sarcoid granulomas in the other.

Patient 1: This 59 y-o woman had been treated for 9 months for plasma cell leukemia with IgG kappa monoclonal gammopathy with melphalan and prednisone when she experienced pains and numbness in all four limb extremities while the leukemia seemed controlled with melphalan. Within a week she developed gradual weakness that predominated in the right hand where there was no sensory deficit. There was a mild distal hypaesthesia in the lower limbs. The tendon reflexes were preserved. Spinal cord MRI and CSF were normal. Motor conduction velocity was 42.5 m/s in the right ulnar nerve with 70 % conduction block in the arm and a 65 % conduction block in the forearm. A 75 % conduction block was found in the left posterior tibial nerve. Distal latencies were normal but F wave latency was prolonged. The patient received IVIGs without significant benefit. Two months later she was re-admitted because of worsening of the neurological deficit. She then had minor sensory loss in the right superficial radial nerve territory which prompted us to biopsy this nerve, which revealed massive, asymmetrical nerve infiltration with plasma cells associated with destruction of neighbouring fibers.

Patient 2 was a 69 y-o man in good health who manifested gradual weakness of dorsiflexion of the right foot since August 1999. A month later he experienced numbness of the second and third fingers on the right side, in the median nerve territory on the left. Numbness extended to the other fingers gradually and to both feet up to midleg level. Muscle strength was at 3/5 in the left peroneal nerve territory, at 4/5 in the right hand, normal in the other territories. Gloves and stockings hypaesthesia were noted, with normal position sense. Ankle jerks were decreased. Routine biological tests and radiograms were normal. CSF showed 0.68 g/l protein, 2 lymphocytes/ml. Electrophysiological testing showed 80 % conduction block on the left median nerve with decreased conduction velocity to 27 m/sec. A 60 % conduction block was noted in the left ulnar nerve in the forearm, and a 40 % block on the median nerve at the ulnar forearm level. No conduction block was found in the lower limbs where nerve action potentials were decreased, which led us to biopsy the superficial peroneal nerve and peroneus brevis muscle. Biopsy specimens showed numerous perineurial sarcoid granulomas with conspicuous lesions of granulomatous angeitis.

We conclude that multifocal granulomatous or malignant cell infiltrates can share many clinical and electrophysiological features with acquired inflammatory demyelinating polyneuropathy, which may delay specific therapy.

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ANTI-GM1-ANTIBODIES CAN BLOCK VOLTAGE-GATED SODIUM CHANNELS OF NHH15-CA2 NEUROBLASTOMA X GLIOMA CELLS. F. Weber, R. Rüdel, P. Aulkemeyer, H. Brinkmeier, German Air Force, Bundeswehrkrankenhaus (Fürstenfeldbruck, Ulm, D)

Anti-GM1 antibodies, frequently found in the serum of patients with Guillain-Barré syndrome (GBS), have been suggested to interfere with axonal function, but this was not undisputed. We report that IgG anti-GM1 antibodies, raised in rabbits, can reversibly block the voltage-gated Na+ channels of nerve cells, thus causing a reduction of the excitatory Na+ current. The block was, however, only substantial when the antibodies were applied together with rabbit complement factors. A solution containing anti-GM1 sera (dilution 1:100) and complement (1:50) reduced the Na+ current to 0.5 ± 0.2 times control (mean value ± SD). Applications of the antibody by itself, complement by itself or of anti-GM2 or anti-GM4-antibodies (1:100) plus complement were nearly without effect. The complexes of anti-GM1-antibodies and complement factors block the channel pore directly. In addition they also increase the fraction of channels that are inactivated at the resting potential and alter channel function by changing the membrane surface charge. In some GBS patients the described effect may be responsible for conduction slowing and reversible conduction failure.

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THE OXALIPLATIN-INDUCED NEUROPATHY IS DUE TO ALTERATION IN INACTIVATION KINETICS OF VOLTAGE-GATED SODIUM CHANNELS IN SENSORY NEURONS. J. Grosskreutz, H. Adelsberger, C. Lersch, S. Quasthoff, Karl-Franzens-Universität Graz, Technical University Munich (Graz, A; Munich, D)

Peripheral neuropathy is the most severe side-effect of chemotherapeutic therapy with oxaliplatin. The neuropathy is characterized by predominantly hyperpathic symptoms (dysaesthesia and/or distal paraesthesia at the fingers, toes and, less frequently, peri-oral region and pharyngo-laryngeal tract, induced or exacerbated by cold). The mechanism underlying this hyperexcitability of sensory nerves was investigated on a cellular level using rat sural, peroneal and vagal nerve preparations, dorsal root ganglia and hippocampal neurons. Oxaliplatin resulted in an increase of the amplitude and duration of compound action potentials of A-fibres (218 ± 68 %; n = 7) while C-fibres compound action potentials were less affected (36 ± 29 %; n = 7). In electrotonus experiments the drug could not mimick the effects caused by blockers of voltage-gated potassium channels but lengthened the refractory period of peripheral nerves suggesting an interaction of the drug with voltage-gated sodium channels. Recordings from dorsal root ganglion neurons with 250 µM oxaliplatin showed an increase of the sodium current by a factor of 2.6 ± 1.45, a block of the maximal amplitude to 0.65 ± 0.23 and a shift of the voltage response relationship towards more negative membrane potentials by 10 mV. The effect was detectable on 13 of 18 tested cells with variable degrees in individual cells. This observation, together with the absence of any effect on sodium currents of hippocampal neurons, suggests that the interaction of oxaliplatin with sodium channels is restricted to one or more channel subtypes expressed in peripheral neurons. The effect of oxaliplatin was antagonised by the sodium channel blocker carbamazepine which could be used to reduce neuropathic side effects of oxaliplatin therapy in patients.

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CLINICAL AND ELECTROPHYSIOLOGICAL CHARACTERISTICS OF CHARCOT-MARIE-TOOTH TYPE2 (CMT2) PATIENTS WITHOUT MUTATIONS IN MYELIN PROTEIN ZERO (MPZ) OR CONNEXIN32 (CX32). J. Berciano, A. García, V. Timmerman, P. De Jonghe, O. Comarros, J. Calleja, Univ. Hospital Marques de Valdecilla, University of Antwerp (Santander, E; Antwerp, B)

Background. Increasing evidence indicates that a subset of patients diagnosed as CMT2 have mutations in the peripheral myelin genes NTZ or Cx32, this accounting for clinico-electrophysiological heterogeneity. Objective: To re-evaluate a CMT2 series after ruling out mutations in MPZ and Cx32. Patients and methods: The series comprises 45 patients (42 patients from 12 pedigrees with dominant inheritance, and 3 patients from 2 sibs) fulfilling the following inclusion criteria: ii) male-to-male transmission or absence of Cx32 and MPZ mutations in the proband; ii) semeiology restricted to the peripheral nervous system; iii) normal or slightly reduced nerve conduction velocity (above 60% of normal); and iv) where available, nerve biopsy indicative of axonopathy. Results: The mean age of onset was 14 years (range 2–69) and the mean age at diagnosis was 35 (range 16–76). Forty percent of the cases were asymptomatic. The majority of patients were scarcely disabled, only recessive ones exhibiting severe weakness. Electromyography was the most sensitive technique showing a neurogenic pattern ranging between 87% for extensor digitorum brevis and 69% for tibialis anterior. Slight reduction of motor NCV, increase of distal motor latency (DNIL) or reduced amplitude of compound muscle action potential of the peroneal nerve occurred in two thirds of cases. Two patients showed a moderate reduction of motor NCV (below 60% of normal) in the median and peroneal nerves, but both had normal motor NCV of ether nerves and normal DNIL of axillary nerve. Sensory NCV abnormalities parallel those of motor NCV.

Conclusions: The clinical picture of CMT2 is usually quite subtle and quiescent. Electrophysiological study is a reliable method of diagnosis of CMT2 patients and especially in separating them from CMT1 patients.

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LONG-TERM FOLLOW-UP STUDY OF 7 FAMILIES WITH HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES, ONE OF THEM WITH A NOVEL MUTATION: PHENOTYPIC DIFFERENCES BETWEEN PATIENTS WITH THE COMMON DELETION AND A NEW SPLICE SITE MUTATION IN THE PMP22 GENE. A. Pou Serradell, J. M. Espadaler, M. J. Téllez, J. Meuleman, V. Timmerman, C. Van Broeckhoven, Hospital del Mar, University of Antwerp. (Barcelona, E; Antwerpen, B)

In 6 families with HNPP an interstitial deletion on chromosome 17p11.2–12 was demonstrated (29 patients) and in a further HNPP family (3 patients), without HNPP-deletion, a new mutation (c. 179–1G> C,3′splice-site, Intron 3 preceding Exon 4, first extracellular domain) in the PMP22 gene was demonstrated, the last one never reported in the literature. These 32 patients with HNPP present with a variability of neurologic symptomes/signes: recurrent peripheral nerve palsies or motor multifocal neuropathy (MMN), brachial plexus palsy (BPP), motor mononeuropathy (MM) precipitated by minor trauma or compression (sometimes after effort), recurrent sensory disturbances (RSD) (often precipitated by forced positions), symmetrical distal sensory neuropathy (SDSN), HMSN I-like phenotype. A follow-up study has been performed in all these patients between 1993 and 1999. An MMN appears in 9/32, BPP in 4/32, RSD in 5/32, SDSN in 8/32 (3 with bilateral carpal tunnel syndrome) and HMSN I-like in 2/32; in 13 patients coexisted at least two forms, essentially RSD or SDSN and MM. Pes cavus were present in 6 patients, five of them belonging to the same family, café-au-lait spots in 3 patients, diabetes in 1 patient. In spite of clinical intrafamilial variability we find a certain interfamilial phenotype homogeneity (12 members in one family presenting RSD). The family with the novel mutation shows the clinical and electrophysiological characteristics of common HNPP but in addition two family members had significantly more neuropathic features, one of them presenting a conduction block lasting for more than 12 years.

Conclusions: the spectrum of phenotypic expression of HNPP patients appears to be broader on a long-term follow-up. If the HNPP-deletion is absent in one family with clinical diagnostic of HNPP, further mutation should be investigated: we demonstrate a novel 5′-splice site mutation in the PMP22 gene giving rise to a phenotype mimicking HMSN I but with some common HNPP clinical features.

Oral session 24

Peripheral Neuropathy – 2

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FREQUENCY OF P0 GENE MUTATIONS IN BRITISH HMSN TYPE II FAMILIES. H. Houlden, M. Lee, M. Sweeney, J. Jacobs, M. Groves, J. Blake, H. Manji, N. Wood, M. Reilly, Neurogenetics Laboratory Institute of Neurology, Neuropathology Laboratory, Neurophysiology Laboratory, Clinical Neurology (London, UK)

Mutations in the P0 (peripheral myelin protein zero) gene have been found to cause typical hereditary motor and sensory neuropathy (HMSN) type Ib and type III. P0 gene mutations have recently been found in a small number of HMSN type II families. The affected patients showed late age of onset with distal muscle wasting clinically. Neurophysiology in these patients is consistent with axonal neuropathy (nerve conduction velocities > 38m/s) although velocities tend to be between 38 and 42 m/s. A subset of these HMSN II patients with P0 mutations and intermediate have been shown to have deafness and pupillary abnormalities as a common feature. To assess the frequency of P0 mutations in British HMSN II patients, we proceeded to sequence the entire coding region and flanking introns of the P0 gene in 40 families and 20 sporadic patients, who fitted the diagnostic criteria both clinically and electrophysiologically for HMSN II. Two HMSN II families were found to have missense coding mutation, a novel mutation in exon 2 and the other previously described in exon 3. These mutations were not present in 100 normal individuals. The first HMSN II family with an exon 2 mutation had four affected members, the proband having clinical and electrophysiological evidence of typical HMSN II. The second HMSN II family with an exon 3 mutation had at least 20 affected members over six generations inherited in an autosomal dominant fashion. In this large family we present detailed clinical, neurophysiology and peripheral nerve pathology data. Therefore, P0 mutations are a rare cause of HMSN II but they do occur at a frequency of 5% in our autosomal dominant families. Based on this data we suggest that all patients with familial HMSN type II and patients with HMSN type II and no family history but suggestive inherited features should be screened for P0 gene mutations.

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STEROID-RESPONSIVE POLYNEUROPATHY IN A FAMILY WITH A NOVEL MYELIN PROTEIN ZERO MUTATION. M. Donaghy, S. M. Sisodiya, R. Kennett, B. McDonald, N. Haites, C. Bell, University of Oxford, University of Aberdeen (London, Aberdeen, UK)

Most myelin protein zero (MPZ) mutations lead to the HMSN type 1 phenotype, with recent reports of Déjérine-Sottas, congenital hypomyelination and HMSN II also ascribed to MPZ mutations. MPZ plays a major role in the compaction of peripheral nerve myelin. Differing phenotypes may reflect the effects of particular mutations on MPZ structure and adhesivity.

We report a novel hereditary motor and sensory neuropathy (HMSN) phenotype associated with a new dominant mutation in the MPZ gene. This produces deterioration resembling chronic inflammatory demyelinating polyneuropathy (CIDP), which was partially steroid-responsive. We undertook clinical, neurophysiological, neuropathological and molecular genetic analysis of 10 members in two generations of a family, 5 of whom exhibited neuropathy. The proband had progressively disabling weakness, with positive sensory phenomena and areflexia, elevated CSF protein and initially responded to steroids. Nerve biopsy in a less severely affected sibling revealed a demyelinating process with disruption of compacted myelin. The younger generation were so far less severely affected, becoming symptomatic only after 30 years. All affected family members were heterozygous for a novel MPZ mutation (Ile99Thr), in a conserved residue.

This broadens the spectrum of familial neuropathy associated with MPZ mutations. It may explain previous reports of steroid-responsive HMSN or familial CIDP. Our family seems to represent the homologue of MPZ knockout mice which develop an age-dependent progressive neuropathy resembling CIDP (Shy ME et al., J Neuropath Exp Neurol 1997, 56:811).

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CHARCOT-MARIE-TOOTH DISEASE AND RELATED NEUROPATHIES: CLINICAL AND MOLECULAR CORRELATION IN A LARGE SERIES OF ITALIAN PATIENTS. D. Pareyson, M. Milani, C. Ciano, V. Scaioli, M. Marchetti, G. Lauria, A. Sghirlanzoni, F. Taroni, Istituto Nazionale Neurologico (Milan, I)

We reviewed our series of patients affected by Charcot-Marie-Tooth disease (CMT) and Dejerine-Sottas disease (DSD) seen at our Institute during the last 12 years. Inpatient and outpatient clinical records, electrophysiologic examinations, molecular tests and (when performed) nerve biopsies were retrospectively reviewed. Overall 128 index cases of CMT and DSD were included; other 45 affected relatives were also evaluated. According to electrophysiologic examination, 82 index cases were classified as CMT1 [Motor Conduction Velocity (MCV) < 38 m/sec in upper limb nerves), 27 as CMT2 (MCV > 38 m/sec); nine other CMT patients who had intermediate MCVs could not be further classified. The 17p11.2 duplication was found in 53/82 CMT1 cases (65 %). If only autosomal dominant CMT1 cases are considered, the duplicated cases were 78 %. On average, non-duplicated CMT1 cases were more severely affected than those carrying the duplication. One large CMT1A family and other two non-duplicated patients had marked upper limb tremor (Roussy-Levy Syndrome). Myelin Protein Zero (MPZ) mutations were found in three CMT1 cases (3.6 %). One of these families showed trigeminal neuralgia in several family members. A mutation in the gene coding for the Schwann cell transcription factor Early Growth Response 2 (EGR2) was found in one CMT1 family (1.2 %); the proband of this family showed involvement of multiple cranial nerves (consistent with a role of EGR2 in cranial nerve development). Inheritance appeared to be autosomal recessive in 3 CMT1 and 2 CMT2 cases and X-linked in other 7 index cases. Search for connexin–32 mutations is currently under way in selected cases. Ten index cases had a diagnosis of DSD. Two of them had MPZ mutations: heterozygous de novo in one case and homozygous in a couple of siblings; interestingly, their consanguineous parents were both affected by mild CMT and were initially thought to have the axonal form CMT2. De novo mutations in Peripheral Myelin Protein 22 (PMP22) and in EGR2 were found in other two DSD patients.

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HEREDITARY MOTOR AND SENSORY NEUROPATHY – RUSSE. P. K. Thomas, I. Tournev, D. Angelechiva, B. Youl, R. H. M. King, L. Kalaydjieva, Institute of Neurology (London, UK)

A large gypsy kindred was investigated in Bulgaria in which over 30 individuals had a peripheral neuropathy with autosomal recessive inheritance. In most this was hereditary motor and sensory neuropathy-Lom (HMSN-L). Two branches of this pedigree failed to display linkage to the HMSN-L region on chromosome 8q24 or to other loci known to be associated with autosomal recessive neuropathy. This newly recognised neuropathy has been designated hereditary motor and sensory neuropathy-Russe (HMSN-R), after the town on the Danube where the cases were first identified. Observations have been made on 16 affected individuals from 10 families. They began with distal lower limb weakness with a mean age of onset at 11 years and distal upper limb weakness with a mean onset at 23 years. This was progressive, leading to severe disability by midlife. There was prominent distal sensory loss in the limbs resulting in neuropathic joint degeneration in 2 cases, and occasional cranial nerve involvement. Upper limb motor conduction velocity was moderately reduced at ~32 m/s. No values were obtainable in the legs. Sural nerve biopsy in 2 cases showed a predominant loss of large fibres and diffuse hypomyelination. The clinical, neurophysiological and neuropathological features distinguish HMSN-R from other autosomal recessive neuropathies.

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NEUROTROPHINS AND TNF DISPLAY DIFFERENT PATTERNS OF AXONAL TRANSPORT IN THE PERIPHERAL NERVE. M. Schäfers, C. Dees, M. J. Lohse, K. V. Toyka, C. Sommer, Neurologische Universitätsklinik Würzburg, Institut für Pharmakologie (Würzburg, D)

The mechanisms by which tumor necrosis factor-a (TNF) generates inflammatory and neuropathic pain are still unclear. TNF is expressed mainly in non-neuronal cells immediately after peripheral nerve injury, whereas in dorsal root ganglia (DRG) it is upregulated several days later. As previously demonstrated for neurotrophins, we hypothesized that TNF might be taken up by peripheral axons and transported centrally. Here we investigated whether exogenous 125-J labelled TNF and nerve growth factor (NGF) (human recombinant, Amersham Pharmacia) is transported by axons when injected into the sciatic nerve (3 µCi/nerve in a volume of 5 µl), gastrocnemius muscle and plantar skin (1,5 µCi in a volume of 50 µl) of Sprague Dawley rats (n=42). Radioactivity was directly measured in ipsi- and contralateral skin, gastrocnemius muscle, sciatic nerve as well as in DRG. After intraneural injection of 125-J labelled TNF, using a double ligation procedure, there was no significant build up of 125-J-TNF at the ligatures (745 CPM ±728 distal vs. 363 CPM ±369 proximal). On the contrary, 125-J-NGF accumulated at the proximal ligature (92 053 CPM ±83 134 distal vs. 17 452 CPM ±16 348 proximal), demonstrating uptake and retrograde transport of NGF as expected. In contrast to 125-J-NGF (517 CPM ±90) there was no accumulation of radioactivity in the sciatic nerve after intradermal injection of 125-J-TNF (17 CPM ±4). Interestingly, after intramuscular injection a significant accumulation of 125-J-TNF could be detected in the distal segments (160 CPM ±75 distal vs. 12 CPM ±4 proximal) of the ipsilateral nerve suggesting a slow retrograde transport of exogenous 125-J-TNF via motor fibers or muscle afferents. In contrast to 125-J-NGF which clearly accumulated in the ipsilateral DRG after all treatments (72 CPM ±36 i. n.; 246 CPM ±83 i. d.; 931 CPM ±527 i. m.), DRG showed no accumulation of 125-J-TNF after intraneural (11 CPM ±1), intradermal (65 CPM ±23) and intramuscular (56 CPM ±14) injection. Thus, retrograde transport of TNF to the DRG is not part of the events causing neuropathic pain, which makes peripheral or spinal mechanisms more likely.

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ROLE OF RESIDENT ENDONEURIAL MACROPHAGES IN PERIPHERAL NEUROPATHY: A STUDY OF WALLERIAN DEGENERATION IN RADIATION BONE MARROW CHIMERIC RATS. M. Müller, K. Wacker, W. F. Hickey, E. B. Ringelstein, R. Kiefer, Westfälische Wilhelms-Universität, Dartmouth Medical School (Münster, D)

Resident endoneurial macrophages of the peripheral nervous system are a poorly characterized but strategically localized cell population that may play a key role during autoimmune demyelination and Wallerian degeneration. To characterize and differentiate these cells from invading haematogenous macrophages we created bone marrow chimaeric rats by transplanting wild-type Lewis rat bone marrow into irradiated transgenic Lewis rats carrying the functionally silent TK-tsa transgene. Resident endoneurial macrophages were identified by in situ hybridization of the transgene and colocalization with macrophage markers on 1 µm thick serial sections of methyl methacrylate-embedded tissue. Following a sciatic nerve crush injury, no activation of resident endoneurial macrophages was yet identified in the distal stump at day one. At day two, identified resident endoneurial macrophages newly expressed the macrophage antigen ED1 normally not expressed in peripheral nerve and took up a rounded appearance. No proliferation of identified resident macrophages was noted in rats injected with bromodeoxyuridine two hours before sacrifice. Colocalization with myelin basic protein revealed activated resident endoneurial macrophages phagocytosing myelin. Similar changes were found at day three. From day four, numerous haematogenous macrophages entered the distal nerve stump, and resident macrophages could no longer be unequivocally detected. In conclusion, resident macrophages of the peripheral nervous system rapidly become activated following peripheral nerve crush prior to the infiltration of haematogenous macrophages. They participate early in the phagocytosis of myelin but, unlike microglial cells of the brain and spinal cord, do not appear to proliferate. The rapid activation of resident macrophages may point towards a key role particularly in the very early pathophysiological steps of degenerative and possibly inflammatory peripheral nerve disease.

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RECOMBINANT TUMOR NECROSIS FACTOR RECEPTOR (P75)-FC FUSION PROTEIN REDUCES HYPERALGESIA IN EXPERIMENTAL PAINFUL NEUROPATHY. C. Sommer, M. Marziniak, K. V. Toyka, Neurologische Klinik der Universität (Würzburg, D)

A recombinant tumor necrosis factor receptor (p75)-Fc fusion protein (TNFR:Fc) competitively inhibits tumor necrosis factor-alpha (TNF) binding to cell surface TNF receptors and thus acts as a TNF antagonist. TNFR:Fc has been successfully used therapeutically in patients with severe rheumatoid arthritis, where it reduces pain and inflammation. We have previously shown that locally produced proinflammatory cytokines play a role in the initiation of pain after nerve injury. In the present study we investigated whether TNFR:Fc reduces pain and hyperalgesia in a mouse model of painful neuropathy, the chronic constriction injury of the sciatic nerve (CCI). Groups of C57Bl/6 mice (n=5) received either 50µg or 87.5µg of TNFR:Fc or sham treatment (human IgG, 87.5 µg). Treatment was applied in a volume of 35 µl intraoperatively and daily after the operation by local injection to the epineurial area of the injured nerve. CCI was performed by placing three loosely constrictive ligatures around one sciatic nerve with a sham operation contralaterally. Withdrawal thresholds to heat and to von Frey hairs were tested at regular intervals. IgG treated mice developed stable thermal hyperalgesia and me-

chanical allodynia from day three after CCI. Treatment with TNFR:Fc reduced thermal hyperalgesia significantly at both doses and mechanical allodynia significantly at the higher dose by about 50%. These results suggest that the potential of TNFR:Fc as a treatment option for patients with neuropathic pain should be further investigated.

Thursday, June 22
Oral session 25

Cerebrovascular disorders – 5

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EARLY BEHAVIORS IN FIRST-EVER ACUTE STROKE. THE LAUSANNE EMOTION IN STROKE STUDY. A. Carota, A. Nicola, S. Aybek, F. Ghika-Schmid, G. Van Melle, P. Guex, J. Bogousslavsky, CHUV (Lausanne, CH)

Studies of emotional responses in stroke patients have shown contradictory findings because of different timing of investigation, methods and patient selection.

METHODS and RESULTS: Our study was a prospective hospital-based study of mood states and behaviors in patients with first-ever stroke admitted within 48 hours. During the first four days patients were evaluated daily with an observational scale for behavioral appraisal (EBIF). The EBIF, which is independent of language abilities, includes 38 rated items (scored from 0 to 4) summarized in 7 classes (overt sadness, passivity, aggressiveness, indifference, disinhibition, denial and adaptation). Mean scores were compared with ANOVA test (p=0.05). Our population consisted in 233 patients whose demographic and nosologic data were identical to the Lausanne Stroke Registry. Signs of overt sadness were present daily in 51.5% of patients, passivity in 48.2%, aggressiveness in 10.4%, indifference in 38.9%, disinhibition in 31.7%, denial in 40.8% and lack of adaptation in 10%. No significant differences of EBIF scores were noted comparing subpopulations with left vs. right hemispheral lesion, cortical vs. sub-cortical lesion, anterior vs. posterior hemispheral lesion, and supra-tentorial vs. infra-tentorial lesion. However, in patients with left lesion we found a significant relation between aphasia and overt sadness (p=0.01) and passivity (p=0.05), while in patients with right lesion, agnostic signs were significantly associated with overt denial and indifference (p=0.05).

CONCLUSION: Our study emphasizes that emotional responses are an important component of acute stroke. We did not define cluster of behaviors related to specific cerebral localization, but preliminary results suggest that patterns of negative and positive behaviors are more frequently associated with aphasia in left lesion, respectively agnosia in right lesion, than other neurologic deficits.

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STROKE MANAGEMENT: TIMING, TRANSPORT AND ARRIVAL TO EMERGENCY ROOM. TWO COMPARATIVE STUDIES IN NICE. M.-H Mahagne, A. Dunac, C. Richier, J.-P. Fournier, F. Bertrand, M. Chatel, Hôpital Saint-Roch, Hôpital Pasteur (Nice, F)

In order to evaluate stroke care, and the opportunity of acute treatment by thrombolysis, we compared the evolution of epidemiology and management of acute stroke. We point out here the peak(s) of stroke occurrence in the nyctohemeral period, delay of arrival to the hospital and mode of transport. We compared evolution between 1991 and 1998.

METHODS: Two studies lead on 6 months periods (May to October), the first prospective in 1991 and the second retrospective, in view to avoid recruiting bias, in 1998. Both studies, led in the emergency department where all patients of Nice are admitted, are compared.

RESULTS: Both studies found the same epidemiological data with an incidence of 284/100,000hab/year. The mean age is 75.81 years in 1998 (74.84 in 1991). We identify two peaks of stroke occurrence in the nyctohemeral period, identical in the two studies: the first from 10:00AM to 02:00PM, and the second from 07:00PM to 10:00PM. Delay of arrival to the hospital is very different in the studies: in 1991, mean delay was 7h05min, whereas in 1998 this delay is reduced to 3h40min. We notice in 1998, two peaks of arrival to the hospital, nearly 3 to 4 hours after the mean stroke peaks: from 02:00PM to 05:00PM and from 10:00PM to 11:30PM. Considering this improvement, we evaluated modification of transport modes in 1998 (vs 1991): 51.65% of patients use ambulance (vs 64.07%), 18.54 calls firemen who assume first care in France (vs 14.37%), 12.58% are transported by reanimation mobile units (vs 15.03%) and 11.92% are transported by relatives and/or taxi (vs 5.88%). Nature and severity of stroke are not related to transport mode neither to the delay of arrival to the hospital in 1998. However, there is difference of delay to arrival, according to the transport mode in 1998, with a mean of 1h46min with firemen and 2h08 with reanimation mobile units who begins medical care and patients conditioning before the transport.

CONCLUSION: Information near practitioners and health care professionals, as well as population, were effective in view to reduce delay of arrival to hospital after stroke. No special mode of transport is needed. With a mean delay of 3h40min, we estimate that a little effort of information is still to continue, to be able to use thrombolysis when possible, but results are already satisfactory.

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PARKINSONISM IN PATIENTS WITH VASCULAR DEMENTIA: CLINICAL, COMPUTED AND POSITRON EMISSION TOMOGRAPHIC FINDINGS. J. De Reuck, B. Siau, D. Decoo, P. Santens, L. Crevits, K. Strijckmans, I. Lemahieu, Ghent University Hospital (Gent, B)

The present study investigates the vascular nature of parkinsonian features in patients with "probable" vascular dementia.

Patients and Methods: Forty patients with vascular dementia were studied with positron emission tomography (PET) using the steady state technique with 15O in order to assess regional cerebral blood flow (rCBF), regional oxygen extraction rate (rOER) and regional metabolic rate for oxygen (rCMRO2) in different brain regions. The findings in 10 patients with (VaDP) were compared to 30 without parkinsonism (VaD).

Results: The clinical and computed tomographic findings in the parkinsonian patients were similar to those described in the literature as "probable" vascular parkinsonism. The PET results showed decreased rCBF and rCMRO2 in the frontal and parietal cortices and in the striatum of the VaDP compared to the VaD group. In the VaDP patients rCBF and rCMRO2 were more decreased and rOER increased in the striatum contralateral to the most affected parkinsonian side.

Conclusion: Our PET findings show that local ischemic changes in the striatum might contribute to parkinsonism in vascular dementia patients.

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DORSOLATERAL THALAMIC INFARCTIONS ABOLISH ACTIVATION OF THE IPSILATERAL VESTIBULAR CORTEX (PET STUDY). M. Dieterich, S. Spiegel, M. Schwaiger, Th. Brandt, Klinikum Grosshadern, University Munich, Technical University Munich (Munich, D)

In an earlier PET study monaural caloric irrigation in healthy volunteers elicited bilateral activation of vestibular cortex areas in the parieto-insular (PIVC) and retroinsular regions. This supports the view that unilateral vestibular input reaches both hemispheres via ipsilateral and contralateral ascending pathways. From monkey studies it is known that vestibular information to the cortex is transduced via the dorsolateral thalamic subnuclei. The aim of this PET activation study was to analyze how acute unilateral infarctions involving the dorsolateral thalamus alter the cortical processing of vestibular information.

Eight right-handed patients with acute infarctions (4 left, 4 right) were studied using the O–15 water-bolus technique and vestibular stimulation by caloric irrigation of the right or left ear (100 ml water at 44°C). Tracer counts were normalized to the global mean, and an automated program was used to transform the image arrays into the stereotactic space of Talairach. Differences between control and activation images as well as averages within subjects and between groups were expressed in z-scores (significance level: $z > 4.0$).

Vestibular stimulation of the ear ipsilateral to the infarction induced no activation of vestibular areas in the infarcted hemisphere and no or only minimal activation within the unaffected hemisphere. Stimulation of the ear contralateral to the infarction caused normal activation patterns within the unaffected hemisphere, and no or minimal activation within the affected hemisphere.

Our PET study shows that contrary to common belief, there is a dominant ipsilateral and a weak contralateral pathway from the vestibular endorgan to the cortex. This finding raises the question of whether bilateral vestibular cortex activation due to monaural vestibular stimulation in healthy individuals is mediated by thalamo-thalamic or cortico-cortical transcallosal connections rather than by bilaterally ascending pathways as hitherto assumed. The dorsolateral thalamus is thus shown to act as a major relay station for the projection to vestibular cortex areas.

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IDENTIFICATION OF SMALL CORTICAL AND SUBCORTICAL ISCHAEMIC TISSUE CHANGE WITH DIFFUSION AND PERFUSION WEIGHTED MRI IN PATIENTS WITH INCONCLUSIVE CRANIAL CT. A. Gass, S. Behrens, J. Hirsch, H. J. Baezner, J. Gaa, M. G. Hennerici, Neurologische Universitätsklinik Klinikum Mannheim (Mannheim, D)

Background: Diagnosis of cerebral ischemia can be impossible without definite confirmation from neuroimaging. Diffusion and perfusion weighted (DW, PW) MRI may be of high value, when CCT and conventional NOEI are inconclusive in regard to the acute clinical deficit. Methods: MRI was performed with a 1.5 T Magnetom VISION, SIEMENS unit: 1. proton density (PD)-, T2-weighted (T,w) (TSE 2620/14–85) 2. T1-weighted (SE 530/12) 3. DW (Echo-planar SE 4000/144, 5 b-values =0_1000S/MM2, diffusion gradients in J orthogonal planes) 4. Perfusion-weighted FIDEP (2000/65/Flip9O, 13 slices, 40 acquisitions, 1:20 min). Eight exemplary case studies with a clinical differential diagnosis of cerebral ischemia with inconclusive CT studies were selected.

Results: DW MRI demonstrated symptomatic lesions < /= 4 mm 0 providing the explanation for the patients' clinical deficits: 1) clinical worsening in a multimorbid patient after almost complete previous MCA infarction due to recurrent ischemic lesions in the small volume of remaining MCA supplied parenchyma; 2) multifocal embolic stroke from a proximal source in a confused patient with multifocal neurological signs, endocarditis was subsequently confirmed; 3) thrombotic stroke in a patient with acute lymphatic leucemia and sudden non-specific clinical worsening with a high white cells (120.000, 85 % eosinophils) count; 4) lateral medullary infarction in a patient with a unexplained headache and slight hemisensory syndrome; 5) recurrent ischemia after previous partial MCA infarction in a patient with clinical worsening and a clinical differential diagnosis of symptomatic focal epilepsy vs. recurrent stroke; 6) small infarction in the head of the caudate in a patient with subcortical vascular encephalopathy and sudden nonspecific worsening of gait and vigilance; 7) infarction in the of the hand knob portion of the left motor cortex in a patient with suspicion of peripheral origin of right hand paresis; 8) small subcortical areas of infarction in the MCA border zone territories after repeated transient sensory symptoms, high grade carotid stenosis was confirmed.

Conclusions: DW and PW MRI can provide important information concerning the underlying pathophysiology facilitating patient management in patients with non-characteristic clinical presentations and negative CCT.

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LACK OF EVIDENCE FOR SPREADING DEPRESSION (SD) IN ACUTE HUMAN STROKE AS MEASURED BY REPETITIVE MAGNETIC RESONANCE DIFFUSION IMAGING. T. Back, J. Hirsch, M. Hennerici, K. Szabo, J. Gaa, A. Gass, Klinikum Grosshadern, Klinikum Mannheim (Munich, Heidelberg, D)

Introduction: Spreading depression (SD)-like periinfarct depolarizations have been demonstrated with diffusion-weighted (DW) MRI in experimental stroke (1). It has been suggested that also in human stroke, SD may be of importance for early enlargement of the ischemic lesions. Methods: To test the hypothesis that SD may play a role in the evolution of human stroke, 10 patients with developing territorial infarction were investigated by imaging of the apparent diffusion coefficient ADC 2–50 h after symptom onset (mean 14.1 h). In each, 20 ADC maps (acquisition time 31 sec, interval 45 sec) were serially measured by echo-planar DW MRI (TR 2200 ms, TE 100 ms, b = 0/160/360/640/1000 s/mm2). Isotropic ADC maps were calculated on a pixel-by-pixel basis by a linear least-squares fit after averaging of the direction-dependent DW images. Data analysis focussed on the spatial and temporal changes in ADC. Postprocessing included structured qualitative analysis, the calculation of subtraction images, serial analysis of regions-of-interest (ROI), positioned in the infarct core and border, and the calculation of hemispheric lesion areas (HLA) depending on various ADC thresholds ranging between 0 and 400, 500, 600, 700 or 800 μm2/s.

Results: Data analysis was unable to disclose any time-dependent changes in ADC which would resemble SD. The ADC reduction was progressively lower in the infarct core (431 ± 104 μm2/s) compared with the infarct border (555 ± 96 μm2/s, $p < 0.001$).

Conclusion: Using a dedicated MRI protocol and postprocessing strategies we were unable to demonstrate a pattern of diffusion changes which would indicate the occurrence of SD in human stroke. The detectability of SD may be different in human and experimental stroke.

Oral session 26

Functional MRI

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RECOVERY OF LANGUAGE FUNCTIONS AFTER A TRANSIENT APHASIA IN MULTIPLE SCLEROSIS. K. Kranada, R. Horowski, Schering AG (Berlin, D)

Aphasia indicates an extensive impairment of cortical function, especially within Broca's area (BA). Small lesions within BA or proximate subcortical lesions are insufficient to cause aphasia and this may explain its apparent scarcity in patients with multiple sclerosis (MS), especially at the onset of the disease. A prerequisite for an MS-induced aphasia is apparently a massive lesion which according to our model could produce enough nitric oxide to block nerve conduction within BA. Transient aphasia reported by a 23 yr. old female became absolute within four days of the MS-onset and subsided ten days later when the recovery of all language functions became almost complete. As the volume of the white-matter lesion remained constant even after the aphasia vanished, we explored the extent of functional recovery in the BA with functional MRI. Comparing regional patterns of neuronal activation within the ≥BA of the patient to the activation patterns of normal subjects failed to show any apparent anomalies. Cortical representation of the mother tongue as well as the spatial representations of later acquired languages seemed to follow typical patterns. Transient loss of cortical function attributed to MS-induced NO thus apparently failed to permanently damage neurones in the BA.

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FMRI AND PET DURING OPTOKINETIC STIMULATION: COMPARISON OF ACTIVATION AND DEACTIVATION PATTERNS. S. Bense, Th. Stephan, T. A. Yousry, M. Schwaiger, M. Dieterich, Th. Brandt, Ludwig-Maximilians-University, Technical University (Munich, D)

In earlier fMRI studies using FLASH sequences during optokinetic stimulation (OKN) we found bilateral activation of the primary visual cortex, motion-sensitive areas in the occipito-temporal cortex (MT/MST), and different ocular motor centers (parietal, frontal, and supplementary eye fields, prefrontal cortex). Additionally, signal changes were observed in the anterior and posterior parts of the insula (1, 2), the human homologue of the vestibular cortex (PIVC). In the only published PET study on OKN, no activation was seen in any region involved in the processing of vestibular information [3]. The aim of our study was to compare the cortical activation and "deactivation" patterns during OKN revealed by 15-O water positron-emission tomography (PET) with blood oxygen level-dependent fMRI. This is relevant, since the significance of relative BOLD MRI signal decreases ("deactivations") is still not clearly understood.

Twenty right-handed healthy volunteers were examined, 10 using 1.5 T MRI (Siemens, Germany) with EPI sequences (20 slices, TR=5sec, voxel size=1.88x1.88x5mm, matrix 128x128), and 10 using a Siemens 951 R/31 PET scanner (CTI, USA) in 3-D mode with an O–15 water-bolus technique (31 slices, voxel size = 2.02x2.02x3.38mm, matrix 128x128). Volumes were realigned, spatially normalized, and smoothed (resulting smoothness ~14mm FWHM in both methods) prior to statistical random effects group analysis (SPM99b, contrasts: OKN-rest, rest-OKN). In both apparatuses, PET and MRI, subjects lay supine and wore prism glasses that allowed horizontal small-field OKN by a rotating drum (visual field 20° x 15°; no self-motion perception).

The activation pattern was similar with both techniques, concentrating on the primary visual cortex V1 (BA 17/18/19), middle temporal and medial superior temporal areas (MT/MST, BA 19/37), and posterior parietal cortex covering BA 7 ($p < 0.001$ uncorrected). The activations in fMRI showed a higher T-value and a larger extent of activation in most of the clusters leading to a confluent cluster in the parietal and occipital cortex areas. Also the pattern of "deactivation" was similar and centered on the posterior insula (fMRI bilaterally: –50/–16/–10, T = 18.66; 54/–20/–2, T = 11.11; PET unilaterally: 40/–12/–2, T = 10.54), and the anterior cingulate gyrus (BA 32/24). Differences between techniques in cluster size and T-value were more evident in the "deactivation" than in the activation contrasts.

This is the first comparative fMRI and PET study of the ocular motor system to show very similar locations of positive as well as negative signal changes. Therefore, it seems justified to interpret negative contrasts in fMRI as "deactivations". However, cautious interpretation is necessary, since there were more voxels for the "deactivations" in fMRI than in PET at the same threshold. (1) Bucher et al., Ann Neurol 44:120–125, 1998, (2) Dieterich et al., Brain 121: 1479–1495, 1998, (3) Galati et al., Exp Brain Res 126: 149–159, 1999.

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A COMBINED PROTON MRS AND SPECT STUDY IN ALS PATIENTS. M. J. Bak, A. Domzal-Stryga, L. Krolicki, H. Kwiecinski, Spcsk (Warsaw, PL)

Many neuroimaging techniques are currently available for in vivo use in patients with amyotrophic lateral sclerosis (ALS). Recently, proton resonance spectroscopy (1H-MRS) has provided a novel means of studying the brain biochemistry of motor neuron disease and the contents of N-acetyl-aspartate (NAA), creatine (Cr) and phosphocreatine (PCr) are being used as a markers of neuronal integrity and viability. The aim of our study was to determine the motor cortex degeneration in ALS by using 1H-MRS and single-photon emission computed tomography (SPECT). We studied 11 patients with El Escorial definite or probable ALS (mean age 44±13 years), and compared them with 8 neurologically normal age-matched control subjects.

Measurements of the metabolic ratios NAA/Cr+PCr, and cerebral blood flow parameters were correlated with clinical findings. Patients with ALS showed a reduction by 19% (P=0.05) in the magnitude of NAA/Cr+PCr metabolite ratios of the motor region when compared with controls. We found that in a subgroup of 7 patients (mean Norris score 99± 13) the NAA/Cr+PCr ratio was reduced to 1.74± 0.07 (P< 0.05). In the other subgroup of patients (n=4) with rapidly progressing severe ALS (mean Norris score 57± 11) the NAA/Cr+PCr was 1.34± 0.08 (P< 0.01). Four of the 11 patients with ALS showed abnormal rCBF with reduced flow in fronto-parietal regions.

We conclude that proton-MRS and SPECT abnormalities in ALS may reflect loss of corticomotoneurons. Our first results suggest that changes in the NAA/Cr+PCr metabolic ratios can be correlated with disease severity.

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CEREBELLAR SIGNAL CHANGES DURING EYE MOVEMENTS: "ACTIVATIONS" AND "DEACTIVATIONS" (FMRI). M. Dieterich, A. Mascolo, Th. Stephan, S. Bense, T. A. Yousry, Th. Brandt, Klinikum Grosshadern, University Munich, University of Pavia (Munich, D; Pavia, I)

Aim of this study was to differentiate between 'activations' and 'deactivations' and further elucidate signal changes first found during optokinetic stimulation (OKN) and saccades in the cerebellar hemispheres, the middle cerebellar peduncle (MCP), and dentate nucleus bilaterally, and medially in the uvula, culmen, and pyramid of the cerebellar vermis (functional magnetic resonance imaging, fMRI, with fast low angle shot, FLASH, pulse sequences).

BOLD signal increases and decreases in 12 healthy right-handed volunteers were analyzed during horizontal small-field OKN and voluntary saccades using EPI sequences (20 slices, TR=5s, voxel size=1.88x1.88x4mm, matrix 128x128). Statistical random effects group analysis and single subject analysis were determined (SPM99b; contrasts: OKN/saccades – rest, rest – OKN/saccades).

Some of the signal changes could be identified as relative BOLD signal decreases (deactivations) localized in different lobuli of the cerebellar hemispheres (9–12/12), the MCP (11–12/12), the superior cerebellar peduncle (6/12), dentate nucleus (7–8/12), and tonsil (6–8/12) bilaterally, and medially in the culmen (4–6/12) and central lobule (7–9/12), but not in structures of the uvula and ocular motor vermis. In contrast, signal increases were concentrated in the flocculus (6–9/12), declive (8–10/12), pyramid (6–8/12), uvula (5–6/12), and culmen (5–6/12) of the vermis. Further activations were seen at different sites of the MCP (8–9/12) and the dentate nucleus (5–6/12). The activation and deactivation patterns were similar in location for OKN and saccades, especially in the hemispheres, but on closer inspection they appeared to differ in size. The size of the activated areas was larger during saccades than during OKN. Some separations were possible in the vermis, the MCP, and dentate nuclei.

Thus, EPI sequences allow the separation of activation and deactivation in the cerebellum as has been shown for the cortex using the same paradigms. Since deactivations were seen mainly in regions without known ocular motor structures, they do not necessarily represent ocular motor function.

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INCREASED THALAMIC ACTIVATION IN PATIENTS WITH COMPLEX REGIONAL PAIN SYNDROME (CRPS): A FMRI STUDY. B. Ertl-Wagner, S. Foerderreuther, C. Helmchen, A. Straube, C. Losert, M. Tiefenbacher, M. Reiser, Department of Radiology, Department of Neurology (Munich, Luebeck, D)

Complex regional pain syndrome (CRPS) is a severe, usually post-traumatic pain syndrome of unknown pathomechanism. Several clinical signs and symptoms (e. g. tremor, central somatosensory deficits) are suggestive of a central nervous system pathomechanism. The thalamus is a critical relay area in acute and chronic nociception. However, since the functional meaning of altered thalamic activation has been controversial in previous chronic pain studies we examined thalamic activation in chronic CRPS patients. We examined four patients with chronic CRPS of the right hand and 10 healthy volunteers with functional magnetic resonance (MR) imaging using a T2*-weighted echo planar imaging sequence on a clinical 1.5 Tesla MR scanner (Magnetom Vision, Siemens, Erlangen, Germany). The patients received thermal noxious stimuli to the finger tips of both the affected and the unaffected hand with a duration of approximately 12 seconds per stimulation. On a visual analogue scale (VAS 0–10, 0=no pain) the stimuli were rated on average 5.9 by stimulation of the affected hand. One patient was additionally examined after a therapeutic sympathetic blockade. A region of interest analysis of the thalamus was performed bilaterally. Only a correlation of over 0.5 was rated as significant. All patients showed a significant increase in activation in the thalamus bilaterally as compared to healthy volunteers, when the affected hand was stimulated ($p < 0.05$), i. e. there was an ipsilateral and contralateral increase in thalamic activity. There was a tendency towards increased activation by stimulation of the unaffected hand, which was not statistically significant, however. One patient was examined twice. After therapeutic sympathetic blockade yielding a 40% subjective improvement of her spontaneous pain this correspondingly showed a significant reduction in activation as compared to the first measurement, even though the activation level was still higher than that of the healthy volunteers. Unlike previous reports about decreased thalamic activation in chronic pain syndromes (Iadarola et al. 1995) our findings suggest a lowering of the thalamic nociceptive threshold in pain processing in CRPS patients as a potential mechanism contributing to the evolution of CRPS. This may be of clinical relevance since these changes could possibly be influenced by therapy.

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HUMAN BRAIN REGIONS INVOLVED IN PASSIVE VISUAL PERCEPTION OF MOTION AND SMOOTH PURSUIT EYE MOVEMENTS. M. A. Rocca, M. Dieterich, T. Stephan, T. A. Yousry, Neuroimaging Research Unit, Neurology, Klinikum Grosshadern (Milan, I; Munich, D)

Several functional magnetic resonance imaging (fMRI) studies have identified MT/V5 as the visual area selectively activated by motion stimulation. Other motion-sensitive areas have been located more anterior or posterior than MT/V5, raising the possibility that there may be different areas in human cortex specialized for processing motion. In this study, we investigated areas involved in motion perception (MP) and/or smooth pursuit (SP) eye movements and the possible role of motion direction and influence of hemispheric dominance on their activity. FMRI was performed in fourteen healthy volunteers using echo-planar imaging (EPI). Stimuli were presented in the scanner through MR-compatible goggles. The following paradigm design was used: MP: subjects had to fixate a blue spot centered on the monitor screen surrounded by white dots moving clockwise or counterclockwise; SP: subjects had to fixate the blue point in the periphery of the screen while moving with the white dots. During the rest phases, the dots were not moving. Image analysis was performed using SPM96. The data were motion corrected, spatially normalized and smoothed with a 10 mm filter prior to statistical analysis. Specific effects were tested by applying appropriate linear contrasts. Significant hemodynamic changes for each contrast were assessed using Z statistical parametric maps. Visual areas V1 and V3a, bilaterally, were activated by all of our stimuli. Additional regions of significant activation were located bilaterally in the parietal lobe, in the region of the intraparietal sulcus. Both paradigms strongly activated an area located in the left and right temporo-parieto-occipital cortex, in the region corresponding to MT/V5 according to earlier studies, with no differences between the two types of paradigm. In each subject, we calculated the differences in MR signal changes and in cluster sizes in right and left MT/V5 in any of the paradigms studied and we did not find any hemispheric dominance or any relationship with the direction of the movement of the dots. During SP paradigm the activation in V1 was larger than in MP and there was also an activation in a frontal region, corresponding to the region of the frontal eye fields (FEF). During MP an additional area located in the temporal lobe was activated. In our study we could identify motion responsive areas detected in previous studies, such as the activation of MT/V5, V3a and the activation in the intraparietal sulcus. We could not confirm differences in the activation of MT/V5 between SP and MP, but other differences were found such as the activation of the FEF in SP and that in the inferior temporal gyrus during MP. These differences confirm the presence of different brain areas specialized for processing motion.

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HETEROGENEITY IN DIFFUSION WEIGHTED IMAGING (DWI) AND PERFUSION IMAGING (PI) ABNORMALITIES IN ACUTE STROKE DIFFERENTIATED BY THRESHOLDING. A. Ritz[1], H. J. Wittsack[1,2], G. Fink[1], F. Wenserski[2], M. Siebler[1], R. J. Seitz[1], U. Moedder[2], H. J. Freund[1], Department of Neurology[1], Institute of Diagnostic Radiology[2], Heinrich-Heine University of Duesseldorf, Germany

Introduction: Diffusion weighted imaging (DWI) and perfusion imaging (PI) nowadays are common tools in acute stroke setting. Regions of PI abnormalities are usually larger than the corresponding regions of DWI abnormalities. Attempts are made to ascribe the region of DWI/PI mismatch to the stroke penumbra while the DWI abnormality is commonly associated with the ischemic core. The aims of this study are (i) to determine volumes of PI as well as DWI abnormalities for stroke patients recruited consecutively over 24 months in the stroke unit (ii) to characterize by thresholding volume fractions which will be recruited in the infarction, and (iii) thereby to find best predictors for the final outcome which are available for the clinician from acute DWI and PI.

Methods: Between January 1998 and January 2000 we studied 52 patients (mean age 62 years) with ischemic stroke in the territory of the middle cerebral artery. Patients received MR imaging in the acute stage (< 24h after symptom onset, mean 7:30h) and after 6 to 12 days. The imaging protocol included a conventional T2-weighted spin echo sequence (T2W), an axial diffusion-weighted single-shot echo planar sequence (DWI), and an axial echo planar perfusion-weighted sequence (PI). Each of the 20 axial DWI slices (thickness 5 mm, interslice gap 1.5 mm) was acquired with b-values of 0 and 1000 sec/mm^2 in all three dimensions of space. For PI (12 slices) 40 T2*-weighted measurements were performed at intervals of 2s. The contrast agent (15 ml Gd-DTPA) was injected at a rate of 5 ml/sec. Maps displaying the time to bolus arrival (time-to-peak, TTP) were used. Contralateral reference values were determined from regions defined by two independent observers. Lesion volumes in the T2W-images after 6 to 12 days were also measured by two independent observers.

Results: 1. The mean lesion volume as determined from DWI and TTP-maps is 37 ± 48 ml and 84 ± 67 ml, respectively. In 85 % of the patients there is a positive mismatch. The mean volume of mismatch in all 52 patients is 46 ± 57 ml.

2. Among the volumes with delay times of 2s, 4s, 6s, 8s, ..., 20s in TTP the one with 6s delay time correlates best with the T2W volume in the follow up (correlation coefficient r = 0.81). In 46 % of the patients the 6s volume in acute TTP is still bigger than the T2W lesion size, in a similar evaluation for 8s and 10s delay times the percentage is reduced to 29 % and 15 %, respectively.

3. A DWI abnormality with DWI-values 23 % larger than the contralateral DWI mean value correlates best with the volume of the chronical lesion as determined from T2W (r = 0.85). The correlation is even higher for measurements performed later than 3h after stroke onset (r = 0.94). For a threshold of 50 % only in 12 % of the patients the T2W lesion is exceeded in volume by the DWI abnormality.

Conclusions: Thresholds in DWI and PI can be helpful in assessing the heterogeneity of DWI and PI abnormalities in acute stroke and in predicting the volume of infarction. DWI as well as PI abnormalities determined in the acute stage comprise brain areas which are not recruited into the T2W lesion volume. The method of thresholding allows to evaluate DWI and PI data by objective means thereby improving the utility of stroke imaging.

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Extrapyramidal disorders – 2

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THE TOPOGRAPHY OF LESIONS OF SECONDARY DYSTONIA. P. Rondot, N. Bathien, P. Tempier, D. Fredy, CHU Bicetre (Le Kremlin-Bicetre, F)

Biological causes provoking dystonia cannot be systematized, with the exception of the small group of dopa-responsive dystonia. Therefore, the pathophysiology of the dystonic syndrome can be approached by considering the site of the lesions.

In 40 cases of uni- or bilateral symptomatic dystonia, this site could be identified with CT Scan or NOEI. Twenty-one were located in the striatum, six in the pallidum, seven in the thalamus and six in the midbrain. Each group is characterized by etiologic and clinical criteria, sometimes associated with abnormal movements. Tumours were eliminated as they do not allow a rigorous topography.

In the striatal group, the most important, dystonia was often accompanied by athetosis or chorcoathetoid abnormal movements. In some cases, in children, lesions were vascular due to impairment of lenticulo-striatal arteries, often following cranial trauma. The pallidal lesions were usually provoked by metabolic or infectious agents. Most thalamic dystonias were of vascular origin, sometimes accompanied by myoclonus. Midbrain lesions were usually vascular with tremor.

Therefore abnormal movements associated with dystonia suggest the site of the lesions. Athetosis occurred after striatal lesions, but not after thalamic or midbrain lesions. It is advisable not to assimilate dystonia and athetosis as both are simultaneously observed only if the lesion is located in the striatum but not in other structures.

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OLFACTORY DYSFUNCTION IN ASYMPTOMATIC SUBJECTS EXHIBITING EXTRAPYRAMIDAL SIGNS WHO LATER DEVELOPPED PARKINSON'S DISEASE. D. Kantor, J. R. Goldsmith, E. Kordysh, Y. O. Herishanu, Soroka University Medical Center Ben-Gurion University of the Negev, Goldman Faculty of Health Sciences (Beer-Sheva, IL)

In a 'cluster' of three kibbutzim (rural communes) in Southern Israel we found a high prevalence of asymptomatic non-PD subjects exhibiting extrapyramidal signs. On five year follow-up we found that 35 % of subjects who exhibited extrapyramidal signs developed more severe signs, 39 % remained constant, and 26 % actually improved (with some subjects no longer displaying any extrapyramidal signs). Approximately 6 % of those with extrapyramidal signs ('preparkinsonism') developed l-Dopa responsive PD. Pesticides and other toxins were implicated in the high incidence of PD and PP in the 'cluster' kibbutzim. Many epidemiological studies have demonstrated that decreased olfactory function is an early sign of idiopathic PD. In the present study we evaluated olfactory function among asymptomatic non-PD subjects who later developed overt PD.

Methods: In 1995 we administered the 40-item, forced choice, microencapsulated odour University of Pennsylvania Smell Identification Test (UPSIT) to PP subjects and matched controls. In the current study we reviewed the results of 10 PP subjects who later developed PD, 7 PP subjects who later demonstrated reduction in the number of sign categories, 4 PP subjects who developed additional extrapyramidal signs, 11 PP subjects who remained stable over the five year time-frame, and 2 PP subjects who reverted to 'healthy' (no extrapyramidal signs). For each of the PP subject groups, we randomly selected controls matched for age, sex, smoking status (current, past, never), and number of pack-years smoked. Statistical analysis was performed on SPSS t tests, regression, correlation, and ANOVA to compare the mean UPSIT score of the subject groups to that of the control groups, as well as the relationship between UPSIT score, demographic data, and measures of PP severity. All participants underwent cognitive function evaluation by Mini Mental Status Examination.

Results: There was a significant ($p < 0.013$) deficit in odour identification among PP subjects who later developed PD, with a mean UPSIT score of 16.5/40 (s. d. of 7.98) compared to a mean of 24.25/40 (6.1) for matched controls. The average age of the subjects was 72.5 years (11.23) compared to 69.3 years (8.77) for the controls ($p < 0.24$). Unlike our findings for the PP subjects who developed PD, there was no significant deficit in olfactory discrimination among the other PP groups as compared to matched non-PP controls.

Conclusions: A subset of asymptomatic preparkinsonism subjects who later developed Parkinson's disease exhibited significant olfactory dysfunction in comparison to two groups of matched controls. This finding suggests that a low UPSIT score may be used as a predictor for the development of PD from PP; it also strengthens the case for the use of pesticide animal models of PD instead of the MPTP model (which displays no olfactory deficit in humans). Further follow-up of non-PP residents of 'cluster' kibbutzim is needed to assess whether olfactory dysfunction predates the development of extrapyramidal signs, and thus to further explicate the possible role of environmental toxins in the etiology of Parkinson's disease.

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LEVODOPA IN PLASMA CORRELATES TO BODY WEIGHT IN PARKINSONIAN SUBJECTS. K. Hellweg, D. Woitalla, W. Kuhn, T. Mueller (Bochum, D)

Antiparkinsonian comedication and/or altered gastrointestinal motility and absorption influence plasma levels of levodopa. Another putative factor may represent body weight. The objective of our study was the relation between body weight and levodopa in plasma of parkinsonian patients.

Methods: We enrolled 26 individuals into this trial on the resorption of levodopa. A standardized protocol was used, which eliminated influencing factors,

such as comedication, activity, food and estimated levodopa plasma levels at fixed timepoints. Results: Levodopa bioavailability (Spearman R = –0.48; p = 0.013) and maximum concentration (Spearman R = –0.50; p = 0.008) in plasma correlated negatively with body weight.

Conclusion: A possibly intensified resorption of levodopa into peripheral body tissue and/or increase of body weight leads to an increase of the levodopa distribution volume may explain our results. Thus severe loss of weight may reduce the need for oral levodopa intake by parkinsonian subjects and may represent a putative factor for the occurrence of dyskinesia in patients without concomitant reduction of oral levodopa administration.

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123-BETA-CIT-SPECT AND PROGRESSION OF PARKINSON'S DISEASE. T. Mueller, E.G Eising, A. Bockisch, S. Peters, D. Woitalla, K. Hellweg, H. Przuntek (Bochum, Essen, D)

Parkinson's disease (PD) is characterized by presynaptic degeneration of nigrostriatal dopaminergic neurons, which may be visualized by single photon emission tomography (SPECT) with a single-head gamma-camera in combination with the radiotracer [123I](1R)–2-beta-carbomethoxy–3-beta-(4-iodophenyl)-tropane ([123I]-beta-CIT). Aim of our study was to monitor progression of PD with [123I]-*-CIT-SPECT and the Unified Parkinson's Disease Rating Scale (UPDRS) in 17 idiopathic parkinsonian patients over a period of two years. Significant differences appeared between ratios of striatum/cerebellum (S/C) (p = 0.02, Wilcoxon test), right S/C (p = 0.02), left S/C (p = 0.03) of [123I]-beta-CIT uptake; UPDRS total score (p = 0.006) and UPDRS motor score (p = 0.02) and the data of these subjects two years ago. [123I]-beta-CIT-SPECT may assess nigrostriatal dopaminergic decline in PD.

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DIFFERENTIAL DIAGNOSIS OF PARKINSONIAN AND ESSENTIAL TREMOR: VALUE OF ACCELEROMETRY. P. H. Kraus, P. Klotz, A. Bigge, J. Andrich, J. Lewe, H. Przuntek, Neurologische Universitätsklinik im St. Josef-Hospital, Psychiatrische Universitätsklinik (Bochum, Essen, D)

Accelerometry is a possibly helpful technique for examination of tremor. Usually frequency and amplitude for measured time series are analysed by use of Fast Fourier Analysis (FFT). Nevertheless frequency of tremor is not specific for differential diagnosis. Therefore also more complicated mathematical approaches for evaluation of e. g. shape of tremor oscillation have been carried out.

We compared accelerometry signals of Parkinsonian tremor (PT, n=32) and Essential tremor (ET, n=15) of the hands.

We found main frequencies of 5.03 Hz (resting) and 5.64 Hz (postural) for PT and of 6.37 Hz (resting) and 6.77 Hz (postural) for ET with a marked overlap of both groups (as expected). It could be observed that PT (75 % right, 79 % left) showed more harmonics in the FFT spectra than ET (36 % right, 22 % left). Change from FFT to spectral analysis improved the selectivity of this parameter ($p < 0.05$). This difference of harmonic peaks between PT and ET is due to a striking deviation of acceleration signal from sinusoidal shape for PT that is not evident in the time series of displacement. These results are in accordance with the hypothesis of a more complex central oscillator in (at least a subgroup of) PT.

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A RANDOMIZED, DOUBLE-BLIND, CROSS-OVER STUDY TO COMPARE THE CLINICAL POTENCIES OF BOTOX® AND DYSPORT® IN CERVICAL DYSTONIA. D. Ranoux, C. Gury, J. Fondarai, JL Mas, M. Zuber, Hopital Sainte-Anne, Sce de Pharmacie, Hopital Sainte-Anne, Statistical Department, Hop Salvator, Sce de Neurologie, Hopital Sainte-Anne (Paris Cedex 14, Marseille, F)

Botulinum toxin type A (BTX-A) is a potent neuromuscular paralysing agent used in various disorders, including dystonia. Two preparations of BTX-A are now commercially available: Dysport® (Ipsen) and Botox® (Allergan). The efficacy and safety of both have been well established, but a strong controversy remains about their respective potencies. Clinical studies have indeed demonstrated that 1 unit of Botox® is not bioequivalent to 1 unit of Dysport®. Different experimental paradigms have been used to find an appropriate conversion factor, but the results were conflicting, the ratio Botox®:Dysport® being found between 1:3 and 1:6. The aim of the study is to determine a more precise conversion factor. Methods. We conducted a monocentric, double-blind, randomized, cross-over study involving 54 patients with cervical dystonia. The patients received successively in a randomized order the following treatments: Botox® at their usual dose (i. e. the dose previously found to be effective), Dysport® at a dose called 1:3 (conversion factor of 3 between Botox® and Dysport® units) and at a dose 1:4 (conversion factor of 4). We assessed the improvement of the Tsui scale and of the TWSTRS-pain scale between baseline and a control visit 1 month after each of the 3 injections. The data of the 3 periods were compared by the ANOVA test. Results. In preliminary results on 41 patients, mean improvement of the Tsui score was 3.26 in Botox group, 4 in Dysport 1:3 group, and 4.6 in Dysport 1:4 group. There was no significant difference between Botox® and Dysport® 1:3 (p=0.22) and Dyport® 1:3 and Dysport® 1:4 (p=0.33) but Dysport® 1:4 was significantly more efficient than Botox® (p=0.04). The differences of TWSTRS-pain scores were non significant when comparing Botox® group to Dysport® 1:3 group (–1.24, p=0.28) and Dysport® 1:3 group to Dysport® 1:4 group (–1.24, p=0.27), but were significant between Botox® group and Dysport® 1:4 group (–2.47, p=0.04). Conclusion. Our results show that one Botox® unit is clinically equivalent to 3 Dysport® units.

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CLINICAL IMPACT OF VARYING ELECTRICAL PARAMETERS IN SUBTHALAMIC NUCLEUS STIMULATION. E. Moro, R. Esselink, J. Xie, V. Fraix, A. L. Benabid, P. Pollak, Joseph Fourier University (Grenoble, F)

Deep brain stimulation is an effective treatment for advanced Parkinson's disease. However, its exact mechanism is still unknown. We have studied the effects on tremor, rigidity and bradykinesia by varying amplitude, pulse width and frequency of subthalamic nucleus (STN) stimulation, in order to optimize the clinical results and to provide clues on the mechanism of stimulation. Twelve parkinsonian patients (8 men and 4 women) with a mean age of 51.9 years and a mean postoperative follow-up of 15 months were evaluated at the most severely affected hemibody after one-night drug withdrawal. Item 20 and 22 of the UPDRS motor part were used to assess tremor and wrist rigidity. Bradykinesia was evaluated by the hand tapping test. Twenty-three combinations for the Itrel II pulse generator (7 patients) and 26 for the Kinetra (5 patients) were randomly studied with a double blind design. Amplitude, pulse width and frequency were changed in two different ways: 1) changing one parameter, which changed the total electrical energy delivered; 2) keeping constant the total energy delivered while two variables were changed. Clinical testing was performed 2 minutes after a new combination was applied. The stimulator was switched off for 1 minute between each combination. The highest voltage (3 V) gave the best results on all three parkinsonian symptoms with a variable energy. The best effect on tremor, rigidity and akinesia was obtained with a frequency equal or more than 130 Hz. A frequency of 185 Hz was better than 130 Hz only for tremor. The best effect on akinesia and tremor was obtained with a pulse width of 120 µsec and of 210 µsec for rigidity. A clinical benefit appeared from a pulse width of 60 µsec whereas no benefit was seen with voltage equal or lower than 1 V and frequency equal or lower than 50 Hz. A frequency of 5 Hz worsened akinesia and tremor. A rate above 100 Hz was necessary to improve tremor with a constant energy delivered, whereas akinesia was improved from 50 Hz and rigidity from 70 Hz. The combination of the higher voltage with the narrower pulse width was the most effective for tremor, rigidity and akinesia. This study confirms that beneficial effects on the parkinsonian triad is obtained only at high frequencies, but some improvement is possible from 50 to 100 Hz. Tremor is better controlled with frequencies up to 185 Hz. The level of voltage appears to be another important parameter which better improves symptoms than the degree of pulse width. We suggest that the neuroinhibition induced by stimulation can only be obtained with high frequencies. The voltage is the critical factor to obtain an adequate volume of electrical field able to inhibit the STN activity.

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GLOBUS PALLIDUS STIMULATION IN PARKINSON'S DISEASE: THE PATIENT'S POINT OF VIEW. F. Lallement, I. Rivier, S. Drapier, Y. Lajat, G. Edan, M. Vérin, CHU Rennes, CHU Nantes, CHU Rennes Hôpital Pontchaillou (Rennes, Nantes, F)

We evaluated by patient self-assessment the improvement of motor fluctuations and quality of life after high frequency stimulation (HFS) of the postero-ventral part of the globus pallidus medialis (GPi) in Parkinson's disease. In the literature, the patient point of view is often neglected to evaluate the efficacy and safety of GPi HFS. Four Parkinsonian patients presenting motor fluctuations with severe and disabling dyskinesias induced by low dose of levodopa and

OFF phenomena, despite optimal pharmacotherapy, were included and received bilateral GPi HFS. The patients estimated their awaked motor situation each 30 minutes during a week. The quality of life was assessed by both the Parkinson's Disease Questionnaire 39 (PDQ 39) and the 36 items Short Form health survey questionnaire (SF 36). The 4 patients were assessed before and 3, 6 and 9 months after surgery. The mean improvement of OFF motor time was 60 %. The disabling OFF states completely disappeared after surgery. The mean ON state slightly increased but 90,4 % of levodopa induced dyskinesias (LID) are controlled by GPi HFS. In both PDQ 39 and SF 36, all the subscores improved at 3rd month, aggravated at 6th month during the depression of 3 patients and finally improved at 9th month. In PDQ 39, the more improved items are the mobility, daily activity, and to be ashamed with the disease. The communication items aggravated in relation with hypophonia in 2 patients and stuttering in 1. All the items of SF 36 improved after surgery and, except the 6th month results, were identical to normal population. From patient point of view, GPi HFS is effective on disabling OFF states and LID in Parkinson's disease. The quality of life is very good after surgery and the sensitivity of the scales used is high to size the frequent postsurgical depression.

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GLOBUS PALLIDUS STIMULATION IN PARKINSON'S DISEASE: THE PHYSICIAN'S POINT OF VIEW. F. Lallement, I. Rivier, S. Drapier, Y. Lajat, G. Edan, M. Vérin, CHU Rennes, CHU Nantes, CHU Rennes Hôpital Pontchaillou (Rennes, Nantes, F)

We evaluated the improvement of motor status assessed by neurologist after high frequency stimulation (HFS) of the postero-ventral part of the globus pallidus medialis (GPi) in Parkinson's disease. The few cases of GPi HFS reported in the literature justify further evaluation of efficacy and safety of this surgical therapy for Parkinson's disease. Four parkinsonian patients presenting motor fluctuations with severe and disabling levodopa induced dyskinesias (LID) and OFF phenomena, despite optimal pharmacotherapy, were studied. Complete UPDRS and neuropsychological battery were assessed before and 3, 6 and 9 months after surgery. Three months after surgery, the mean levodopa test (UPDRS-part III) in the OFF drug condition without stimulation (stimulator switch off 1 hour before) showed an improvement of 23,4 % versus baseline before surgery suggesting a long term effect of HFS. This retentive effect lasts about a week (unexpected stimulators switch off). With stimulation, improvement of the OFF drug condition was better (45 %). One patient had a pure akinesia status, resistant to levodopa, when stimulation was performed on the lower contacts of the electrodes, more anterior than those of the 3 other patients. There was no difference between the pre- and post-operative levodopa test in the ON drug condition. The mean UPDRS part-II in OFF drug condition improved of 58,7 %. There was no difference for the ON drug condition. The mean LID items of UPDRS-part IV improved of 91 %. The mean UPDRS-part IV improved of 64 %. The Hoehn & Yahr and Schwab & England scales were also improved after surgery. Three months after surgery the average weight gain was 8,25 kg. The cognitive evaluation was not modified by GPi HFS. HFS is a promising therapeutic approach for parkinsonians who have disabling LID with low doses of levodopa. We suggest that levodopa resistant akinesia may occur with the most anterior electrodes. The retentive effect after stimulators were switched off is possibly caused by modification of number and sensitivity of the neuromediator receptors (GABA?) but not the dopamine receptors because the levodopa response is not modified by GPi HFS.

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QUALITY OF LIFE AND SUBTHALAMIC NUCLEUS STIMULATION IN PARKINSON'S DISEASE. S. Drapier, I. Rivier, M. Coustans, F. Lallement, Y. Lajat, G. Edan, M. Vérin, CHU Rennes, CHU Nantes, CHU Rennes Hôpital Pontchaillou (Rennes, Nantes, F)

High-frequency stimulation (HFS) is a promising therapeutic approach for patients with severes Parkinson's disease (PD). Therefore, evaluation of patient's quality of life (QoL) after surgery is often neglected in the literature. The purpose of this study is to evaluate by patient self-assessment the improvement of QoL after HFS of subthalamic nucleus (STN) in PD. Six patients with mean age 56,6 years  age range 39–70 presenting a disabled PD with mean duration of disease 14,6 years 12–24 were included and received bilateral HFS of STN. The QoL was assessed by both the Parkinson's Disease Questionnaire 39 (PDQ39) and the Short Form 36 health survey questionnaire (SF36) before and 6 months after surgery. The SF36 measures health on eight dimensions covering functional status, well being and overall evaluation of health. The PDQ39 covers eight dimensions of health that patients with PD report as adversely affected by the disease. Both questionnaires are scored on a scale of 0 to 100. For the PDQ39, lower scores indicate better perceived health status but in the SF36, a high score indicates better perceived health state. The mean pre- and postoperative scores of PDQ39 were respectively estimated at 52,2 % and 33,1 %. The postoperative improvement was 37 %. All the subscores improved at 6th month, mainly mobility (40 %), activities of daily living (40 %), bodily discomfort (42 %) and stigma (40 %). In SF36, the mean preoperative score was estimated at 40,4 % and six months later at 57,4 %. The postoperative improvement was 42 %. Four dimensions showed a significant improvement: physical role (100 %), emotional role (124 %), physical function (115 %) and pain (41 %). From patient point of view, QoL is significantly improved after surgery. Analysis of the sum-score dimensions reveals that the global reduction in perceived impairment was apparent for both the physical and psychosocial dimensions of QoL. These findings demonstrate the functional efficacy of STN HFS in PD and illustrate that subjective quality of life instruments, such as PDQ39 or SF36, offer information on important patient's concerns that are neglected by traditional Parkinson's disease rating scales.

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DYT1 GENERALIZED DYSTONIA: NEUROSURGICAL TREATMENT BY CONTINUOUS BILATERAL STIMULATION OF THE INTERNAL GLOBUS PALLIDUS IN NINE PATIENTS. A. Roubertie, L. Cif, N. Vayssière, S. Tuffery, S. Hemm, M. Claustres, A. Bonafé, P. Frerebeau, B. Echenne, P. Coubes (Montpellier, F)

Primary generalized dystonia is a hyperkinetic movement disorder with poor response to pharmacological treatment. In 1996, electrical stimulation of the internal globus pallidus (GPi) was applied in our department to a first patient with intractable generalized dystonia, with successful results. Twenty-five other patients with severe generalized dystonia, including nine patients with the DYT1 mutation, benefited from this procedure. Here, we report the results of continuous electrical stimulation of the GPi in these nine patients with severe early-onset generalized DYT1 dystonia. The study received the approval of the National ethical committee. All the patients or their parents gave written informed consent. Method. Eight children and one adult with medically intractable generalized dystonia lasting from 1 year to 18 years 3 months underwent deep brain stimulation. Two patients had a severely impaired walking, seven patients were unable to walk or stand, one of them was bedridden before surgery. Mean age at surgery was 14 years 4 months (ranging from 8 years 6 months to 27 years). The two electrodes were stereotactically implanted using Leksell frame and MRI. Targets and trajectories were calculated using SGPR sequences with gadolinium contrast enhancement and a dedicated software. Electrical pulse generators (ITREL II, Medtronic), delivering continuous high frequency stimulation, were implanted in the abdominal region in children. Clinical evaluation was assessed pre- and postoperatively at selected intervals by the Burke-Marsden-Fahn's Dystonia Rating Scale (BMFRS); objective functional abilities and pain were also evaluated. Mean follow-up is 12 months (ranging from 6 to 32 months). Results. The mean value of the BMFDRS was reduced from 56 preoperatively to 6,6 postoperatively, resulting in an average improvement of 88 % of the BMFDRS at last follow-up. This improvement is progressive and durable. Subsequently, functional abilities were progressively improved; eight of the patients managed to walk without aid, all of the nine patients are independent in their daily living activities. Pain rapidly and completely disappeared under stimulation. Withdrawal of the pharmacological treatment was rapidly possible in seven patients, with improvement of their side-effects (drowsiness especially) but without relapse of the dystonic symptoms. No side-effect of the deep brain stimulation was reported. Conclusion. Deep brain stimulation of the GPi is a dramatically effective and durable treatment of young patients with DYT1 generalized dystonia. This new treatment gives rise to a new future for the patients with such a devastating disease.

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BILATERAL EFFECT OF UNILATERAL PALLIDOTOMY IN PARKINSON'S DISEASE – A PILOT STUDY. W. Koszewski, A. Friedman, The Medical University of Warsaw (Warsaw, PL)

Unilateral pallidotomy was performed in 9 patients with bilateral manifestation of idiopathic Parkinson's disease, with severe dyskinesia and fluctuations related to L-DOPA treatment. Stereotactic operation was performed under local anesthesia and macrostimulation control. The side of surgery was determined by the side of onset of the symptoms and perfectly corresponded to the side of the body more affected at the time of the procedure. Radiofrequency permanent lesion was made according to CT and MRI based preoperative target localisation, modified by clinical effect of stimulation assessed intraoperatively. Several parallel trajectories have been used within the pallidum to achieve the best, patient's tailored, clinical effect and possibly the bilateral alleviation of parkinsonian symptoms. Postoperative clinical improvement was assessed with the use of UPDRS and ADL scales and determined by independent observer – a neurologist. In all patients a bilateral improvement of parkinsonian symptomatology was seen immediately after the surgery. However, in the course of time ipsilateral improvement tended to fade in most of patients, but remained per-

manent in some aspects in 4 of them. Permanent bilateral improvement concerned in these 4 patients hypokinesia and rigidity, but not tremor. MRI revealed that in all these 4 patients the lesion was placed more laterally compared to classical postero-ventral pallidotomy target, and involved the posterolateral pallidum and partly the putamen. Authors suggest that the combined pallido-putaminal lesion may have more bilateral influence on hypokinesia and rigidity. Side-effects were seen in 2 patients of the series, and involved hemianopia contralateral to the side of surgery. No psychological postoperative deterioration was found in this series, despite that in one patient some degree of dementia was seen preoperatively.

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Oral session 29

Genetics – 3

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TWO DIFFERENT MUTATIONS AFFECTING THE D393 AMINOACID RESIDUE IN THE ND5 SUBUNIT OF COMPLEX I ARE BOTH ASSOCIATED WITH COMPLEX MITOCHONDRIAL ENCEPHALOMYOPATHIES. C. Antozzi, F. Carrara, E. Lamantea, L. Morandi, Istituto Nazionale Neurologico (Milano, I)

We found two different heteroplasmic mtDNA point mutations affecting the same amino acid residue in the ND5 subunit of complex I. The first mutation, 13513G-> A, leading to a D393N amino-acid change, has already been reported in one case of MELAS and in 4 cases of MELAS/LHON overlap syndromes. At age 39 yrs, our D393N patient had pes cavus, optic atrophy, ataxia of the four limbs, mild distal muscle atrophy, increased deep tendon reflexes, a positive Babinski sign, and bilateral vestibular hyporeflexia. PEVs and BAEPs were both altered. Lactate concentration was normal in the blood but slightly increased in the CSF. Brain MRI showed signs of diffuse supra- and infra-tentorial atrophy. No EEG abnormalities were found. A muscle biopsy disclosed several ragged-red/ragged-blue fibers. Biochemical analysis of the respiratory chain in muscle was normal. The second mutation, 13514A-> G, leading to a D393G amino-acid change, was found in two unrelated patients. The first D393G patient was a 24-year-old female. At age 17 yrs she experienced daily episodes of tingling paresthesias, involving her left hand and arm and lasting several minutes. A CT scan disclosed a hypodense area in the right occipital lobe, confirmed by MRI. At age 18 yrs she experienced sudden visual loss in her left eye with no significant recovery, and repeated episodes of throbbing headache. At age 19 years she experienced visual loss also in her right eye, prickly paresthesias and weakness of the upper left arm lasting several days, and myoclonic jerks of the right limbs. Blood lactate and pyruvate were normal, but CSF examination showed increased lactate levels. MRI scan disclosed several areas of increased signal intensity in the cortico-subcortical regions of cerebral and cerebellar hemispheres. The previously observed occipital lesion was not found. A muscle biopsy showed no morphological alteration except for a slight increase of lipid droplets in some fibers. A partial reduction of the activity of complex I was found in muscle homogenate. The third patient was a 26-year-old male. At the age of 13 years he noticed scintillating scotoma in his right visual field, followed by headache, and several episodes of loss of consciousness. A CT scan disclosed a hypodense occipital lesion. At the age of 18 years he presented intention tremor of the right upper limb, myoclonic jerks of his left face, severe dysarthria, bilateral hearing loss, mild cognitive impairment, slight weakness of upper left limb, and mild diffuse muscle hypotrophy. Lactate concentration in blood and CSF was normal. A muscle biopsy was normal; biochemical examination confirmed a partial reduction of the activity of complex I. The discovery of two different disease-associated mutations affecting the same amino acid residue establishes conclusively their pathogenicity, and demonstrates that the D393 amino-acid position is indeed crucial for function of ND5 subunit and of complex I as a whole.

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RETROSPECTIVE STUDY, OF GENETIC RISK FACTORS IN 22 CASES OF PAEDIATRIC STROKE. A. Ferro, J. Pinto Basto, S. Barreirinho, M. Santos, C. Barbot, E. Costa, A. Sousa, J. Barbot, J. Sequeiros, P. Maciel, Instituto de Biologia Molecular e Celular, Hospital de Crianças Maria Pia (Porto, P)

Paediatric stroke is more common than previously thought. Awareness of aetiological factors is essential because recurrence is significant and sequels are frequent, endangering quality of life. Numerous conditions have been associated with stroke in children, including various inherited and acquired coagulation abnormalities that predispose to thrombotic complications.

The aim of the study is to identify thrombophilic conditions that might be related to the development of stroke in children. A retrospective study performed at Hospital de Crianças Maria Pia identified 22 children with ischaemic stroke in the last 12 years.

Acute hemiplegia was the most common presenting clinical manifestation in 13/20 patients and epileptic seizures were associated with 6/20. CT and/or MRI scans confirmed ischaemic stroke in all patients. Medical and surgical conditions, described as associated to thrombosis, were present in 16/22. Coagulation abnormalities were detected in 10/22, and included factor XII deficiency in 1/22, protein S deficiency in 1/22, activated protein C resistance in 3/22, elevated antiphospholipid antibodies in 8/22 (anticardiolipin antibodies in 4, lupus anticoagulant in 4), hyperhomocysteinemia in 1/20 and elevated lipoprotein (a) in 7/22. All 3 children with APCR were carriers of a factor V Leiden mutation (G1691A). Testing for the C677G mutation in the MTHF reductase gene and the G20210A mutation in prothrombin gene is currently under way in all 22 cases. Medical/surgical risk factors associated with coagulation abnormalities were present in 13/22, medical/surgical risk factors alone were present in 5/22, and in 4/22 no risk factors were detected.

Stroke in children is frequently associated with a combination of predisposing conditions including the presence of one or more risk factors. These findings emphasize the importance of such alterations in the pathogenesis of ischaemic cerebrovascular disease in children.

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CANDIDATE GENES FOR HEREDITARY MOTOR NEURONOPATHY AT 9Q34 (ALS4). A. Abel, C. L. Bennett, I. P. Blair, B. A. Rabin, J. W. Griffin, D. R. Cornblath, K. H. Fischbeck, P. F. Chance, NINDS, National Institutes of Health, Univ. of Washington School of Med., Johns Hopkins Univ. School of Med. (Bethesda, Seattle, Baltimore, USA)

Inherited motor neuron diseases are important clues to the pathogenesis of sporadic amyotrophic lateral sclerosis. Several of these disorders have been mapped to specific loci in the genome, and a subset of the genes, which are important for motor neuron survival, have been identified and functionally characterized. An early-onset motor neuronopathy observed in a large pedigree in Maryland, USA, has been mapped to chromosome 9q34. The candidate region is confined to a 500 kb interval between the markers D9S149 and D9S1198. As part of the former tuberous sclerosis (TSC1) candidate region, this genomic interval has been cloned in a cosmid contig, from which we have initiated a search for the disease gene. Methods: In order to map transcripts to the candidate region, expressed sequence tags (ESTs) from the Genemap99 database were tested through the BLAST search for matches with the previously sequenced cosmids (Whitehead Institute/MIT genome project). ESTs without a match were further screened by polymerase chain reaction (PCR) with unsequenced cosmids covering the remaining candidate region. Positively identified transcripts were checked by Northern blot for expression in brain and spinal cord. Selected candidate genes are being sequenced in patient and control samples to detect disease-specific mutations. Results: Ten genes, 3 Unigene EST clusters, and 4 anonymous ESTs have been identified in the interval between D9S149 and D9S1198. The genes designated GFI1B, ENG, TTF-1, TSC1, CEL and one EST were considered unlikely as candidates on the basis of their function and expression pattern. Mutation screening of several candidate genes, including two transcription factors, has been unrevealing so far. The analysis of six remaining transcripts, most of them EST clusters without any known sequence homology, is under way. Conclusion: Our characterization of the candidate region for an early-onset motor neuronopathy has revealed a high density of transcripts in this segment of 9q. Many of these genes could be excluded, leaving only a few as possible candidates for the disease gene. We are seeking additional families with early-onset, slowly progressive, predominantly distal motor neuronopathy with sparing of bulbar muscles and autosomal dominant inheritance that may be linked to 9q34, in order to facilitate the disease gene identification and confirm the pathogenicity of any mutation we detect. We hope that identification of the gene responsible for this rare disease will provide new insights in the mechanism of motor neuron degeneration.

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EVIDENCE FOR TAP2 GENE AS A SECOND MHC MARKER INDEPENDENT OF HLA-DRB1*1501, IN SUSCEPTIBILITY TO MULTIPLE SCLEROSIS (MS): A FRENCH FAMILY-BASED STUDY. J. Yaouanq, E. Quelvennec, B. Fontaine, M. Alizadeh, M. Clanet, G. Semana, G. Edan, University Hospital Pontchaillou, Hospital La Salpêtrière Paris, Hospital Purpan (Rennes, Paris, Toulouse, F)

Aim. As part of a continuing candidate gene approach, the French MS genetics group found of interest to examine the influence of DRB 1, DQB 1, LMP7 and TAP2 gene polymorphisms in MS susceptibility.

Background. The demonstration of significant linkage between MS and DRBI (1) raises the possibility that any functional gene of the HLA class II region may influence susceptibility to MS. Genes encoding the large multifunctional protease (LMP) and transporter associated peptide (TAP) which are involved in antigen processing and presentation to T lymphocytes are attractive candidates for T-cell mediated auto-immune diseases like MS.

Methods. A total of 154 simplex families of French origin ascertained for the presence of only one MS patient per family with both parents living were included. HLA-DRB1, DQB1, LMP7 and TAP2 genotypes were defined by PCR-based methods. Association with MS was tested by using parental haplotypes as controls, according to the Affected Family-Based Control (AFBAC) method. The transmission/disequilibrium. test (TDT) was used as a test of linkage for MS-associated alleles. Linkage disequilibrium. (LD) between DRB1 and TAP2 was measured by the D' coefficient of Lewontin.

Results. Besides the well known linkage with the DRBI*1501, DQB1*0602 haplotype we found an additional linkage with the DRB 1 * 13 02 allele (TDT: 17 of 21 transmitted from norr-DRBI*1501 parents, $p< 0,01$), specifically with the DRBI*1302, DQBI*0605/0609 haplotype (Il of Il transmitted). LMP7 variants randomly segregated with MS. By contrast, the TAP2–01 allele was linked with MS (TDT: 91 of 149 transmitted, $p< 0.01$), and its predispositional effect was independent froin that of DRBI*1501. Indeed, TAP2*01 showed a marginal LD with DRBI*1501 ($D'= +0.30$, $p< 0.05$) and was associated with a significant increased risk of MS when present on non-DRB1*1501 haplotypes. Furthermore, the strong positive LD of TAP2*01 with DRBI*03 ($D'= +0.80$, $p< 10–3$) and negative LD with DRBI*01 ($D'= –0.87$, $p< 10–5$) could explain the trend towards a predispositional effect of DRB1*03 and protective effect of DRB 1 *0 1 in our population.

Conclusion : We demonstrate that non-DRBI*1501 haplotypes conferring predisposition or protection to MS may rely on the presence or absence of TAP2*01 on the haplotype. Our data enlighten the complex HLA-linked susceptibility to MS with a prominent role of the DRBI*1501, DQB1*0602 haplotype and, in a lesser extent, a significant contribution of TAP2*01 haplotypes negative for DRBI*1501.

(1) Yaouanq et al. *Science* 7, 276: 661.

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SMALL IN-FRAME DELETIONS AND MISSENSE MUTATIONS IN CADASIL:3D MODELS PREDICT MISFOLDING OF NOTCH3 EGF-LIKE REPEAT DOMAINS. M. Dichgans, H. Ludwig, A. Messerschmidt, T. Gasser, Klinikum Grosshadern, Max-Planck-Institut für Biochemie (Munich, D)

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary microangiopathic condition due to mutations within the Notch3 gene. Notch3 encodes a large transmembrane receptor with 34 extracellularly localized epidermal growth factor-like (EGF) repeat domains. Mutations are highly stereotyped and are clustered in two exons coding for the first five EGF-like repeat domains. The mechanisms by which these mutations become pathogenic are unknown.

Purpose: To extend the spectrum of mutations and to evaluate the potential molecular consequences of the observed mutations.

Methods: Seventy-one unrelated CADASIL families were screened for mutations in two exons coding for the first five EGF-like repeat domains. 3D homology models of EGF-like domains were generated on the basis of NMR data from human fibrillin–1.

Results: Mutations were found in 70 % of the families (n=50). Two types of mutations were identified: 48 families (96 %) had missense mutations and 2 families (4 %) had small in-frame deletions. Nine mutations are novel. All mutations, including the two deletions result in the gain or loss of a cysteine residue. As shown by the 3D homology models of EGF-like domains some of the mutations are predicted to destroy sequences involved into beta-strand formation and domain stabilization.

Conclusion: This study extends the spectrum of CADASIL mutations by adding small in-frame deletions. The deletions substantiate the pivotal role of an odd number of cysteine residues within EGF-like repeat domains of Notch3 in the pathogenesis of this disorder. The 3D models predict domain misfolding for a subset of mutations.

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FRIEDREICH'S ATAXIA WITH MINIMAL GAA EXPANSION PRESENTING AS ADULT ONSET SPASTIC ATAXIA. J. Berciano, I. Mateo, C. De Pablos, J.M. Polo, O. Combarros, Univ. Hospital Marques de Valdecilla (Santander, E)

Background: Around a quarter of Friedreich's ataxia (FA) patients, despite being homozygous for GAA expansion within the X25 gene, show atypical clinical presentations. Objective: To describe three brothers with long-term follow-up suffering from FA manifested with spastic ataxia. Historical note: These patients belong to a family with occipital dysplasia (OD) and Chiari 1 malformation previously reported by us (cases 11–6, 11–8 and 11–9 in Coria et al., J Neurol Sci 1983, 62: 147–158). Patients, methods and results: Onset with gait ataxia occurred between 24 and 35 years. Serial examinations have revealed progressive spastic gait, truncal and limb ataxia, dysarthria, nystagmus, hyperreflexia with extensor plantar responses and distal hypopallesthesia. Ages at present vary between 50 and 60 years. The proband (11–9) is chairbound but his brothers are able to walk with support. Leaving aside OD, skeletal malformations are not prominent. All three patients showed subclinical cardiomyopathy with extensive T wave inversion. Electrophysiological studies revealed normal motor and sensory nerve conduction velocities of upper and lower limbs and disturbed central conduction time of both motor and somatosensory pathways. MR imaging demonstrated moderate to severe atrophy of the spinal cord with lesser involvement of the cerebellum. Molecular genetic analysis showed that all three patients were homozygous for the GAA expansion, the shorter expanded allele ranging between 130 and 170 repeats. Four heterozygotic carriers were detected among non-ataxic relatives including one with OD; furthermore and asymptomatic OD patient showed normal genotype. Conclusions: Adult onset spastic ataxia is a distinctive FA phenotype associated with minimal GAA expansion. The present concurrence of OD and FA reflects coincidental cosegregation of two inherited disorders.

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Oral session 30

General Neurology

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CHANGES IN HEADACHE CHARACTERISTICS AFTER A MIGRAINEOUS STROKE. E. Linetsky, R. Leker, T. Ben-Hur, Hadassah – Hebrew University Hospital (Jerusalem, IL)

Objective: To evaluate headache patterns in patients after migrainous stroke (MIGS). Background: MIGS is a rare complication of migraine. Headache characteristics following MIGS and its prognosis are not well documented, as previous studies did not adhere to IHS criteria and included a heterogeneous population. Methods and Patients: We prospectively evaluated 6 patients with MIGS. Patients were selected according to IHS criteria, i. e. the stroke evolved during a typical migraine attack, the neurological deficit lasted over 24 hours and was of similar vascular distribution as the aura. Patients underwent a standard evaluation including CT scan, echocardiography, carotid duplex, transcranial doppler and hypercoagulability tests. They were questioned regarding migraine characteristics, frequency and severity (rated 0–10) before, during and after the stroke. Patients were followed for 24–48 months. Results: All patients (5 women, 1 man; mean age 52.7±11.5, range 39–65 years) had a long history of migraine with aura (31±10 years). Two patients had mild, well-controlled hypertension. All other patients did not have risk factors for stroke (including negative anticardiolipin antibodies). Initial CT was normal in 5 patients and showed a major hemispheric stroke in one. MRI performed in 3 patients showed hyperintense T2 lesions. Five patients fully recovered within a month. A major change in headache frequency and intensity occurred following MIGS: Three patients remained free of migraine attacks during the follow-up period after MIGS and the remaining 3 had significant reduction in frequency of attacks. The mean migraine attack frequency dropped from 2.5±0.8 attacks per month to 0.14±0.15 attacks per month ($p=0.0021$). The patients also reported on significant improvement in severity of headache from severe headaches (7.1±0.8) to mild headaches 1.3±1.5, $p< 0.01$). Conclusions: Headache frequency and severity are significantly reduced after MIGS. Possible explanations include reduced excitability and vasodilatatory reactivity of the affected blood vessels, resulting in decreased nociceptive transmission.

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MRI, MTI AND DWI STUDY OF THE OPTIC NERVE, BRAIN AND CERVICAL CORD FROM PATIENTS WITH LEBER HEREDITARY OPTIC NEUROPATHY. M. Inglese, M. Rovaris, S. Bianchi, G.L. Mancardi, A. Ghezzi, F. Salvi, P. Cortelli, L. La Mantia, M. Filippi, Neuroimaging Research Unit, University of Genoa, Ospedale Sant'Antonio Abate, Ospedale Bellaria, Istituto Neurologico "Carlo Besta", Neuroimaging Research Unit Scientific Institute Ospedale San Raffaele (Milan, Genoa, Gallarate, Bologna, I)

Leber's hereditary optic neuropathy (LHON) is a mitochondrial disease characterized by acute or subacute bilateral loss of central vision. A clinical subtype of LHON (LHON "plus") presents T2-weighted magnetic resonance imaging (MRI) lesions indistinguishable from those of multiple sclerosis (MS). Aims of this study were: a) to assess the severity of optic nerve (ON) damage in patients with (LHON) using conventional (MRI) and magnetization transfer imaging (MTI); b) to assess the presence and extent of microscopic pathology in the brain and cervical cord of these patients using MT ratio (MTR) and mean diffusivity ($\bar{D}$) histogram analysis.

Fourteen LHON patients (10 with isolated ON involvement and 4 with LHON "plus") and 20 age- and sex-matched controls were studied. The following sequences were acquired: a) brain: dual-echo, T1-weighted, MT and echo planar diffusion-weighted (DW); b) ON: T1-weighted and MT; c) cervical cord: fast-short tau inversion recovery (STIR) and MT. We measured the ON volumes and average MTR at the level of the chiasm, the intracranial (ICR), intracanalicular (ICL) and intraocular (IO) tracts. MTR and $\bar{D}$ histograms of the normal-appearing brain tissue (NABT) and MTR histograms of the whole cervical cord tissue were obtained from all patients and controls. For each histogram, the peak height, the peak location, the average MTR and the average $\bar{D}$ were analysed.

The mean values of ON volumes and MTR at the level of the chiasm and the anterior tracts were significantly lower in LHON patients than in healthy controls (p values ranging from 0.002 to 0.001), with the exception of ICR tract MTR. ON volumes and MTR values were lower in LHON "plus" than in LHON patients. All the four patients with LHON "plus" showed brain and cervical cord MRI lesions. Mean NABT-MTR ($p = 0.02$) and peak height ($p = 0.024$) were significantly lower in LHON patients than in controls whereas there was no significant difference for NABT peak location and cervical cord MTR histogram-derived measures. Average $\bar{D}$ was lower ($p = 0.04$) in LHON patients than in controls. Patients with LHON "plus" had lower values of all NABT and cord MTR histogram metrics than those with LHON.

It is feasible to quantify tissue loss in the ON of LHON patients using ON size measurements and MTR. These changes seem to be more pronounced in patients with LHON "plus" than in those with LHON. MTR and $\bar{D}$ histogram analysis suggest that microscopic brain damage occurs in LHON and that it is more severe in the MS-like form of this disease. In patients with LHON "plus", the cord pathology is confined to macroscopic lesions.

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HEADACHE IN THE EMERGENCY DEPARTMENT—A PROSPECTIVE OBSERVATIONAL STUDY. L. B. Morgenstern, J. C. Huber, H. Luna-Gonzales, S. Shaw, J. C. Grotta, University of Texas, Houston (Houston, Texas, USA)

Clinicians employ a variety of therapies for patients presenting to the emergency department for severe headache with little information supporting which agent to choose. Goal: To perform a prospective observational study to determine the demographics of patients presenting to a busy urban U. S. emergency department for severe headache, and to study the efficacy of specific therapies for severe headache presenting to the emergency department. Methods: We screened all 38,730 patients presenting to Hermann Hospital, Houston Texas, USA, during a 16 month period and found 440 (1.1%) presenting with a chief complaint of severe headache. We systematically reviewed the demographic, clinical and treatment data for each patient. This abstract report results on the first 250 patients; data on the full cohort of 440 will be available for presentation at the meeting. Response to medication for headache relief was categorized as resolved, improved, unchanged or worsened. Results: The median age was 36 years, 76% were women. 51% were African American, 29% non Hispanic white and 18% Hispanic. 30% had a previous diagnosis of migraine, 22% had hypertension, 3% diabetes and 17% were current smokers. Non Hispanic whites were more commonly discharged with a diagnosis of migraine than African Americans ($p=0.004$) or Hispanics ($p=0.094$). Photophobia was seen in 25%, stiff neck in 6%, nausea/emesis in 38%, blurred vision in 10%. The average time spent in the emergency department was 240 minutes. 37% of patients received anti-emetics (prochlorperazine, metoclopramide or promethazine), 24% received ketorolac, 13% acetaminophen and 11% narcotics. The most effective therapy was a combination of IM ketorolac and anti-emetics which led to complete resolution in 53% and improvement in an additional 44%. The combination of anti-emetics and rigorous hydration led to resolution in 48% and improvement in an additional 38%. When used alone anti-emetics led to resolution of headache symptoms in 39% and improvement in 58%, and ketorolac led to resolution in 36% and improvement in 58%. Narcotics had the poorest performance. When used alone or in combination resolution was found in 24% and improvement in 62%. Acetaminophen and ibuprofen had mixed results. Sumitriptan was used just four times and ergots were not employed. Conclusions: Patients presenting to the emergency department with severe headache are commonly young women. Patients with headache spend a long time in the emergency department and receive a variety of treatments and treatment combinations. Anti-emetics and ketorolac seem especially effective in relieving headache pain. A clinical trial may follow from this data so that a more evidence-based approach can be utilized to treat severe headache patients in the emergency department.

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CLINICAL HETEROGENEITY IN FAMILY MEMBERS OF A PATIENT WITH ACETAZOLAMIDE-RESPONSIVE EPISODIC ATAXIA. C. Gordon, N. Gadoth (Kfar Saba, IL)

Familial episodic atàxia with interictal nystagmus (EA–2) is an uncommon neurologic disorder which responds to acetazolamide treatment. Goals: To report clinical heterogeneity and oculographic features in a family of an unusual severe case of episodic ataxia with interictal ocular movement abnormalities who dramatically responded to acetazolamide. Methods and Results: A complete neuro-otological examination was performed in a 24-year-old woman referred for recurrent episodes of severe vertigo, ataxia, nausea and vomiting starting at the age of 2 years. Each episode lasted several hours and occurred 5 to 10 times a week. Her college studies were interrupted by frequent absence periods and she was found unsuitable to serve the obligatory Israeli army service. She was unable to keep a stable job. Paroxysmal vertigo of childhood, basilar migraine, epilepsy and psychogenic vertigo were some of the diagnoses considered. A variety of drugs and extended psychological treatment were ineffective. Her present ictal and interictal examination showed a slight gaze-evoked nystagmus, impaired pursuit with frequent catch-up saccades, impaired optokinetic nystagmus and impaired fixation-suppression of the vestibulo-ocular reflex. She had severe truncal ataxia during the attacks with no additional cerebellar signs. The rest of her neurological examination was normal. She was started on acetazolamide 250 mg b. i. d. with excellent results. On 6 months follow-up, she is totally free from attacks and is working as a janitor four hours a day. Her mother who is totally asymptomatic has identical ocular movement abnormalities. Her father and two asymptomatic sisters have normal neuro-otological examination. A maternal aunt has recurrent episodes of dizziness and headaches diagnosed as migraine. A search for mutations in the CACNA1A gene is now in progress. Conclusions: The diagnosis of acetazolamide-responsive ataxia could easily be missed in the lack of family history and the presence of only mild findings on formal neurological examination. Careful examination of asymptomatic family members and a therapeutic trial with acetazolamide are recommended in patients with long lasting history of paroxysmal vertigo and ataxia.

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MRI FINDINGS IN CHILDREN AFFECTED BY LEIGH'S DISEASE WITH SURF–1 MUTATIONS. M. Savoirado, L. Farina, L. D'Incerti, A. Costa, M. Zeviani, G. Uziel, Ist. Naz. Neurologico C. Besta (Milano, I)

Purpose: Magnetic resonance imaging (MRI) studies of 17 children affected by Leigh disease (LD) were reviewed to possibly identify specific features that might differentiate patients with SURF–1 mutations (LD-SURF–1) from patients with LD due to other genetic conditions (LD-not SURF–1).

Patients and methods: The 8 patients with LD-SURF–1 (4 males and 4 females) were aged between 1 and 10 years. Only the oldest patient, with the mildest clinical course, was examined twice, at age 4 and 10. The other group of LD patients (9 cases) included 4 patients with cytochrome-c-oxidase (COX) deficiency not SURF–1, 4 with other respiratory chain defects (2 of complex I, 1 of complex III, 1 with multiple complexes defects), and 1 in whom the biochemical defect remained undefined. Five were males, 4 females, with age ranging from 8 months to 9 years. Four patients were examined twice.

MRI studies had been performed with different units and various techniques, but all included T1-, proton density and T2-weighted images that, at least in one plain, covered the whole brain. No post-contrast studies were obtained. Results: The lesions were characterized by high signal intensity in proton density and T2-weighted images. The lesions were less evident (as hypointensity) in T1-weighted images. LD-SURF–1: All 8 patients had lesions in the brainstem: 8 in the medulla oblongata, 7 in the pontine tegmentum, 8 in the midbrain. Six patients had lesions in the cerebellum, located in dentate nuclei with different involvement of the surrounding white matter. Only 2 patients had lesions of the lenticular nucleus that involved the posterior part of the putamen. All 8 patients had lesions in the subthalamic nuclei. LD-not SURF–1: 5 patients

had lesions in the brainstem, with minimal or mild evidence except in 1 case: 3 in the medulla oblongata, 4 in the pontine tegmentum, 3 in the midbrain. Four patients had lesions in the cerebellum, located in the dentate nuclei with different involvement of the white matter. Three patients had lesions in the thalami; 7 in the basal ganglia (7 in the putamina, 3 in the pallida, 4 in the caudate nuclei). Only 1 patient (with COX deficiency) had mild abnormalities in the subthalamic nuclei. Conclusions: The MRI pattern in our series of LD-SURF–1 patients is very uniform with constant involvement of the brainstem and subthalamic nuclei, while putaminal involvement is rare. Involvement of the basal ganglia is the most common finding in LD-not SURF–1 patients. Symmetric lesions in the subthalamic nuclei, very rarely seen in other mitochondrial disorders, have been thought to be a hallmark of COX deficiency. With this series, we demonstrate that lesions in the subthalamic nuclei particularly occur in LD patients with COX deficiency associated with SURF–1 mutations.

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PREDICTORS OF LONG-TERM NEUROPSYCHOLOGICAL DEFICITS IN BACTERIAL MENINGITIS (BM). S. Merkelbach, H. Sittinger, C. Kölmel, M. Müller, University Hospital (Homburg / Saar, D)

Background: The long-term prognosis in BM is frequently complicated by lasting neuropsychological disturbances. We investigated, whether clinical conditions in the acute stage may be useful predictors of neuropsychological deficits.

Patients and methods: 24 patients (15 men, 9 women, mean age 51±18 years) were investigated 33±12 months after acute BM neuropsychologically using Wechsler Intelligence Test (WIP), Wechsler Memory Scale (WMS), Number-Connection-Test (ZVT), Aufmerksamkeit-Belastungstest (d2), and Benton Test (BVRT). Results were compared to healthy controls and related to clinical conditions in the acute stage of BM.

Results: Patients performed most neuropsychological tests significantly worse as compared to controls. Patients with pneumococcal meningitis performed WIP (subtests 2,3), and WMS (subtests 6,7) significantly worse than patients with different pathogens. Age was significantly correlated with BVRT, WIP (subtest 4), WMS (subtests 3,4,6,7), and ZVT. Neuropsychological deficits were not related to initial pleocytosis or total protein content, the clinical condition (scored as Glasgow coma score), and especially decreased consciousness on admission. However, when the clinical condition on days 3–14 is considered, an increasing number of clinical scores were significantly correlated with test results (predominantly assessing memory).

Conclusion: Neuropsychological outcome after bacterial meningitis is determined by causative pathogens. On admission, the clinical severity of BM does not allow any prediction of neuropsychological outcome. During the following acute stage, the clinical condition overweighs the influence of age (using multivariate analysis). Our results emphasize the relevance of BM's acute stage course and complications for long term outcome.

Oral sessi<on 31

Multiple Sclerosis – 5

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MOLECULAR MECHANISMS OF LYMPHOCYTE-ENDOTHELIUM INTERACTIONS IN BRAIN MICROCIRCULATION. L. Piccio, C. Giagulli, B. Rossi, C. Magagna, C. Laudanna, G. Scarlato, E. Scarpini, G. Constantin, University of Verona, University of Milan (Verona, Milan, I)

Lymphocyte migration into the brain represents a critical moment in the pathogenesis of multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE). Current data proposed a multistep model for lymphocyte migration through endothelium involving: 1) tethering and rolling; 2) lymphocyte activation mediated by a pertussis toxin (PTX)-sensitive Galpha-i protein signaling pathway; 3) activation-dependent arrest; 4) diapedesis. Aspects of this model have been confirmed in lymphoid organs, but the interactions between lymphocytes and brain endothelium in situ have not yet been characterized. OBJECTIVE: The study proposes to identify the molecular mechanisms controlling the interactions between activated lymphocytes and endothelium in situ in brain microcirculation by intravital microscopy. METHODS: PLP139–151 T cell lines and concanavalin A activated lymphocytes were fluorescent labeled and injected into SJL mice through an incannulated carotid artery. Intravital microscopy observations were made through the intact skull by using an immersion objective with long focal distance, epifluorescence microscopy, and a silicon-intensified target camera. RESULTS: In situ analyses revealed that lymphocytes interact with brain endothelium by combinatorial events: tethering and rolling and firm (> =30sec) or transient arrest. L-selectin is not responsible for rolling of activated lymphocytes, while alpha–4 integrins participates in both rolling and arrest. Beta–1 integrin participates in a less extent than alpha–4 to lymphocyte stable adhesion. The involvement of other adhesion molecules will be discussed. Integrin-dependent arrest is not abolished by PTX, implicating that a Galpha-i-protein-linked signaling is not required. Moreover, tyrphostin AG490, a Jak–2 kinase inhibitor, blocks lymphocyte arrest but has no effect on rolling. CONCLUSIONS: The results suggest that alpha–4 integrins play a central role in lymphocyte-brain endothelium interactions, and signaling pathways involving tyrosine kinases are required for integrin-dependent arrest. Our findings show important differences from previously described adhesion cascades, and may help to define new pharmaceutical targets in MS/EAE based on inhibition of signaling mechanisms involved in lymphocyte recruitment into the brain.

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MICROGLIA VERSUS MACROPHAGE EFFECTS ON LESION DEVELOPMENT IN MYELIN OLIGODENDROCYTE GLYCOPROTEIN (MOG) INDUCED EAE. MK Storch, R Weissert, R Birnbacher, K. de Graaf, E. Wallström, A. Stefferl, C. Linington, T. Olsson, H. Lassmann (Graz, A; Tuebingen, D; Vienna, A; Stockholm, S; Munich, D)

The extent of activated microglia and macrophage contribution in autoimmune experimental encephalomyelitis as well as in human inflammatory demyelinating disease remains up to now poorly defined. We provide for the first time a detailed quantitative analysis of microglia/macrophage participation in chronic EAE lesions and demonstrate the consequences of activation of different effector cell populations. Myelin oligodendrocyte glycoprotein induced experimental autoimmune encephalomyelitis (MOG-EAE) is a chronic inflammatory demyelinating disease, in which demyelination is accomplished by the interaction of antibodies and complement with activated macrophages. In the rat species, there are strong MHC haplotype effects on clinical course and lesional pathology on MOG-EAE, in part mapping to the class II region. We here determined the role of macrophages and microglia for demyelination and tissue damage in relation to different regions of the MHC complex by using intra MHC recombinant rat strains between the RT1a and u haplotype on the EAE permissive Lewis background. Activated microglia/macrophages in these animals were identified by their expression of ED1 and acute inflammatory protein–2 (AIP–2) as well as their phenotype determined according to morphological criteria. In most rat strains demyelinating lesions in the white matter were dominated by effector cells with macrophage phenotype, whereas in gray matter lesions a high proportion of cells with microglia morphology was found. Overall the macrophage response was more pronounced in active stages of demyelination, whereas in inactive stages higher proportions of microglia were present. In two rat strains the demyelinating lesions were dominated by microglia. In these strains a prominent expression of AIP–2 in microglia was found in and around inflammatory demyelinating lesions, which was absent in strains with macrophage dominated lesions. Both, the class II and class Ib region (telomeric to the class III region) regulated the macrophage/microglia phenotype. RT1 a in the class II region correlated to a macrophage predominance, resulting in demyelinated lesions with a high degree of axonal damage. RT1 u in the Class Ib region was associated with a microglia predominance with high AIP–2 expression and demyelinated plaques with little axonal loss. Thus, 1) MOG induced EAE in these different strains provide excellent tools to compare the effect of microglia compared to macrophage activation in inflammatory demyelinating CNS disease and 2) we document for the first time a non Class II gene region, telomeric, MHC haplotype influence on an MS-like experimental disease.

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APOE GENOTYPE IS A MAJOR PREDICTOR OF PROGRESSION IN MULTIPLE SCLEROSIS. J. Chapman, S. Vinokurov, A. Achiron, D. M. Karusis, D. M. Michaelson, M. Birnbaum, A. D. Korczyn, Tel Aviv University, Hadasah Medical Center, Hebrew U (Tel Aviv, Jerusalem, IL)

The APOE gene codes for apolipoprotein E which has been implicated in CNS repair and inflammation. We have recently reported that the APOE epsilon–4 allele is associated with progression of disability in a 2 year follow up of multiple sclerosis (MS) patients. In the present study we extended these findings by examining a larger group of patients followed for up to 40 years.

DESIGN/METHODS: In the present study, 213 consecutive patients from 3 MS clinics with clinically definite MS were genotyped for the APOE epsilon–4 carrier state. Groups of patients with (n=43) and without (n=170) APOE epsilon–4 alleles were compared for latency to expanded disability status scale (EDSS) scores of 4.0 and 6.0 by Kaplan-Meier survival analysis. RESULTS: The APOE e4 allele frequency in the MS patients (0.13) was similar to the general Israeli population. The two groups of patients did not differ significantly in

gender distribution or duration of disease although there was a 4 year earlier onset of disease in the APOE epsilon–4 group (p=0.015). There was a significant effect of APOE genotype on the latency to reach EDSS 4 and 6 (p< 0.0001 by Log Rank test). Median latencies were shorter by 12 years in the APOE e4 group for either outcome. These results were similarly significant when adjusted for gender though the effect of the epsilon–4 allele seemed more pronounced in males.

CONCLUSIONS: The APOE epsilon–4 allele is associated with significantly faster progression of disability in MS. This is the first genetic factor to be identified with a major impact on the progression of disease. We suggest that APOE genotype be considered as significant cofactor in the analysis of clinical and therapeutic trials in MS, especially those with long term follow up.

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ELEVATED LEVELS OF CHLAMYDIA PNEUMONIAE SPECIFIC IMMUNOGLOBULINS IN A SUBGROUP OF PATIENTS WITH MULTIPLE SCLEROSIS. JDE. Parratt, R. Tavensdale, D. Parratt, R. Swingler, J. O'Riordan, Tayside University Hospitals Trust (Dundee, UK)

Chlamydia pneumoniae is an obligate intracellular bacterial pathogen. Recently, in the U. S. A., the organism was identified frequently in the cerebrospinal fluid (CSF) of patients with Multiple Sclerosis (MS). We attempted to verify these results and identify whether infection is common in MS patients in Scotland by conducting a retrospective analysis of CSF. Stored samples from 15 patients with MS and 5 with other neurological diseases were examined for evidence of the bacteria. Patients were identified by the presence of oligoclonal bands in the CSF and a diagnosis of MS was confirmed, according to Poser's criteria, after examination of their medical records. We examined the CSF for evidence of Chlamydia pneumoniae specific IgA and IgG immunoglobulins using a commercial enzyme linked immunoassay (ELISA). Chlamydia pneumoniae specific IgA was not identified in the CSF of patients or controls (mean optical density (OD) patients 0.275; controls 0.233; Labsystems positive control 1.522). There was a trend towards higher levels of specific IgG antibodies in MS patients (mean OD 0.418) over controls (mean OD 0.229, p = 0.10) and in a subgroup of MS patients there were very high levels of IgG (mean OD 1.306). Thus, we proceeded to try and identify Chlamydia pneumoniae antigen in the CSF of patients and controls using a specific polyclonal antibody and alkaline phosphatase label. Chlamydia pneumoniae antigen was not identified in either group (mean OD patients; 0.970; controls 0.984; commercial antigen (Savyon 1: 50) 1.762). Conclusion. There is evidence that Chlamydia pnenmoniae infection occurs in a subgroup of patients with MS.

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SPECIFIC TH2 CELLS ARE PRESENT IN THE CENTRAL NERVOUS SYSTEM OF MICE PROTECTED AGAINST EAE BY COPOLYMER 1. R. Aharoni, D. Teitelbaum, M. Sela, R. Arnon, The Weizmann Institute of Science (Rehovot, IL)

Copolymer 1 (Copl, CopaxonJ, glatiramer acetate) suppresses experimental autoimmune encephalomyelitis (EAE), reduces relapse rate and slows progression of disability in multiple sclerosis (MS). We previously demonstrated that Copl is a potent inducer of Th2 suppressor cells. However this reactivity was demonstrated in the periphery i. e. spleens and lymph nodes, and not in the organ in which the pathological process of EAE and MS occur. In this study we attempted to demonstrate that Copl specific Th2 cells are present in the central nervous system (CNS). For this aim we isolated T cells from the CNS of mice rendered unresponsive to EAE by injection of Copl, and studied their proliferation and cytokine responses, in comparison to cells isolated from CNS of mice immunized with lysozyme. The level of the inflammatory cytokine INF-g secreted in response to the encephalitogen myelin basic protein (MBP) was reduced by half, while the antinflammatory cytokine IL–10 was elevated, in brains of EAE induced mice that were treated with Copl. Lymphocytes isolated from brains of Copl treated mice demonstrated a specific response to Copl by proliferation and Th2 cytokine secretion. The cross reactivity of Copl with the autoantigen MBP on the level of Th2 cytokine secretion demonstrated before in T cells from the periphery, was found also in cells originated in the CNS. Highly reactive Copl specific T cell lines that secrete high amounts of IL–4, IL–5, IL–6, IL–10 and TGF-B in response to Cop 1 and cross react with MBP, were established from both brains and spinal cords of mice treated with Copl, with or without EAE induction. In contrast, no reactivity to lysozyme could be obtained in the CNS of mice after injection of lysozyme by either proliferation or cytokine secretion. This lack of response to lysozyme was observed in CNS isolated cells and was confirmed by the inability to grow lysozyme specific T cell lines from the CNS of lysozyme treated mice. Thus, while lysozyme specific cells are absent in the CNS, Copl induced cells accumulate in the CNS, where they can be stimulated in situ by MBP to secrete Th2 anti-inflammatory cytokines, and thereby exert therapeutic effect in the diseased organ.

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T2 LESION LOAD IN MULTIPLE SCLEROSIS USING STANDARD 2D-FSE AND 3D-FFLAIR: RELATIONSHIP TO DISABILITY. O. Ciccarelli, P. A. Brex, K. A. Miszkiel, A. J. Thompson, D. H. Miller, NMR Research Unit, UCL (London, UK)

Imaging with three-dimensional fast fluid attenuated inversion recovery (3D-fFLAIR) has been shown to detect larger cerebral T2 lesion loads (T2LL) in Multiple Sclerosis (MS) than imaging using a standard fast spin-echo (FSE) sequence with 5mm contiguous slices. The aim of this study was to compare the lesion loads derived from these two sequences and to determine if the use of 3D-fFLAIR improved the correlation between T2LL and disability. Methods: 33 MS patients who had been followed prospectively since their initial presentation with a clinically isolated syndrome were studied with both FSE [TR 2000ms, TE 19/95, 5mm contiguous slices] and 3D-fFLAIR [TR 4600ms, TE 136.8ms, TI 15ms, 1.5mm slices]. A clinical assessment to determine the disease course and disability, as measured on the expanded disability status scale (EDSS), was also performed. T2LL were determined using a semi-automated local thresholding technique. Results: The mean age of the patients was 46 years (range 35–62 years). Median disease duration was 13.5 years (range 12.5–16.5 years). There were 20 women and 13 men. Three of the patients had clinically probable and 30 clinically definite MS (24 relapsing remitting and 6 secondary progressive). The median EDSS score was 2 (range 0–8). The median T2LL was 21% higher on 3D-fFLAIR images than on the FSE images (3D-fFLAIR: median 11.8cm^3, range 0.7–65cm^3, FSE: median 9.8cm^3, range 0.5–52.4cm^3; $p < 0.001$). There was a strong correlation between the T2LL derived using each sequence ($r = 0.99$, $p < 0.001$). The T2LL from both sequences correlated with EDSS (3D-fFLAIR: $r = 0.55$, $p = 0.001$; FSE: $r = 0.56$, $p = 0.001$). Conclusions: Although 3D-fFLAIR did detect a substantially higher T2LL than the FSE sequence, the T2LL derived using each sequence very strongly correlated with each other and both correlated equally with disability. The robust correlation between T2LL and EDSS most likely reflects the prospective nature of the cohort studied which ensured homogeneity with regard to disease duration.

Oral session 32

Multiple Sclerosis – 6

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THE RELATIVE CONTRIBUTIONS OF BRAIN AND CERVICAL CORD PATHOLOGY TO MS DISABILITY: A STUDY WITH MTR HISTOGRAM ANALYSIS. G. Iannucci, M. Rovaris, M. Bozzali, G. Santuccio, M. P. Sormani, M. Rodegher, G. Comi, M. Filippi, Neuroimaging Research Unit, Clinical Trials Unit, IRCCS HSR, Neuroimaging Research Unit Scientific Institute Ospedale San Raffaele (Milan, I)

Magnetization transfer (MT) imaging is sensitive to the most destructive aspects of multiple sclerosis (MS) pathology. MT ratio (MTR) histogram analysis encompasses the macro- and the microscopic lesion burdens. We assessed a) the correlations between MTR histogram-derived measures of the brain and the cervical cord from patients with different MS phenotypes and b) the correlation between these metrics and clinical disability. We studied 77 MS patients (40 relapsing-remitting [RR], 28 secondary progressive [SP] and 9 primary progressive [PP]). For the brain, we obtained dual-echo, T1-weighted and gradient-echo (GE) scans (with and without an MT saturation pulse). For the cervical cord, we obtained fast-short tau inversion recovery (STIR) and GE scans (with and without an MT saturation pulse). Brain T2- and T1-weighted lesion volumes (LV) were measured. The number and length of cord lesions on fast-STIR scans were assessed. MTR maps were created from GE images and MTR histograms of the entire brain and cervical cord were obtained. Brain T2 LV, number and size of cord lesions were significantly higher and brain MTR histogram peak location was significantly lower in SPMS than in RRMS and PPMS patients. Cord MTR histogram peak location was also significantly lower in SPMS than in RRMS patients. The univariate correlations between MTR histogram-derived metrics obtained from the brain and the cervical cord were all not significant, with the exception of that between average brain MTR and cord MTR histogram peak location. On a multivariable analysis, both brain T2 LV and cord MTR histogram peak location fitted two models significantly separating patients with RRMS and SPMS and MS patients with and without locomotor disability. This study shows that the extent and severity of tissue damage in the brain and cervical cord are both relevant to determine disability in MS and that the assessment of brain and cord pathology provides complementary information.

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CYTOTOXIC T-LYMPHOCYTE ANTIGEN 4 (CTLA4) EXON 1 DIMORPHISM IN MULTIPLE SCLEROSIS. A. Ponath, M. Mäurer, N. Kruse, K. V. Toyka, P. Rieckmann, Department of Neurology (Würzburg, D)

The cytotoxic T-lymphocyte antigen 4 (CTLA4) is an important modifier of T-cell activation with downregulatory properties upon B7 engagement. As dysregulated T-cell activation plays an important role in the pathogenesis of multiple sclerosis (MS) CTLA4 is a possible candidate gene in MS. We investigated whether a functional A/G substitution in exon 1 (+49) is associated with disease susceptibility, disease course and severity. Patients and Methods: We investigated genomic DNA of 247 MS patients (relapsing-remitting MS n=154, secondary-progressive MS n=72, chronic progressive MS n=17) and 131 controls with allelic discrimination PCR (AD-PCR) capable to detect a single base pair exchange. Disability was assessed by using Kurtzke's Expanded Disability Status Scale (EDSS), the rate of accumulation of neurological disability was expressed by the progression index (PI). In addition, the progression to important clinical landmarks EDSS 3.5 and EDSS 6 was recorded. Results: We found no differences in the allelic distribution of the G49 allele between the MS patients and the control group (57.6% vs 59.5%). However, the G49 allele occurred in a significantly higher percentage in patients with chronic progressive MS than in patients with bout onset of the disease (82.3% vs 56%, $p < 0.05$). Analysis of the PI did not reveal any statistically significant difference between the groups with the different exon 1 (+49) genotypes ($p > 0.05$). In addition we were unable to detect any difference for the progression to the EDSS landmarks 3.5 and 6. Conclusion: Our results suggest that dysregulation of CTLA4 driven downregulation of T-cell activation due to a genetic dimorphism in exon 1 could be involved in the pathogenesis of different MS disease subtypes.

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PROVIGIL® (MODAFINIL) FOR THE TREATMENT OF FATIGUE IN PATIENTS WITH MULTIPLE SCLEROSIS (MS): RESULTS OF A 9-WEEK, PLACEBO-CONTROLLED STUDY. J. H. Rosenberg, A. Blumenfeld, D. J. Lynn, C. P. Pollak, H. N. Nagaraja, K. W. Rammohan, Kaiser Permanente (San Diego, Columbus, USA)

Fatigue is common and a main cause of disability in MS. Modafinil is effective and well tolerated for the treatment of excessive daytime sleepiness in patients with narcolepsy. We evaluated modafinil for the treatment of fatigue in patients with MS. Methods: Patients aged 18–65 years with MS, a disability level of *6 on the Expanded Disability Status Scale, and a mean Fatigue Severity Scale (FSS) score of *4 were eligible. Exclusion criteria included a diagnosis of narcolepsy, sleep apnea, or clinically significant major disease and use of medications affecting fatigue. Patients received placebo during weeks 1–2 (placebo baseline), 200 mg/d modafinil plus placebo during weeks 3–4, 400 mg/d modafinil during weeks 5–6, and placebo during weeks 7–9. Efficacy was evaluated with the FSS, a visual analogue scale for fatigue (VAS-F), and the Modified Fatigue Impact Scale (MFIS). The Epworth Sleepiness Scale (ESS) was self-administered at baseline and after treatment with modafinil 200 and 400 mg/d. Measures were self-administered by patients blinded to treatment. Adverse events (AEs) were recorded. Results: 72 patients (MS type: 74% relapsing/remitting, 7% primary progressive, 19% secondary progressive) received treatment. Modafinil 200 mg/d significantly improved fatigue vs placebo baseline; mean scores were: FSS, 5.5 vs 4.6 for placebo ($p < 0.0001$); VAS-F, 5.4 vs 4.5 ($p=0.0031$); and MFIS, 37.7 vs 44.7 ($p=0.0002$). Scores for modafinil 400 mg/d were not significantly different from placebo. Both modafinil dosages significantly ($p < 0.0001$) decreased daytime sleepiness vs baseline. The most common AEs were headache, asthenia, and nausea. No serious AEs occurred. Conclusions: Modafinil 200 mg/d significantly improves fatigue and is well tolerated in patients with MS.

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INFRATENTORIAL HYPOINTENSE LESION VOLUME ON T1-WEIGHTED MAGNETIC RESONANCE IMAGING CORRELATES WITH DISABILITY IN PATIENTS WITH CHRONIC CEREBELLAR ATAXIA DUE TO MULTIPLE SCLEROSIS. S. J. Hickman, C. M. H. Behan, N. C. Silver, I. F. Moseley, N. J. Scolding, D. A. S. Compston, D. H. Miller, Institute of Neurology, Cambridge Centre for Brain Repair, The National Hospital, Frenchay Hospital (London, Cambridge, Bristol, UK)

In multiple sclerosis (MS) hypointense lesions on T1-weighted magnetic resonance imaging (T1HL) are thought to represent areas of tissue disruption and axonal loss. In previous studies of MS patients infratentorial T1HL were found to be rare. We present data to suggest that, in MS patients selected to have chronic cerebellar ataxia, infratentorial T1HL are more common than previously thought and that the lesion volume correlates with disability. METHODS – We recruited 9 patients with chronic cerebellar ataxia due to MS. An expanded disability status scale (EDSS) assessment was performed on each. The patients' brains were then imaged with an axial-oblique T2-weighted fast spin echo sequence, and a post-Gadolinium axial-oblique T1-weighted conventional spin echo sequence. The number and total volume of infratentorial high signal lesions on T2-weighted images (T2HSL) and infratentorial T1HL were calculated by a blinded observer using a computer-assisted contouring technique. RESULTS – A total of 96 infratentorial T2HSL were present, of which 62 (64.6%) appeared isointense and 34 (35.4%) hypointense with respect to the surrounding white matter on the T1-weighted images. There was a median 3 (range 0–10) and median volume of 0.43 ml (range 0–0.85 ml) infratentorial T1HL per patient. The EDSS score correlated with both the number per patient of ($r=0.68$, $p=0.043$) and the volume per patient ($r=0.89$, $p=0.001$) of infratentorial T1HL but not T2HSL. CONCLUSIONS – Infratentorial T1HL are often seen in MS patients with chronic cerebellar ataxia. They may play a significant role in the disability suffered by these patients.

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PHARMACODYNAMICS PROFILE OF WEEKLY INTRAMUSCULAR INTERFERON BETA–1A IN RELAPSING REMITTING MULTIPLE SCLEROSIS. F. Bagnato, F. Bellomi, C. Scagnolari, C. Gasperini, M. Spadaro, C. Pozzilli, G. Antonelli, University La Sapienza, S. Camillo Hospital (Rome, I)

It has been well established that the interferon (IFN) beta treatment may induce the expression of a variety of proteins, including neopterin, beta–2 microglobulin, 2–5 oligoasynthetase (2–5OAS) and MxA protein. In vivo studies on healthy volunteers have shown that these proteins may represent biological markers of IFN beta activity and that their measurement may be useful to study the pharmacodynamics of IFN beta. However, only few longitudinal studies are currently available in patients with relapsing remitting multiple sclerosis (RRMS). Aim of the study is to define the pharmacodynamics of IFN beta–1a in RRMS treated patients. Thirty-three RRMS patients with a mean (SD) disease duration of 4.3 (0.9) years and mean EDSS of 1.3 (1) are treated with IFN beta–1a (Avonex, Biogen) 6 MIU intramuscularly once a week for 12 months. Patients' samples are collected at baseline, 24 and 48 hrs after the injection of IFN beta–1a, at the time 0 (beginning of the study) and then at 3, 6, 9 and 12 months of therapy. Levels of neopterin, beta–2 microglobulin, 2–5 OAS and MxA protein, IL–10, IFN gamma, circulating interferon beta, neutralizing and binding antibodies to IFN beta are analyzed. So far, results on neopterin serum levels are available at 0, 3, 6, and 9 months of therapy. Baseline values are 9.2 (3.3), 9.8 (3.8), 8.3 (4.0), 7.0 (2.4) nmol/L at 0, 3, 6, and 9 months of therapy, respectively. After 24 hrs from drug-injection, the mean fold increase at 0, 3, 6, and 9 months of therapy is 2.4 (0.9), 1.6 (0.6), 1.7 (0.6), 2.0 (0.5), respectively; significant differences are observed between the increase at time 0 and those observed at month 3, 6, and 9 ($p< 0.05$, by t paired test). Similar results are obtained 48 hrs from the administration of the drug at each time point examined. These preliminary data indicate that the circulating neopterin levels significantly increase after 24 hrs and 48 hrs from the first IFN beta–1a injection. Later, the increase is less marked but stable during time. A trend towards progressive decrease in absolute neopterin value up to 9 months is also observed. The biological meaning of these findings, as well as their relevance from the clinical and therapeutical point of view, are still to ascertain; probably new insight will be provided when the measurement of the other IFN-induced proteins as well as the analysis of the 12-months follow-up will be completed.

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PROTON MAGNETIC RESONANCE SPECTROSCOPY IN NORMAL APPEARING WHITE MATTER OF MULTIPLE SCLEROSIS PATIENTS WITH BENIGN AND MALIGNANT COURSE. I.-L. Simone, C. Tortorella, D. Carrara, M. Trojano, M. Liguori, I. Pavone, University of Bari (Bari, I)

A metabolic impairment of normal appearing white matter (NAWM) in multiple sclerosis (MS) patients has been detected by using proton magnetic resonance spectroscopy (1H-MRS). In particular, NAWM of primary progressive MS patients showed decreased N-acetyl Aspartate (NAA) as marker of axonal damage, whereas no changes were found in benign MS. Goal: To evaluate the brain metabolic pattern in the NAWM of two clinically opposite MS populations: benign forms with a favorable clinical course and malignant forms with a rapid clinical deterioration. Design and methods. Two hundred and ten MS patients have been selected, 36 were defined as malignant MS (EDSS score > 6 and disease duration < 5 years) and 174 as benign MS (EDSS score < 3 and disease duration > 10 and < 15 years in 102 patients, > 15 and < 20 years in 53 patients and > 20 years in 19 patients). To date MR spectroscopy has been performed in 18 patients, 13 benign MS (4 male and 9 women) and 5 malignant MS (4 male and 7 women). Twenty two healthy subjects matched for sex and age with MS patients were used for the comparison of spectroscopic data. MRI was performed by using a Magnetom Siemens (1.5 Tesla). Contiguous proton density and T2 scans were acquired (TR/TE: 2200/20–80 msec); T1 scans

(TR/TE: 600–15 msec) were performed before and after Gd administration. Proton spectra were obtained by means of single voxel technique (SE sequence, TE 135 msec) on volume of interest (8 ml) localized on frontal NAWM. Choline (Cho), Creatine (Cr) and NAA were evaluated in each spectrum. Results. The examined benign MS patients had relapsing remitting course, whereas 2 malignant MS had secondary progressive course and 3 primary progressive. Median disease duration was 17.5 (range: 11.3–26.9) in benign MS and 8.3 (range: 7.9–10.3) in malignant MS. Median age at onset and progression index were significantly lower in benign MS than in malignant MS (p=0.04 and p=0.001 respectively). No difference in NAA/Cr, NAA/Cho and Cho/Cr was found between benign MS and controls, whereas malignant MS showed a significant reduction of NAA/Cr in comparison to controls (p=0.03). A trend towards the reduction of NAA/Cr was found comparing benign and malignant MS (p=0.07). In addition, in the benign form the longest disease duration (> 20 years) was associated with the highest NAA/Cr levels (rs: 0.6; p=0.02) Conclusions. Our data confirm an axonal damage in the NAWM of malignant MS, whereas in benign MS, especially in the form with longer disease duration, NAWM seems to be preserved, according to a low degree of clinical disability.

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GENOMEWIDE SCAN OF MULTIPLE SCLEROSIS IN SARDINIAN MULTIPLEX FAMILIES. F. Coraddu, S. Sawcer, A. Hensiek, S. Broadley, M. Lai, M. Pugliatti, M. G. Marrosu, DAS. Compston, Neurology, Centro Regionale sclerosi multipla, Clinica Neurologica (Cambridge, UK; Cagliari, Sassari, I)

Multiple sclerosis has a much higher prevalence in Sardinia than in surrounding Mediterranean countries, suggesting that the island's isolated population growth has concentrated factors increasing susceptibility to the disease. The special nature of the genetic basis for susceptibility to multiple sclerosis in Sardinia is reflected in the established association of the disease with the DR3 (DRB1*0301, DQA1*0501, DQB1*0301) and DR4 (DRB1*0405, DQA1*0501, DQB1*0302) HLA class II haplotypes, which are distinct from those seen in Northern Europeans. In order to utilise the special opportunity represented by this population we are performing a whole genome screen for linkage in 57 multiplex Sardinian families, 28 of which were previously studied (D'Alfonso et al., 1999) with 69 markers from regions of linkage suggested by previous MS genome screens.

The 57 families include 46 sibling pairs and 7 other pairs typed with an additional 289 microsatellite markers. Non parametric linkage analysis of these data is being performed using the Genehunter program. So far, work on Chromosome 8, 20 and X is completed with a region of potential linkage detected on the chromosome X where the NPL score reaches 1.3.

Oral session 33

Neuro-oncology – 1

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CRMP/ULIP PROTEINS RECOGNISED BY ANTI-CV2 ANTIBODIES ARE NOVEL PERIPHERAL NERVE ANTIGENS ASSOCIATED WITH PARANEOPLASTIC PERIPHERAL NEUROPATHY. J. P. Camdessanche, J. C. Antoine, J. Honnorat, L. Absi, M. Aguera, V. Rogemond, J. F. Mosnier, D. Michel, Hôpital Bellevue, Hôpital Neurologique, Inserm 433 (Saint-Etienne cedex 02, Lyon, F)

The paraneoplastic syndrome associated with anti-CV2 antibodies includes cerebellar degeneration, uveitis and for half of patients, an axonal and demyelinating peripheral neuropathy suggesting that the CV2 antigen is expressed in both the central and peripheral nervous systems (CNS/PNS). In the CNS, anti-CV2 antibodies react with the cytoplasm of an oligodendrocyte subpopulation and a 66 kDa protein belonging to the family of Collapsin Response Mediator Protein / Unc 33 like phosphorylated protein (CRMP/ULIP). These proteins are possibly involved in axonal growth and guidance, but their expression in the PNS has not yet been established in adults. The aim of this work is to investigate the expression of the CRMP/ULIP proteins and their mRNA in the adult rat and human PNS. For this study, we used an immunohistochemical method and western blot with the biotinylated IgGs of a patient with anti-CV2 antibodies and a polyclonal rat antiserum reacting with a peptidic sequence common to the four CRMP/ULIP proteins. Controls include biotinylated IgGs from a normal blood donor and rat serum obtained prior to immunisation with the CRMP/ULIP peptide. Reverse Transcriptase – Polymerisation Chain Reaction (RT-PCR) was performed with primers of the four rodent and human CRMP/ULIP proteins. Immunohistochemistry in rat and human peripheral nerve gave the same results. In the dorsal root ganglion, biotinylated anti-CV2 IgGs and the rat anti-CRMP/ULIP peptide serum immunolabeled the cytoplasm and axon of sensory neurons and the cytoplasm of their satellite cells. In the peripheral nerve, axon of both myelinated and unmyelinated fibers was immunolabeled but not the myelin sheath. Anti-CV2 IgGs and the rat CRMP/ULIP peptide antiserum recognised a 66 kDa protein in western blotting of rat and human endoneurium. By RT-PCR, CRMP/ULIP mRNAs were detected in rat and human peripheral nerve. Our results emphasise the expression of the CV2-antigen and CRMP/ULIP proteins in the P. N. S. These proteins are the first paraneoplastic antigens to be recognised in the peripheral nerve by the immune system in patients with paraneoplastic neurological syndrome and carcinoma. These findings support the immune mechanism of the neuropathy of patients with anti-CV2 antibodies and give arguments for a role of CRMP/ULIP proteins in the PNS.

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NEURAL REPRESSOR REST/NRSF IS A CRITICAL REGULATOR IN MEDULLOBLASTOMA CELLS. S. Majumder, P. Lawinger, A. Immaneni, Z. Zhao, L. Rastelli, University of Texas MD Anderson Cancer Center (Houston, TX, USA)

Medulloblastoma is the most malignant pediatric brain tumor, and is believed to arise mainly due to the abnormal arrest of neuroectodermal stem cells in their differentiation pathway by some unknown mechanism. Utilizing three different human medulloblastoma cells, here we show that they are arrested at different levels of neural differentiation, and they contain the neural repressor REST/NRSF activity at a level that is inversely proportional to their level of differentiation. Expression of REST-VP16, a recombinant mutant of REST/NRSF, in least differentiated Daoy medulloblastoma cells by transient transfection not only blocked REST-dependent repression, but also activated neural promoters present as transfected plasmids. High efficiency expression of REST-VP16 in these cells through adenoviral vectors (Ad.REST-VP16) was found to cause activation of multiple neural differentiation genes, triggering of apoptosis through caspase cascade in a p53-independent manner, and blockage of tumorigenic potential of these cells in nude mice. Intratumoral injection of Ad.REST-VP16 was also found to cause growth inhibition of established tumors in nude mice. Therefore, these experiments indicate that REST is a critical biological regulator in these cells, and suggest that it is potentially a novel target for intervention of medulloblastoma.

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CNS INVOLVEMENT BY SYSTEMIC NON-HODGKIN'S LYMPHOMAS (NHL): TREATMENT WITH HIGH-DOSE METHOTREXATE (HD-MTX)-BASED COMBINATION CHEMOTHERAPY. F. Bokstein, A. Lossos, I. Lossos, T. Siegal, Hadassah University Hospital (Jerusalem, IL)

Objective: To evaluate response to pre-radiation chemotherapy in CNS involvement by systemic NHL. Background: CNS involvement in NHL is associated with dismal prognosis. Standard treatment includes radiotherapy (XRT), intra-CSF and systemic chemotherapy. Despite a high rate of initial response, the median survival is about 4 months with 1-year survival rate of 12–23 %. Aggressive systemic pre-XRT chemotherapy may offer an advantage in this clinical setting since it treats both the systemic and the CNS disease. Methods: 23 consecutive adult patients with systemic NHL and a newly diagnosed CNS involvement were evaluated by CSF cytology and neuroaxis MRI. Treatment included HD-MTX 3.5 g/m2 weekly, oral PCZ 100 mg/m2 days 2–15 and weekly intra-CSF ARA-C. The cycle was repeated q 28 days. Dose adjustments were often required for older patients (age > 70) and for heavily pretreated patients. XRT to the CNS was deferred for responding/stable CNS disease. Response to treatment was evaluated before and after XRT. Results: All patients with leptomeningeal seeding responded to treatment prior to XRT with 33 % achieving a complete response (CR). Concomitant response of systemic disease was noted in 36 % with 9 % CR. Addition of XRT to the CNS did not change significantly the overall rate of response nor the CR. Progression free survival for CNS disease was 5 months and for systemic disease 2 mos. All patients with parenchymal involvement responded to therapy prior to XRT with only 9 % achieving CR. The addition of XRT increased the rate of CR to 24 %. Progression free survival was 3 months for both CNS and systemic disease. For the whole group relapse rate was 96 % with 61 % CNS relapses and 70 % systemic relapses. Median survival was 6 months, 1-year survival 32 % and 2-year survival 15 %. Conclusions: Systemic HD-MTX-based combination chemotherapy yields an initial response rate of 100 % in the CNS and a 50 % concomitant systemic response. A complete CNS response can be obtained prior to XRT which adds little to the overall rate of CR. Durable responses are rare and occur in patients

whose CNS and systemic disease can be controlled by the treatment. Since both CNS and systemic relapses appear in tandem, future trials should evaluate alternative modalities to enhance drug delivery into the CNS.

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TREATMENT OF INTRACRANIAL GLIOMAS WITH DELTA–24 ADENOVIRUS. J. Fueyo, A. Khan, C. Gomez-Manzano, T. Sano, X. Shi, M. Lemoine, A. P. Kyritsis, W. K. A. Yung, University of Texas M. D. Anderson Cancer Center (Houston, Texas, USA)

In a previous work we characterized the oncolytic effect of delta–24 adenovirus on glioma cells. The delta–24 mutant adenovirus is a replication-competent adenovirus whose range of host cells is restricted to dividing cells with an abnormal Rb pathway. The delta–24 adenovirus showed potent anti-glioma effect in vitro and in gliomas growing subcutaneously in nude mice. In the work reported here we examine the anti-cancer efficiency of the delta–24 adenovirus in gliomas growing intracranially in nude mice. Thus, U–251 MG human glioma cells were implanted in 14 nude mice (day 0). Seven days after the implantation the mice were treated with a single intracranial injection of 10e8 plaque-forming units of delta–24 adenovirus or an ultraviolet light-inactivated form of delta–24 adenovirus. The animals were monitored daily for survival. All animals treated with the control virus were dead or needed to be sacrificed by the 28th day of the experiment, with the majority of them dying before the 20th day of the experiment (18.7±2.4). However, animals treated with delta–24 adenovirus had a significant increase in median survival (28.7±3.6) ($p< 0.05$). The experiment was performed by duplicate in independent conditions. To correlate the anti-cancer effect with the injection of the adenovirus, the progressive spread of the delta–24 adenovirus was assessed using intracranially implanted gliomas in nude mice. After the intracranial injection of the glioma cells, 2 animals were sacrificed every 4 days, and the tumors were extracted, fixed and processed for immunohistochemistry. Immunohistochemical examination of the viral hexon proteins showed a progressive spread of the adenovirus indicating intratumoral viral replication in vivo. Taken together these data indicate that delta–24 is an efficient anti-glioma tool, and the selectivity and potency of this adenovirus suggest that this approach should be tested in the clinic.

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INCREASED ANTI-GLIOMA EFFECT BY ADENOVIRUS CONTAINING MODIFICATION IN THE FIBER PROTEINS. C. Gomez-Manzano, J. Fueyo, R. Alemany, P. Mitlianga, A. P. Kyritsis, W. K. A. Yung, University of Texas M. D. Anderson Cancer Center, University of Alabama (Houston, Texas, Alabama, USA)

Delivery of the therapeutic tool is one of the main problems of current gene-therapy of gliomas. Tumor-specific or conditionally replicative adenoviruses show anti-glioma effects and are able to spread from cell to cell within the tumor. However, low levels of the primary adenovirus receptor might limit the efficacy of replication-competent adenoviruses. In this study, we enhanced the infectivity of a mutant adenovirus unable to bind the Rb protein by incorporating a sequence encoding an Arg-Gly-Asp (RGD) motif into the viral fiber structure. The RGD insertion allows the virus bind and infect cancer cells expressing alfa-V integrins, and thus, to infect cells that do not express or express low concentration of the adenoviral receptor in their surface by using an alternative receptor during the cell entry process. The double modified adenovirus showed higher viral DNA replication and virus production in U–87 MG (homozygous deletion of p16) and D–54 MG (homozygous deletion of p16) glioma cells. Thus, crystal violet assays showed that 10 MOI of the delta–24 adenovirus were required to induce complete cytopathic effect 7 and 14 days after the infection of 10 MOI D–54 MG and U–87 MG glioma cells, respectively. In addition, the delta–24-RGD adenovirus was able to infect cell lines that require high dose (> 300 MOI) of replication-deficient adenoviral vectors to be infected. Furthermore, a single intratumoral injection of delta–24-RGD in subcutaneous U–87 MG xenografts in athymic nude mice showed high efficacy of the double-modified virus compared to the single-modified adenovirus. This study demonstrates that genetically altered adenoviruses with modified tropism are capable of more efficient cell killing in the contest of neoplasms, like gliomas, characterized by deficiency of the primary adenoviral receptor.

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INDUCTION OF S PHASE BY E2F–1, E2F–2 AND E2F–4 ENHANCES THE EFFECT OF TEMOZOLOMIDE ON GLIOMA VIABILITY. J. Fueyo, C. Gomez-Manzano, M. Lemoine, P. Mitlianga, W. K. A. Yung, A. P. Kyritsis, University of Texas M. D. Anderson Cancer Center (Houston, Texas, USA)

Numerous studies using conventional proliferation markers have showed that gliomas harbor a variable population of non-cycling cells. Temozolomide is a second-generation imidazotetrazinone with activity against a spectrum of tumors including gliomas. Since the mechanism of action of temozolamide requires active DNA replication in the target cell, strategies that enhance the ability of cells to enter into S phase should favor the anti-cancer effect of the drug. E2F–1, E2F–2, and E2F–4 are members of the E2F family of proteins able to promote S phase. In addition, E2F–1 induces apoptosis. In this study, we transduced high doses of E2F–1, E2F–2, or E2F–4 to glioma cells and then we challenged them with temozolomide. Thus, U–251 MG and U–87 MG cells were transduced with E2F–1, E2F–2 or E2F–4 using an adenoviral vector, and treated with temozolomide at a concentration of 0, 10, 25, 50 or 100 microM. Cells were monitored daily by optic microscopy, and tested for viability and cell-cycle analysis. The two cell lines used in these experiments showed similar IC50 values. The combination of these genes and the drug increased significantly cell kill ($p< 0.05$). The experiments with lower doses of the drug showed a synergistic effect between temozolomide and E2F–1. In addition, higher doses of the E2F–2 and E2F–4 viruses resulted in a marked increase of the sensitivity of the cells to temozolomide. Flow cytometric analyses of the cell cycle showed a correlation between size of the population of cells in the S phase and cell death ($p< 0.01$). These results may be of considerable therapeutic benefit in glioma, because the dose of temozolomide is limited due to dose-related toxicity.

Oral session 34

Neuro-oncology – 2

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INTRAOCULAR LYMPHOMA (IOL) TREATED BY A STANDARD PROTOCOL OF INTRAVITREAL INJECTIONS OF METHOTREXATE AND WITHOUT IRRADIATION. J. Pe'er, F. Bokstein, A. Lossos, Y. Sherman, T. Siegal, Hadassah University Hospital (Jerusalem, IL)

Objectives: To use a standard protocol of intravitreal injections of methotrexate for the treatment of intraocular lymphoma and to defer ocular radiation therapy. Background: IOL can be regarded as one of the sites of multiocular CNS involvement by primary CNS lymphoma (PCNSL). Up to 25% of all patients with PCNSL will develop IOL, which may precede or follow the occurrence of PCNSL. Standard therapy includes ocular radiation therapy with or without cranial irradiation and systemic chemotherapy. Significant ocular toxicity may follow in long term survivors. Intravitreal application of methotrexate was previously reported in only 4 patients with IOL (Fishburne, Arch Ophthalmol 115:1152,1997). Methods: Since January 1997 we treat HIV negative patients, who have a pathologically verified IOL (by vitreous cytology) or IOL with a verified PCNSL, by a standard protocol of intravitreal injections of 400 microg. of methotrexate given intravitreally twice weekly for one month, then once a week for 2 months and once a month for 9 months. Results: Twelve eyes of 9 patients were treated (220 injections). The initial diagnosis was PCNSL in 6 and IOL in 3 patients. All had vitreous cells at presentation and in 3 patients retinal lesions were found as well. Six patients received concomitant systemic therapy for their PCNSL (3 for a relapsed PCNSL). For 2 patients the diagnosis of PCNSL has not been made yet, and they are treated with intravitreal methotrexate as the only modality. Four patients completed the treatment protocol, all with complete disappearance of vitreous cells and no relapse occurred during the follow up period of 6–29 mo. After 220 injections no endophthalmitis or retinal detachment were observed. There was no change other than some improvement in the visual acuity of the treated eyes. One 77-year-old pt with multiple ischemic CNS episodes had suspected ischemic optic neuropathy in the treated eye. During the initial period of intensive injections (first month) most patients experienced mild to moderate conjunctival congestion which resolved later. Conclusions: Intravitreal chemotherapy with methotrexate may serve as a promising alternative to external beam radiation therapy in IOL. However, its long-term effects, impact on relapse rate and patients' survival require further studies.

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WHAT DOES LATE CNS RELAPSE OF SYSTEMIC NON-HODGKIN'S LYMPHOMA (NHL) SIGNIFY? A RESIDUAL PRIMARY DISEASE OR A SECOND NOVEL LYMPHOMA? A. Lossos, D. Ben-Yehuda, F. Bokstein, G. Amir, T. Siegal, Hadassah University Hospital (Jerusalem, IL)

Objective. To determine whether late CNS relapse of systemic NHL is related to residual resistant primary disease or whether it represents a second de novo lymphoma. Background. CNS relapse is a well-recognized complication of NHL with risk ranging from 5% to more than 30% in aggressive lymphomas. Most relapses occur within 2 years after the initial diagnosis, however, patients with aggressive NHL may have a persistent rate of 7%–9% per year of late relapse occurring beyond the complete remission period of 2 years. Some of these patients relapse in the CNS. It is indeed difficult to explain why these patients relapse after so many years but it could be argued that residual NHL clones persist which are resistant to the primary treatment. An alternative possibility could be the emergence of a second de novo lymphoma. Methods. We studied 8 patients with systemic NHL with late CNS relapse. At the initial diagnosis, 5 had diffuse large cells, 2 immunoblastic and 1 blastic variant of mantle cell NHL. 6/8 patients had extranodal disease and 1 had leptomeningeal involvement. The median time to CNS relapse was 72 months (range 40–142). All pts had parenchymal brain involvement and 2 had both brain and leptomeningeal involvement. In 7 patients, the initial and relapse histology were the same, but the patient with systemic mantle cell NHL had diffuse large cells in the brain. 3 pts died 4–13 months after the relapse, while 5 are still alive 8–30 months post relapse. To determine whether the late CNS relapse represents resistant disease or a new lymphoma, we studied and compared the immunoglobulin (Ig) gene rearrangements in these cases. Using PCR, we analyzed the Ig heavy chain gene in the primary disease and in the relapsed brain lymphoma. Results. In 2 cases, we found the same heavy chain rearrangement in the primary systemic tumor and in the brain tumor, suggesting that the relapse originated from a resistant disease. In 3 cases, a different rearrangement was detected in the CNS when compared to systemic NHL, indicating development of a second novel lymphoma. 3 cases failed control amplification and were considered uninterpretable. Conclusions. Our results suggest that at least some of the late CNS relapses in NHL represent a second de novo neoplasm. Potential pathogenetic and therapeutic implications of this finding may be significant and should be prospectively addressed in the future.

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SALVAGE CHEMOTHERAPY WITH TEMOZOLOMIDE FOR RECURRENT ASTROGLIAL AND OLIGODENDROGLIAL TUMORS. R. Soffietti, M. Nobile, R. Rudà (Torino, I)

BACKGROUND. Temozolomide is a new oral methylating agent that is able to cross the blood-brain barrier and has been shown to have clinical activity in malignant gliomas.

OBJECTIVE. To assess in phase II studies the benefits and toxicity of temozolomide as salvage treatment for patients with recurrent astroglial and oligodendroglial tumors after conventional therapies.

DESIGN/METHODS. Since April 1998 temozolomide was given to 28 patients with recurrent enhancing gliomas. There were 15 astroglial tumors (originally low grade or anaplastic) and 13 oligodendroglial tumors (originally low grade or anaplastic oligodendrogliomas and oligoastrocytomas). All patients had been previously treated by surgery and most of them by radiotherapy and PCV chemotherapy; 5 patients with oligodendroglial tumors had received second line treatment with carboplatin. The schedule of temozolomide was 150–200 mg/m2 per day for 5 days at 4-week intervals. Response was evaluated on MRI according to Macdonald's criteria.

RESULTS. A median of 4 cycles of temozolomide were administered (range 2–12). Among patients with astroglial tumors (median age 39 yrs) we observed CR in 0/15, PR in 3/15 (20%), SD in 7/15 (47%) and PD in 5/15 (33%). Among patients with PR 2/3 displayed an improvement in their neurological status; 2 had previously responded to PCV and 1 was unresponsive. Median time to tumor progression was 5 months (2–9). Among patients with oligodendroglial tumors (median age 45 yrs) we observed CR in 0/13, PR in 4/13 (30%), SD in 6/13 (46%) and PD in 3/13 (24%). Two patients with PR (one with a CSF spreading) displayed an improvement in their neurological status. Three of the 9 responders and 1 of the 4 non responders to PCV responded to temozolomide. Time to tumor progression was 5 months (2–13+). Toxicity (especially myelotoxicity) was mild.

CONCLUSIONS. Temozolomide has shown activity in a heavily pretreated group of patients with recurrent astroglial and oligodendroglial tumors. Patients unresponsive to PCV may respond to temozolomide.

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RADIOTHERAPY AS SALVAGE TREATMENT FOR IMMUNOCOMPETENT PRIMARY NON-HODGKIN'S CNS LYMPHOMAS: AN ITALIAN STUDY. R. Rudà, M. Borgognone, A. Boiardi, L. Bove, C. Carapella, R. Marra, M. Scerrati, S. Storti, F. Spagnolli, R. Soffietti (Torino, Milano, Roma, Bologna, I)

Chemotherapy is increasingly used as an upfront treatment for newly diagnosed Primary Central Nervous System Lymphomas (PCNSL), with whole brain radiotherapy (WBRT) as a second line treatment.

OBJECTIVE. To assess the value of WBRT as a salvage treatment in patients with PCNSL unresponsive to or progressive after methotrexate (MTX)-based chemotherapy.

DESIGN/METHODS. We report 19 patients with a biopsy proven PCNSL, who were treated with salvage WBRT (median dose 50 Gy) because unresponsive to or progressive after an induction chemotherapy regimen including both intravenous and intrathecal MTX and cytarabine. There were 10 males and 9 females, with a median age of 48 years and a median Karnofsky score of 60 (range 40–100). Lesions were multiple in 60% of patients and single in 40%. Response to RT was evaluated on MR performed 4–6 weeks after the end of treatment, basing on conventional criteria of Macdonald.

RESULTS. Responses to salvage RT were as follows: CR 7/19 (37%) and PR 7/19 (37%) with an overall response rate of 74%. Two patients had a stable disease (10%) and 3/19 (16%) a progressive disease. Most patients who responded to WBRT had a neurological improvement. Time to tumor progression is 13 months (4.5–30 months), with a median survival of 17 months (5–36 months). One long surviving patient developed dementia.

CONCLUSIONS. Salvage WBRT is effective in a significant proportion of patients unresponsive to or progressive after chemotherapy.

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Abstract withdrawn

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COMBINED SYSTEMIC AND INTRAVENTRICULAR THERAPY OF PRIMARY CNS LYMPHOMA: A PILOT STUDY. H. Pels, J.A. Kraus, I. Schmidt-Wolf, U. Schlegel, Dpt Internal Medicine Univ Hospital, Dpt Neurology Univ Hospital (Cologne, Bonn, D)

Objective: To evaluate response rate, response duration and toxicity after systemic and intraventricular chemotherapy in primary central nervous system lymphoma (PCNSL).

Background: Radiotherapy (RT) alone in PCNSL results in a median survival of about one year. Combination chemotherapy and RT is much more efficient but potentially neurotoxic. Therefore, novel chemotherapy based treatment regimens need to be developed.

Patients and Methods: From 9–95 to 9–98, 20 consecutive patients with PCNSL (mean age 59 years, range 27–71) were enrolled in a pilot study evaluating chemotherapy without RT. A high dose methotrexate (MTX) (cycles 1,2,4,5) and cytarabine (ara-C) (cycles 3,6) based systemic therapy (including dexamethasone, vinca-alkaloids, ifosfamide and cyclophosphamide) was combined with intraventricular MTX, prednisolone and ara-C.

Results: Complete response (CR) was achieved in 12 and partial response (PR) in two patients (70%). Four showed progressive disease (PD) and two (70,71ys) died of treatment-related complications. Observation time is two to 51 months (median 26, mean 26 months). Four patients relapsed (10 to 22 months after first diagnosis) and two died from lymphoma. Kaplan Meier esti-

mate for median time to treatment failure (TTF) is 22 months, median survival is not yet estimable. Four patients, who did not receive intraventricular therapy all showed either PD or early relapse. Systemic toxicity was mainly hematologic. Ommaya reservoir infection occurred in four patients and acute (subacute) transient MTX induced encephalopathy in two (one). Cognitive dysfunction due to treatment was seen in only one patient after 12 cycles (six at relapse).

Conclusion: High dose MTX and ara-C based chemotherapy alone is highly efficient in PCNSL. The permanent response rate is possibly higher, if systemic chemotherapy is combined with intraventricular triple therapy. Toxicity is manageable in patients younger than 70 years.

Oral session 35

Peripheral neuropathy – 3

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MRI AND SKIN BIOPSY FINDINGS IN SENSORY GANGLIONOPATHIES. G. Lauria, D. Pareyson, M. Grisoli, R. Lombardi, A. Sghirlanzoni, National Neurological Institute C. Besta (Milan, I)

Ganglionopathies should be distinguished from sensory axonal neuropathies because of different pathogenesis. Evidence of both central and peripheral sensory pathway degeneration in a fashion that is not length-dependent localizes the disease to sensory neurons of dorsal root ganglia (DRG).

Methods: Thirty-one patients with predominantly sensory disturbances underwent cervical spine MRI and 3 of them also thoracic and lumbar MRI scanning. Nineteen patients underwent skin biopsies at the proximal thigh and the distal leg. In 5 of them further skin biopsies were taken at C5 dermatome and at the hand. In 3 sections from each biopsy, immunostained with PGP9.5, linear density of intra-epidermal nerve fibers IENF was quantified and compared by analysis of variance (ANOVA).

Results: Neurological features: In 23 patients, sensory ganglionopathy was suspected. Limb and gait ataxia and proprioceptive sensory loss dominated their clinical picture, while positive sensory symptoms involved face, trunk, and limbs in a patchy or asymmetrical fashion. Five patients had autonomic dysfunctions and 3 patients showed nystagmus. Disease was idiopathic in 8 cases, paraneoplastic in 3 cases and associated with Sjögren, AIDS, autoimmune chronic active hepatitis, and cisplatin neurotoxicity in the others. One patient had a hereditary sensory autonomic neuropathy. Seven patients developed sensory and cerebellar dysfunction in childhood: 4 of them had vitamin E deficiency, 1 a Friedreich ataxia and 2 a spinocerebellar syndrome. In 8 patients, sensory axonal neuropathy was diagnosed. Disease was related to diabetes, alcoholism, AIDS on antiretroviral treatment, and monoclonal gammopathy of undetermined significance.

MRI findings: All ganglionopathy patients showed high signal intensity in the posterior columns on cervical T2-weighted MRI scanning. Signal abnormality was found at the dorsal and lumbar levels as well. Conversely, MRI was negative in all axonal neuropathy patients.

Skin biopsy findings: Neuropathy patients had significantly lower IENF density at distal leg than at proximal thigh. Ganglionopathy patients did not show any change of IENF density with respect to the rostral:caudal orientation in the leg. Similarly, in the arm neuropathies had a length-dependent loss of IENF while ganglionopathies did not show differences between proximal and distal site.

Discussion: Unlike peripheral motor disorders, sensory disturbances are less frequently diagnosed by the probable site of pathology. Ganglionopathy should be suspected when gait ataxia, pseudoathetosis, and cutaneous sensory symptoms involving the proximal regions of the body dominate the clinical picture. These features reflect the impairment of sensory afferents from muscle spindles and skin in a fashion that is not length-dependent. The predominant loss of IENF at the proximal site of limbs confirmed this pattern of denervation. Moreover, ganglionopathies showed T2-weighted hyperintensity in the posterior columns, reflecting the degeneration of central sensory projection. These findings definitively localized the pathological process to T-shaped sensory neurons and strongly supported the clinical diagnosis of ganglionopathy.

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EXPRESSION OF SPECIFIC CHEMOKINE RECEPTORS IN THE GUILLAIN-BARRÉ SYNDROME AND CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY. B. C. Kieseier, M. Tani, N. Oka, J. W. Griffin, K. V. Toyka, R. M. Ransohoff, H.-P. Hartung, Karl-Franzens-University, Cleveland Clinic Foundation, University of Kyoto, Johns Hopkins University, Julius-Maximilians-University (Graz, A; Cleveland, USA; Kyoto, J; Baltimore, USA; Würzburg, D)

Chemokines represent a group of chemoattractant molecules involved in the process of leukocyte entry into the nervous system during immune-mediated inflammation. To investigate the expression of their specific receptors in the inflamed human peripheral nervous system (PNS) sural nerve biopsies from patients with Guillain-Barré syndrome (GBS), chronic inflammatory polyradiculoneuropathy (CIDP), and, for comparison, various non-inflammatory neuropathies were studied. Expression pattern and distribution of the alpha-chemokine-receptor CXCR3 and the beta-chemokine-receptors CCR1, CCR2, CCR4, and CCR5 were investigated immunohistochemically using an avidin-biotin detection system. A consistent chemokine receptor expression pattern was detected: CXCR–3, CCR–2, and CCR–4 were primarily expressed by invading T lymphocytes, whereas CCR–1 and CCR–5 could be localized to endoneurial macrophages, as demonstrated on serial sections. Significantly elevated cell counts in GBS and, to a lesser degree, CIDP cases in comparison to controls were found after quantitation of labeled mononuclear cells. Demonstrating consistent alterations of specific chemokine receptor expression in inflammatory demyelination of the PNS, the present study supports the concept that chemokines and their receptors participate in the pathogenesis of immune-mediated demyelinating neuropathies in human.

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A NOVEL CONNEXIN–32 GENE MUTATION IN AN ITALIAN FAMILY WITH X-LINKED CHARCOT-MARIE-TOOTH NEUROPATHY. C. D'Avino, G Siciliano, A. Pellegrinetti, A Rocchi, F. Sartucci, M. Mostacciuolo, L Pellegrinetti, University of Pisa, University of Padova (Pisa, I)

X-linked Charcot-Marie-Tooth is an inherited motor and sensory neuropathy associated with mutations in GJB1, a gene on chromosome X coding for the gap junction protein "connexin 32" (Cx32). Cx 32 gene is expressed in both peripheral and central nervous system myelins.

We report the case of a family affected by X-linked CMT neuropathy in which a novel point mutation in Cx32 gene has been detected. The mother, the putative carrier, three affected sons and one healthy daughter referred at the Neuromuscular Unit of the Department of Neuroscience in Pisa. They all were examined: the affected sons (32, 35, 38 yrs) presented a motor-sensory slowly progressive neuropathy mainly involving lower limbs. Nerve conduction study showed both axonal and demyelinating pattern of denervation. Evoked potentials indicated visual and brainstem auditory pathway involvement. The mother showed subclinical electrophysiological abnormalities in nerve conduction velocities, whereas the daughter resulted unaffected. The transmission modality was suggestive for an X-linked disease.

By mutational analysis of GJB1 using SSCP and sequencing of candidate regions a previously undescribed missense mutation in the exon 2, codon 151, was found. This mutation was due to a transversion (TAT-> TCT) leading to a Tyr-> Ser substitution in the 2nd extracellular domain.

Our findings further stress the wide variability in the spectrum of Cx32 mutations associated to CMTX, making it worthy to deepen knowledge about genotypic-phenotypic interrelationship in this disease.

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PERIPHERAL NEUROPATHY DURING HEPATITIS-C VIRUS (HCV) INFECTION. F.J Authier, Ch. Payen, J.M Pawlotsky, L. Guillevin, L. Belec, R.K Gherardi, Hôpital Henri-Mondor Ap-Hp, Chu D'anger, Hôpital Avicenne Ap-Hp, Hôpital Broussais Ap-Hp (Creteil Cedex, Anger, Bobigny, F)

Peripheral neuropathy is a complication of HCV infection, usually ascribed to mixed cryoglobulinemia. The pathogenesis of nerve injury remains unclear. Since HCV-associated cryoglobulinemia was shown to contain viral RNA, it may be hypothesized that direct infection of nerve tissue by HCV play a role in nerve injury. In the present study, we described the clinical, electrophysiologic and nerve biopsy findings in 30 patients with HCV-associated peripheral neuropathy and we evaluated whether HCV was directly involved in peripheral nerve lesions. All patients underwent nerve and muscle biopsies. Detection of genomic HCV RNAs and replicative strands in nerve and muscle tissues was performed using two distinctive RT-nested (N)-PCRs. Neuropathy was symptomatic in 29/30 patients, and was consistent with distal symmetrical polyneuropathy (DSPN) in 24/30 (predominently sensory: 18/24; sensorimotor: 6/24), mononeuropathy multiplex (MM) in 3/30 or demyelinating polyneuropathy in

2/30. Pain was present in 17/29 symptomatic patients. Biopsy disclosed inflammatory lesions in 26/30 patients (87%) including perivascular inflammatory infiltrates (8/30; 27%), lymphocytic vasculitis (9/30; 30%), leucocytoclasic vasculitis (3/30; 10%) and necrotizing angeitis (6/30; 20%). Patients with MM (n=3) had lymphocytic (2/3) or leucocytoclasic (1/3) vasculitis and patients with necrotizing angeitis (n=6) presented with sensory (4/6) or sensorimotor (2/6) DSPN. RT-N-PCR disclosed genomic HCV RNA in 10 cases (muscle: 9; nerve: 3), including 2 cases with positive detection in both nerve and muscle. In contrast no replicative strands were found. We conclude that DSPN is the most frequent form of neuropathy in HCV-infected patients, usually associated with vascular inflammatory lesions of nerve. The lack of replicative HCV in nerve suggests that neuropathy may be due to immune-mediated process rather than nerve infection.

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INVESTIGATION OF SERUM RESPONSE TO MYELIN AND NON-MYELIN NERVE COMPONENTS IN INFLAMMATORY NEUROPATHIES. M. S. G. Kwa, I. N. Van Schaik, R. R. De Jonge, F. Baas, M. Vermeulen, Academic Medical Center (Amsterdam, NL)

Guillain-Barré Syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) are thought to be caused by an auto-immune reaction to peripheral nerve epitopes leading to myelin breakdown and nerve conduction block. We investigated whether serum antibodies against both myelin and non-myelin components are involved in the pathogenesis of immune mediated neuropathies. Firstly, recombinant myelin protein zero (MPZ, P0), peripheral myelin protein 22 (PMP22) and connexin 32 (Cx32) were produced in CHO-K1 cells using a transient expression vector based on Semliki Forest Virus (pSFV). Screening of a panel of GBS and CIDP patient sera showed no apparent serum immune reactivity towards these major myelin constituents. Secondly, we tested whether sera contained antibodies directed against Schwann cells, which normally are responsible for myelin synthesis and maintenance. We present evidence that 23–25% of GBS and CIDP patients have circulating auto-antibodies against proliferating non-myelinating human Schwann cells. In contrast, healthy donors showed positive staining in only 2 out of 34 sera. No reaction was found in sera from patients with other neurological disorders, including other neuropathies. Cells derived from non-neural origin (tumors) did not show this staining. Immunofluorescence was localized strongly at the distal tips (leading lamella) of the Schwann cell processes. Distal tips of neurites (nerve-growth-cones) of in vitro differentiated human neurons (hNT2 cells) were stained strongly as well. These findings suggest that the immune reactivity is not directed against myelin, but towards proteins and epitopes involved in Schwann cell-axon interaction. Several of those nerve-growth-cone and leading lamella associated proteins were investigated. Furthermore, the correlation between clinical manifestation, intravenous immunoglobulin treatment and high serum titers of anti-Schwann cell antibodies (IgG) will be discussed.

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TREATMENT OF EXPERIMENTAL AUTOIMMUNE NEURITIS BY A RAS INHIBITOR, S-FARNESYLTHIOSALICYLIC ACID (FTS). M. Kafri, V. E. Drory, I. Wirguin, N. Wang, Y. Kloog, A. D. Korczyn, J. Chapman, Tel Aviv University, Tel Aviv University Sackler Faculty of Medicine (Tel Aviv, IL)

Intracellular signaling is a novel target for the immunomodulatory treatment of autoimmune disease. A specific target for such therapy is Ras, a GTP-binding protein important in lymphocyte activation. A recently described novel compound, FTS, inhibits the activity of Ras with minimal toxicity in experimental animals. We have examined the use of FTS in the experimental autoimmune neuritis model, which is a short monophasic disease similar to the Guillain Barre Syndrome. EAN was induced in 3 month old Lewis rats (5–10 rats per group) by immunization with a bovine spinal roots myelin preparation in adjuvant. The rats developed weakness from day 10 following immunization as confirmed by a standard clinical scale, a Rotarod test and by neurophysiological studies. FTS was administered intraperitoneally (5 mg/kg 1–2 times daily) in protocols which included treatment from day 0, and treatment from day 10. EAN animals treated with saline alone and non-immunized rats served as controls. Two main effects of FTS treatment were noted. In the acute phase, the onset of disease and peak disability scores were significantly attenuated by continuous FTS treatment begun at day 0. Mean (±SE) peak clinical scores, days 16–18 were 4.1±0.5 and 2.5±0.5 in the control and continuous FTS treatment groups respectively (p=0.018, t-test). In the recovery phase (days 30–40) however, the animals treated continuously with FTS (clinical score 1.75±0.45) improved very little in comparison to the untreated controls (2.4±0.6, p=0.19). The best overall results were obtained with FTS treatment started on day 10 and continued for 10 days. This resulted in a significantly reduced peak of disease (2.5±0.6, p=0.032 compared to saline treated controls) followed by a marked improvement on days 30–40 (0.84±0.42, p=0.028). Similar results were obtained with Rotarod and electrophysiological measures. These findings indicate the potential use of FTS and other inhibitors of intracellular signaling in autoimmune disease and especially GBS.

Oral session 36

Peripheral Neuropathy – 4

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DORSAL ROOT GANGLION NEURON BEHAVIOUR IS IMPAIRED BY DIABETES. Z. J. Luo, R. H. M. King, J. Lewin, P. K. Thomas, Royal Free & University College Medi (London, GB)

Diabetic sensory polyneuropathy involves a progressive loss of axons accompanied by impaired regeneration. Hyperglycaemia leads to the nonenzymatic glycosylation (NEG) of proteins which correlates with the severity of diabetic complications. NEG of extracellular metrix (ECM) proteins can cause structural and functional changes leading to altered cell behaviour. Intracellular components may also be modified. It is not known whether the failure of axonal regeneration is because of impaired axonal growth or because an abnormal endoneurial microenvironment does not support axonal elongation. We have used a dissociated dorsal root ganglion (DRG) neuron culture model to investigate the behaviour of diabetic sensory neurons on normal and glycated substrates. Neuron survival and neurite extension were assessed. Dorsal root ganglia were obtained from normal neonatal and normal and streptozotocin (STZ)-diabetic adult Lewis rats. Laminin was from EHS mouse tumour and collagen I / III was extracted from STZ-induced diabetic and non diabetic rat tails. Glycation of collagen was checked using luminescence spectrometry. Neurons were plated evenly into culture dishes coated with laminin for adults and collagen for neonates. After 1 h incubation, the total numbers of viable neurons and neurite-bearing neurons were counted and again after 24 h in the same area. Some cultures were plated on glass coverslips for 24 h for immunostaining and scanning electronic microscopy (SEM). Neuron survival and the number of neurite-bearing neurons were reduced by 10% and 15% respectively when adult diabetic neurons were cultured on laminin. When normal neonatal neurons were cultured on a diabetic collagen substrate, the same measures were significantly reduced by 20% and 13%. No significant morphological changes were found by SEM. It is therefore concluded that both the presence of diabetes and glycation of the ECM appear to affect the survival of sensory neurons and neurite extension.

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TREATMENT OF CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY AND MULTIFOCAL MOTOR NEUROPATHY WITH HIGH DOSE INTRAVENOUS IMMUNOGLOBULIN WITH IGM, IGA IN ADDITION TO IGG. K. Scheglmann, E. Rentz, Zentralklinikum Dep. of Neurology, Biotest-Pharma (Augsburg, Dreieich, D)

Positive Effects of treatment with high-dose Immunoglobulins (IVIG) are demonstrated in controlled studies in chronic inflammatory demyelinating polyneuropathy (CIDP) and in open studies in multifocal motor neuropathy (MMN). In most, but not all cases, this treatment was effective. In some patients you can realize secondary loss of response to IVIG-treatment. In this group we changed therapy in 5 patients using a different type of Immunoglobulin (IVIM), containing IgM 12%, IgA 12% and IgG 76% for intravenous administration (Pentaglobin).

3 patients with CIDP: The first patient was treated with IVIG, initial 150 g, followed by 30 g every 6 weeks over 9 months. Accidently IVIM was administered, surprisingly with better effect than IVIG, then continued over 6 months. One patient showed no effect with IVIG and steroid-treatment, but positive response to 120 g IVIM, followed by 20 g every 4 weeks over a period of 6 months. After that time we realized again secondary loss of IVIM-treatment response. 3rd patient showed secondary loss of treatment response to IVIG after 18 months, but moderate effect of IVIM 120 g over 4 days.

2 patients suffered with MMN: First patient treated with IVIG over 4 years, 30 g every 6 weeks, until we saw secondary loss of effectiveness, with progressive paresis of M. extensor digitorum communis and M. biceps brachii of the other side. Using IVIM 120 g over 5 days, followed by 30 g every 6 weeks there was a good effect was at the beginning of IVIG-treatment 4 years ago. The 2nd patient was treated with IVIG, but his paresis was progredient over a period of 1 year. With IVIM 30 g every 4 weeks progression has been stopped for 7 months.

This report showed better effects of treatment with Immunoglobulins containing IgM and IgA in addition to IgG in 5 cases without response to classic IVIG-treatment. This data evoke further questions: Why is there a positive effect of IgM or IgA in treatment of CIDP and MMN? Is IVIM an alternative treatment in primary or secondary loss of response to IVIG?

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RITUXIMAB AND ANTI-MAG-ASSOCIATED POLYNEUROPATHY – A PILOT STUDY. S. Renaud, M. Gregor, P. Fuhr, A. J. Steck, A. Gratwohl, University Hospital Basel (Basel, CH)

The treatment of anti-MAG-associated polyneuropathy remains unsatisfactory. Although the relationship between paraproteinaemia, anti-MAG-antibodies and the development of a polyneuropathy is well understood, no causative or curative therapy exists so far. Rituximab is a mouse-human chimaeric antibody, directed against the CD20 protein, that eliminates specifically normal and malignant B-cells and B-cell precursors. It has been proven effective in the treatment of relapsed or refractory follicular B cell lymphoma and preliminary results suggest that it may be effective in autoantibody-related polyneuropathies.

Objective: To show whether rituximab has a beneficial effect on the clinical outcome of anti-MAG-associated polyneuropathy, on electrophysiological parameters and antibody titers.

Methods: In a pilot study with 6 patients with an anti-MAG-associated IgM polyneuropathy, rituximab was administered intravenously 375 mg/m^2 once weekly for 4 weeks. Clinical follow-up consists in neurological examination (NDS and NSS) at baseline, month 1, 3, 6, 9 and 12. Electroneurography is done at baseline, month 6 and 12. In addition regular white and red blood cell counts, blood chemistry and measurement of IgM levels and anti-MAG-antibodies are performed.

Results: Rituximab is well tolerated. The only side effects were fever and hypotension in one patient each. In all patients the B-cells in the peripheral blood circulation were completely depleted, without any side effects observed so far. Follow-up after 6 months will be presented.

Conclusion: Rituximab is a promising new drug that effectively and safely eliminates B-cells in patients with anti-MAG-associated polyneuropathy.

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COMPARATIVE STUDY ON PRECEDING CAMPYLOBACTER JEJUNI INFECTION IN GUILLAIN-BARRÉ SYNDROME BETWEEN JAPAN AND THE NETHERLANDS. M. Koga, C. W. Ang, N. Yuki, B. C. Jacobs, F. G. A. Van Der Meche, P. Herbrink, K. Hirata, P. A. Van Doorn, Dokkyo University, Erasmus University Rotterdam, SSDZ Diagnostic Centre (Tochigi, J; Rotterdam, Delft, NL)

Campylobacter jejuni infections have emerged as the most common antecedent event in Guillain-Barré syndrome (GBS). Serological studies showed that the frequency of C. jejuni infection in GBS ranged from 17% to 66%; frequencies in Asian countries were higher than those in western countries. However, all previous studies used different assay systems with variable sensitivity and specificity, making it impossible to compare the incidence of C. jejuni infection in GBS among those countries. This cooperative project by Dokkyo University and Erasmus University Medical Centre Rotterdam was planned to compare the frequencies of C. jejuni-associated GBS between Japan and the Netherlands. Serological examinations were performed independently in two laboratories. In the assay system at Dokkyo University, there was no difference of incidence of C. jejuni serology between the Japanese (17/88, 19%) and Dutch (21/132, 16%) GBS patients. Investigation at Erasmus University showed that the incidence of C. jejuni serology in the Dutch GBS patients (45/132; 34%) was higher than that in the Japanese GBS (20/88; 23%), although the difference did not reach significance (p=0.07). In both systems, no differences were shown between Japanese and Dutch disease controls and between Japanese and Dutch healthy subjects as well. The results of Dokkyo's and Erasmus' systems showed good correlation with each other in Japanese ($p< 0.0001$, rs=0.77) and Dutch ($p< 0.0001$, rs=0.76) populations. However, there was significant difference of positive frequency between Erasmus' (22%) and Dokkyo's (11%) assay systems (p=0.00003). These results indicate that the incidence of C. jejuni infection in GBS did not differ between Japan and the Netherlands in our collaborative study.

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MONOCYTE-MACROPHAGES INFILTRATION AND INDUCTION OF IL–1B IN THE NERVE OF STREPTOZOTOCIN DIABETIC RATS. G. Conti, M. De Riz, E. Scarpini, S. Bussini, R. Bianchi, S. Livraghi, P. Baron, G. Stoll, G. Scarlato, IRCCS – Ospedale Maggiore, Mario Negri Institute, Heinrich-Heine-University (Milano, I; Düsseldorf, D)

Inflammatory cells have been involved in the ethio-pathogenesis of diabetic neuropathy, and activated macrophages have been found in the peripheral nervous system of diabetic rats, playing a possible role in chemotaxis and regeneration. In this study sciatic nerves have been obtained from diabetic rats at different time points following STZ administration. Monocyte-macrophage infiltration and IL–1b induction were analyzed by immunocytochemistry on frozen sections and on teased nerve fibers, and these data were compared to concomitant p75NTR induction. Furthermore, apoptosis was detected in some specimens by TUNEL and DAPI staining performed on teased nerve fibers, and the cell phenotype was characterized by double-staining with antibodies specific for Schwann cells, and macrophages. The nerves obtained from STZ-diabetic rats showed macrophages infiltration by day 14 following STZ administration with complete clearance by day 35. The 15% of these cells was TUNEL positive. IL–1B induction was concomitant with macrophages infiltration and not detectable by day 35. p75NTR expression began by day 21, peaking by day 35. These findings seem to indicate that these processes may be crucial in the regulation of nerve damage and in promoting an attempt of regeneration in STZ diabetic neuropathy.

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DETECTION AND PREVALENCE OF THE ALPHA-LATROTOXIN-LIKE EFFECT IN SERA FROM PATIENTS WITH MILLER FISHER AND GUILLAIN-BARRÉ SYNDROME. B. C. Jacobs, R. W. M. Bullens, G. M. O'Hanlon, J. J. Plomp, C. W. Ang, H. J. Willison, University Hospital Rotterdam (Rotterdam, NL)

Anti-GQ1b positive sera from patients with Miller Fisher syndrome (MFS) induce muscle fibre twitching, an increase of miniature endplate potentials (MEPP) frequency and blockade of transmission at the neuromuscular junction (NMJ) in the mouse diaphragm in vitro. These effects are very similar to those of alpha-latrotoxin (LTx) and are induced by antibody-mediated activation of complement at the NMJ. In this study we developed an assay for detection of muscle fibre twitching as an indicator of the LTx effect and investigated the prevalence of this effect in sera from patients with Guillain-Barré syndrome (GBS), MFS and controls. We studied the relationship between the presence of the LTx-like effect and clinical symptoms, serum anti-ganglioside antibodies, micro-electrode physiology and deposition of activated complement at NMJs.

METHODS. Mouse diaphragms were cut in 8 equivalent strips, pinned out in incubation wells, and incubated with heat-inactivated serum samples followed by incubation with normal human serum as a complement source. Twitching was scored visually by stereomicroscopy by one or two observers. The assay was optimized and standardized using LTx, mouse monoclonals and serum samples with anti-GQ1b activity. Thereafter, serum samples from 90 patients, including MFS (17), GBS (50), neurological, infection and normal controls (23) and mouse anti-ganglioside monoclonals were tested in duplicate. 34 samples were tested with standard micro-electrode methods. Sections from each strip were double-stained with fluorescently labelled bungarotoxin and anti-complement C3c for microscopic analysis. C3c-deposition at NMJs was measured using image analysis techniques.

RESULTS. The intra- and interobserver agreement of detection of twitching was 96% and 90% respectively. Twitching was observed with 3/3 anti-GQ1b monoclonals, 13/17 (76%) of MFS, 5/50 (10%) of GBS and none of the control samples. Twitching was highly associated with the presence of ophthalmoplegia, increased MEPP frequency, serum anti-GQ1b antibodies and C3c-deposition at NMJs (all items, $P< 0.001$). Serum from one GBS patient without anti-GQ1b antibodies induced twitching and C3c-deposition at NMJs. Convalescence samples were all negative for twitching.

CONCLUSION. This study strongly suggests that antibodies to GQ1b but not to other gangliosides are responsible for the LTx-like activity in serum from GBS and MFS patients, and that the muscle fibre twitching assay is a valuable biophysiological test for detection of this effect.

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HETEROGENEITY OF PERIPHERAL NEUROPATHY ASSOCIATED WITH IGM MONOCLONAL GAMMOPATHY. D Adams, P Labauge, K Rerat, C Lacroix, C Théodore, G Said, Hôpital de Bicêtre, Univ. Paris-Sud (Le Kremlin-Bicêtre, F)

We reviewed the files of 69 patients with neuropathy and IgM monoclonal gammopathy seen over the last 20 years. Mean age was 65.5±10 years (range, from

29 to 83), sex ratio (M/F) was 1.5. Fifty three patients (78 %) presented initially with monoclonal gammopathy of undetermined significance, 11 had Waldenström's disease (16 %), 4 had a low grade lymphoplasmacytic proliferation (6 %) and one had a solitary plasmacytoma (1 %). Light chain type was of the kappa type in 76 %, of the lambda type in 24 %. Fifteen patients (22 %) had purely sensory polyneuropathy, with ataxia in 4. Twenty two patients (32 %) had distal symmetrical sensory-motor polyneuropathy. Twenty three patients (33 %) had a multifocal neuropathy which was sensory-motor in 19 and sensory in 4. Nine patients (13 %) had a predominantly motor neuropathy. Electrophysiological study and nerve biopsy showed that the neuropathy was demyelinating in 43/69 patients (62 %), axonal in 16/69 (23 %), mixed axonal and demyelinating in 8/69 (12 %), associated with lymphocytic perivascular epineurial infiltration in one. Among the 16 patients with axonal loss, 5 had amyloidosis including 3 patients with Waldenström's disease, 4 a probable vasculitis and one a solitary plasmacytoma. Anti-MAG activity of the paraprotein was found in 8/23 patients, including one with AL amyloid neuropathy. This study underlines the heterogeneity of both of the peripheral neuropathy associated with monoclonal IgM gammopathy, and of the nature of the gammopathy itself.

Poster session – 1

Cerebrovascular disorders – 1

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SERUM INSULIN-LIKE GROWTH FACTOR 1 IN ACUTE ISCHEMIC STROKE. A. Szczudlik, A. Slowik, J. Krupinski, University Hospital, Jagiellonian University (Cracow, PL)

Objective: To compare serum insulin-like growth factor 1 (IGF-I) levels in acute stroke patients and age-matched controls. To assess the relationship between serum IGF-I levels and clinical pattern and volume of ischemic lesion on CT in acute stroke patients. Background: Experimental studies showed increased expression of IGFs after hypoxic injury. The secretory dynamics of IGF-I serum levels in acute stroke patients has not been studied systematically. Design/methods: 19 consecutive patients with a first ischemic stroke (mean age: 72±13 years) and admitted within 12 hours after stroke onset and 11 age-matched controls with a similar stroke risk factors profile were included in the study. The following data were collected in stroke patients: patient characteristics, risk factors, clinical stroke syndrome (TACS, PACS, LACS – Oxfordshire criteria), stroke aetiology (TOAST criteria), comorbidities, complications, treatment and stroke severity (Scandinavian Stroke Scale – SSS) on admission, on the next, 3rd, 7th and 14th day after stroke onset. CT scans were performed between day 3 and 10 to estimate the volume of the lesion. Serum IGF-I levels (Octeia® IGF-I ELISA kit) in stroke patients were measured sequentially on the day of admission, on the next, 3rd, 7th and 14th day after admission and once in controls. Plasma glucose and white blood cell (WBC) count were also measured on the first day of hospitalisation in stroke patients. Results: Serum IGF-I levels in all measurements in stroke patients were significantly higher than in controls ($p< 0.05$). Serum IGF-I levels decreased in the consecutive measurements in patients with TACS and PACS, and increased – in patients with LACS. The increase of IGF-I levels between day of admission and day 14th correlated significantly with the improvement of neurological status as measured by the difference in SSS score between day 14th and the day of admission ($R=0.48$, $p< 0.05$). IGF-I serum levels correlated adversely with the size of the ischemic lesions on CT ($R=-0.47$, $p< 0.05$) and were not related to glucose levels, WBC count and body temperature. Serum IGF-I was not influenced by the ACE inhibitors treatment. Conclusions: The study showed that acute stroke patients had significantly higher IGF-I serum levels than controls. IGF–1 secretory dynamics in acute stroke patients was related to the volume of ischemic lesion on CT and stroke clinical pattern.

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KNOWLEDGE OF STROKE ONSET. S. Santos, J. Lòpez del Val, L. F. Pascual, C. Tejero, J. A. Mauri, C. Iñiguez, Hospital Clinico Universitario (Zaragoza, E)

Background: the aims of the study were to analyse and to identify factors associated with notknowing the time of the day of stroke occurrence. Methods: We prospectively studied 540 consecutive acute stroke patients admitted in a 1-year period; a standardized questionnaire was completed for every study patient. Initial stroke severity was assessed on admission with the Canadian Stroke Scale CSS. Stroke onset time was defined as the earliest moment the patient or an observer first noticed neurological dysfunction. Other variables were also documented (age, sex, risk factors, type of stroke). All patients were divided into two groups: patients who knew stroke onset and those patients in whom stroke onset time was not available (patients awaking with symptoms, patients with aphasia or those with dementia). Exact multiple logistic regression was used to predict knowledge. Results: Stroke onset was unknown in 206 patients (mean age 72.23 DS: 11.41). Most frequent reasons were: dementia (n=79), aphasia (n=17), stroke symptoms present on waking (n= 101) and others (n=9). Patients that did not know stroke onset had diabetes mellitus ($p=0.038$) and non-transient stroke ($p=0.00010$) more frequently. Stroke occurred more often in their own house ($p=0.00$). Initial stroke severity (CSS) was decreased in this group ($p=0.0219$) and small-vessel lesions seem to be the relevant mechanism ($p=0.013$). In the multivariate model the variable type of stroke ($p=0.0005$), mechanism ($p=0.0028$) and where the stroke occurred ($p=0.000$) were identified as the only predictors of knowledge of stroke onset. Conclusions: Our results suggest that being at home is a significant independent risk factor for notknowing time of stroke onset. We found also association with small and lacunar infarcts in whom a hypothetical treatment might be more effective.

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VASCULAR MALFORMATIONS IN PATIENTS WITH INTRACEREBRAL HAEMORRHAGE. A. Slowik, U. Wyrwicz-Petkow, W. Turaj, K. Kasprzyk, M. Bosak, H. Uhl, A. Szczudlik, University Hospital (Karakow, PL)

Purpose: the study was prospectively designed to assess the frequency of vascular abnormalities and to determine features that might require the need for angiography in patients with intracerebral haemorrhage (ICH). Design/methods: 56 patients with ICH, confirmed by CT, without a history of trauma or known pre-existing brain abnormality, admitted to Stroke Unit Department of Neurology, Jagiellonian University, Krakow, entered the study. 38 (67.9 %) of patients underwent conventional angiography and/or angio-NMR within 5 days after stroke. Angiography and/or angio-NMR were not performed for clinical reasons in 18 patients. Results: Vascular malformations were found in 11 from 38 patients (31,6 %); ruptured aneurysm in 8 patients (21 %), arteriovenous malformation (AVM) in 1 patient (2.6 %), angioma venosum in 1 patient (2.6 %) and angioma cavernosum in 1 patient (2.6 %). In 1 patient angiography showed haemorrhage into metastases. Angiographic findings were negative in 9 from 19 (47.5 %) patients with lobar haematoma, in 5 from 6 (83.3 %) with haemorrhages originating in the thalamus, in 1 from 2 patients (50 %) originating in pons and in all 5 patients with haemorrhage originating in basal ganglia, 3 patients in deep periventricular white matter and 2 in cerebellum. Intraventricular haemorrhage accompanied ICH in 30 % of patients independently of whether they had or had not vascular malformation. Hypertension was found in 63 % of patients with vascular malformation and 95 % of patients without vascular malformation.

Conclusions: (1) Vascular malformation is the cause of about 30 % of ICH's. (2) Vascular malformations are found in about 50 % of patients with lobar haemorrhage. (3) The history of hypertension is frequently associated with vascular malformation.

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DECREASED CEREBROVASCULAR CO_2-REACTIVITY IN CADASIL PATIENTS. T. Pfefferkorn, S. von Stuckrad-Barre, J. Herzog, G. F. Hamann, M. Dichgans, Klinikum Grosshadern, LMU München (München, D)

Background: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukencephalopathy (CADASIL) is a hereditary angiopathy caused by mutations within the Notch3 gene. Patients develop recurrent strokes or transient ischemic attacks and progressive cognitive deficits in early adulthood. Pathologically, CADASIL shows some typical microangiopathic features: lack of macroangiopathic changes, lacunar infarct types, leukencephalopathy. Electron microscopy shows osmiophilic deposits in the smooth muscle cell layer of intracerebral arterioles. To elucidate functional impairment of the affected cerebral microvessels, we investigated the cerebrovascular CO_2-reactivity of CADASIL patients by transcranial Doppler sonography.

Patients and methods: 12 CADASIL patients with the diagnosis proven by either skin biopsy or genetic testing were investigated. Macroangiopathic changes were excluded by extracranial Duplex sonography. Cerebrovascular CO_2-reactivity was measured by bilateral transcranial Doppler sonography insonating the middle cerebral artery (MCA). CO_2-reactivity was calculated as the percent change in MCA mean blood flow velocity (MFV) after breathing carbogen (5 % CO_2, 95 % O_2) compared to room air. Values were compared to age matched control subjects without cerebrovascular disease.

Results: CO_2-reactivity was significantly decreased in CADASIL patients compared to controls (32.8 ± 14.3 % vs. 47.3 ± 12.9 %; $p< 0.05$, Mann-Whitney-U-test) while other parameters showed no significant differences (MCA MFV, mean arterial blood pressure).

Discussion: Our findings demonstrate functional impairment of cerebral vasoreactivity in CADASIL patients. These results confirm that small, but not larger vessels, are involved in the pathological process. The microvascular impairment may be caused by smooth muscle cell dysfunction due to or associated with osmiophilic deposits.

P235
LEUKOCYTE SUBTYPES AND OUTCOME IN PATIENTS SUFFERING ACUTE STROKE. M. Gomis, J. Roquer, A. Rodriguez Campello, E. Munteis, J. Izquierdo, A. Pou, Hospital del Mar (Barcelona, E)

There is increasing evidence that the inflammatory response plays an important role in brain ischemic injury and that leukocyte count is positively associated with a worse outcome in patients with acute stroke. In the present study we analyze the relationship between the leukocyte subtypes (LS) and outcome in patients with atherothrombotic stroke (ATS) and in patients with intracerebral hemorrhage (ICH). Methods and results: In 198 patients (100 with ICH, and 98 with ATS) blood samples were obtained 0 to 24 hours after stroke debut to determine the peripheral white blood cell count (total leukocyte count and leukocyte subtypes: neutrophils, monocytes and lymphocytes). We correlated these findings with the patient's outcome: in-hospital mortality (fatal/non fatal stroke) and in-hospital morbidity using Barthel index and Canadian Score at admission and discharge. In-hospital patient's mortality was positively related with the neutrophil count ($p< 0.04$; OR: 6.5, in ATS cases; $p< 0.1$; OR: 1.85 in ICH cases). Disability was also positively related with the neutrophil count ($p< 0.03$ for Canadian Score at admission in ATS patients and $p< 0.001$ in ICH patients; $p< 0.004$ for Barthel at discharge in ICH cases; $p< 0.006$ for Canadian Score at discharge in ICH cases). Monocytes and lymphocytes did not correlate with mortality nor morbidity.

Conclusions: 1. Mortality is higher in patients with leukocytosis during the acute stroke, and this is mainly related to the neutrophil rise; 2. Neutrophil rise is also a marker of poor functional recovery in patients suffering ICH or ATS. 3. There is no relationship between monocytes or lymphocytes and mortality or morbidity.

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THE ULTRASOUND PICTURE OF INTIMA-MEDIA CAROTID ARTERY COMPLEX AND THE CHARACTERISTICS OF BLOOD PLATELET ACTIVITY IN ISCHAEMIC STROKE PATIENTS. W. Kozubski, C. Watala, R. Kazmierski, M. Lukasik, University of Medical Sciences (Poznan, PL)

In order to estimate the influence of blood platelet activity and their released proteins on the development of atherosclerotic plaque we have estimated the status of subendothelium layer in common carotid artery and the expression of blood platelet surface antigen in ischaemic stroke patients. Seventeen patients with first-ever stroke were examined between 6th and 8th weeks after brain ischaemic accident. The control group consisted of 12 sex- and age-matched subjects without neurological symptoms and signs. The intima-media thickness (I-M T) and plaque existence were estimated by the High-Resolution B-mode ultrasonography. All the patients have had bilateral intima-media measurements within 20 mm proximal to the carotid bulb on the far wall in the anterioposterior and laterolateral plans. The expression of selectin-P (CD62 antigen) was measured by flow cytometry with the use of human platelet monoclonal antibodies as well as the fractions of platelet microparticles and aggregates. All the characteristics were estimated in the resting and thrombin-activated platelets. There were significant correlations between microparticles platelet fraction and I-M T ($p< 0.02$) and between platelet aggregates fraction and plaque existence ($p< 0.02$). The most significant discriminate functions that best differentiated the patients' and control groups were: I-M T ($p< 0.00006$), CD62 antigen expression in the resting ($p< 0.04$) and activated ($p< 0.05$) platelets, and aggregates fraction after thrombin activation ($p< 0.004$). In the patients' group the best discriminate parameters according to the existence of plaque were: I-M T ($p< 0.0008$), aggregates ($p< 0.004$) and microparticles ($p< 0.004$) fractions, selectin-P expression in the resting ($p< 0.008$) and activated ($p< 0.044$) platelets. The authors conclude that functional status of blood platelets may strongly influence carotid subendothelium morphology in ischaemic stroke victims.

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PAINFUL HORNER'S SYNDROME AND IPSILATERAL IX AND X CRANIAL NERVES PALSY IN A CASE OF SPONTANEOUS INTRAPETROUS CAROTID DISSECTION: RELEVANCE OF MRA IN THE DIAGNOSIS AND FOLLOW UP. D. Tessarolo, A. Pingi, R. P. Cioffi, P. Scarano, M. Liguori, San Camillo Hospital (Rome, I)

Spontaneous or post traumatic acute onset of Horner's syndrome is a neurologic emergency. Painful Horner's syndrome should be considered a relevant sign in the diagnosis of internal carotid artery dissection. Carotid dissection may be associated to ipsilateral lower cranial nerves dysfunction, but isolated glossopharyngeal and vagal nerves involvement has not been frequently reported. Brain magnetic resonance angiography scan (MR angioscan) has been proposed as a first choice investigation in the diagnostic assessment of carotid dissection, in order to avoid invasive arteriography.

METHODS AND RESULTS: A 60 year old male was admitted to the neurologic ward of our Department because of the acute onset of fronto-orbital headache, dysphonia and dysphagia. Neurologic examination showed incomplete right Horner's syndrome and ipsilateral soft palate and vocal cord dysfunction. A plain brain CT scan gave normal results. A standard brain MRI scan ruled out brainstem lesions which could mimick the observed clinical picture, and showed hyperintense signal in the right internal carotid artery. Doppler ultrasound scan of carotid arteries was unable to recognize arterial stenosis but showed sign of distally increased resistance on the right side. A brain MR angioscan using a 3D phase contrast sequence (vs 30 cm/s) disclosed hyperintense signal in the intrapetrous and extracranial segments of the right internal carotid artery (replacing the normal flow void signal pattern), indicating a markedly reduced blood flow. A treatment with sucutaneous heparin (25,000 U/day) was started. A second MR angioscan performed a week later was compatible with the presence of an intramural hematoma of the dissected artery, and showed a partial rehabilitation of vasal lumen. The patient partially recovered and was discharged two weeks after the onset of symptoms.

CONCLUSIONS: Each painful Horner's syndrome should be considered highly suggestive of internal carotid artery dissection until proven otherwise. Lower cranial nerve involvement, in particular of hypoglossal, is thought to be secondary to nerve compression by intramural hematoma or to ischemia. Vagal and glossopharyngeal nerve dysfunction has been rarely reported in association to carotid dissection and may have the same explanation. The coexistence of Horner's syndrome and ipsilateral lower cranial nerves palsy require a careful differential diagnosis with brainstem lesions. MRA study resulted a safe, not invasive procedure able to correctly diagnose carotid dissection and to properly monitor the evolution of the disorder.

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VALIDATION OF A STANDARDIZED ASSESSMENT OF POSTURAL CONTROL IN STROKE PATIENTS. C. Benaim, D. Pérennou, J. Villy, M. Rousseaux, J. Y. Pelissier, CHU, CHRU Hôpital Swynghedauw (Nimes, Lille, F)

Few clinical tools available for assessing posture abilities are especially designed for stroke patients. Most have major floor or ceiling effects, and their metrological properties are not always completely known. The Postural Assessment for Stroke Patients (PASS) was elaborated in concordance with three main ideas. (1) Basically, postural control relies upon two domains which both have to be assessed: the ability to maintain a given posture and to ensure equilibrium in changing position; (2) a useful scale should be applicable for all patients, even those with very poor postural performances; (3) a sensible scale should contain items with increasing difficulty. On this basis, we have adapted the 'BL Motor Assessment' (Lindmark et al., 1988). This new scale, which contains twelve four-level items assessing postural abilities in lying, sitting and standing positions, has been validated in 70 patients tested at D30 and/or D90 post stroke onset. Normative data obtained in 30 age-matched healthy subjects are also presented. The PASS meets the following requirements: good construct validity, excellent predictive validity, high internal consistency as well as high inter-rater and test-retest reliabilities. Among the different postural scales dedicated to stroke patients, it undergoes one of the most complete validation phases. With a view to assessing postural control of stroke patients in a clinical context, we recommend using the PASS during the first three months following the cerebrovascular accident.

P239
CAROTID ANGIOPLASTY: TECHNIQUES TO PREVENT EMBOLIC COMPLICATIONS. H. Sievert, K. F. Beykirch, R. Theis, I. Bösenberg, W. Pfeil, C. Rubel, A. Fach, H. Spies, H. Merle, R. Ensslen, Cardiovascular Center Bethanien (Frankfurt, D)

Since February 1994, 97 high-grade lesions of the internal carotid artery in 88 patients were treated with primary implantation of a stent. The first balloon inflation was performed (whenever possible) after stent placement. In 25 lesions a balloon protection device (PercuSurge) for temporary occlusion of the distal internal carotid artery was used to prevent embolic complications.

No lesions were excluded for morphological reasons. Clinical indication for angioplasty was a previous stroke in 14 and one or more TIA's in 22 lesions. 61

lesions had non-specific symptoms or were asymptomatic. 55 patients had additional stenoses or occlusions of other cerebral vessels. In 76 197 lesions stent implantation (87 Wall-, 2 Palmaz-, 1 Multilink, 1 Jo-Stent, 7 Bard-Memotherm Stent) was possible before the first balloon inflation. In the remaining lesions pre-dilatation with a small (2.5–3 mm) balloon had to be performed before stent implantation. Together with the protection device, primary stenting was possible in 92 % of the procedures.

All procedures were angiographically successful. Mean stenosis diameter decreased from 77 +1- 11 to 6 +1- 17 %, MLD increased from 1.2 +1- 0.6 to 4.8 +1- 1.0 mm. In 16 125 procedures with protection device atherosclerotic debris could be collected. Only two cerebral complications (1 stroke and 1 central retina artery occlusion) occurred (2.1 %), both in procedures without embolic protection device.

In conclusion, complications are rare with primary carotid stent implantation. Embolic protection devices further reduce the risk of carotid angioplasty.

P240
TRANSCATHETER CLOSURE OF PATENT FORAMEN OVALE (PFO) FOR PREVENTION OF RECURRENT EMBOLIC STROKE – ACUTE RESULTS AND FOLLOW-UP. H. Sievert, U. Krumsdorf, K. Horvath, R. Schräder, U. Babic, A. Fach, H. Merle, R. Ensslen, H. Spies, D. Scherer, Cardiovascular Center Bethanien (Frankfurt, D)

Patients with a patent foramen ovale and a cerebral embolic event are at an annual risk of a recurrence of 3 to 4 %. Catheter closure of PFO has been proposed as an alternative to anticoagulation or surgical closure. Several devices for transcatheter PFO-closure have been developed.

Between Aug 1994 and Dec 1999 transcatheter PFO closure was attempted in 183 patients aged from 17 to 75 years (mean 46 ± 13). The PFO was suspected to have caused 1–5 paradoxical embolic events (stroke in 100, TIA in 101 and peripheral embolism in 9 patients). Other sources of embolism were excluded. Balloon sizing of the PFO revealed a diameter between 4 and 24 mm.

PFO-closure was successfully performed in 23 126 patients with SIDERIS-But toned-Devices, in 11 111 patients with the ASDOS double-umbrella, in 19 119 patients with ANGEL WINGS occluder (2 devices in one patient), in 30 130 patients with the CardioSeal/CardioSeal-Starflex occluder, in 65 165 patients with the PFO-Star occluder, in 26 126 patients with an Amplatzer-PFO occluder and in 616 patients with a Helex occluder. The overall primary success rate was 98.4 %. During follow-up one SIDERIS-Device was surgically explanted because of partial unbuttoning and two patients suffered recurrent embolism. Arm fractures occurred in four ASDOS and one ANGEL WINGS system, thrombus-formation was diagnosed after implantation of an ASDOS, ANGEL WINGS and CardioSEAL system and on 4 PFO-Star devices. One patient died during surgical explantation of an ASDOS-umbrella due to septicemia. During 190 patient-years only five patients suffered from a recurrent embolic event.

In conclusion, all systems are effective for transcatheter PFO closure. The results of catheter based PFO closure have improved with the newer systems. Like in any interventional procedure severe complications may occur. Randomized studies to compare catheter closure and anticoagulation andlor surgery are justified and required.

P241
POST-TRANSFUSION POSTERIOR LEUCOENCEPHALOPATHY SYNDROME. P. Perrone, M. V. Calloni, R. Freschi, A. Giorgetti, G. Mariani, R. Morini, P. Secchi, A. Sermoni, Hospital of Legnano (Milan, I)

Reversible posterior leucoencephalopathy (RPLS) is a rare syndrome characterized by extensive white matter abnormalities suggested by CT or MRI studies, of bilateral edema involving primarily the occipital and parietal regions. Clinical signs include headache, confusion, seizure, visual field defect. EEC abnormalities are typically remarkable. PLS has generally been reported in association with HTN encephalopathy, eclampsia, renal diseases or immunosuppressive therapy and only occasionally after blood transfusion. In general PLS is a reversible condition. We report two cases of PLS following blood transfusion. Case I is a 47 year old woman presenting severe anaemia secondary to massive vaginal bleeding (uterine myoma). Six days after receiving 4 red blood cell transfusions, she developed nausea, headache, confusion, anopsia and focal seizure with secondary generalization. Her blood-pressure remained normal. Case II is a 49 year old man treated with steroids and azathioprine because of hemolytic anaemia. He presented acute renal failure and HTN and received 3 blood cell transfusions for severe anaemia. Six days after he developed status epilepticus and anopsia. MRI studies showed in both patients diffuse areas with abnormal T2 signal in the occipital and temporoparietal regions suggesting cerebral edema. The MRI studies performed 4 months after the initial presentation, proved in one patient (CASE I) persistence of abnormalities in posterior regions. These cases indicate that RPLS is not always a reversible condition. Moreover symptoms suggesting development of PLS after multiple blood transfusion should induce prompt aggressive treatment including vasoactive therapy.

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SHOULD TRANSIENT ISCHAEMIC ATTACKS PATIENTS BE ADMITTED IN A STROKE UNIT? B Fuentes, E Diez-Tejedor, Fj Mora, G Suarez, M Lara, P Barreiro, University Hospital La Paz, University Hospital La Paz Universidad Autónoma De Madrid (Madrid, E)

The efficacy of Stroke Units (SU) in the management of stroke in-patients is known though at present, there are only few studies analysing specifically their diagnostic and therapeutic implications in the transient ischaemic attack (TIA) patients. Methods and Results: We compared the outcome of four homogeneous samples of patients before (1994) and after (1995–97) the establishment of a SU in our department. Patients were admitted with the same inclusion criteria and cared for by the same health professionals. We analysed length of stay, etiological diagnosis, type of treatment (antiplatelet versus anticoagulant agents) and acute stroke care costs during in-hospital period. Statistics: t-student, Chi-square. 2032 stroke in-patients were admitted during the study period. 331 patients had a TIA. The SU determined an increment in the number of hospital admissions (up to 41 %), a reduction in the average length of stay (up to 36,8 %; $p < 0,001$), an improvement in the diagnosis of carotid artery stenosis as well as cardiac sources of embolism (6,9–12,5 % vs 3,3 % and 30,4–60 % vs 13,3 % of the studies performed respectively). In the SU we found a significant increment in the prescription of anticoagulant agents (up to 32,2 % vs 9,1 %; $p < 0,001$). There was a reduction in acute stroke care costs (cost per patient 1951,8–2289,1 vs 3084,3 euros) in favour of the SU, which represents a saving of 25,8–36,8 %. Conclusions: The admission of TIA patients in a SU determines an increment in the number of patients attended, reduction of average length of stay and an improvement in the diagnostic sensibility, that is, an improvement in the efficacy and efficiency in the management of TIA patients.

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INFLUENCE OF DEMENTIA ON MORTALITY IN STROKE PATIENTS: A 3-YEAR FOLLOW-UP STUDY. H. Henon, I. Durieu, O. Godefroy, G. Guerouaou, C. Lucas, F. Pasquier, D. Leys, Hopital Roger Salengro (Lille, F)

Objective: to evaluate the influence of pre- and of post-stroke dementia on the 3-year mortality rate in stroke patients.

Background: the risk of death is increased in demented patients. Pre- and post-stroke dementia are frequent. Methods: In 202 consecutive stroke patients > = 40 years, the prevalence of pre-stroke dementia was determined using the Informant Questionnaire on Cognitive decline in the Elderly (IQCODE) with a cut-off of 104. At month–6, the diagnosis of dementia was based on ICD–10 criteria in survivors who underwent the visit with the neurologist, on the IQ-CODE score obtained by telephone contact in survivors who did not. Patients were followed-up during 3 years. Kaplan-Meier analysis was used to estimate the cumulative proportion of survivors in function of dementia. Cox proportional hazards analysis was used to estimate the risk of death associated with pre- and post-stroke dementia, after adjustment for other potential predictors of stroke mortality. Results: of 202 patients, 33 had pre-stroke dementia. Of 142 survivors at month–6, 42 were demented. At year–3, the cumulative proportion of survivors was 27.27 % in patients with pre-stroke dementia and 62.12 % in patients without ($p=0.0007$). Pre-stroke dementia was not an independent predictor of death within 3-years. At year–3, the cumulative proportion of survivors was 54.55 % in patients with post-stroke dementia and 91.54 % in patients without ($p=0.0001$). Post-stroke dementia was an independent predictor of long-term death, the other predictors being aging and stroke recurrence. Conclusion: post-stroke dementia adversely influenced long-term survival. Although pre-stroke dementia was not an independent predictor of death within 3 years, the mortality rate was higher in patients with pre-stroke dementia. Both cognitive and physical functions should be assessed in clinical studies of stroke outcome.

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THE SYNDROME OF SPONTANEOUS INTRACRANIAL HYPOTENSION. P. Perrone, M.V Calloni, R. Freschi, A. Giorgetti, G. Mariani, R. Morini, P. Secchi, A. Sermoni, Hospital of Legnano (Milan, I)

We report four cases of orthostatic headache related to the syndrome of intracranial hypotension. The clinical picture was for all of them characterised by severe headache, accentuated by erect position and relieved assuming a recumbent position and not responding to analgesic therapy. Associated with nausea, dizziness, tinnitus, generalised malaise. The neurological examination was normal. LP revealed low CSF opening pressure and high protein without cells.

Gadolinium-enhanced MRI revealed an extraordinary degree of dural enhancement and only in two cases downward displacement of the cerebellar tonsils. Three cases were spontaneous with no evidence of CSF leak or systemic illnesses, including autoimmune processes. One patient showed CSF leaks following discectomy. All have been treated with non-invasive therapy: bed rest, hydratation, caffeine, brief trial of steroids with reported improvements over the following months (6–12 months), including the patient who underwent spinal surgery. Our experience encourages non invasive treatment despite several reports about epidural blood patch also in patients without epidural spinal leak.

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CEREBROVASCULAR MANIFESTATION OF SYSTEMIC INVASIVE ASPERGILLOSIS – REPORT OF FOUR CONSECUTIVE PATIENTS AND REVIEW OF THE LITERATURE. H. K. Spiss, E. Taferner, E. Luginger, B. Pfausler, A. Kampfl, H. Maier, E. Schmutzhard, University Hospital for Neurology of Innsbruck, University Institute for Pathology (Innsbruck, A)

In recent years lipid formulations of Amphotericin-B provide a better therapeutic approach towards systemic aspergillosis. However, invasive aspergillosis still remains a fatal disease in most of the cases, especially in its disseminated form with involvement of the central nervous system with a mortality rate of approximately 80–100%. Most of the patients are immunosuppressed following organ transplantation and an increasing number of patients suffer from HIV. Importantly however, recent reports provided evidence that even immunocompetent patients may develop systemic and/or cerebral aspergillosis. This report gives an overview of four consecutive patients with systemic aspergillosis, admitted at our Neurological Intensive Care Unit. All of them had symptoms of vascular disorders of the central nervous system. One patient presented with a syndrome of the anterior spinal artery, two patients were diagnosed with a thrombosis of the basilar artery and one patient suffered from subarachnoid hemorrhage and intracerebral hemorrhage due to a mycotic aneurysm of the left middle cerebral artery. Although three of our four patients were treated with specific antimycotic therapies, none of the patients survived. In summary, our data suggest that systemic anticoagulation may have a therapeutic implication in patients with central nervous system (CNS) aspergillosis. However, future studies have to further investigate the therapeutic potential of this treatment, in particular as cerebral aspergillosis may not only cause ischemic complication but also mycotic aneurysm and intracerebral bleeding.

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THERAPEUTIC EFFECT OF RASAGILINE IN STROKE-PRONE SPONTANEOUSLY HYPERTENSIVE RATS. S. Eliash, Z. Speiser, A. Slovis, S. Cohen, Sackler School of Medicine Tel Aviv University (Ramat Aviv, IL)

Stroke prone sprontaneously hypertensive rats (SP-SHR) administered 1% NaCl drinking solution and Stroke-Prone Rodent Diet develop severe hypertension as well as glomerular and cerebrovascular lesions with prominent pathological changes in the brain and kidney with a high incidence of stroke. The aim of this study was to determine whether chronic treatment with the MAO-B inhibitor, Rasagiline, can prevent or delay stroke as well as ameliorate the outcome of stroke in salt-loaded SP-SHR. Male SP-SHR aged 6 weeks were used in the study, which lasted 12 weeks. Two groups of rats were studied. Group 1 (n=26) was untreated and Group 2 (n=26) was treated with Rasagiline 3 mg/kg/day in the drinking fluid. Rasagiline significantly prolonged survival from 54.35 to 73.96 days (Kaplan Meier survival analysis). Stroke incidence was also decreased from 14/26 in the untreated rats to 5/26 in the Rasagiline group. Stroke severity was determined by neurological severity score (NSS). NSS was significantly reduced from 7.0 in the untreated rats to 4.8 in the treated rats on the day of the stroke; 24 hrs after the stroke it was 4.8 vs 2.1 respectively. Histological evaluation also showed decreased severity of brain pathology. Decreased kidney damage was demonstrated both by urine protein concentration which was reduced in the Rasagiline-treated rats, as compared to the untreated rats, as well as decreased tubular nephropathy observed in the histological examination of the kidneys. Salt-loaded SP-SHR developed malignant hypertension during the 12-week course of the study. This drastic rise in blood pressure was attenuated in the Rasagiline-treated rats. In the untreated group blood pressure rose from 122 at the start of the study to 231 mmHg at the end of the study. In the Rasagiline-treated group, from 127 to 184 mmHg. HR also increased in the untreated rats (388 to 420 beats/min), but not in the Rasagiline-treated rats (383 to 385 beats/min). Our results show that chronic Rasagiline therapy exerts protective effects against stroke and severe vascular lesions in the kidney of salt-loaded SP-SHR. Moreover, when stroke did occur its neurological outcome was less severe in the Rasagiline-treated rats. The mechanism of action of Rasagiline in stroke has yet to be elucidated. Contributing factors could be its protective actions on the brain, kidney and its antihypertensive effect.

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GENDER INFLUENCES STROKE OUTCOME. B Fuentes, E Díez-Tejedor, G Suarez, FJ Mora, M Lara, P Barreiro, University Hospital La Paz (Madrid, E)

There are known the differences in the predisposing factors and the subtypes of stroke between man and female. Our goal is to analyse if there are also gender-related differences in the stroke outcome. Methods and Results: We analysed the data of 2032 consecutive stroke in-patients from our stroke databank corresponding to the patients admitted in our department during 1994–1997. Patients were admitted with the same inclusion criteria and cared for by the same health professionals. We analysed mortality, average length of stay, functional state (modified rankin scale) and destiny at discharge. 1128 male and 904 female patients were admitted during the study period. Women were older than men (71,8 ±11,6 vs 67,5 ± 11,6; $p < 0,001$). There were no differences in mortality rate: 5,2% men, 6% women; $p = 0,4$). Average length of stay was significantly shorter in men (12,2 ± 9,4 vs 13,9 ± 11; $p < 0,001$). At discharge, 69% of men and only 55,4% women were independent (modified rankin scale $< = 2$) ($p < 0,001$). There were also important differences in destiny at discharge, in favour of men: 78% of men vs 64,1% of women could go home ($p < 0,001$), and only 4,3% of men vs 10,8% of women were transferred to nursing home ($p < 0,001$). On the other hand more women were transferred to rehabilitation wards at discharge (18% vs 11,3%, $p < 0,001$). Conclusions: There are important gender-related differences in stroke outcome with better functional prognosis and shorter length of stay in men than in women. This fact could be due, in part, to the different mean age. The fewer transference to home and the more interest in rehabilitation in women could be explained for by the difference in functional outcome as well as social factors (family disposal).

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THE PREDICTIVE VALUE OF THE PLASMATIC AMINO ACID LEVELS IN THE BRAIN HEMORRHAGE PATIENTS, AND THEIR CORRELATION WITH CT AND SPECT FINDINGS. G. Suarez, F. J. Mora, E. Diez-Tejedor, A. Hernanz, J. Coya, A. Frank, P. Barreiro, University Hospital La Paz (Madrid, E)

Objectives: To analyze during the acute phase of intracerebral hemorrhage (ICH) the relationship among the hematoma volume (HV) and perilesional hypodensity (PH) in CT, with the plasmatic amino acid levels and cerebral blood flow (CBF) changes. To determine their predictive value on the patients' outcome.

Methods and Results: We include patients with spontaneous ICH in the first 24h of onset; and exclude traumatic or not hemispheric ICH. We analyze the following variables: 1) Previous Barthel scale. 2) Admission: Canadian scale; HV and PH; plasmatic amino acid levels (PAL) (n = 23); and SPECT. 3) One week later: SPECT. 4) Outcome after one month: both neurological and functional scores (Canadian, Barthel and Rankin scales). 11 patients were included; mean age 66,9 ± 15,6 years. The PAL that showed a higher percentual increment compared with their standard values were glu, leu, lys and hys. The HV and PH showed statistically significant correlation with the increase of PAL (hys, val, met, phe, iso, trp, lys [$p < 0,01$] and ala, val, iso, phe[$p < 0,05$] respectively). There was a correlation among the outcome after one month with the HV ($p < 0,01$) and the increment of PAL (hys, val, met, iso and phe [$p < 0,05$]); however the PH didn't show relationship with the outcome. The reduction of the CBF was related only with the HV. There was no correlation among the CBF changes with the PH, neither with the outcome. Conclusions: Our findings suggest that the highest predictors in the outcome in the ICH are, besides the hematoma volume, the plasmatic amino acid levels. However the PH seems to have no correlation with the outcome. On the other hand, the SPECT detects a cerebral blood flow decrease that related only with the hematoma volume.

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URINARY TRACT INFECTION IN ACUTE STROKE. J. Roquer, C. Jericó, X. Sanz, A. Rodríguez Campello, M. Gomis, J. Izquierdo, A. Pou, Hospital del Mar (Barcelona, E)

Urinary tract infection (UTI) is a common medical complication in patients with stroke. However little information about mechanisms, risk factors and outcome in patients with UTI in the acute phase of stroke is available.

MATERIAL AND METHODS: We report the results of a study on UTI in a consecutive series of 1420 patients with acute stroke admitted in our stroke unit. We compared patients with UTI during the acute phase of stroke (UTI patients) with those without (non-UTI patients). Age, sex, vascular risk factors, stroke subtype and outcome were analyzed.

RESULTS: 1.- We found 152 cases of UTI (10.70%); 2.- No differences

were seen in age (74.5±10.6 versus 73.4±11.2, p< 0.2), and vascular risk factors (diabetes, hypertension, atrial fibrillation and ischemic cardiopathy); 3.- UTI was more frequent in women than in men (63.8 % versus 36.2 %; p< 0.001. OR:2.2); 4.- UTI was diagnosed in 143/1096 (13 %) of patients with major strokes and in 9/324 (2.8 %) in minor strokes (TIA or RIND). 5.- In-hospital mortality was 15.8 % in UTI patients and 11.5 % in non-UTI patients (p< NS; OR:1.4). 6.- Stroke severity was higher in the UTI patients than in the non-UTI patients, according to the Barthel index at discharge (p< 0.001) and Canadian score at discharge (p< 0.001). 7.- 54.7 % of UTI patients had urinary bladder catheter and 60 % were incontinent.

CONCLUSIONS: 1.- UTI was detected in 10.7 % of patients in the acute phase of stroke; 2.- Women had a higher risk of UTI (OR:2.2), but age and vascular risk factors didn't play any role in the development of UTI; 3.- UTI were more frequent in patients severely impaired, probably due to urinary bladder catheter necessity. However the presence of UTI was not related to a statistical significant in-hospital mortality increase.

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RAPIDLY PROGRESSIVE DEMENTIA REVEALING ANGIITIS OF THE CENTRAL NERVOUS SYSTEM. G. Castelnovo, B. Biolsi, A. Barbaud, C. Marty-Double, P. Labauge, Dpt Of Neurology, Dpt D'anatomopathologie, Dpt Of Neurology Chu Montpellier-Nîmes (Nîmes, F)

Angiitis of central nervous system (SNC) is a heterogenous group of diseases which are characterized by histological evidence of vascular inflammation. The clinical presentation is protean. Usually the SNC is involved with focal to diffuse manifestations and acute to chronic evolution.

OBJECTIF: We report a rapidly progressive dementia reveling an angiitis of SNC. Case report: A 70-year old woman was admitted to hospital for evaluation of a mental confusion and stupor. In the two months preceding admission she exhibited a behaviour and intellectual decline and a diagnosis of dementia has been proposed. On admission laboratory investigations and CSF examination were normal. MRI showed multiple brain infarctions. The patient rapidly progressed to death. Necropsy showed central nervous leucocytoclastic angiitis.

DISCUSSION: Angiitis of nervous system consists of wide spectrum of disorders which have in common inflammatory lesions of the vascular wall. The diagnosis is usually difficult because of the high variability of the clinical presentation. The main complementary exames are not specific of angiitis. Headache, seizures and focal neurological deficits are usually observed. Our report is characterized by a rapidly progressive dementia without any focal symptoms. The diagnosis was affirmed by autopsy findings.

CONCLUSIONS: This report confirms that angiitis of CNS should be considered as differential diagnosis of rapidly progressive dementia.

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BILATERAL VERTEBRAL ARTERY OCCLUSION: REPORT OF 7 CASES. S. J. Rüegg, E. W. Radü, A. Hetzel, A. J. Steck, P. A. Lyrer, Neurology Dept., Neuroradiology (Basel, CH; Freiburg, D)

Bilateral vertebral artery occlusion (BVAO) is a rare cerebrovascular disorder and accounts for about 0.1–0.2 % of all strokes. Methods: Seven cases of BVAO are presented. Emphasis is given to the etiologies and the clinical course of BVAO.

Results: BVAO was diagnosed in seven patients (3 women, 4 men, mean age 63 years (54–74)). They are younger than patients with cerebrovascular disease of the anterior circulation (70 years). The causes of BVAO were in 4 cases atherothrombotic disease and in 3 cases giant-cell arteritis (GCA). Hallmarks of the clinical course were either intermittent (dizziness, blurred vision; in 3 patients), remitting (vertigo, headaches, diplopia, TIA/PRIND; in 2 patients) or stepwise progressive signs of vertebrobasilar ischemia (limb paresis/hypaesthesia, gait disorder, multiple (lower) cranial nerve palsies; in 6 patients) which was followed by a more pronounced, rapid deterioration (either hemi-/tetraparesis, -ataxia, -hypesthesia, or locked-in syndrome). Except for fever, headache and laboratory results indicating acute inflammation, BVAO due to atherothrombotic disease and GCA did not differ in signs and symptoms. All seven patients had anticoagulation. Two patients with GCA had immediate and one patient delayed immunosuppressive therapy with steroids and cyclophosphamide. This patient died later of recurrent strokes leading to locked-in syndrome. The outcome was serious too in the six surviving patients with persisting disability (modified Rankin-Scale 3–4).

Conclusion: The clinical picture of BVAO is characterised by sudden onset of nonspecific and later stepwise progressive neurological signs and symptoms of impaired vertebrobasilar perfusion. Such a course of disease together with fever and headache should raise the suspicion of an inflammatory vessel disease, especially GCA. This has important consequences since BVAO is a serious condition and requests rapid diagnostic work-up. In cases of suspected GCA immunosuppressive therapy should be started without delay. Despite the functional basilar occlusion due to BVAO, this disorder shares a better prognosis than acute thrombotic basilar occlusion.

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THE ADVANTAGES OF LACUNAR INFARCTION MANAGEMENT IN STROKE UNITS. FJ Mora, E Díez-Tejedor, G Suarez, B Fuentes, A Frank, P Barreiro, University Hospital La Paz (Madrid, E)

Stroke Units (SU) have been demonstrated to improve management of acute ischaemic stroke patients. Outcome and clinical features of lacunar infarctions seem to be different from atherothrombotic and cardioembolic strokes. We compared the results of stroke in-patients with lacunar infarction treated by Stroke Team (ST) with those treated in a SU in the Department of Neurology. Methods and results: We analysed the outcome of four homogeneous samples of lacunar infarction patients, from our stroke data-base, before (1994) and after (1995–1997) the establishment of a SU in our department. We analysed functional state at discharge (modified Rankin Scale (RS)), average length of stay, and acute stroke care costs during in-hospital period. Statistics: Chi-square, t-student. 2032 patients have been admitted at Neurology Dept. during the study period. 341 were diagnosed as lacunar infarctions; 75 in 1994 (17,2 %) and 266 in 1995–97 (16,62 %). There were no statistical differences in terms of functional state between SU and ST in the neurology department (RS ≤ 2–82,6 % (ST) vs 82–93 % (SU); p = 0.087). We found a reduction in average length of stay in favour of SU (33–45 %; p < 0.0001), and a saving of 1120 euros for each patient.

Conclusions: The management of lacunar infarction patients in SU does not determine a clear benefit in functional state at discharge but implies a high reduction in average length of stay and in acute stroke care cost. These data could help to select the stroke subtype patients for Stroke Unit.

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STENOSIS OF THE MIDDLE CEREBRAL ARTERY: LONG TERM OUTCOME, ROLE OF TRANSCRANIAL DOPPLER ULTRASOUND AND CORRELATION WITH MR-ANGIOGRAPHY. N. Niedermaier, O. Jansen, K. Lowitzsch, R. Winter, Klinikum Ludwigshafen, University of Heidelberg (Ludwingshafen, Heidelberg, D)

Arteriosclerotic disease of the intracranial cerebral vessels with stenosis of the middle cerebral artery (MCA) is a well known cause for ischemic stroke. The long term outcome of stenosis of the MCA is nonetheless discussed partly inconsistently, and little is known about the correlation of transcranial doppler (TCD) ultrasound with magnetic resonance angiography (MRA) in diagnosis of MCA stenosis.

Methods: The medical records of 74 patients with MCA stenosis, that were routinely followed up both clinically and with TCD for 2–6 years, were analyzed and the patients included in the study. 33 of these patients were then examined again physically, with TCD and MR-angiography. Results: One patient died of MCA stroke and one patient had multiple transitory ischemic attacks over the surveillance period of 2–6 years, the remaining patients were clinically stable. The degree of MCA stenosis as diagnosed by TCD did not significantly change. TCD and MRA correlated in 90 % with regard to detection of MCA stenosis in general and in 77 % with regard to detection of the grade of the stenosis.

Conclusions: Our study demonstrates a surprisingly good long term outcome of MCA stenosis with stable TCD results over the period of surveillance. It also shows a good correlation of TCD and MRA in the diagnosis of MCA stenosis.

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AUDIT OF MORTALITY IN A STROKE UNIT. A. Verdelho, J. Ferro, V. Oliveira, T. Pinho E Melo, P. Canhão, F. Falcão, Hospital Santa Maria (Lisboa, P)

Stroke units decrease stroke mortality and dependence and provide less need for institutional care. We audited stroke characteristics and causes of death of patients who died in an acute stroke unit. Methods. File review of all ischaemic and intracerebral haemorrhagic stroke patients who died in the stroke unit between May 1996 and May 1999.

Results. From 1087 stroke patients admitted to the stroke unit during 3 years, 30 (3 %) died during hospitalisation. Patients who died were older than surviving patients (57,7 vs 54 years old), and had a longer medium stay (9 vs 7,6 days). Half of the patients died up to the 4th day of stroke. Fatal stroke types were parenchymal haemorrhagic (14 cases: hemispheric, 9 left, 3 right; 5 lobar, 7 deep; 2 brainstem), primary intraventricular haemorrhage (1), ischemic (14 patients: hemispheric, 4 left, 3 right, 2 bi-hemispheric; 3 medium cerebral

artery (MCA), 2 MCA and anterior cerebral artery (ACA), 2 MCA and posterior cerebral artery, 2 MCA bilateral, 5 vertebrobasilar) and cerebral venous thrombosis (1). In 19 patients Glasgow Coma Scale Score at admission was > 9, but 20 (67 %) of the patients had at least one of the following bad prognostic signs on admission: decreased consciousness, gaze deviation, dysphagia and urinary incontinence. Causes of death were neurological (47 %: 10 patients with stroke progression and 4 with re-bleeding), systemic complications (27 %) and both neurological and systemic causes (27 %). Systemic complications were mainly respiratory infections and cardiac complications. Five patients had previous life threatening systemic conditions.

Conclusions. In our stroke unit, mortality was low and mainly due to neurological causes. Further reduction of death rate can eventually be achieved by better prevention and intensive care of respiratory infections, aggressive (surgical?) interventions to reduce intracranial pressure and mass effect and local thrombolysis of vertebrobasilar stroke.

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INTRACEREBRAL HEMATOMA REVEALING OCCULT ENDOCARDITIS. H. Rossillol, S. Crozier, X. Vandamme, E. Houdart, R. Manai, Y. Samson, G. Rancurel, Hôpital de la Salpêtrière, Hôpital Lariboisière (Paris Cedex 13, F)

A 52 year-old man, without medical past history, was admitted in our stroke unit for the sudden onset of a left hemiparesis associated with persistent headache. Cerebral CT-scan showed a right frontal hematoma and subarachnoid hemorrhage.

Cerebral angiography revealed a mycotic aneurysm of an anterior branch of the right middle cerebral artery. Trans-oesophageal echocardiography demonstrated a mobile aortic valvular vegetation consistent with the diagnosis of infectious endocarditis. There was initially no clinical or biological inflammatory syndrome (no fever, no cardiac murmur, normal white cell count and CRP). One of the nine blood cultures was positive at Streptococcus faecalis. Endocarditis was treated with adapted antibiotherapy; and mycotic aneurysm by endovascular procedure. A microcatheter was placed 10 mm proximal to the aneurysm neck, and embolization was performed using Histoacryl glue. Neurological outcome of the patient greatly improved.

Causative factors in intracerebral hemorrhage are trauma, hypertension, congenital vascular malformations, angiopathies, blood dyscrasias, collagen vascular disease, venous thrombosis, drugs and sepsis (including endocarditis). Intracranial hemorrhage, either intracerebral or subarachnoid, occurs in 2,7 % – 7 % of patients with endocarditis, and is usually linked to rupture of a mycotic aneurysm. The majority of these aneurysms are related to a subacute bacterial endocarditis, and develop after septic emboli. Rare cases of ruptured mycotic aneurysm as the first manifestation of endocarditis have been described in the literature, with a high mortality rate (60 % – 80 %). In our case a voluminous frontal hematoma was the presenting symptom of an occult infectious endocarditis. The good and unusual prognosis here is probably due to the endovascular treatment. Angiography and rapid endovascular procedure should be performed in infectious endocarditis, because of the high risk of recurrent hemorrhage of these aneurysms.

P256
NEUROPSYCHOLOGICAL IMPAIRMENT AFTER STROKE. J. Köster, J. Berrouschot, B. Eggers, A. Wagner, D. Schneider, University of Leipzig (Leipzig, D)

Background: Cognitive decline after stroke is frequent. The influence of various vascular risc factors, e. g. prior transient ischemic attacks (TIA), atrial fibrillation (AF), Diabetes mellitus (DM), an hypertension in development of post stroke cognitive impairment is still not clear.

Method: Prospective study with 114 patients (65 men, 49 women, age 60–85 years, mean age 69 years) suffering from infarction of middle cerebral artery (MCA), were investigated 3 and 12 months after stroke. Inclusion criteria were: age > 60 years, no dementia in history, functional independence (Barthel Index 100 points), Scandinavian Stroke Scale (SSS) £ 50 points 7 days after stroke (= exclusion of transient ischemic events with full neurological recovery), no aphasia and expectation of testing eligibility. Clinical and neuropsychological follow up examinations included: Structured Interview for Diagnosis of Dementia of Alzheimer's or Multi-Infarct-Type (SIDAM), Mini Mental State Examination (MMSE), Hamilton Depression Rating Scale, SSS, Barthel Index (BI).

Results: Using SIDAM cut-offs we found 8 patients with dementia and 43 patients with mild cognitive impairment 3 months after stroke. Nine months later 17 patients were suffering from dementia and 60 patients from mild cognitive impairment. In statistical analysis (Chi-square) after 90 days none of the examined risc factors (age, sex, diabetes mellitus, hypertension, atrial fibrillation, smoking, transient ischemic attacks, location of infarct) showed significant influence on neuropsychological outcome. One year after stroke only atrial fibrillation was an independent risc factor for dementia and mild cognitive impairment ($p < 0,01$)

Discussion: In our study only atrial fibrillation had significant influence on cognitive decline 12 months after stroke.

P257
FREQUENCY OF CARDIOEMBOLISM IN STROKE PATIENTS – CLINICAL STUDY. S. Gvozdenovic, K. Bozic, K. Gebauer, M. Zikic, M. Jerkovic, Institute of Neuropsychiatry (Novi Sad, YU)

The purpose of the study was to investigate the frequency of cardioembolism in patients who suffered an ischemic stroke. Methodology: We investigated 410 patients, both sexes, aged 28–75 years, hospitalized at The Clinic of Neurology in Novi Sad during year 1998. The including criteria which confirmed the diagnosis of cardioembolic stroke were: the presence of the cardiac diseases; absence of other potential causes of cerebral ischemia, particularly the carotid occlusive disease; the other clinical findings in significant correlation with cerebral embolism; and the specific characteristics of the ischemic brain lesion on the computerized tomography and/or magnetic resonance imaging findings. Results: Using these criteria, the diagnosis was confirmed with significant reliability in 104 out of 410 patients. Among 38 out of 410 patients the diagnosis was only possible due to the presence of other etiopathogenetic factors of cerebral ischemia. Conclusion: Our results suggest that applied criteria prove high reliability of the set criteria for diagnosing this type of ischemic stroke.

P258
HEMODYNAMIC RESPONSES OF THE EARLY AMBULATION IN ACUTE HEMIPLEGIC PATIENTS. S. Aksu, K. Armutlu, A. Guclu, O. Saribas, Hacettepe University (Ankara, TR)

Background: After cerebrovascular accidents (CVA) early ambulation is important to prevent the bed rest complications on the circulatory, respiratory, mental and metabolic functions. Although physical therapy is generally recognised as beneficial in the treatment of stroke patients, early initiation of therapy program might have some risks. Because, there are not any commonly acceptable measurements criteria of mobilisation ability.

The purpose of the study was to evaluate hemodynamic responses during early ambulation in acute hemiplegic patients and to determine the factors which may play an effective role in ambulation.

Material and Method: 35 subjects for the study were randomly selected from acute stroke patients. Hemodynamic responses of the hemiplegic patients were evaluated in following 5 days initiation of the ambulation. Firstly, sitting in bed with legs extended and normal sitting positions were used. Blood pressure, heart rate and breath frequency measurements were recorded every three minutes following position changes. When the patients' conditions were stable, the same measurements were done while the patients stood still and walked.

Results: As a result of this study, hemodynamic responses of ambulation during the first and second days showed a significant difference ($P < 0.05$) with resting values. On the other hand the factors which can effect ambulation; etiology, involved brain area, hypertension, coronar artery disease were found to have negative effect on the hemodynamic responses.

Conclusion: According to the findings, the ambulation of the acute hemiplegic patients must be started as soon as possible and for safe ambulation, hemodynamic response must be controlled at the initial stage of ambulation.

Child Neurology

P259
PARENTS' AND CHILD'S EXPOSURE TO SMOKING AND RISK OF CENTRAL NERVOUS SYSTEM TUMOURS IN CHILDREN. G. Filippini, M. Farinotti, Neurological Institute "C. Besta" (Milan, I)

The objective of this case control study is to investigate the role of parental smoking on the risk of central nervous system (CNS) tumors in children. A positive association between CNS tumors in the children and maternal passive exposure to tobacco smoke during pregnancy was found in our previous study. It seems biologically plausible that the developing foetus exposed transplacentally to tobacco smoke might be at increased risk of further cancer risk. In fact, tobacco smoke contains carcinogens, including pre-formed N-nitroso compounds, which are transported across the placenta and can produce DNA adducts in human placenta and haemoglobin adducts in foetuses. Passive smoking exposure is used to describe the involuntary exposure of non-smokers to tobacco combustion products generated by smokers. Although the exposures to

active smoke and passive smoke are not identical, the latter appears to include most of the tobacco combustion by-products, especially the carcinogens.

We included 244 children up to 15 yr of age, diagnosed with a CNS tumor between 1988 and 1993, and resident in the Region of Lombardy Northern Italy. Two population controls matched to each case by date of birth, sex, and residence area were randomly selected from the record office of municipalities. A total of 502 controls were interviewed.

The mother was interviewed and asked about the smoking habits of both parents before and during the pregnancy. We defined two periods of exposure: early pregnancy (approximately the first five weeks), before the mother knew she was pregnant and likely she didn't modify her smoking habit and late pregnancy after the pregnancy was known.

Odds ratios (OR) and their 95 % confidence intervals (CI) were calculated. As the results of the conditional and unconditional analyses were similar the final analysis used unconditional logistic regression on the complete dataset.

The tumor was histologically confirmed in 82 % of the participating cases. We found no association between parental smoking before the pregnancy and the risk of tumors. Significant elevated risks were found for maternal passive exposure to tobacco smoke both in early and late pregnancy. However, a dose-response effect was not found. Slight increased risks were associated with active smoking by the mother in both periods. When the data were analysed by histological tumour type, a significant association with passive maternal exposure was confirmed only for astroglial tumors, during both early (OR, 2.0; 95 % CI 1.2–3.4) and late pregnancy (OR, 1.8; 95 % CI 1.1–3). There was no association between child's exposure to tobacco smoke and the risk of CNS tumors.

The results of this case-control study confirm our previous findings and suggest the existence of an increased risk of developing CNS tumors in children and regular passive smoking by the mother during pregnancy. In view of the sensitivity of the foetus to the harmful effects of tobacco smoke, and against the background of increasing cigarette smoking in young people around the world, our study highlights the need for more information about this possible etiological association.

P260
SLOW CORTICAL POTENTIALS (SCPS) IN THE PATHOGENESIS OF MIGRAINE IN CHILDHOOD. M. Siniatchkin, P. Kropp, W. D. Gerber, Institute of Medical Psychology (Kiel, D)

It has been demonstrated that adults suffering from migraine are characterized by increased amplitude and reduced habituation of SCPs. The contingent negative variation (CNV) – a SCP – was recorded in 43 families with a migraine child ($N = 57$, age 12.4 ± 3.7) and 40 families with healthy children ($N = 44$, age 12.8 ± 3.2) to investigate the pathogenesis of migraine in childhood. The influence of psychosocial factors on neurophysiological abnormalities in migraine was assessed by analysis of parent-child interactions. There was only a tendency towards significance for the differences in CNV parameters between migraine and healthy children ($P < .1$ for all comparisons) during the pain-free interval, if the distance to the migraine attack was not considered. Comparison of the children's data with adult data showed that increased CNV amplitude and reduced habituation characterize the process of sensory maturation, and are common phenomena in childhood. Repeated recordings of CNV parameters in children during the interval, however, showed a maximum increase of CNV amplitude and most pronounced loss of CNV habituation only 1–2 days before the next migraine attack. These CNV abnormalities increased 5 days prior to an attack in young migraineurs and, in the pre-attack phase, differed significantly from the CNV parameters of healthy children ($P < .05$ for CNV amplitude and $P < .01$ for habituation). Periodic changes of CNV amplitude and habituation represent attack anticipation and the variance of the attack "threshold". Analysis of familial contribution described the factors influencing this threshold. On the one hand, there were close similarities in morphology and habituation of the CNV between migraine children and parents with migraine ($r = .60$ and $r = .44$ respectively), and between migraine children and healthy parents with first-degree relatives with migraine ($r = .76$ and $r = .64$ respectively). The genetic influence on CNV features in migraine was supported by the association between the CNV and familial history of migraine ($r = .54$, $P < .05$). On the other hand, abnormal features of parent-child interactions (excessive control and activities inhibiting the child's independence) were significantly related to the variance of the CNV. Genetic and psychosocial familial factors, therefore, may exert an influence on cortical information processing in migraine and constitute a disposition to this disorder. Finally, migraine children were treated with CNV-feedback and instrumental conditioning. The training, associated with normalisation of the CNV amplitude and habituation ($P < .05$ compared to the pre-treatment data), was clinically effective (50 % responder rate and 80 % reduction of the attack frequency compared with the pre-treatment data). The results demonstrated that CNV is an appropriate parameter for investigation of migraine pathogenesis in childhood, describing two important variables – disposition to development of this disorder and the threshold of the migraine attack.

P261
N-ACETYL ASPARTATE METABOLISM IN RAT NEURAL CELLS – IMPLICATIONS FOR CANAVAN DISEASE. Ashkenazi, T. Ben-Hur, T. Brenner, V. Barash,

Objective: To study the transport and degradation of N-acetylaspartate (NAA) in neurons and in glial cells of the rat brain. Background: Canavan Disease (CD) is an autosomal recessive fatal disease, associated with a mutation in the gene for aspartoacylase, the degrading enzyme of NAA. It is characterized by postnatal CNS dysmyelination. NAA, however, is generally considered as a neuronal marker. This apparent discrepancy suggests a cross-talk between neurons and glial cells in the metabolism of NAA. Methods: Glial cell and neuron cultures were prepared from newborn and embryonic rat brains. Transport of NAA into the cells was examined by incubation with 10mM [3H]NAA at 370c and at 50c, followed by counting radioactivity within the cells. Aspartoacylase activity in the various cell populations was assayed by measuring spectrophotometrically aspartate levels derived from NAA hydrolysis. Results: At 37oc, transport of NAA into oligodendrocytes, astrocytes and neurons was similar (20, 35 and 22 pmol/min/mg protein, respectively). At 5oc, transport was negligible in all cell populations. Aspartoacylase activity in astrocytes and in oligodendrocytes was 50 and 250 nmol/min/mg protein, respectively, but in neurons it was below threshold of detection. Conclusions: These results suggest a cross-talk between neurons and glial cells in the metabolism of NAA. While most NAA is concentrated in neurons, the main site of degradation is in oligodendrocytes. We speculate that dysmyelination in CD may be due to toxic accumulation of NAA in oligodendrocytes or due to insufficient supply of vital metabolites.

P262
ALTERNATING HEMIPLEGIA OF CHILDHOOD – A MIGRAINE RELATED DISORDER?. M. v. Maravic, U. Maschke, H. W. Koelmel, Klinikum Erfurt GmbH (Erfurt, D)

Background: Alternating hemiplegia of childhood (AHC) is a very rare clinical disorder of unknown origin. The clinical manifestations typically occur before 18 months of age. The symptoms are characterized by transient attacks of hemiplegia, changing from one side to the other, by tetraplegia, or by attacks of the oculomotor-, extrapyramidal or cerebellar system. Two pathophysiological hypotheses are under discussion: the concept of a mitochondropathia versus the concept of AHC as a migraine related disorder. According to the migraine hypothesis we investigated the cerebral blood flow velocities of AHC-children with the question for vasospasm in AHC-attacks.

Methods and Results: The German self-help-association of parents with AHC-children (15 known children in Germany) enabled us to investigate up to now 8 AHC-children by means of transcranial dopplersonography (TCD). Standard TCD-insonations of all basal cerebral arteries were repeatedly performed during symptom-free intervalls and during AHC-attacks. The ultrasound datas were compared with those of age-matched normals. As results the blood flow velocities were significantly elevated in the symptomatic MCAs and reduced or unchanged in the contralateral MCAs in 6 of 8 children during AHC-attacks. Furthermore we found vasospasm-like changes of the blood flow velocities in the basilar artery during a tetraplegic episode, and in two children a normalizing of the elevated symptomatic MCA blood flow was recorded simultaneous to the recovery from a hemiplegic attack.

Conclusions: For the first time a strong relation could be observed between vasospasm-like blood flow variations of the basal cerebral arteries and the evolution and recovery of neurological symptoms in AHC. Therefore we support the hypothesis that neurological symptoms in AHC are caused by vasospasm of the basal cerebral arteries resulting in intermittent cerebral hypoxia with disturbed neuronal function, followed by transient neurological deficiency. Because of these pathogenetical considerations we may assume AHC as a migraine related disorder.

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MÖBIUS SYNDROME; A DEVELOPMENTAL DISORDER OF THE LOWER BRAINSTEM. H. T. F. M. Verzijl, G. W. Padberg, University Hospital Nijmegen, St. Radboud (Nijmegen, NL)

Möbius syndrome is defined as a congenital palsy of the facial nerve, frequently accompanied by dysfunction of other cranial nerves. The abducens nerve is regularly affected and often also the hypoglossal nerve. In addition, orofacial and limb malformations, defects of the musculoskeletal system, and mental retardation can be present. Since the original paper of J. P. Möbius in 1888, authors have used different diagnostic criteria for Möbius syndrome, varying from congenital facial palsy, with or without loss of ocular abduction, and with or without congenital abnormalities of the extremities. The pathogenesis is unclear, but by absence of a clear hereditary cause prenatal brain stem ischemia is consid-

ered as a possible mechanism. In view of the difficulties of definition, each attempt to make a ruling on clinical aspects, etiology, pathogenesis, and genetics of the Möbius syndrome understandably remains uncertain. In order to shed more light on both the clinical aspects and the definition of the condition, and to arrive at a more directed opinion on etiology and pathogenesis, we examined thirty nine Dutch patients diagnosed as having Möbius syndrome. Of 39 patients with unilateral or bilateral facial palsy, 35 patients had a bilateral and 1 patient had a unilateral abducens paresis. Eleven patients demonstrated features of the Duane retraction syndrome. In 7 cases a complete and in 17 cases an incomplete conjugated horizontal gaze paresis was present. External ophthalmoparesis such as occurring in 4 patients was interpreted to be caused by a congenital fibrosis of the extraocular muscles. Involvement of the hypoglossal nerves occurred in 15 patients and twenty patients suffered from swallowing difficulties because of glossopharyngeal involvement. Thirty of 34 examined patients had motor disabilities such as retardation in motor development, awkward motor performances, clumsiness, and hypotonia. Twenty five persons had problems with coordination varying from disturbed tandem walk, dysdiadochokinesis, and axial imbalance. Associated systemic findings included flattened nasal bridge, epicanthic folds, high arched palate, micrognathia, microglossia, speech problems, talipes equinovarus and branchial malformations, Poland anomaly, epilepsy, and mental retardation. Detailed neurological examination revealed that Möbius syndrome shows considerable overlap with other brainstem developmental syndromes. Möbius syndrome is a metencephalic developmental syndrome; myelencephalic extension of signs frequently occurs and in a lesser degree mesencephalic and telencephalic extension. In extreme cases the caudal part of the brainstem is insufficiently developed leading to respiratory failure; milder cases reveal respiratory failure early in life. Many cases showed mild dysfunction of the long tracts leading to clumsiness and poor dexterity, suggesting that the brainstem lesion is not limited to the cranial nerve nuclei but is more extended and may be interpreted as a regional lower brainstem development restriction. The associated findings in Möbius syndrome suggest a continuum of different brainstem developmental syndromes, and suggest a wider involvement than brainstem nuclei only.

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SEVERE TACROLIMUS LEUKOENCEPHALOPATHY AFTER LIVER TRANSPLANTATION. J. Schuuring, A. Verrips, P. Wesseling, J. Tolboom, Ch. Bijleveld, St. Radboud Academic Hospital Nijmegen, University Hospital Groningen (Nijmegen, Groningen, NL)

Tacrolimus is an immunosuppressive agent frequently used after organ transplantation. A wide variety of neurological complications have been described, resembling those during cyclosporin A therapy. We present a 12 year old girl who presented six months after liver transplantation (biliary artresia) with a secondarily generalized seizure. Her medication included prednison, 15 mg daily and tacrolimus, 3 mg daily. General examination was normal. Neurological examination revealed a slight weakness of the left side. Deep tendon reflexes were brisk on the left side. The left plantar response was extensor, the right flexor. There was a moderate tremor on both hands. Laboratory findings, including liver and renal function and cerebrospinal fluid were normal. PCR on JC virus was negative. Tacrolimus bloodlevel was 14,90 nanogram/ml. A CT- scan of the brain showed extensive bilateral areas of hypodensity of the white matter. MRI of the brain demonstrated multiple bilateral focal areas of hyperintensity on both proton-density and T2 weighted images, throughout the cerebral and cerebellar hemispheres and the brain stem without mass effect or Gadolinium enhancement. Because of the possibility of the presence of a progressive multifocal leukoencephalopathy, a stereotactic biopsy was performed. Light microscopically the brain tissue was normal. After lowering the daily dose of tacrolimus the MRI lesion load and intensity lessened. Leukoencephalopathy is a well known complication of tacrolimus use with a predilection for posterior white matter lesions. So far the etiology is unknown. A correlation between bloodlevels of tacrolimus and toxic effect is not clear, although in most case reports high bloodlevels were measured. The prognosis is good: after cassation of tacrolimus or dose reduction a complete recovery clinical as well as on neuroimaging usually occurs. In experimental settings the toxic effect of cyclosporin A is far greater than that of tacrolimus. The clinical reports of encephalopathy for both drugs are comparable. Direct cytotoxic effect on brain capillary cells and an enhancement of permeability across the blood brain barrier have been suggested as possible mechanisms. Hypocholesterolaemia and hypomagnesaemia may predispose, as is well known for cyclosporin A. Coexisting pathology, such as hepatic or hypertensive encephalopathy may add to the neurotoxicity.

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RESTORATION OF ARYLSULPHATASE A ACTIVITY IN MURINE METACHROMATIC LEUKODISTROPHY OLIGODENDROCYTES BY RETROVIRAL VECTOR-MEDIATED GENE TRANSFER. A. Consiglio, S. Martino, D. Dolcetta, A. Trojani, G. M. Severini, G. Benaglia, L. Wrabetz, G. Cusella, An. Orlacchio, A. Orlacchio, S. Marchesini, P. Aebischer, C. Bordignon, telethon institute for gene therapy, scienze biomediche e biotecnologiche, Biology of myelin lab, dibit-HSR, Div.of surg.res.and gene ther.cent. (Milano, Brescia, I; Lausanne, CH)

Metachromatic Leukodystrophy (MLD) is a neurodegenerative disease caused by the deficiency of Arylsulfatase A (ASA), a lysosomal enzyme which catalyzes the first step in the degradation pathway of cerebroside sulfate. Absence of ASA activity leads to the accumulation of sulfatide mainly within lysosomes of oligodendrocytes (OL) and Schwann cells. The basis for correcting MLD by gene therapy is to use vector-corrected cells to secrete normal ASA for mannose–6-phosphate receptor-mediated uptake by target cells. A promising approach to the treatment of this, as well as other inborn errors of metabolism, is the use of polymer-encapsulated genetically engineered cells implanted into the ventricular space, in order to obtain overexpression and a continuous release of the therapeutic enzyme in the cerebrospinal fluid. To explore this possibility, the retroviral vector LASATIN was used to transduce C2C12 mouse myoblasts. As result, C2C12 increased 20-fold the intracellular enzyme activity and 35-fold the enzyme secretion. In primary culture of murine OL isolated from ASA knockout mice, which contain large amount of undegraded sulfatide, vector-encoded ASA secreted by C2C12 restored normal processing of the sulfatide in the lysosomes compartment of the treated cells. A thin-layer chromatography revealed that treated OL convert most of the sulfatide to the normal final products. Our data provide strong evidence that vector-encoded ASA is secreted by C2C12 at therapeutic levels and normally sorted as biologically active protein to the lysosomes. The implantation of encapsulated transduced C2C12 in an appropriated animal model will allow us to verify the long-term survival of these cells and their potential use for the treatment of MLD. These results represent a first level of feasibility of a drug delivery system to the CNS based on the use of a polymer-encapsulated transduced xenogenic cell line.

Higher function disorders

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NEUROPSYCHOLOGICAL TESTING OF PATIENTS WITH PEO AND KEARNS-SAYRE SYNDROME REVEALS DISTINCT FRONTAL AND PARIETO-OCCIPITAL DEFICITS. C. Kornblum, S. Bosbach, M. Wagner, P. Seibel, T. Klockgether, R. Schröder, University Hospital of Bonn, University of Dresden (Bonn, Dresden, D)

Objective: To study the range and extent of putative cognitive dysfunction in 18 patients with mitochondrial disorders by comprehensive neuropsychological testing.

Methods: Genetic analysis of muscle tissue from 18 patients with progressive external ophthalmoplegia (PEO) and Kearns-Sayre syndrome (KSS) included screening for mtDNA point mutations (3243/8344) and large-scale deletions. All patients were examined by a neuropsychological test battery covering general intellectual capabilities and the following focal cognitive functions: verbal and visual memory, concentration, vigilance, attention, language, visuospacial perception, visual construction, abstraction and flexibility.

Results: Genetic analysis revealed large-scale deletions in 13/18 patients and the "common" 3243 MELAS mutation in 2/12 patients. However, in 3/12 patients none of the frequently encountered mtDNA mutations could be detected. Neuropsychological testing revealed that the mean level of intelligence was scored by 96 (±12) IQ points indicating no general intellectual deterioration in our group of patients. However, 17/18 patients scored below the 10th percentile of performance in various subtest settings. The following focal higher cerebral impairments were detected: disturbance of visual construction in 50 %, of vigilance and concentration in 38 % and of abstraction/flexibility in 35 % of our patients. 72 % of all patients displayed severe impairment of visual motor skills. Additionally, mild deterioration of visual and verbal memory was detected in 33 %.

Conclusion: In our series of 18 patients with mitochondrial disorders neuropsychological testing did not reveal any signs suggesting general intellectual decline. However, subtests demonstrated markedly poor performances in flexibility tasks as well as visuo-constructive deficits. These findings indicate distinct cognitive deficits due to impairment of supervisory attentional control associated to the prefrontal cortex as well as parieto-occipital cortical dysfunction.

P267
ATYPICAL NEUROPSYCHOLOGICAL AND INSTRUMENTAL FEATURES IN A CASE OF PRIMARY DEGENERATIVE DEMENTIA. M. Guidi, L. Paciaroni, S. Paolini, P. Civerchia, S. Castellani, O. Scarpino, I. N. R. C.A. (Ancona, I)

Our report concerns the 16 months follow up of a woman who came to our attention for a language disorder and a calculation difficulty, which interfered with her working capability. She was 56 years old, 10 years educated and she worked as administration clerk. The patient underwent the following examinations: neurological examination, MRI and SPECT of the head, Apolipoprotein E (ApoE) genotyping and neuropsychological evaluation.

A bilateral selective atrophy of parietal lobe was found at MRI, whereas SPECT showed a left marked frontal, parietal and temporal hypoperfusion, which was less evident on the controlateral side. She was homozygous for the ApoE epsilon3 allele. The Mini Mental State Examination score (M. M. S.E) resulted 19. The neuropsychological evaluation showed impairment on both verbal and visuo-spatial memory span and working memory. The episodic memory test was in the normal range and she resulted well oriented. It was not possible to classify the aphasic disorder on the base of the Aachen aphasia test. The repetition and the comprehension of single words were relatively preserved; the increasing stimulus complexity worsened the performances. The naming trial showed the same trend, pointing out that the deficit was prevalently phonological whereas the semantic system resulted relatively preserved. An accurate evaluation of reading showed a phonological impairment. The executive and attentive functions resulted impaired as praxic-constructional and visuo-spatial tasks.

On the base of the neuropsychological evaluation, the cognitive impairment was not compatible with an Alzheimer's disease for the relative integrity of orientation, episodic memory and semantic store. Furthermore, the spatial deficit excluded a diagnosis of progressive non-fluent aphasia. Only the neuropsychological pattern of the frontal-temporal dementia seems closer to the clinical aspect, but the neuroimaging investigations, especially MRI, do not support this hypothesis.

After 16 months the M. M. S. E. score was 17. The patient lives at home. She is able to carry out her daily living activities.

This case suggests the presence of a degenerative dementia not included in the current criteria of classification, which involves primarily the parietal lobe functions, opening the discussion to more complex pattern.

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BETA-AMYLOID 1–42 LEVELS IN CEREBROSPINAL FLUID OF PATIENTS WITH CREUTZFELDT-JAKOB DISEASE. M. Otto, L. Cepek, H. Esselmann, W. Schulz-Schaeffer, M. Neumann, A. Schröter, P. Ratzka, P. Steinacker, J. Kornhuber, H. A. Kretzschmar, S. Poser, J. Wiltfang, Neurology, Georg-August-University, Psychiatry, Georg-August-University, Neuropathology, Georg-Aug.-University (Göttingen, D)

Background: As early stages of Creutzfeldt-Jakob disease (CJD) and Alzheimer's disease (AD) share several clinical features, we investigated amyloid-beta (Ab)1–42 levels in cerebrospinal fluid (CSF) of these groups, inferring that this might give additional help in differentiating patients with CJD from AD patients. Especially as decreased levels of Ab1–42 are found in CSF of patients with AD.

Methods: We investigated 27 patients with CJD, 14 patients with AD, 19 patients with other dementias (OD) and 20 non-demented control patients (NDC) for Ab1–42 in CSF. Twenty-four of the 27 CJD patients were neuropathologically verified. All of the neuropathologically verified patients presented with a type 1 prion-protein pattern. CJD patients were all homozygous for methionine at codon 129. Except for five CJD patients, no beta-amyloid plaques were seen. Additionally, the ApoE status was determined in patients with CJD.

Results: Levels of Ab1–42 in CSF were decreased in patients with AD as well as CJD. Levels of Ab1–42 in CSF of patients with CJD and AD were significantly different from the OD and NDC groups. But there was no substantial difference between the CJD and the AD group (p=0.66). Decreased levels of Ab1–42 did not correlate with the ApoE–4 load in patients with CJD.

Conclusion: Low levels of Ab1–42 in CSF do not exclude a diagnosis of CJD. And decreased levels of Ab1–42 in CSF can occur without beta-amyloid plaque formation in the brain.

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PARKINSON'S DISEASE AND MITOCHONDRIAL DNA DELETIONS: COINCIDENTAL ASSOCIATION OR CAUSE-EFFECT RELATIONSHIP? G. Siciliano, M. Mancuso, R. Ceravolo, V. Lombardi, L.E. Pollina, U. Bonuccelli, L. Murri, University of Pisa (Pisa, I)

There is growing evidence for the involvement of oxidative chain respiratory in Parkinson's disease (PD), suggesting a possible role, genetically or environmentally determined, of mitochondria in both aetiology and pathogenesis of the disease.

We describe two cases of Parkinson's disease in two different pedigrees characterised by diverse phenotypic expression of mitochondrial disease. The first, a 45 yrs old man, came to our observation with liver cirrhosis, Parkinson's disease and diabetes mellitus. Family history was positive for chronic external ophthalmoplegia, diabetes mellitus and liver cirrhosis. The second, a 52 yrs old man, was affected by multiple symmetric lipomatosis and Parkinson's disease. Both patients were affected by typical Parkinson's disease with predominant rigid-akinetic symptomatology. The first patient was under treatment with levodopa, complicated by motor fluctuations and dyskinesias. The second one, treated by levodopa and ropinirol, showed stable response to levodopa. Muscle biopsy revealed scattered ragged red fibers and citochrome c oxidase negative fibers in both cases, while Southern Blot analysis revealed multiple mitochondrial DNA deletions in skeletal muscle of the first, a single deletion in the second one.

Our data support the hypothesis that mitochondrial involvement can be a significant contributor to nigral neuronal death in PD.

P270
ALαA-D-MANNOSIDASES IN PATIENTS WITH ALZHEIMER'S DISEASE (AD). A. Orlacchio, S. Latorraca, L. Parnetti, V. Gallai, P. H. St.George-Hyslop, S. Sorbi, A. Orlacchio, C. Emiliani, University of Toronto, University of Firenze, University of Perugia (Toronto, CDN; Firenze, Perugia, I)

Alzheimer's disease (AD) is an irreversible progressive brain disorder genetically heterogeneous. Familial aggregation has been reported for the more aggressive form of early onset of the disease and for the most common late onset form of AD. Genetic studies have identified in a larger proportion of early onset AD cases pathogenetic mutations in the PS–1 (Presenilin–1), PS–2 (Presenilin–2) and Amyloid Precursor Protein (APP) gene, located on chromosome 14,1 and 21 respectively. The precise function of the related proteins is not known, however PS–1 has been implicated in trafficking and processing of proteins, including amyloid precursor protein (APP), within the endoplasmic reticulum and Golgi apparatus of neuronal cells. There are several studies demonstrating abnormalities of the lysosomal-endosomal system in relation to the development of the diffuse plaques within the cerebellum and striatum in AD patients. In this study we have surveyed in fibroblasts from Familial Alzheimer's disease (FAD) patients the activity of the glycohydrolase alαa-D-mannosidase, a complex enzyme system involved in both the biosynthesis and catabolism of the N-linked glycoproteins. We have taken into account fibroblasts from families carrying mutations in the genes encoding for PS1, PS2 and APP, respectively. In normal human fibroblasts, as in other normal cells and tissues, the predominant alαa-D-mannosidase activity has an acidic pH optimum of 4–4.5 and is located in the lysosomal fraction of cells; a second soluble activity is associated with the endoplasmic reticulum membrane and has a neutral optimum pH; a third activity, which has a pH optimum of 5.5–6, is located in the Golgi compartment. Activity of all forms of alαa-mannosidases varied in FAD patients with the most dramatic changes related to the lysosomal form of the enzyme. The most remarkable increase was detected in 2 AD patients with mutations in the PS2 gene. Two of the three AD patients carrying the same mutations in APP gene, and coming from the same family, displayed very different levels of lysosomal alαa-mannosidase activity. Our data suggest that an accurate analysis of alαa-mannosidases in AD might contribute to the physiopathological knowledge of the disease.

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CEREBROSPINAL FLUID PATTERN IN PATIENTS WITH DEFINITE CREUTZFELDT-JAKOB DISEASE. C. Jacobi, I. Zerr, S. Arlt, A. Schröder, M. Otto, S. Poser, University of Göttingen (Göttingen, D)

Creutzfeldt-Jakob disease (CJD) is a rare neurodegenerative disease caused by the pathologic form of prionprotein. Patients can be clinically classified as probable, possible and other cases. Definite diagnosis can only be made by neuropathological examination. 4–14% of patients classified as other cases suffered from acute and chronic inflammatory diseases of the nervous system. These patients usually have typical findings like pleocytosis, blood-CSF barrier dysfunction and/or intrathecally synthesized immunoglobulins in CSF. In literature CSF pattern of cell count, albumin, IgG, IgA, IgM and oligoclonal bands in CJD was examined in small, not well defined groups or single case reports up to now. The aim of this study was to review the CSF pattern of CJD patients and to examine if CSF changes of acute or chronic inflammatory origin can be found.

We analyzed CSF pattern of 148 patients with definite CJD altogether. Patients are divided into two groups. Albumin, IgG, IgA, IgM and oligoclonal bands in CSF/serum pairs of 25 patients were measured in our laboratory (group I). Of the remaining 123 patients CSF/serum pairs were not available and we had to rely on the CSF reports of the external hospitals (group II). CSF/serum pairs of this group were analyzed in different laboratories.

In group I six of 25 cases (24%) had blood-CSF barrier dysfunction (range Q Alb: 7,8–17,6). Oligoclonal bands, a sensitive sign of intrathecally synthesized IgG, were found in two of 25 patients (8%). No intrathecally synthesized IgA or IgM was detected. CSF analysis of group II was in accordance with the results of group I. Mild pleocytosis (range: 5–11 cells) was found in 6 of 110 patients (5,4%). A blood-CSF barrier dysfunction (range Q Alb: 8,0–22,7) could be shown in 27 of 100 cases (27%). Five of 75 cases (6,7%) had positive oligoclonal bands in CSF.

We describe the complete CSF pattern of albumin, IgG, IgA, IgM and oligoclonal bands in patients with definite CJD. Apart from blood-CSF barrier dysfunction mild pleocytosis and positive oligoclonal bands are rare findings in CSF of CJD patients and do not exclude this diagnosis. Previous inflammatory disorders of the nervous system may lead to persistent oligoclonal bands in the CSF, as shown in one case with lyme disease in the medical history.

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DONEPEZIL SLOWS SYMPTOM PROGRESSION IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE: RESULTS OF A ONE YEAR, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL. P. Subbiah, K. Engedal, H. Soininen, F. Verhey, G. Waldemar, A. Wimo, A-L. Wetterholm, R. Zhang, A. Haglund, P. Subbiah, Pfizer Pharmaceuticals Group Pfizer Inc., Clinic for Geriatric Rehabilitation, University of Kuopio, Department of Psychiatry, The Neuroscience Center, Umeå University, Pfizer AB (NY, USA; Oslo, N; Kuopio, FIN; Maastricht, NL; Copenhagen, DK; Umeå, Taby, S)

Background: To date, the cholinesterase inhibitors (ChE) are the only available treatments for the symptomatic treatment of mild to moderate Alzheimer's disease (AD). Previous studies of ChEs have demonstrated beneficial effects on cognition, activities of daily living (ADLs) and global function in AD patients for up to 6 months. More evidence from placebo-controlled clinical trials of the prolonged effects of ChE inhibitors on symptom progression is awaited. Objectives: This one year, double-blind, placebo-controlled study evaluated the clinical efficacy and safety of the once-daily acetylcholinesterase inhibitor, donepezil, versus placebo, for the symptomatic treatment of patients with mild to moderate AD. Methods: Patients with possible or probable AD from five Northern European countries were randomized to receive either donepezil (n=142; 5 mg/day for 28 days followed by 10 mg/day as per the clinician's judgement) or placebo (n=144). In addition to the primary efficacy assessment of global function, the Gottfries-Bråne-Steen (GBS) scale, secondary efficacy assessments included the Global Deterioration Scale (GDS), a hierarchic scale for the delineation of disease severity, the Mini-Mental State Examination (MMSE), a brief evaluation of cognition, and the Progressive Deterioration Scale (PDS), a disease specific scale constructed to measure changes in patients' ADLs and quality of life. Results: Mean baseline MMSE scores for donepezil- and placebo-treated patients with a mean age of 72.5 years (range: 49–88) were 19.4 and 19.3, respectively. Statistically significant differences in global function in favor of donepezil over placebo for mean change from baseline on the GBS total score were observed at Weeks 24, 36 and 52 ($p< 0.05$). Significant differences in favour of donepezil over placebo were also observed at Weeks 24, 36 and 52 and Endpoint (Week 52 LOCF) for mean change from baseline on the GDS ($p< 0.05$) and MMSE ($p< 0.02$) total scores. After 52 weeks of therapy, significantly more patients treated with donepezil (14%) improved from baseline according to the GDS scale than those receiving placebo (5%; p=0.047). Significant differences were also observed for ADLs on the PDS score at Week 52 and Endpoint ($p< 0.05$). Over one year, 66.9% of donepezil- and 67.4% of placebo-treated patients completed the study. Treatment-emergent adverse events (AEs) were observed for 81.7% donepezil- and 75.7% placebo-treated patients, which, consistent with previous findings, were mainly cholinergic-induced, gastrointestinal in nature and generally transient and mild in severity. Seven percent donepezil- and 6.3% placebo-treated patients discontinued due to AEs. Conclusions: This unique, one year, double-blind study advances previously published data that donepezil slows symptomatic progression in AD patients and is well tolerated.

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CREUTZFELDT-JAKOB DISEASE IS A RARE NEURODEGENERATIVE DISEASE CAUSED BY THE PATHOLOGIC FORM OF PRIONPROTEIN. PATIENTS CAN BE CLINICALLY CLASSIFIED AS PROBABLE, POSSIBLE AND OTHER CASES. DEFINITE DIAGNOSIS CAN ONLY BE MADE BY NEUROPATHOLOGICAL EXAM. B. Paradowski, T. Dobosz, M. Szczepaniak, M. Sasiadek, Medical University (Wroclaw, PL)

Background: The pathologic background of Alzheimer Disease (AD) is loss of neurons, accumulation of senile plaques and presence of neurofibrillar tangles. These tangles consist of hyperphosphorylated TAU protein. In 1993 Vandermeeren at al. reported the presence of Tau protein in cerebro-spinal fluid (CSF) in patients with AD. The aim of our study was to estimate the diagnostic value of Tau protein measurement in CSF of the demented patients. Material and methods The examined group contained 32 patients with AD, meeting the NINCDS/ADRDA criteria, and 15 with diagnosed vascular dementia (VD). The control group consisted of 46 patients without dementia. The TAU protein was measured in CSF using the immunoreactive assay (Innotest TAU-antigen, Innogenetics) Results The level of Tau protein in CSF was 54.20 pg/ml ± 35.46 in the group of patients with AD, and 33.50 pg/ml ± 26.89 in the group of vascular dementia. The difference between the levels of Tau protein in AD patients and control group was statistically significant (p=0.001). The difference in results in group of AD and VD was not significant. However, the level of statistical significance was 0.06 slightly exceeding critical value. Conclusions The authors underline the usefulness of TAU protein level measurement in the early diagnosis of dementia.

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THE TAU PROTEIN IN DIAGNOSIS OF DEMENTIA. B. Paradowski, T. Dobosz, M. Szczepaniak, M. Sasiadek, Medical University (Wroclaw, PL)

The pathologic background of Alzheimer's disease is loss of neurons, accumulation of senile plaques and presence of neurofibrillar tangles. These tangles consist of hyperphosphorylated TAU protein. In 1993 Vandermeeren at al. reported the presence of Tau protein in cerebro-spinal fluid (CSF) in patients with AD. The aim of our study was to estimate the diagnostic value of Tau protein measurement in CSF of the demented patients.

Material and methods. The examined group contained 32 patients with AD, meeting the NINCDS/ADRDA criteria, and 15 with diagnosed vascular dementia (VD). The control group consisted of 46 patients without dementia. The TAU protein was measured in CSF using the immunoreactive assay (Innotest TAU-antigen, Innogenetics)

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Conclusions. The authors underline the usefulness of TAU protein level measurement in the early diagnosis of dementia.

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COGNITIVE DYSFUNCTION RELATED TO HORMONAL AND IONIC LEVELS IN A PATIENT DIAGNOSED OF CONN SYNDROME. M. Gudin, C. Sanabria, B. Legido, F. Bustos, R. Ibàñez, A. Hernàndez, P. de Luis, M. Del Real, J. Vaamonde, Ntra Sra de Alarcos (Ciuda Real, E)

BACKGROUND. The influence on cognition of hormones and electrolytes has been extensively studied on different endocrinological diseases. Reports on dementia due to Conn syndrome are scarcely found in literature. A patient with a dementia and a suprarenal adenoma is presented. Clinical follow up after medical and surgical treatment is studied in order to determine if improvement was related to ionic anomalies or the hormonal ones.

PATIENT AND METHOD. A 64 year old woman was admitted at Hospital because of a confusional state. Two years before admission she was studied because of a seven year history of depression and a decline in cognitive function with abnormal neuropsychological testing. She had hypertension dating 7 to 8 years. CT brain scan showed mild vascular changes; and general blood tests, thyroid hormones, and serology did not show any anomaly. She was diagnosed of a mild vascular dementia. Two weeks prior at Hospital admission she began with disorientation, apathy, and a confusional state. General blood tests were performed at admission. Repeatedly low potassium levels with normal sodium levels and metabolic alkalosis were found. Aldosterone plasma levels were 295 pgp/ml, cortisone basal levels were 1162 mmol/l. A CT pelvic scan showed a suprarenal adenoma.

EVOLUTION. The patient was treated with conservative measures including ion replacement, and spironolactone during several months. The confusional state ameliorated but cognitive function did not. Eight months later the patient was surgically treated removing suprarenal adenoma. Cognitive function improved after surgery. After a year follow up, cognitive testing was normal.

CONCLUSION. Conn syndrome must be recognized as treatable cause of dementia. In this patient cognitive function has not been related to ion levels, but to cortisone and aldosterone blood levels. Cognitive improvement was related to the suprarenal adenoma removal and the hormone blood levels.

Epidemiology

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AMYOTROPHIC LATERAL SCLEROSIS INCIDENCE IN THE PROVINCE OF FERRARA, ITALY, 1964–1998. V. Govoni, E. Granieri, J. Capone, P. Ruppi, M. Manconi, University of Ferrara (Ferrara, I)

Objective. To determine if the incidence of amyotrophic lateral sclerosis (ALS) is changing.

Background. ALS incidence rates may be useful in assessing etiologic theories. Some surveys indicated that the frequency of ALS has increased. A previous population study in the province of Ferrara, Italy, found an annual incidence of 1.0/100,000 (95% CI: 0.8–1.3) for the period 1964–1982. Methods. The incidence of ALS in the province of Ferrara in the years 1964–1998 (13,178,200 person-years) was updated. Multiple case-collection sources were used (all the neurological services serving the community and other sources of potential case material). Only patients resident in the study area were eligible for incidence estimate. The El Escorial diagnostic criteria for ALS were applied. Estimated annual incidence of symptom onset was calculated by five-years period. Results are age-adjusted to the 1981 Italian population. Results. The study found 240 ALS cases: 167 (87 males and 80 females) of them (69.6%) were resident in the study area and eligible for incidence estimate. For the entire period 1964–1998, the incidence was 1.3/100,000 (95% CI:1.1–1.5), 1.1/100,000 when age-adjusted. The incidence was 1.4/100,000 for males (95% CI: 1.1–1.7) and 1.2/100,000 for females (95% CI: 1–1.5). The mean age at onset was 61.2 ± 9.6 (SD) years (60.1 ± 9.2 for males and 61.5 ± 9.4 for females). Incidence (per 100,000) by five-year period was 0.8 (95% CI: 0.4–1.3) in 1964–68, 1.0 (95% CI: 0.6–1.6) in 1969–73, 1.1 (95% CI: 0.7–1.7) in 1974–78, 1.4 (95% CI: 0.9–2) in 1979–83, 1.4 (95% CI: 0.9–2) in 1984–88, 1.5 (95% CI: 1–2.1) in 1989–93, 1.7 (95% CI: 1.2–2.4) in 1994–98 (chi-square test for trend = 9.84, $p < 0.01$). Conclusions. This increase in ALS incidence may reflect changing medical practice, although an increase in exposure to etiologic agents cannot be excluded.

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FREQUENCY OF MIGRAINE IN PATIENTS WITH EPILEPSY AND THEIR FIRST DEGREE RELATIVES. T. Leniger, S. von den Driesch, K. Isbruch, U. Bingel, I. Kavuk, A. Hufnagel, University of Essen (Essen, D)

A relationship between migraine and epilepsy has been discussed for many years. It has to be considered that the prevalence for migraine is much higher than for epilepsy. The aim of our study was to compare the frequency of migraine in epileptic patients with that of their first degree relatives without epilepsy.

Methods: In a 10-month, prospective study 94 patients, who were treated in our outpatient clinic for epilepsy, were interviewed for epilepsy and migraine as well as for their first degree relatives (parents, siblings, children > 18 years) having migraine and/or epilepsy. The diagnosis of migraine was based on the criteria of the International Headache Society. The epilepsy syndromes were diagnosed according to the classification of epilepsies and epileptic syndromes of the International League against Epilepsy and categorised into partial epilepsy (PE) and idiopathic generalised epilepsy (IGE). In case of positive familiar history in first degree relatives the diagnosis of migraine and epilepsy was confirmed by telephone interview according to the criteria mentioned above.

Results: Ninety-four patients (48F, 46M) with epilepsy (63.8% PE, 36.2% IGE) were included. Thirteen of the 94 patients (13.8%) had a comorbidity of epilepsy and migraine, which was characterised as follows: 6 patients migraine with aura and 7 patients migraine without aura, 2 patients with PE and 11 patients with IGE.

Of the 295 first degree relatives 2 were diagnosed for epilepsy (0.7%) and 15 for migraine (5.1%). The 2 relatives with epilepsy had a PE, 4 of the 15 relatives with migraine a migraine with aura and 11 a migraine without aura. Comorbidity in the relatives was not observed. The frequency of migraine in the 94 patients with epilepsy compared with the 293 relatives of the patients without epilepsy was significantly higher (p= 0,005, Mann-Whitney-U Test).

Conclusion: We found a significantly higher frequency of migraine in patients with epilepsy (13.8%) compared with the frequency of migraine in their first degree relatives without epilepsy (5.1%). This preliminary evaluation of an ongoing study was too small to specify the observed comorbidity by aetiology, onset and classification of epilepsy.

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CONCUSSION IN HIGH SCHOOL SPORTS: BEGINNING THE EDUCATION PROCESS. Brooks, UMDNJ-Robert Wood Johnson Medical School (New Brunswick, New Jersey, USA)

In an effort to identify points for emphasis in the concussion education process, this study reports data obtained via survey of high school student-athletes. Survey components included demographics, information sources regarding concussion, reasons for and barriers to reporting concussion. The sample (n=269, mean age=15.54 years, 63% male) was composed of participants in football, boys and girls soccer, ice and field hockey and cheerleading. Student-athletes consistently reported greater frequencies of concussive symptoms (headache, diagnosis of concussion, loss of consciousness, dazing and memory problems) due to sports than due to accidents. Although most student-athletes were knowledgeable about symptoms of concussion, 68% wrongly assumed that a concussion required a direct blow to the head. Student-athletes noted that the most important reasons for reporting a head injury would be diplopia (87%) and disorientation (75%). The most important reasons for not reporting an injury to the team physician or athletic trainer were thinking it not necessary or serious (53%) and concern over losing a scholarship (51%). Although almost all of the student-athletes (99%) believed the most common symptom of concussion was headache, few student-athletes (8%) would report a headache to a team physician or athletic trainer. Based on this information, it is apparent that more formalized concussion education is needed at the high school level, emphasizing both the significance of headache in concussion and the potential seriousness of concussion in sports.

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PREVENTION OF CONCUSSION IN SPORTS PROGRAM. Brooks, UMDNJ-Robert Wood Johnson Medical School (New Brunswick, New Jersey, USA)

Concussion is a common consequence of trauma to the head in contact sports, but can also result from collisions or fall in all forms of athletics and recreational sports. The Center for Disease Control and Prevention estimates that 3–25% of all head injuries are sports-related. It is estimated that 10% of all US college football players and 20% of all high school players will sustain a brain injury in the course of a season. Repeated concussions have been shown to result in cumulative neuroanatomic and neuropsychological damage even when concussions are separated by months or years. Second impact syndrome (SIS) is thought to be the result of a second concussion occurring while an individual is symptomatic from an earlier concussion. Concern regarding concussion and SIS prompted a pilot program at a local high school which included three components: education, surveillance and prevention. Ongoing systematic collection of preseason baseline data was completed on the football team (=48) utilizing the Standardized Assessment of Concussion (SAC). The concussion Grading Scale published by the American Academy of Neurology (AAN) was utilized to define concussion. Test scores obtained post-concussion were compared to baseline scores. Practice parameters developed by the AAN were utilized to guide team physicians' decisions regarding return to play. Education regarding concussion was provided preseason and again at time of concussion. Analysis of surveillance data indicated that 15% of the student-athletes reported a history of Grade 3 concussion. More importantly, 50% reported a history of Grade 1 or 2 concussion (involving no loss of consciousness). A total of eight Grade 2 concussions in seven student-athletes were identified. There were no Grade 3 concussions (involving a loss of consciousness) documented. This program was designed to identify concussions without loss of consciousness and objectively evaluate the existence and severity of cognitive and neurologic findings. These concussions might otherwise be missed. As many student-athletes cross-train and are involved in multiple sports, a tracking system for surveillance of concussion adds another level of protection.

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INCREASING INCIDENCE OF THE GUILLAIN-BARRÉ SYNDROME ON THE CARIBBEAN ISLAND CURAÇAO. R. Van Koningsveld, C. W. Ang, R. Rico, R. Rico, I. S. J. Merkies, I. Gerstenbluth, H.Ph. Endtz, P.A Van Doorn, F. G. A. Van der Meche, Erasmus Medical Centre Rotterdam, Sint Elisabeth Hospital, Public Health Service Curaçao (Rotterdam, Willemstad,)

Purpose: Over the last ten years the number of new Guillain-Barre syndrome patients (GBS) seems to increase in Curaçao. The disease appears to run a more severe course with a high mortality rate. In this study we explored this observed increase by inventarisation of epidemiological, clinical and serological parameters.

Patients and Methods: Curaçao is the largest island of the Netherlands Antilles and is located near the coast of Venezuela. Patients from the only neurological department on the island were identified from hospital discharge records

and where possible serum- and stool samples were collected. Data from a recent epidemiological survey (n=476) carried out in the Netherlands were used for comparison.

Results: The number of inhabitants in Curaçao was approximately 150.000 and 49 GBS cases were identified in the period under study. The overall crude incidence rate (IR) was 2.53/100.000 inhabitants (95% CI 1.87–3.35). From 1987 to 1991, the IR in Curaçao was stable with an IR of 1.62/100.000 inhabitants. From 1992 to 1999, the IR showed a linear increase with an overall IR of 3.10/100.000, resulting in a relative risk of 5.22 compared with the period 1987–1991 (95% CI 2.48–10.2, p=0.02). Especially in recent years, the IR within the year showed a curve linear shape with a top in the colder months and a decline towards zero in the warmer months (p=0.06). Compared with the Dutch study, patients from Curaçao were characterized by a more severe course with a mortality rate of 23% (3.5% in the Dutch group, p< 0.001), a higher percentage of preceding gastro-enteritis (55% versus 20% in the Dutch group, p< 0.01) and less sensory involvement (17% versus 67% in the Dutch group, p< 0.001). From the ten collected serum samples in 1999, nine showed evidence for a recent Campylobacter jejuni infection.

Conclusions: This study shows a seasonal related increase in IR of GBS over a longer period. Serology and the severe clinical course with minor sensory involvement indicate a role for C. jejuni. Prospective studies are initiated to assess whether this is due to a more violent strain, to an increase of C.jejuni from a specific source or whether environmental factors and host factors play a role.

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PREVALENCE AND COMORBIDITY OF PATENT FORAMEN OVALE IN THE YOUNG. C. Gandolfo, S. Angeli, G. L. Bruzzone, C. Finocchi, S. Pretta, M. Del Sette, Dept. of Neurosciences (Genoa, I)

The presence of patent foramen ovale (PFO) is a well-known risk factor for ischemic stroke in the young, being present in 40–60% of young stroke patients as opposed of 15–25% of normal subjects. It can be diagnosed by means of transesophageal echocardiography (TEE) or transcranial Doppler (TCD) with gaseous contrast injection. According to the literature and to our experience TCD, when done with established diagnostic criteria, has high sensitivity and specificity compared to TEE. Recent data suggest that the risk of stroke in presence of PFO is correlated to the size of foramen and thus to the magnitude of right-to-left shunt quantified by TCD. Comorbidity of PFO could be very important in identifying high-risk subgroups: we evaluated comorbidity of PFO examining 73 patients younger than 50 with ischemic stroke (IS), 50 controls asymptomatic for cardio- or cerebral vascular disease (CO), 44 patients suffering from migraine with aura (MA), and 38 migraine without aura (Ma), and 50 subjects with obstructive apnoea (OA). We evaluated also 23 subjects with cluster headache (CH). All the subjects underwent TCD (Multipod DWL, Sipplingen, Germany) with injection of contrast medium in an antecubital vein (agitated solution of 9 ml saline and 1 ml of air). The test was performed with patients at rest and during Valsalva manoeuver. Criterium for diagnosing PFO was presence of at least 3 microembolic signals within 15 seconds from injection. PFO was found in 26 out of 73 IS (35%), 8/50 CO (16%), 18/44 MA (41%), 14/38 Ma (37%), 13/50 OA (26%), 11/23 CH (48%). The difference between CO and IS was significant, as well as with MA, Ma, and CH, while no significant difference was found between CO and OA. Large PFO was associated with higher stroke risk. In conclusion: 1. PFO is a risk factor for ischemic stroke in the young; 2. larger PFO carries a higher risk of stroke; 3. comorbidity should be evaluated to identify subgroups at possible higher risk of stroke; 4. further studies are needed to clarify the definite strategy for stroke prevention in subjects with PFO.

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CLINICAL ONSET-DIAGNOSIS INTERVAL (ODI) IN A PROSPECTIVE COHORT OF AMYOTROPHIC LATERAL SCLEROSIS (ALS) PATIENTS (SLAP REGISTRY). G. Logroscino, G. Benedetto, G. Cacudi, L. Cavone, A. Cazzato, P. Colamartino, S. De Rosa, P. Di Viesti, G. Giausa, V. Guerra, F. Lincesso, B. Maggio, V. Monitillo, C. Nozzoli, A. Osella, G. Palagano, S. Pasca, R. Pulimeno, G. Russo, R. Sambati, V. Santamato, P. Tota, F. Valluzzi, G. Ventura, S. Zoccolella, P. Lamberti, G. Iliceto, E. Beghi, L. Serlenga (Casamassima (BA) Bari, Milano, I)

Objects: To assess possible clinical determinants of delay in ALS diagnosis. Design and Methods: A multicenter registry was established in Puglia to collect all ALS incident cases who came to medical attention through the calendar year 1998. Cases were ascertained through a network comprehensive of all neurological departments, outpatient neurological clinics and EMG (electromyography) units present in the geographic area of interest (23 centers). All patients were evaluated by a neurologist at the entry in the study according to a clinical protocol. Clinical diagnosis was made according to El-Escorial Criteria (1995). ODI was defined as time interval between the first symptoms, according to patients recall, and first ALS diagnosis. Results: We identified 119 ALS patients (35 males, 29 females) among the inhabitants of Puglia (4.025.392 inhabitants). The ODI median was 14.9 months (Range = 1–70.6). The ODI was 16.1 months (1- 54.5) for males and 13.4 months (1- 70.6) for females. The diagnosis was established more rapidly for patients < 39 years (9.9 months; 7.4–12.5) than for patients between 60–69 years (19.1 months; 1–70.6). Patients with bulbar onset were diagnosed more rapidly (6.1 months) than patients with other localizations, particularly than patients with onset in both upper/lower limbs and trunk (28.6 months; 19.9–37). Conclusions: Localization of clinical onset, sex and age are determinants of ODI in a cohort of ALS patients.

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STROKE MORTALITY IN POLAND – ARE THERE ANY DIFFERENCES BETWEEN INDUSTRIAL AND AGRICULTURAL AREAS? D. Ryglewicz, D. Milewska, W. Lechowicz, M. Roszkiewicz, Institute of Psychiatry and Neurology (Warsaw, PL)

Although Poland is known as one of the countries with a high stroke mortality, precise epidemiological data about stroke mortality concerning the whole country are still very limited. The most quoted study are Warsaw Stroke Registry (WSR) and Pol-MONICA which collected data only from selected regions, in majority the cases from different parts of Warsaw. The aim of our study was to analyze stroke incidence and stroke fatality in different parts of Poland.

All identified incidents of stroke treated in the hospitals in 1993 and 1996 (code 430–434, 436–437, International Classification of Diseases 9th version) were included into the study group. Hospital based questionnairies were used for the analysis since previous reports (WSR and Pol-MONICA) have shown that 85% to 99% of stroke patients in Poland had been treated in the hospitals.

The performed analyses revealed that the annual stroke incidence rates were higher in industrial areas (Warsaw, Cracow, Lodz, Poznan) – 274, 222, 426, 228 per 100000 population than in agriculture areas (Elblag, Koszalin, Pila, Suwalki) – 130, 110, 158, 110 per 100000. Stroke fatality rates were also higher in industrial areas (23%, 23.5%, 18%, 26% – accordingly) than in agriculture areas (8.2%, 15.5%, 13.1%, 9.2%). These differences are statistically significant. The analysis revealed also that stroke incidence and stroke fatality had not changed between 1993 and 1996.

It seems likely that the different prevalence of stroke risk factors is probably one of the reasons of these differences. Pol-MONICA showed that prevalence of stroke risk factors is lower in agriculture areas than in industrial ones. It is however not clear whether the observed differences depict a constant or fluctual trend.

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CREUTZFELDT-JAKOB DISEASE IN POLAND: EPIDEMIOLOGICAL, CLINICAL AND NEUROPATHOLOGICAL STUDY. J. Kulczycki, W. Lojkowska, K. Niedzielska, M. Rakowicz, Institute of Psychiatry and Neurology (Warsaw, PL)

The study was established at the beginning of 1996 and was partly sponsored by European Commission (programme Biomed 1). It was preceded by a wide informative action among neurologists and psychiatrists in the whole country. Within four years over 80 cases were referred to us with tentative diagnosis of CJD, several of them for postmortem examination. The probable or possible clinical diagnosis of the illness was confirmed neuropathologically in 38 cases. In nearly all confirmed cases full inquiry form after the model indicated by E. C., including control individuals, was filled. During four years of collecting and processing of cases suspected clinically for CJD we were able to define 35 of them as sporadic and three as presenting familial type of the disease. In the last group one patient belonged to a family with Gerstmann-Streussler-Scheinker syndrome (with mutation in codon 102 of PrP gene), and two others – to a family of clinical and neuropathological features typical for sporadic CJD. No case of the new variant of CJD was found during the study.

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AGE AND SEX DEPENDENCY OF TRANSCRANIAL DOPPLER ASSESSED CEREBRAL HEMODYNAMIC PARAMETERS IN THE ELDERLY. F-E. de Leeuw, T. den Heijer, P. J. Koudstaal, A. Hofman, M. M. B. Breteler, Epidemiology & Biostatistics, Neurology (Rotterdam, NL)

Background and Purpose: The cerebral hemodynamic parameters assessed by means of transcranial Doppler ultrasound may be influenced by age and gender. Results on the relationship between age and gender and these parameters are scarce, especially in the elderly.

Methods: We investigated the relation between age and sex, and the trans-

cranial Doppler assessed cerebral hemodynamic parameters in 826 consecutive participants from the Rotterdam Study. The Rotterdam Study is a prospective population-based cohort study among 7983 participants aged 55 years and over (response 78%), which focuses on neurological, cardiovascular, endocrine and ophthalmologic diseases in the elderly. From the third survey on (1997), cerebral blood flow velocities and pulsatility index measurements by means of transcranial Doppler ultrasonography were incorporated in the study protocol. The relationship between age and sex and the cerebral hemodynamic parameters was analyzed by means of multiple linear regression analysis with the cerebral hemodynamic parameter as the dependent variables and age and sex as the independent variables. These analyses were performed in both the whole study population as well as for men and women separately.

Results: Mean end diastolic cerebral blood flow velocity was 30.3 cm/sec; 29.3 for men and 31.3 for women (p=0.001). Mean of the mean cerebral blood flow velocity was 47.6 cm/sec; 46.2 for men and 49.0 for women (p< 0.001). Mean peak diastolic cerebral blood flow velocity was 82.2 cm/sec; 79.9 for men and 84.5 for women (p< 0.001). Mean pulsatility index was 1.04; 1.05 for men and 1.03 for women (p=0.05). Cerebral blood flow velocity (CBFV) decreased with increasing age: –0.3 cm/sec per year for the mean CBFV; p< 0.001, –0.4 cm/sec per year for the end diastolic CBFV; p< 0.001 and –0.1 cm/sec per year for the peak systolic CBFV; p=0.14. The inverse association between peak systolic and mean CBFV and age was statistically significant in women but not in men. No sex difference was found regarding the end diastolic CBFV. The pulsatility index increased with increasing age: 0.01 per year; p< 0.001. This association was statistically significant in both men and women.

Conclusions: Our data confirm that age is associated with a decrease in cerebral blood flow velocities and a concomitant increase in the pulsatility index. A sex related difference in cerebral hemodynamic parameters probably does exist but the direction of these associations varies.

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ELEVATED SERUM TRIGLYCERIDES ARE AN INDEPENDENT PREDICTOR OF ISCHEMIC STROKE: PROSPECTIVE ASSESSMENT IN CORONARY HEART DISEASE PATIENTS. D. Tanne, N. Koren-Morag, U. Goldbourt, Sheba Medical Center, Sackler School of Medicine (Tel Hashomer, Ramat Aviv, IL)

Background – Little is known about the association between serum triglycerides and cerebrovascular disease. Our aim was to evaluate whether elevated serum triglycerides constitute a risk factor for subsequent ischemic stroke or TIA in a large group of patients with coronary heart disease (CHD).

Methods and results – Patients with documented CHD that were screened for but not included in the Bezafibrate Infarction Prevention (BIP) study and had no history of stroke or TIA (n= 11,177) were followed-up. At baseline medical histories were obtained and blood lipids assessed at a central study laboratory. During a 6 to 8-year follow-up period 965 cases were identified with non-hemorrhagic cerebrovascular disease, of which, after reviewing hospital records with diagnoses of cerebrovascular disease, 487 cases had verified ischemic stroke (per clinical findings and brain CT) or TIA. Age-adjusted rates of non-hemorrhagic cerebrovascular disease (per 1000 persons years) increased with increasing quintiles of baseline triglycerides (9.4, 9.9, 11.1, 12.2 and up to 17.3 for triglycerides in the upper quintile). A similar trend was found for the end-point of ischemic stroke/TIA. In a logistic regression model, adjusting for clinical covariates, the relative risk (95% CI) for developing an ischemic stroke/TIA associated with triglycerides above 200 mg/dl versus lower triglyceride levels was 1.51 (1.23, 1.85). In a separate model adjusting for clinical covariates, total cholesterol and HDL cholesterol, serum triglycerides above 200 mg/dl remained an independent predictor of ischemic stroke/TIA with a relative risk of 1.30 (1.03, 1.64).

Conclusion – High serum triglycerides constitute an independent predictor of ischemic stroke/TIA among patients with established CHD.

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IS DISEASE DURATION RELATED TO THE DEGREE OF DIAGNOSTIC ACCURACY IN AMYOTROPHIC LATERAL SCLEROSIS? E. Beghi, G. Logroscino, A Millul, R. Riva, A. Micheli, F. Salmoiraghi, E. Vitelli, G. Filippini, M. Perini, V. Bonito, D. Baldini, M. Ceroni, D. Testa, M. Poloni, L. Manfredi, G. Bogliun, V. Silani, M. Corbo, P. Perrone, A. Cheldi, G. Mariani, M. Rezzonico, G. Meola, Istituto Ospedale "Miulli", Istituto "Mario Negri", Fondazione "Maugeri", Ospedale di Lodi, Istituto Nazionale Neurologico, Ospedale di Gallarate, Ospedali Riuniti, Ospedale di Sondrio, Istituto "Mondino", Ospedale "Valduce", Ospedale "San Gerardo", Ospedale Policlinico, Ospedale "San Raffaele", Ospedale di Legnano, Ospedale di Desio, Ospedale di Como, Clinica "San Donato" (Milano, Acquaviva delle Fonti, Bari, Gussago, Brescia, Lodi, Gallarate, Varese, Bergamo, Sondrio, Pavia, Como, Monza, Legnano, Desio, San Donato, I)

This study aimed to assess whether disease duration can predict the degree of diagnostic accuracy in newly diagnosed amyotrophic lateral sclerosis (ALS). Patients with ALS firstly diagnosed during the calendar year 1998 in seven provinces of the Lombardy region of Italy (total population 3,992,391) were traced through a regional registry of the disease. The sources of the registered cases included neurological departments, physical therapy and neurophysiology units, located in the entire regional territory. The diagnosis of ALS was made using the El Escorial criteria (J Neurol Sci 1994; 124 (suppl): 96–107). These criteria are based on the topographical location of upper and lower motor neuron signs in four CNS regions (brainstem, brachial, thoracic, crural), the progression of these signs, and the absence of other diseases. The degree of diagnostic accuracy (definite, probable, possible, suspected ALS) is based on a different combination of the above signs. The diagnosis was made by the caring physicians who filled ad-hoc semistructured abstract forms including relevant demographic (age and sex) and clinical data (disease duration and site of onset of symptoms, ie bulbar or spinal).

A total of 64 patients were recruited in the target provinces (overall annual incidence rate 1.6 per 100,000). The sample included 28 women and 36 men aged 29 to 83 years (mean 64.0). Thirty-eight patients had spinal-onset and 26 had bulbar-onset ALS. Disease duration at first diagnosis ranged from one to 84 months (mean 14.4). The El Escorial diagnostic categories were the following: definite 35, probable 15, possible 3, suspected 11. Mean disease duration varied significantly across ALS diagnostic groups: definite 12.1 months, probable 5.4, possible 5.7, suspected 36.5 (p=0.036). However, no positive correlation was found between diagnostic accuracy and disease duration. Mean age, sex, and site of onset of symptoms were similarly distributed across groups.

Based on these findings, the degree of diagnostic accuracy is not related to the duration of ALS. By contrast, disease duration may be an indicator of the heterogeneity of the clinical features and the rate of progression of the disease. Suspected ALS probably includes ALS varieties with a benign, long-lasting course as well as non-ALS forms of motor neuron disease, which will be identified through an appropriate follow-up.

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EPIDEMIOLOGY AND MANAGEMENT OF STROKE IN NICE: TWO COMPARATIVE STUDIES BETWEEN 1991 AND 1998. A. Dunac, M.-H Mahagne, C. Richier, J.-P. Fournier, F. Bertrand, M. Chatel, Hôpital Pasteur, Hôpital Saint-Roch (Nice, F)

OBJECTIVE: Few informations about stroke epidemiology in France are available. The aim of these two studies is to evaluate stroke epidemiology in Nice, as well as to compare data evolution over 7 years.

METHODS: Two epidemiologic studies were performed in the unique department of emergency in the city; the first (prospective) from May to October 1991, and the second (retrospective in view to avoid recruiting bias), from May to October 1998.

RESULTS: In both studies, 600 patients are admitted per year. That makes a high rate of incidence of 284/100,000hab/year. Sex ratio M/F=0.84 in 1998 (0.81 in 1991). As expected, in 1998 (versus 1991), vascular risk factors (VRF) were as follows: hypertension 51.65% (vs 50.34%), heart rhythm diseases 35% (vs34%), medical history of stroke 26.49% (vs 32%), dyslipidemia 18.5% (vs30%), diabetes 17.22% (vs 14.7%), coronary diseases 16% (vs 17.65%), smoking 15% (vs 22%), heart insufficiency 11% (vs 14.68%), arteritis 11% (vs 7.33%). Most patients had at least two VRF (24.5%). Among the 80/302 patients in 1998, with a medical history of stroke, only 10.59% had a secondary prevention by an anti-platelet agent and 2.98% had oral anticoagulation. In 1998, 84 out of 302 (27.81%) stroke, were transient ischemic attacks, and 181 (59.93%) were completed ischemic stroke. Only 29 (9.6%) were hemorragic. Regarding patients' exploration, we noticed a great improvement between 1991 and 1998; 50% of patients were oriented to the department of neurology, where management was quite different from other departments. Cerebral tomodensitometry is done in 95.37% in 1998 (vs 77% in 1991), carotid ultrasonography is applied in 54% in 1998 (81.04% in neurology) vs

39% in 1991. Heart ultrasonography is done in 37.09% in 1998 (50.96% in neurology) vs 21% in 1991. 24 hours ECG monitoring: 15% vs 10% in 1991. Angiography (conventional or by MRI) in 14% (quite exclusively in Neurology) vs 10% in 1991. The average of hospital discharge is 9.95 days vs 15 days in 1991.

OUTCOME: 31 out of 302 patients (10.26%) died in the first week and 64 (21.19%) died in the first month with a mean age of 80.20 years. In 1991, this rate was equal with 20.35%.

CONCLUSION: Nice holds a high stroke incidence, and only half of patients can be managed by the department of neurology, with a fair rate of exploration; populations risk factors are quite similar to previously reported studies. However, we point out an improvement in the management of the patients between 1991 and 1998, and that could be greatly emphasized by the creation of a stroke unit in the frame of a stroke department.

P289
PREVALENCE OF DIABETES AND DIABETIC NEUROPATHY. O. Bolukbasi, R. Yildiz, Adnan Menderes University, Karadeniz Technical University (Aydin, Trabzon, TR)

In a hospital based study, we had found the prevalence of diabetic neuropathy as 31% in Trabzon (Bolukbasi 1998). To estimate the prevalence of diabetes mellitus, diabetic neuropathy and its relationship age, obesity and hypertension, a population based cross sectional survey was conducted in Central Province of Trabzon, Turkey. Cluster sampling of 2642 adults aged 20 years and above (1324 men, 1322 women) was done. After fasting glucose levels, oral glucose tolerance tests were performed to suspected cases for diabetes. The diagnosis of diabetes was made according to World Health Organization (WHO) criteria. All patients with diagnosis of diabetes were evaluated with defined electrodiagnostic investigation to detect neuropathy. History of any medication predisposing to neuropathy were evaluated and on the basis of this information, non-diabetic neuropathies were eliminated. The prevalence of diabetes was found as 6.04% (160/2646). Advanced age, positive family history of diabetes, hypertension and obesity were associated with higher rates of diabetes. Prevalence of diabetic neuropathy was calculated as 11.25% (18/160). The prevalences found in this Northeastern Region (Black Sea) are similar to that of Central Anatolia of Turkey.

Epilepsy

P290
VIGABATRIN-ASSOCIATED VISUAL DISTURBANCES. J. A. Mauri, S. Santos, C. Rios, C. Iñiguez, I. Escalza, F. Morales, Hospital Clinico Universitario (Zaragoza, E)

Vigabatrin VGB is an effective antiepileptic drug AED that selectively increases brain gamma aminobutyric acid GABA. Several patients recently developed constricted visual fields during VGB treatment suggesting the possibility of GABA-associated retinal dysfunction. Objective: to determine the frequency of visual disturbances in a series of 8 patients taking VGB. Methods: Eight patients treated chronically with VGB underwent visual field examination; visual evoked potentials VEP and electroretinogram ERG were made in six patients (75%). We report four patients who showed visual system toxicity. In all cases we discontinued therapy. Results: We found visual disturbances in four patients and pathological ERG in two patients. Case 1: A 34-year-old man had frequent partial seizures before starting VGB. For the first 16 months he had received VGB 2 g/day and the last months he was treated with VGB 1 g/day added to AEDs. ERG a- and b-waves were negative. VEP was normal bilaterally. Visual fields showed severe peripheral constriction (missed points 62 of 81). Ophthalmoscopy revealed optic disk pallor. Case 2: A 56-year-old man had secondary partial seizures due to a great left hemispheric arteriovenous malformation. Six years ago he began VGB 2 g/day along with sodium valproate 2 g/day. Visual fields showed moderate peripheral constriction (missed points: 47 of 79). Case 3: A 33-year-old man had complex partial seizures beginning at age 6. He began VGB 1 g/day added to carbamazepine 1,2 g/day 2 years ago. VGB dosage was gradually increased to 3 g/day. Visual fields showed mild to moderate and bilateral peripheral constriction (missed points: 12 of 79). Latencies of ERG were delayed and VEP was normal in both eyes. Case 4: A 15-year-old girl with longstanding partial epilepsy had onset at age 8. Four years ago she started VGB 2 g/day as monotherapy. Visual fields showed mild to moderate and bilateral peripheral constriction (missed points: 17 of 81). Conclusions: Our results suggests that visual disturbances are common (50%) among patients treated with VGB. Cases 1 and 2 (those with several visual disturbance) noted gradual constriction in their peripheral vision so it would be necessary to follow-up patients treated with VGB in order to prevent retinal dysfunction before they notice visual abnormalities.

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PATTERNS OF FAMILIAL EPILEPSY IN ISRAËL. A. Mazarib, M. Y. Neufeld, A. D. Korczyn, E. Kahana, S. Kivity, I. Blatt, T. Sagi, S. Walid, J. Manelis, R. Shalev, I. Mator, Z. Shorer, I. Goikhman, U. Kramer, A. El Qadra, S. F. Berkovic, Tel-Aviv Sourasky Medical Center (Tel-Aviv, IL)

BACKGROUND: Identification of epilepsy genes depends on clinical characterization of families with a single type of epilepsy. Recent recognition of new syndromes including autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), generalized epilepsy with febrile seizures plus (GEFS+) and familial temporal lobe epilepsy led to finding molecular defects in ADNFLE and GEFS+. We investigated familial epilepsies in the racially diverse Israeli population.

DESIGN/METHODS: Families with two or more affected individuals were ascertained. Two investigators (AM, SFB) personally examined affected individuals and classified the epilepsy syndromes based on clinical, EEG and radiological studies.

RESULTS: 43 families were ascertained of Ashkenazi, Sephardi, Arab or Druze origin. In 17 families unclassified or mixed syndromes were observed, whereas a single syndrome existed in the remainder comprising idiopathic generalized epilepsy (11 families), GEFS+ (6), severe generalized epilepsy (2), familial temporal lobe epilepsy (3) and others (4).

CONCLUSIONS: The ethnic diversity and variable family structures in Israel provide an ideal opportunity for understanding the genetics of the epilepsies and for identifying epilepsy genes.

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MODULATION OF GABA-ACTIVATED CURRENTS BY PHENAZEPAM AND ITS METABOLITES IN ISOLATED RAT PURKINJE NEURONES. M. Kopanitsa, S. Zbarska, Y. Boychuk, O. Krishtal, Bogomoletz Institute of Physiology (Kyiv, UKR)

Phenazepam (7-bromo-5-(2-chlorophenyl)-1,2-dihydro-3H-1,4-Benzodiazepin-2-one) has become one of the most widely prescribed benzodiazepine drugs in the former USSR. It possesses potent anxiolytic, sedative and anticonvulsant properties and is superior to standard benzodiazepines in a number of behavioural tests. Since psychotropic activity of benzodiazepines is thought to correlate with their effects on GABAa receptors, we studied the action of phenazepam and its metabolites, 3-hydroxyphenazepam and 5-bromo-(2-chlorophenyl)-2-aminobenzophenone, on GABA-gated conductance. Experiments were carried out on enzymatically isolated Purkinje neurones from cerebellar slices of 12–13 days old Wistar rats. GABA-activated currents were recorded at –80 mV by standard whole-cell patch clamp in response to rapid applications of 10 microM GABA. Both phenazepam and 3-hydroxyphenazepam potently enhanced GABA-gated currents in the range of concentrations 0.3–1000 nM. Maximal potentiation of GABA currents by saturating concentrations of phenazepam, 3-hydroxyphenazepam and a reference benzodiazepine, diazepam, was in the range of 194–203% without significant differences between drugs. However, the EC50 value of phenazepam (6,1±0,8 nM) was lower than that of diazepam (13,5±1,8 nM), and 3-hydroxyphenazepam (10,3±1,4 nM). At concentration 10 microM, 5-bromo-(2-chlorophenyl)-2-aminobenzophenone increased peak current amplitude to 123,1±6,2% of control and substantially accelerated desensitisation of currents. It is concluded, that phenazepam and 3-hydroxyphenazepam are full positive modulators of the GABAa receptor complex, whereas the exact mode of action of 5-bromo-(2-chlorophenyl)-2-aminobenzophenone remains to be elucidated. Supported by INTAS 97–0382 and Wellcome Trust grants.

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FREQUENCY AND CLASSIFICATION OF SEIZURE ASSOCIATED HEADACHE (SAH). T. Leniger, K. Isbruch, S. von den Driesch, U. Bingel, I. Kavuk, A. Hufnagel, University of Essen (Essen, D)

Seizure associated headache (SaH) is mostly neglected in the treatment of patients with epilepsy. Only a few studies exist reporting a frequency of SaH up to 51% of patients with epilepsy. A recommended therapy is missing, although some antiepileptic drugs seem to be effective in the treatment of different types of headache. Aim of our study was to determine frequency and classification of SaH in respect of further investigations about specific therapy of SaH. Methods: In a 10-month, prospective study all patients with epilepsy, who were treated in our department, were interviewed for SaH. SaH was defined as follows: headache, which occurs almost always within the hour before or after the seizure. Classification of headache was based on the criteria of the International Headache Society (IHS). Pain intensity was assessed by the patients with a visual analogue scale 0–10 (0= no pain, 10= strongest pain). The epilepsy syndromes were categorised into partial epilepsy and idiopathic generalised epilepsy. Results: 178 patients (84 M, 94 F) were included; 45 patients (25%)

complained of SaH. The patients with SaH were comparable to the total population with regard to age and sex. 25 patients with SaH (56 %) had partial epilepsy and 20 patients with SaH (44 %) idiopathic generalised epilepsy. In 71 % of the patients with SaH (n= 32) the seizures were always associated with headache. The duration of SaH was 13.7 h ± 2.4 SE. The intensity of pain was 6.2 ±0.2 SE. In 98 % of the patients SaH was reported after the seizure. 27 % of the patients had SaH before and after the seizure. In one patient the SaH only occurred before the seizure. The time of onset of SaH (pre- and/or postictal) was not significantly associated with the type of epilepsy syndrome. The headache was combined with following symptoms: sensibility for noise (87 %) and light (49 %), dizziness (42 %) and vomiting (24 %). According to the criteria of the IHS SaH could be classified as migraine-like headache in 60 % of the patients (n= 27) and as tension type-like headache in 29 % (n= 13). In 5 patients (11 %) the SaH could not be classified according to IHS criteria. There was no significant association between the type of epilepsy syndrome and the type of SaH. Conclusion: 25 % of 178 patients with epilepsy complained about SaH with an average duration of 13,7h and moderate pain intensity. This is in contrast with the previously reported frequency of up to 51 % possibly due to the different definition concerning the time of onset of SaH. In the majority of patients (60 %) the SaH could be classified as a migraine-like headache, followed by tension type-like headache (29 %). In conclusion 1 of 4 patients with epilepsy is additionally affected by SaH. In the case of SaH the choice of the antiepileptic drug should also take into account its efficacy in treatment of the different types of headache.

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Abstract withdrawn

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COGNITIVE IMPAIRMENTS UNDER ADD-ON THERAPY WITH TOPIRAMATE. H.-J. Huppertz, A. Quiske, A. Schulze-Bonhage, Epilepsy Unit, Clinic of Neurosurgery, University of Freiburg (Freiburg, D)

Topiramate (TPM) is regarded as one of the most potent of the new antiepileptic drugs. However, TPM-related cognitive impairments have been reported both in healthy adults and epilepsy patients. The present study was aimed at investigating the frequency and severity of adverse cognitive effects under add-on therapy with TPM. Methods: In 1999, 26 patients (11 w, 15 m, age 12–78 ys) with symptomatic or cryptogenic focal epilepsy, treated in the Epilepsy Unit of the University of Freiburg, Germany, were put on TPM in addition to the pre-existing antiepileptic medication. During the titration phase, TPM was increased by 25 mg/week (b.i.d.). Concomitant antiepileptic medication consisted of 2 or 3 of the following drugs: CBZ (800–2400 mg/die; 15 patients), VPA (1050–4300; 10), LTG (125–800; 5), CLB (15–35; 3), PB (50–200; 3), DPH (250–375; 2), OCB (10–3000; 2), PRM (125; 1) and/or BBC (25; 1). Cognitive deficits noted by the patient or doctor were assessed by a neuropsychological test battery. Results: In 14 patients (54 %), cognitive impairments (i.e. decreased attention and concentration, slowing, decreased verbal fluency, anomia, and dysphasia) were observed during TPM-therapy. Cognitive deficits became apparent under dosages of 50–575 mg TPM/die and were at least in part reversible after dose reduction of TPM (by 50 mg/die on average; 5 patients) or one of the concomitant antiepileptic drugs (3 patients). In 5 patients, cognitive impairments led to withdrawal of TPM, in 2 other patients, TPM was discontinued because of nausea and weight loss, respectively. Major cognitive deficits were seen in the following neuropsychological tests: verbal fluency (Test No. 6, 'Leistungsprüfsystem'), psychomotor processing speed (Trail Making Test), and verbal memory (Auditory Verbal Learning Test by Rey). In 2 patients, verbal fluency (decline of percentage rank from 50 to 16 and from 16 to < 10, respectively) as well as verbal learning and memory performances (decline of percentage rank from 50 to 15 and from 35 to < 5, respectively) were severely reduced under TPM. Seven of 19 patients in whom TPM-therapy was continued became seizure-free, 3 showed a major (> 90 %), 2 a moderate (> 50 %) reduction in seizure frequency. Conclusion: In summary, the present study showed a higher incidence of cognitive side effects under TPM than reported in the past. In some patients, these adverse effects led to substantial impairments in everyday life and at work. For early recognition of cognitive impairments, neuropsychological baseline- as well as follow-up investigations in the subtests mentioned above are recommended.

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EPILEPTIC SEIZURES AND EPILEPSIES IN THE ELDERLY. J. Nikl, A. Gombos, Zala Megye Korhaz County Hospital (Zalaegerszeg, H)

The epidemiological studies show the accumulation of epileptic seizures and syndromes in childhood and in the elderly. The prevalence of the epilepsies in old age is 0,8–1,2 %. Despite these facts there are few data about epilepsies of elderly people. Methods – In a prospective study of 165 consecutive patients (> 60 years) admitted to a neurological department after their first epileptic seizure, we evaluated the etiological factors, the types of seizures, the characteristics of EEG patterns and some special aspects in the care of elderly. Results – The most frequent etiological factor is cerebral ischemia (47 %). The rate of white matter lesions is higher than expected (17 %). The proportion of tumors (15 %) and posttraumatic causes (8 %) is relatively low. The partial seizures and epileptic syndromes predominate in this age group (50 %). The comorbidity rate is very high (42 %). The rate of epileptic potentials is quite low (31 %) and the proportion of non-specific EEG findings is rather high (56 %). Conclusions – Epilepsy appears to be a major cause of morbidity in the elderly. The comorbidity rate, social status, some biological factors, the influence of age on the pharmacokinetics and the pharmacodynamics of antiepileptic drugs should be taken into consideration. Arrangements for sharing care of epilepsy patients between specialists and GPs should be formally established to encourage more effective management of old patients.

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PROGNOSTIC FACTORS INFLUENCING LONG-TERM RETENTION OF TOPIRAMATE IN CHRONIC EPILEPSY. S. D. Lhatoo, I. C. K. Wong, J. W. A. S. Sander, Epilepsy Research Group (London, UK)

Purpose: To determine the long-term retention rate of topiramate (TPM) therapy in patients with chronic epilepsy and to identify the relevant prognostic factors that influence retention. Methods: All patients with chronic epilepsy (n=393) prescribed TPM between 1st October 1995 and 31st December 1998 at a tertiary referral centre for epilepsy were analysed. The retention rate for TPM was calculated using Kaplan Meier survival analysis and the prognostic factors influencing retention were analysed using Cox regression. Results: 30 % of patients prescribed TPM continued on the drug beyond 3 years. Discontinuation was mainly due to adverse events and lack of efficacy. Use of more than 1 new concurrent antiepileptic drug (AED) and lower maximum daily doses were more likely to result in treatment discontinuation due to adverse events. Older age at onset of epilepsy, a history of having previously been on more than 1 new AED (lamotrigine, gabapentin or vigabatrin), and lower maximum daily doses were more likely to lead to discontinuation due to lack of efficacy. Conclusion: A 3rd of patients with chronic epilepsy started on TPM therapy will continue on treatment for more than 3 years. Absence of learning disabilities, late age at onset of seizures, previous use of more than one new (AED), 2 or more concurrent AED usage and low maximum daily doses of TPM are more likely to result in withdrawal from medication. These factors should be taken into account when considering the use of TPM for the treatment of chronic epilepsy.

Extrapyramidal disorders

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LATE ONSET DISULFIRAM-INDUCED ENCEPHALOPATHY WITH PARKINSONISM, OPTIC NEURITIS AND BI-PALLIDAL LESIONS. Y. Boukriche, I. Weisser, P. Aubert, C. Masson, Beaujon, Beaujon Hôpital (Clichy, F)

Disulfiram is an alcohol aversive drug used in the treatment of alcohol dependency. Various adverse effects on the nervous system have been reported. We report on a man with a three years history of disulfiram treatment, who developed optic neuritis and an acute encephalopathy with parkinsonism. CT scan and MRI disclosed lesions of both pallidal nuclei. Case report: A 52 year-old man had been treated for three years with disulfiram, 500 mg daily. Three months before admission, he had a severe loss of the left eye visual acuity to 2/10. Two months later he experienced similar symptoms on the right eye. He was admitted to our hospital because of drowsiness. Neurological examination revealed severe hypophonia, difficulties in swallowing and mild rigidity of the limbs. Disulfiram was then withdrawn. Drowsiness improved within five days, but the patient remained bradykinetic with extrapyramidal hypertonia and facial hypomobility. He also had abnormal posture and the gait was slow and shuffling. Ophthalmologic examination showed severe bilateral loss of visual acuity to 1/10 with central scotomas. Funduscopic examination was normal.

Initial EEG showed diffuse theta activity combined with pseudorhythmic sharp waves. CT scan revealed symmetrical hypodensities of both pallidal nuclei, whereas a CT scan performed three months before was normal. There was no carbon monoxide intoxication. Brain MRI examination showed no significant lesion, neither on T1-weighted nor T2-weighted sequences. On the other hand, there was a strong bilateral and symmetrical enhancement of both pallidal nuclei after gadolinium injection. Drowsiness disappeared within one week, gait gradually became normal and signs of parkinsonism spontaneously improved. Two months after onset, there was persistent very low visual acuity and the patient was still hypophonic with difficulties in swallowing. Conclusion: We emphasize that in cases of disulfiram neurotoxicity, MRI examination should include gadolinium administration to detect blood-brain barrier disruption. The physiopathology is discussed.

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SECONDARY NON-RESPONSIVENESS TO BOTULINUM TOXIN TYPE A IN PATIENTS WITH OROMANDIBULAR DYSTONIA. C. H. Adler, M. Brin, S. A. Factor, K. D. Sethi, S. Newman, Mayo Clinic Scottsdale, Mt. Sinai Medical Center, Albany Medical College, Medical College of Georgia (Scottsdale, New York, Albany, Augusta, USA)

Intramuscular injection of botulinum toxin type A (BTX-A) (Botox) is the treatment of choice for most forms of focal dystonia, including blepharospasm, torticollis, and oromandibular dystonia (OMD). A small number of patients with torticollis have developed secondary non-responsiveness (immunoresistance) to BTX-A. This has rarely been seen with other focal dystonias. We report 4 cases of OMD who have also developed secondary non-responsiveness. There were 3 women and 1 man, 3 were idiopathic, with onset at ages 17, 28, and 42, and one was secondary to viral encephalitis at age 1. Duration of disease at the time of first BTX-A injection was 2, 10, 18, and 36 years. All patients received Botox from the original formulation, Lot #79–11 (Allergan, USA). Three cases were jaw-closing and injections were mainly in the masseter and temporalis muscles, and one case was jaw-opening with injections in the external pterygoids, digastrics, and platysma. Case 1 received 21 sets of injections 1–4 months apart, 30–385 U per session, total dose = 4,305 U. Case 2 received 11 sets of injections 2 weeks (3 times) to 6 months apart, 15–80 U each, total dose = 498 U. Case 3 received 15 sets of injections 1–3 months apart, doses of 30–340 U, total dose = 2,210 U. Case 4 received 8 sets of injections 2–7 months apart, 80–355 U each, total dose = 1,347 U. All but case 4 had booster injections at some point. All patients responded to initial injections and eventually lost all response. Three had frontalis testing (15 U to the forehead) which showed lack of response and 2 had positive mouse neutralization antibody testing. Development of secondary non-responsiveness to BTX-A is not isolated to torticollis patients. Factors that likely lead to secondary non-responsiveness to BTX-A in OMD patients include frequency of injections, high doses at individual sessions, cumulative dose, and possibly young age of onset. Whether the new lot of BTX-A is associated with a lower incidence of resistance and antibody formation is unclear.

P300
ESSENTIAL TREMOR IN JEWISH AND ARABIC POPULATION IN ISRAEL. P.F Nisipeanu, R Inzelberg, R. Strugatsky, RL. Carasso, Hillel Yaffe Medical Center (Hadera, IL)

The prevalence of essential tremor (ET) differs depending on study methodology. In our Movement Disorders Clinic serving both Jewish (JW) and Arabic (AR) population, with similar access possibilities, we noticed the paucity of AR patients with ET. To neutralize the referential bias, we examined the frequency of ET among patients (> 40 years) hospitalized for any diagnosis, in internal medicine and neurology departments during 1993–1998. Hospital records review may provide important information about ET in the general population, since ET is extremely rare as the sole cause of hospitalization. Patients diagnosed as ET, senile tremor and familial tremor were detected by computerized search. Their in- and out-patient files were reviewed. Among 37,195 hospitalized patients, 28,194 (75.8%) were JW and 9,001 (24.2%) were AR. The proportion JW/AR was 3.13 (range 2.41–3.92 each year; similar to the proportion of the inhabitants of the area). Among the 38 patients diagnosed as ET, 37 were JW (17 males, 12 familial history) and one AR (male, no familial history). ET occurred in 0.102% of all hospitalized patients; in 0.131% of JW and only in 0.011% of AR (chi-square=9.646, p< 0.01). Our data suggest that not only ET occurs in AR patients significantly less than in JW, but that it is very rare in AR.

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ACUTE MANIC EPISODE AND HEMIBALLISM DUE TO A SUBTHALAMIC INFARCTION. R. Inzelberg, P.F Nisipeanu, M. Sarkantyus, R.L Carasso, Hillel Yaffe Medical Center (Hadera, IL)

Lesions of the subthalamic nucleus (STN) are known to cause hemiballism. Recently the STN has gained particular interest since its high frequency stimulation is successfully used for Parkinson's disease (PD) therapy. However, very recently, high frequency stimulation 2 mm below the STN has been shown to cause acute depression, which was reversed by stimulation interruption.* We aim to describe for the first time a patient who developed acute mania and hemiballism consequent to an STN infarction. A 60 years old, very decent man, with diabetes and no psychiatric history, suddenly became inadequate and euphoric. Few hours later, he developed involuntary jerky movements of the left limbs. On admission, he was euphoric, inadequately talkative, disinhibited, with flight of ideas. He was distractable, but his memory, calculation and abstraction abilities were normal. He had no hallucinations or delusions. Neurological examination showed only left hemiballism. He was treated with haloperidol, which alleviated the hemiballism, but due to his disinhibited and hypersexual behavior, he had to be transferred to the psychiatric ward, where he was treated with antipsychotic drugs for 3 weeks. On discharge, the hemiballism had disappeared; antipsychotic medication was gradually reduced and the manic episode resolved within two months. Alterations in the connections of the STN might induce acute mood changes such as mania in our patient and depression as previously reported.* These observations raise concerns about potential complications of STN surgery currently used for PD therapy, as well as new theoretical treatment options for mood disorders which remain to be challenged. * Bejjani B-P et al. N Engl J Med 1999; 340:1476–1480.

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THE CLINICAL CHARACTERISTICS OF NEUROLEPTIC INDUCED PARKINSONISM. S Hassin-Baer, P Sirota, AD Korczyn, TA Treves, H Shabtai, B Epstein, T Martin, Y Litvinjuk, N Giladi, Tel-Aviv Medical Center, Abarbanel Mental Health Center (Tel-Aviv, Bat-Yam, IL)

Parkinsonism often complicates neuroleptic therapy. The pathophysiology of neuroleptic induced parkinsonism (NIP), beyond dopamine receptor blockade, is not fully understood and its relation to Parkinson's disease (PD) is controversial. Objective: To characterize the clinical spectrum of NIP. Methods: The study population was composed of consecutive psychiatric patients treated with neuroleptics for at least two weeks, who were diagnosed by their psychiatrist as having parkinsonism. The patients were examined by a movement disorders specialist after anticholinergic therapy had been discontinued for at least 24 hours, and parkinsonism was confirmed. The presence of at least two of the four cardinal parkinsonian symptoms: rest tremor, rigidity bradykinesia or postural instability, were required for inclusion. The neurological assessment included the motor examination and the activities of daily living (ADL) sections of the Unified Parkinson's Disease Rating Scale (UPDRS), and the Hoehn and Yahr (H&Y) staging. Results: A total of 75 patients (54 males), with a mean age of 46 (range 21 to 73 years) were included in the analysis. The mean duration of neuroleptic therapy was 15 years, while 61% were treated for more than 10 years. Most of the patients (n=66, 88%) were in H&Y stage 2.5 or less. Rest tremor was present in 44% of the patients, and usually persisted in action. Action tremor without a rest component was present in 13 of the patients (17%). Forty-one patients (61%) had symmetrical involvement and a linear relationship between the abnormalities on the right and left was found, with a slope of 0.95 (p=0.0001). Parkinsonian signs were significantly more common and pronounced in the upper limbs in comparison with the lower limbs (p=0.0001). Gait disturbances were mild and freezing of gait was very rare (n=2). No other preferential clinical features could be identified. Bradykinesia, tremor and rigidity were found to be intercorrelated, while they were not associated with postural and gait disturbances. Neither age nor duration of therapy or their interaction had an affect on the total motor score or on any of the motor subscores.

Conclusions: NIP seems to have in its early stages its own clinical profile: it is different from PD for more bilateral involvement with relative symmetry, and by affecting upper body more often. NIP tends to be associated with the triad of bradykinesia, tremor and rigidity while PD tends to involve gait and posture more often. NIP develops unrelated to duration of neuroleptic treatment or age of the patient, suggesting a personal predisposition or hypersensitivity to blockage of the dopaminergic receptors.

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OLFACTORY FUNCTION IN DRUG INDUCED PARKINSONISM. A. E. Hensiek, K. Bhatia, C. H. Hawkes, The National Hospital for Neurology, Essex Neuroscience Centre (London, UK)

Drug induced parkinsonism (DIP) is among the commonest causes of parkinsonism and the clinical features may be indistinguishable from idiopathic Parkinson's Disease (PD). The distinction is important because treatment is different. It has been shown that about eighty percent of patients with Parkinson's Disease have a profound disorder of olfactory function. We have conducted a pilot study on ten patients with DIP to assess olfactory function. Methods: A standardised odour identification test (University of Pennsylvania Smell Identification Test) was used in addition to clinical assessment and Mini Mental Test Score Examination. Results: Causative drugs were dopamine antagonists in all patients and one patient took Amiodarone. Average Mini Mental Test Score was 28.7 /30. Five patients had made a complete recovery after the offending drug had been discontinued and five patients had improved but still exhibited signs of parkinsonism at the time of the assessment. Five patients were outside the 95% limit of normal on the smell identification test for our age matched controls. Average age in these patients was 54.8 years and four of the five showed residual signs of parkinsonism. The pattern of smell impairment was similar to that previously described for patients with PD. The remaining five patients scored at the lower range of normal and had an average age of 64.6 years. Conclusions: This small study suggests patients with DIP may have a similar type of smell impairment as those with PD. It has been suggested previously that DIP is associated with an increased risk of PD and common causative mechanisms may contribute to the development of both clinical syndromes. Further investigations are needed to assess the relation of DIP and PD.

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FREEZING OF GAIT IN MULTIPLE SYSTEM ATROPHY (MSA). T. Gurevich, N. Giladi, Movement Disorder Unit (Tel-Aviv, IL)

Freezing of gait (FOG) is a mysterious symptom, observed in different parkinsonian syndromes. It was considered to be a rare symptom in Multiple System Atrophy (MSA) based on database data and literature review of confirmed cases (Giladi et al.,1997). Objective: To assess the frequency of FOG in patients with MSA. Method: We studied the presence of FOG in 28 patients (17 women, 11 men) with clinical diagnosis of MSA, 22 patients with MSA-Parkinsonism (MSA-P) and 6 with MSA-Cerebellar (MSA-C). 21 patients had probable MSA (15 MSA-P and 6 MSA-C) and 7- possible (MSA-P), according to Quinn's criteria. Mean current age was 66.8 ± 10.2 years, mean disease duration 5.2 ± 3.9 years, and mean Hoehn and Yahr stage 3.8 ± 0.8. Patients' clinical diagnosis was based on neurological examination performed by at least two experienced movement disorders specialists as well as on the results of ancillary examinations and course of the disease. The diagnosis was reconfirmed by recent chart review and clinical examination. FOG was assessed by the FOG questionnaire (FOGQ), consisting of 6 subjective questions concerning FOG, with maximal score of 24. The FOG questionnaire was given to all patients at their last office visit or through the phone. Results: 22 patients (80% of total; 16 with MSA-P and 6 with MSA-C) were able to walk at the time of the study, 18 of them (60%) experienced FOG. Among 6 currently bedridden patients, 4 reported presence of FOG in the past. FOG appeared in 81% of patients with MSA-P and in 50% patients with MSA-C. Disease duration was about the same among "freezers" and "non-freezers" in the MSA-P group (6.9 vs. 7.5 years, respectively), while among the MSA-C it was 5.0 year for "freezers" and 0.8 for "non-freezers". Mean FOGQ total score for MSA-P patients was 13.6 and for MSA-C 10.2. Conclusion: Freezing of gait is a common and disabling symptom in MSA. In MSA-P, FOG was unrelated to disease duration, while in MSA-C it was associated with longer disease duration.

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CLINICAL CHARACTERISTICS OF OPPENHEIM'S DYSTONIA IN ISRAEL. M. Anca, T. Falik, A. D. Korczyn, E. S. Simon, S. Badarna, S. Honigman, N. Giladi, Movement Disorders Unit, TASMC, Neurology, TASMC, Tel-Aviv Sourasky Medical Center (Tel-Aviv, IL)

Background: The clinical course of Oppenheim's dystonia (OD) is highly variable but updated data on genetically confirmed cases have not been presented. Objective: To characterize the clinical spectrum of genetically confirmed patients with OD. Subjects and methods: 33 patients (19 males) with OD and the GAG deletion in the DYT1 gene were evaluated. We based our data on detailed history and all available charts. The Dystonia Rating Scale (DRS) and Disability Scale (DS). Results: The current age of our patients range between 11–63 years (mean 27.8±15.24). The age of disease onset ranged between 7–28 years (mean 10.7±4.6 years) and the disease duration between 3–54 years (mean 15.5±13.8 years). The current DRS score was 5–65 (mean 22.7±14.7) and DS score 2–17(mean 7.7±4.3). Dystonia first presented in the limbs in 30 patients (91%). Nine patients (27.2%) have progressed into generalized dystonia. Five patients (15%) are wheel chair bound and three (9%) are using walking aids. Six patients developed cranio-cervical dystonia (3 of whom have spastic dysphonia). Fifteen patients did not develop new symptoms for at least 3 years. All patients have normal cognitive function. The most commonly used drug was baclofen given to 19 patients (57.6%) at maximal dose of 140 mg/d and a mean dose of 102 mg/d, followed by trihexyphenidyl, prescribed to 17 patients (51.5%) with a maximal dose of 120 mg/d and mean dose of 30 mg/d. Fifteen patients are currently being treated with baclofen, 9 as monotherapy and 6 in combination with trihexyphenidyl with prolonged benefit. Twelve patients (36.4%) were successfully treated for focal symptoms with Botulinum toxin. Nine patients (27%) underwent neurosurgical intervention: 6 thalamotomy (2 bilateral) and 4 pallidotomy (3 bilateral) with significant improvement.

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PROCREATION ABILITY IN WILSON'S DISEASE. A. Czlonkowksa, B. Tarnacka, M. Rodo, S. Çichy, Institute of Psychiatry and Neurology (Warsaw, PL)

Objectives: The clinical manifestations of Wilson's disease (W. D.) take form of hepatic, neurological, renal as well as hormonal disturbances. Infertility and amenorrhea are reported in women and hypogonadism in men with W. D. Our study was designed to analyse the procreation abilities of patients with W. D. Material and Methods: We investigated by a questionnaire the course of pregnancy and delivery in 31 untreated (27 asymptomatic and 3 with mild neurological signs) women (mean age 22.5 years, 82 pregnancies) and 15 women (mean age 26.2, 25 pregnancies), treated with D-penicillamine (D-p) or zinc sulphate (ZnS). We studied also procreation ability of 27 men (mean age 27.2 years). We analysed the congenital abnormalities and frequency of W. D. in children of our patients. Results: One of ten untreated women had difficulties with conception. The number and type of pathology (imminent abortion, gestosis, stillbirth, preterm births) were similar in treated and untreated patients. In both mentioned groups the most frequent pathology were spontaneous abortions, which were found in 26% of untreated and in 26.6% of treated women. This percentage is higher than general population. Most of deliveries in patients with W. D. were spontaneous. Neither developmental malformations nor serious disorders were noticed in the offspring of our treated patietns, 3 children of untreated patients were born with congenital heart disease. In 78 of the 110 children of our patients we examined the copper metabolism and we diagnosed W. D. in 5 cases (from 3 families). Among 27 investigated men only 1 was impotent. Conclusion: The risk of complications during pregnancy in asymptomatic and treated patients is higher than in general population, but it does not make the procreation impossible.

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INDOMETHACIN DIMINISHES IMPAIRMENT OF DOPAMINERGIC NEURONS FOLLOWING 1-< ETHYLO-4-PHENYLO-1,2,3,6-TETRAHYDROPIRYDINE (MPTP) INTOXICATION IN MICE. M. Babiuch, I. Kurkowska, A. Czlonkowski, A. Czlonkowska, Institute of Psychiatry and Neurology Medical Academy (Warsaw, PL)

There are a number of evidence for inflammatory reaction in impaired brain structures of patients with neurodegenerative processes, such as Parkinson's and Alzheimer's diseases. When mice were given MPTP toxin (1-methylo–4-phenylo–1,2,3,6-tetrahydropirydine) and thus developed nigrostriatal system impairment, in our previous experiments we observed inflammatory reaction in the form of glial activation and lymphocytic infiltration. We expected that Indomethacin as an anti-inflammatory agent would diminish this reaction. Methods and Results: By means of immunohistochemical methods we investigated glial cells reaction and dopaminergic neurons degeneration which reflected impairment of the substantia nigra and striatum. On the second day after MPTP treatment a lesser impairment of dopaminergic cells was observed in mice which were injected with indomethacin. This difference was not observed 7 days after MPTP treatment. We also noticed on the 2nd day after MPTP treatment smaller lymphocyte infiltration and APP protein expression in glial cells. No difference was observed in the extent of micro- and astroglial activation and expression of MHC class I and II, adhesive molecules, ICAM–1 and LFA–1alpha. Conclusions: Indomethacin temporarily diminishes impairment of dopaminergic neurons (second day after MPTP) and produces anti-inflammatory effect. This can lead to a conclusion that the inflammation partially contributes to the extent of impairment of dopaminergic system following MPTP intoxication. Further investigation is needed to explain why the Indomethacin protective effect is only transitory.

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IS IRON INVOLVED IN THE PATHOPHYSIOLOGY OF MULTIPLE SYSTEM ATROPHY? A MRI STUDY. F. Lallement, Y. Rolland, C. Prunier, I. Rivier, G. Edan, M. Vérin, CHU Rennes, CHU Tours, CHU Rennes Hôpital Pontchaillou (Rennes, Tours, F)

The aim of this work is to study the localisation and the evolution of hyposignals in patients who underwent high field magnetic resonance imaging (MRI) in multiple system atrophy (MSA). According to its paramagnetic effect, iron appears as a hyposignal in T2 weighted with high field MRI. The presence of such hyposignal has been previously described in the posterior part of the putamen in Parkinson's disease, progressive supranuclear palsy and MSA. Twenty eight patients with MSA (according to Quinn's criteria) were evaluated with 1.0 Tesla MRI (n=24) and 1.5 Tesla MRI (n=4). An obvious bilateral hyposignal was found in the posterior part of putamen (85.7%), in substantia nigra (57.1%), red nucleus (50%) and dentate nucleus (50%). These hyposignals were always present (100%) when the disease duration is less than 2 years except for dentate nucleus (87,5%). Between 3 and 5 years of disease duration, this hyposignal seemed to disappear in substantia nigra (37,5%), red nucleus (37,5%) and dentate nucleus (62,5%) but was still present in putamen (100%). Between 6 and 7 years of disease duration, the hyposignal still continues to decrease in putamen (77,7%), substantia nigra (55,5%), red nucleus (33,3%) and dentate nucleus (22,2%). After 8 years, no hyposignal was found. Accumulation of iron is always detected with high field MRI in MSA patients at the beginning of the clinical history of the disease in the striatonigral system but also in the red and dentate nuclei, which are usually spared by the degenerative process in pathological studies. The disappearance of the hyposignal in T2 weighted high field MRI with the evolution of the disease is a new clue for the role played by iron in cells apoptosis in MSA.

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FRONTAL CORTEX DYSFUNCTION IN PARKINSON'S DISEASE: AN EVALUATION BASED ON PROTON MAGNETIC RESONANCE SPECTROSCOPY. A. Hozumi, B. Mihara, S. Gomi, K. Hirata, Institute of Brain and Blood Vessels, Aoyama Gakuin University, Dokkyo University School of Medicine (Isesaki, Gunma, Aoyama, Tokyo, Mibu, Tochigi, J)

The cognitive dysfunction of Parkinson's disease is considered to have a particular relationship with frontal lobe dysfunction. Recently proton magnetic resonance spectroscopy (1H MRS) has been used to evaluate brain metabolism in neurological disease. This study was carried out to clarify brain metabolism in the frontal cortex of Parkinson's disease patients (PDPs) using 1H MRS. METHODS: The study participants were 19 PDPs (11 males and 8 females; mean age 68.4 years, S.D.=10.5, range 48–85) and 15 age-matched normal controls (NCs). Clinical disability of the PDPs assessed with the Hoehn and Yahr (H-Y) rating scale. T1-weighted imaging of the brain and 1H MRS (single-voxel method) of the frontal cortex were performed with a 1.5-tesla MR system (Magnetom Vision, Siemens) in all subjects. Then N-acetylaspartate (NAA)/creatine (Cr) ratio in the frontal cortex were calculated. All the PDPs were evaluated by the Mini-Mental State Examination (MMSE) which measures the cognitive function. RESULTS: NAA/Cr ratio in the PDPs did not show any correlation with patient's age or duration of the disease. In the advanced stages PDPs (H-Y; ≠V-≠X), NAA/Cr ratio was significantly lower than that in the early stages PDPs (H-Y;≠T-≠U) or in NCs ($p< 0.02$, $p< 0.05$). On the other hand, in the early stages PDPs, NAA/Cr ratio was slightly higher comparing to that of NCs, however, there is no statistical significance. In the PDPs, NAA/Cr ratio significantly correlated with MMSE score. CONCLUSIONS: The degree of damage to the frontal cortex, as shown by the magnitude of NAA loss, correlates well with the cognitive decline in the PDPs. Elevated NAA/Cr ratio in the frontal cortex of early stages PDPs may reflect to hyperactivity of EEG ascribable to the disinhibition as reported previously. This study suggests that 1H MRS can detect frontal dysfunction in the PDPs.

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THE QUALITY OF THE SEXUAL LIFE IN PARKINSON'S DISEASE. O. Moore, T. Gurevich, M. Anca, E. Simon, H. Shabtai, Y. Villa, AD. Korczyn, N. Giladi, Tel-Aviv Sourasky Medical Center (Tel-Aviv, IL)

The Parkinson's Disease Questionnaire (PDQ–39) became the gold standard instrument to assess the impact of Parkinson's Disease (PD) on patients' quality of life (QoL). Sexual functioning and data on the quality of sexual life (QSL) are not included in the PDQ–39. Objective: To evaluate the relationships between QSL in PD patients and general QoL assessed by the PDQ–39. Methods: 100-consecutive patients with PD were asked to grade their General Satisfaction from Life (GSL) on a scale from 1 to 10. All patients also self-completed the PDQ–39 and a QSL questionnaire (QSL-Q) consisting of 5 items (Bruner, 1983). Clinical data were evaluated on the same visit. Cronbach's alpha analysis was used for reliability of the QSL-Q and Spearman's test for total-item correlation. Results: Out of 100 patients, 20 did not have partners and 6 refused to answer the QLS-Q. 74 patients (57% men) were included in the analysis. Their mean age was 66.7 ± 10.3 years, mean disease duration 8.8 ± 6.1 years, and mean Hoehn & Yahr (H&Y) score 2.6 ± 0.9. The reliability of the QSL-Q was 0.72, similar to some of the PDQ–39 dimensions; social support–0.66, cognition–0.70 and body discomfort–0.72 (Jenkinson et al., 1995). Satisfaction from sexual life as reflected by the QSL-Q significantly decreased with aging ($p< 0.01$). Gender, disease duration or disease progression as reflected by the H&Y did not effect QSL. Significant correlation was found between the PDQ–39 index and the GSL grading ($p< 0.001$), and also between the QSL-Q index and GSL grading ($p< 0.05$). However, no correlation was found between the PDQ–39 index and the QSL-Q index. These results indicate that the QSL-Q assessed a unique problem not evaluated by the PDQ–39. The correlation between PDQ–39 to GSL ($r = 0.466$) was improved by adding the QSL-Q as a 9th dimension to the PDQ–39 ($r = 0.469$). Conclusions: Quality of sexual life is an important dimension that is not assessed by the PDQ–39. QSL-Q is a reliable and practicable tool that can improve the PDQ–39 for assessment of QoL in PD patients.

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PERSISTENT POSTPUMP CHOREA BEGINNING AFTER CHILDHOOD: A CASE REPORT. J. M. Polo, I. Mateo, R. Muñoz, R. Bermúdez-Cañete, O. Combarros, J. Berciano, University Hospital Valdecilla, Hospital Ramón y Cajal (Santander, E)

Postpump chorea is the development of choreidoathetoid movements within two weeks following cardiopulmonary bypass. Its precise pathophysiological mechanism is unknown. It may be an age-related phenomenon, with the most vulnerable period starting at 6–9 months and ending after 5–6 years; no patient has been reported outside early childhood. Here we describe the case of a girl who suffered a choreic syndrome after cardiac surgery when she was 10 and her evolution during a six year follow-up. A girl born in 1984 with congenital pulmonary atresia and ventriculoseptal defect, underwent total correction in 1994; cardiopulmonary bypass time was 130 minutes and minimum rectal temperature 20 °C. Five days after surgery she began with progressive abnormal movements, at its onset considered as psychogenic. On the 39th day postsurgery, after a 10 day home discharge, she was readmitted because of generalised choreoathetosis, which was initially confused with a convulsive status epilepticus due to its severity. Extrinsic ophthalmoparesis, anarthria and dysphagia were also present. No cognitive deficit was evident. Electroencephalography and neuroimaging failed to detect any cerebral abnormality. We tried treatment with several drugs, but only pimozide had some effect in decreasing chorea. An endoscopic gastrostomy was unavoidable. A severe neurological deficit persisted in the follow-up period, and comprehensive psychological, pedagogical and physiotherapy support was necessary. Six years after surgery some improvement has occurred. She walks independently with a puppet-like gait, oral feeding has been re-established and some verbal communication is now possible. But an important motor impairment persists and she needs a lot of help in her daily life activities. As this patient shows, postpump chorea may exceptionally affect an adolescent. In addition to movement disorder, the clinical picture includes other cranio-bulbar motor abnormalities. Pharmacological treatment may be useless, management requiring a multidisciplinary support.

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HUNTINGTON'S CHOREA SINE CHOREA. D. Paleacu, A. Plopsky, H. Shor, A. Elizur, Abarbanel Mental Health Center (Bat Yam, IL)

Objective: To describe the unusual onset and follow up of a patient with longstanding Huntington's Disease. Background: HD is a neurodegenerative disease, which manifests with a triad of symptoms including a movement disorder, a dementia syndrome and psychiatric symptoms. The most characteristic psychiatric symptoms include mood disorders such as depression or anxiety, personality changes, aggressive behavior or psychotic episodes. Case: A 29 years old Caucasian male of Jewish/Georgian origin had a psychotic episode at age 19, including delusions of persecution and visual and auditory hallucinations. He was treated with ECT and neuroleptics never attaining a complete remission. At ages 24, 26 and 27 he had additional psychotic episodes that required hospitalization and remitted following medical treatment but the patient never returned to his pre-psychotic baseline. He was diagnosed as suffering of paranoid schizophrenia. The patient had normal cognitive capacities with a Minimental State Examination (MMSE) of 28/30, normal neurological examination and on repeated psychiatric exams showing a syndrome of predominantly negative symptoms including blunted affect, social isolation, withdrawal and decreased initiative despite treatment. He scored 13 points on the positive and 30 points on the negative and 51 on the general psychopathology subsets of the Positive and Negative Syndrome Scale (PANNS). His father had a pro-

gressive neurological syndrome with gait ataxia and dementia and died at age 41, history which prompted a genetic testing of our patient. The test revealed a 44 CAG repeat expansion in the IT15 gene, which was diagnostic of HD. Conclusion: We present an unusual case of longstanding HD (10 years) and treatment resistant psychiatric symptoms as the only manifestation of the typical triad of HD.

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FESTINATING GAIT IN PARKINSON'S DISEASE. H. Shabtai, E. Rozenberg, D. Kowaneshter, E. Shabtai, N. Giladi, Tel-Aviv Sourasky Medical Center (Tel-Aviv, IL)

Festinating gait (FSG) was first associated with parkinsonism in Sir James Parkinson's first assay on "The Shaking Palsy". It's frequency and relation to other parkinsonian features has never been assessed. Objective: To study the relationships between gait festination and other parkinsonian clinical features among patients with Parkinson's disease (PD). Method: During an open lecture to patients with PD who are followed at the Movement Disorders Unit of Tel-Aviv Sourasky Medical Center one of us explained verbally and imitated festinating gait on stage. All attending patients with the help of their care-givers or family members, were asked to answer 3 written questions regarding their own experience with FSG as well as the degree of disability it causes. By using this approach we made sure that all patients got the same explanation and saw the same demonstration of FSG. Clinical features on each patient were taken from their chart and missing data was added during the last office visit, or from the family physician. Statistical analysis was performed using t-test for comparison between groups, Chochran-Armitage for trends and logistic regression. Results: Eighty-one patients (58 males, mean age 67.5±10.7 years) answered the short FSG questionnaire. Our study population's mean disease duration was 8.5±6.4 years, mean Hoehn & Yahr (H & Y) clinical stage of 2.6±0.8 and mean levodopa dose of 608± 375 mg/day (15 patients were not on levodopa). Twenty six patients (32.1 %) experienced FSG during the previous month and 56 % of them reported that FSG was a significant and disabling symptom. FSG was strongly associated with higher stage of H&Y ($p< 0.001$) with a significant trend $p = 0.001$ and longer disease duration ($p< 0.001$) but was not affected by age of disease onset. There was no association between significant postural reflex abnormalities as rated on the objective part of the UPDRS (Unified Parkinson's Disease Rating Scale) (> 1) and the presence of FSG. Thirty seven percent (37 %) of the patients with FSG reported frequent falls with significant association between occasional or frequent falls, as reported on the activity of daily living (ADL) part of the UPDRS, and the presence of FSG. There was a significant association between the presence of freezing of gait (FOG) as reported in the ADL part of the UPDRS (> 1) and the presence of FSG ($p< 0.0001$) as well as a significant trend towards more frequent FSG in patients with more severe FOG ($p< 0.001$). Conclusion: FSG was clearly associated with higher disease progression and longer duration of symptoms. The relationships between FSG and postural reflexes abnormalities is unclear but FSG is frequently associated with falls and freezing of gait.

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TREATMENT WITH INTRAVENOUS IMMUNOGLOBULINS IN TWO CASES OF PROGRESSIVE MYOCLONIC ATAXIA. J. J. Vilchez, L. Bataller, C. Valero, V. E. Villanueva, Hospital Universitari La Fe (Valencia, E)

Progressive myoclonic ataxia (PMA) or Ramsay Hunt syndrome is defined by the association of cerebellar ataxia, myoclonus and infrequent seizures, in absence of dementia. The causes of this syndrome include genetic, mitochondrial and storage diseases as well as coeliac disease associated encephalopathy among others. However, no specific diagnosis can be made in some patients. An immunopathogenetic influence has been proposed in some cases. Objective. To present two "idiopathic" cases of PMA that improved after treatment with intravenous immunoglobulins (IVIG). Case reports. Case 1. A 29 year old woman had cerebellar ataxia and action myoclonus that evolved in the previous 8 years leading to severe disability. There was no family history nor consanguinity. Complementary investigations including routine serum analysis, CSF, cerebral MRI, somatosensory evoked potentials, EEG, muscle and skin biopsies and biochemical studies were unremarkable. Serum harboured antibodies to parietal gastric cells but no anti-neuronal or anti-gliadin antibodies could be detected. A slight benefit could be observed after clonazepam, L-hydroxytryptophan and piracetam. Treatment with cycles of IVIG every three months started with a progressive and notorious improvement of clinical and functional status. Case 2. A 30 year old man presented with cerebellar ataxia, action myoclonus and infrequent generalized seizures. This syndrome had started 10 years ago and slowly progressed to a chairbound situation. Complementary investigations, including routine serum analysis, cerebral MRI, EEG, study of CSF, muscular and skin biopsies and biochemical studies were all normal. No serum anti-neuronal or anti-gliadin antibodies could be detected. There was a partial response to clonazepam, piracetam and L-hydroxytryptophan. Treatment with IVIG (during 5 days) was administered with an immediate improvement in his clinical status. Three months later ataxia and myoclonic jerks worsened and were again satisfactorily treated with IVIG. Conclusions. An autoimmune neuronal damage could be the underlying mechanism in some cases with the Ramsay Hunt syndrome. IVIG could play a role in their treatment.

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MOTOR POTENTIAL IN PATIENTS WITH PRIMARY DYSTONIA. O. Orlova, A. Morenkova, L. Petrova, G. Tabeeva, V. Golubev, A. Vein, M. Vendrova, Moscow Medical Academy (Moscow, RUS)

It has been shown that in dystonia there is a segmental interneuronal hyperactivity, which could arise from the motor cortical hyperexcitability or lack of descending cortical inhibition. To test this hypothesis we studied the functioning of cortical motor areas by means of the motor potential recording (1) in 13 patients with cervical dystonia (mean age 45.2 years) and 9 patients with cranial dystonia (mean age 53.4 years); 15 age-matched healthy subjects were studied as a control. In registered curve we measured the early phase of Bereitschaftspotential (BP) previous to EMG in the interval of 1380"b 230 msec and the late phase of BP (NS_i:) previous to EMG in the interval of 350"b 26 msec. The areas of BP and NS_i: were analyzed. In healthy subjects, fulfilling the task by the right hand yielded in BP=4.3 and NS_i:=2.9 in contralateral hemisphere and fulfilling the task by the left hand yielded in BP=8.0 and NS_i:=6.0 in contralateral hemisphere. In patients with cranial dystonia fulfilling the task by the left hand yielded in BP=10.2 and NS_i:=8.0 (recorded from the contralateral hemisphere) and in patients with cervical dystonia fulfilling the task by the left hand yielded in BP=11.2 and NS_i:=9.0 (recorded from the contralateral hemisphere); these data differed significantly from results seen in the control group (pf" 0.05). In fulfilling the task by the right hand, the significant (pf" 0.05) increase in components of BP was observed in ipsilateral hemisphere both in cranial and cervical dystonia unlike the control group (correspondingly, BP=3.6, NS_i:=2.2 and BP=4.3, NS_i:=5.4). CONCLUSION. Motor potential study showed common neurophysiologic pattern of changes in various forms of dystonia ¡V the increase of BP components. Such findings prove the hypothesized motor cortical overactivity in dystonia which may be responsible for segmental interneuronal hyperactivity. References: 1. Shibasaki H. Movement-related potentials. In: Evoked potentials in clinical testing, 1993, p. 523–537

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ELECTROCONVULSIVE THERAPY IN PATIENTS WITH PARKINSON'S DISEASE. T. Ujovic, B. Miljanovic, M. Blagojevic, V. Tepšic, N. Bjelica, Medical Military Academy (Belgrade, YU)

For over 25 years electroconvulsive therapy /ECT/ has been reported as helpful in many patients with Parkinson's disease receiving this therapy for psychiatric indications /mostly for depression/. Lately there are many reports of successful treating of Parkinson's disease patients without psychiatric disorders. There was a highly positive association between the age of the patient and the scored degree of ECT induced improvement. Also, severe disability such as bedridden, on-off syndrome may be favorable prognostic features for ECT response. Possible explanation could be that ECT alters central dopaminergic system fundamentally involved in Parkinson's disease. Also, apomorphine induced suppression of prolactin release, that is dopamine mediated response, is greater after than before ECT and ECT induced prolactin levels fall across a course of ECT. We report two patients with Parkinson's disease with positive response to ECT. The first patient was 70y old woman treated for the last 12y for Parkinson's disease who had also depressive symptoms, receiving various antiparkinsonian medications during this period. She exhibited severe rigidity, gait disturbance, masked face and bradykinesia and underwent the course of ECT – 8 bilateral ECT with a brief pulse device – Thymatron. Each of ECT induced seizures lasted more than 30 sec with posticta1 suppression index ranging from 85–98 %. This treatment largely resolved both neurologic and depressive symptoms. Rigidity and gait disturbance were markedly improved after 5th application of ECT but we proceeded till 8th application when depressive symptoms were resolved. The second patient was 61y old woman with 18y long history of Parkinson's disease with cognitive impairs. She was bedridden, had severe rigidity, masked face and she spoke in slow, monotonous voice, stretching each word. She received 6 bilateral ETC and responded well to this therapy with significant improvement of gait, speech and rigidity but without changes in cognitive functions. Although many reports of case studies show positive effects of ETC in patients with Parkinson's disease both with or without psychiatric symptoms, further efforts should be done to define general principle of the optimal administration of ETC in this group of patients.

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FREEZING OF GAIT IN PATIENTS WITH ADVANCED PARKINSON'S DISEASE. N. Giladi, T. A. Treves, A. D. Korczyn, Y. Orlov, B. Kandinov, D. Paleacu, E. S. Simon, H. Shabtai, Tel-Aviv Sourasky Medical Center, Sieratzky Chair of Neurology, Tel-Aviv University (Tel-Aviv, IL)

To study the relationships between freezing of gait (FOG) clinical features and therapeutic modalities in patients with advanced Parkinson's disease (PD). Background: FOG is one of the most disturbing and least understood symptoms in PD. The contribution of the underlying pathological process and the antiparkinsonian treatment to the development of FOG is controversial. Method: 172 consecutive patients with 5 years or more of PD symptoms (99 men 73 women, mean age at symptoms onset 58.3±13.2 years, mean symptoms duration 11.8±5.6 years) were studied. Clinical data were collected during the last office visit through physical examination, detailed history, review of patients charts, and outside documents. A patient was considered as "freezer" if he reported recent feeling of the legs getting stuck to the floor while trying to walk. Presence of dyskinesia was assessed and duration of treatment with antiparkinsonian drugs was calculated from history, chart and outside records. Chi square and t test were used to compare the patients characteristics among those with and without FOG. Logistic regression was used for the comparison of association between the presence of FOG (dependent variable) and duration of treatment with antiparkinsonian drugs and disease stage (explanatory variables). Results: The study population consisted of 45 patients at Hoehn and Yahr (H&Y) stage < = 2.5 (26%), 104 patients at stage 3 (60.5%), and 23 patients at H&Y stages 4–5 (13.5%). Ninetyone patients (53%) experienced FOG at the time of the study. Progression of the disease expressed by H&Y staging was the most important contributing factor for FOG with significant trend ($z = 4.38$, $p< 0.0001$). Duration of levodopa treatment was the second most significantly associated factor ($p< 0.001$) and duration of treatment with dopa agonist drugs was the third contributing factor ($p< 0.03$) for the presence of FOG. Treatment with Amantadine, Selegiline and anticholinergic drugs did not have an effect on the presence of FOG. There was a significant association between FOG and the presence of dyskinesia ($p< 0.005$), early morning foot dystonia ($p< 0.003$), postural instability ($p< 0.0005$) and dementia ($p< 0.005$). Conclusion: FOG is a common symptom in advanced PD. It is mainly related to disease progression and dopaminergic treatment.

P318
CHRONIC HIGH FREQUENCY GLOBUS PALLIDUS INTERNUS STIMULATION IN DIFFERENT TYPES OF DYSTONIA. A CLINICAL, VIDEO AND MRI REPORT OF 3 PATIENTS PRESENTING WITH SEGMENTAL AND GENERALIZED DYSTONIA. B. Bereznai, M. Jäger, K. Seelos, T. Gasser, U. Steude, K. Bötzel, LMU Munich (Munich, D)

Bilateral globus pallidus internus (GPI) stimulation is an experimental treatment for patients with medication-resistant severe dystonia. We report pre- and postoperative assessments of one patient with generalized inherited dystonia and two patients with idiopathic segmental dystonia. Depth electrodes were implanted with MRI-guided stereotaxy after multiple medications had failed to relieve the symptoms of the patients and antibodies against botulinum-toxin were found in one patient. Clinical symptoms were evaluated before and 3 months after surgery using the Tsui-scale for cervical dystonia. Also, neurological status was documented by video before and under chronic stimulation. MRI studies were carried out to show the anatomical localization of the electrodes. Results: Although the patients had no immediate benefit from surgery, progressive improvement began in two patients within 7 days. The symptoms of generalized dystonia in one patient disappeared mainly, so that the patient is now able to walk. One patient with segmental dystonia improved considerably and could return to work. The patient with cervical dystonia and Meige syndrome showed no improvement despite correct electrode positioning. No permanent side effects were seen. We conclude that chronic high frequency GPI stimulation is an effective treatment for certain patients with different types of dystonia. Future clinical research should be directed to finding preoperative signs to predict the success of the operation.

P319
THE EQ–5D – A GENERIC QUALITY OF LIFE MEASURE – IS A USEFUL INSTRUMENT TO MEASURE QUALITY OF LIFE IN PATIENTS WITH PARKINSON'S DISEASE. AE Schrag, M Jahanshahi, C. Selai, NP Quinn, Institute of Neurology (London, GB)

Background: The EQ–5D is a widely used generic, i.e. disease non-specific, instrument to measure quality of life (QoL), which allows comparisons between different patient groups and the general population. Objective: We tested the feasibility and validity of the EQ–5D to assess QoL in a population-based sample of patients with Parkinson's disease (PD). Methods: All 124 patients with PD seen in a population-based study on the prevalence of parkinsonism were asked to complete a QoL battery comprising the EQ–5D, the Medical Outcome Study Short Form (SF–36), the PDQ–39, a disease-specific instrument to assess QoL in PD, and the Beck Depression Inventory. A structured questionnaire interview and a complete neurological examination including the Hoehn and Yahr stage of illness scale, the Schwab and England disability scale, the motor section of the Unified Parkinson's disease rating scale (UPDRS) and the mini-mental state examination (MMSE) were performed on the same day. Results: The response rate was 78% and the completion rate of the EQ–5D among responders was 96%. The EQ–5D summary index correlated strongly with the PDQ–39 ($r=-0.75$, $p< 0.0001$) as well as the physical score of the SF 36 ($r=0.61$, $p< 0.0001$). There was a significant correlation of the EQ–5D summary index with disease severity, as measured by Hoehn and Yahr stage of illness, the Schwab and England disability scale, the motor section of the UPDRS and the depression score. The EQ–5D summary index also distinguished between patients with and without depression, falls, postural instability, cognitive impairment hallucinations, and those with deterioration of health over the previous year. Conclusion: The EQ–5D is a feasible and valid instrument to measure QoL in PD and reflects severity and complications of disease.

P320
A CLINICAL ANALYSIS AND EFFICACY OF DIFFERENT TREATMENTS IN TARDIVE SYNDROMES (TS) A CLINICAL ANALYSIS AND EFFICACY OF DIFFERENT TREATMENT IN TARDIVE SYNDROMES (TS). A. Stern, S. Honigman, S. Badarny, Carmel Medical Center (Haifa, IL)

Objective: To study the clinical features of TS and their response to tetrabenazine (TBZ), botulinum toxin – A (Botox-A) and other treatments. Background: TS is an iatrogenic syndrome of persistant abnormal involuntary movements that occur as a complication of drugs that competitively block dopamine receptors, particulary D2 receptors. Methods: Clinical features and response to treatment with TBZ, Botox-A and other drugs were analyzed in 40 patients with TS. Mean age 49.7±19.1 years, 60% female, 40% male, diagnoses at the movements disorder clinic "Carmel" Medical Center between 1990–1998. Results: 40% of patients had orobucolingual dyskinesia (OBLD), 32.5% cervical and axial dystonia, 12.5% blepharospasm, 12.5% cranial dystonia, 2.5% severe bruxism. 50% of patients were treated with TBZ by a mean dose of 75 mg/d, 20% with Botox-A, the rest with anticholinergic, Benzodiazepines anticonvulsive and neuroleptic drugs (Sulpiride). Good response was noted in 80% of patients treated with TBZ in comparison to 50% of patients treated with other drugs ($p< 0.05$). The best response to TBZ was observed in patients with OBLD compared to cervical dystonia and blepharospasm which responded well to Botox-A. 20% of twenty patients treated with TBZ developed mild parkinsonian symptoms, and 7.5% transient headache. None of the patients discontinued medications because of side effects. Conclusion: In our patients OBLD was the most common form of TS and showed a good response to TBZ treatment. Tardive Dystonia, cervical and blepharospasm responded to Botox-A as expected without serious side effects.

P321
ELEVATION OF HOMOCYSTEINE IN DYSTONIA. K. Hellweg, W. Kuhn, D. Woitalla, S. Peters, T. Mueller (Bochum, D)

Objective: Homocystinuria appeared in subjects with dystonia in combination with various neurological disorders. We investigated relations between plasma homocysteine, age, severity and duration of primary idiopathic torsion dystonia.

Material & Methods: We measured homocysteine levels in blood samples drawn from 24 subjects with dystonia and controls.

Results: Patients with dystonia (19.3  8.5, range 8.4–37  mol/l) showed significantly ($p = 0.008$, t-test) increased levels of total homocysteine compared with age- and sex-matched controls (13.9 ± 4.2, range 5.8–24.5  mol/l). No significant influence of age, severity and duration of dystonia appeared.

Conclusions: Our study supports previous reports on subjects with dystonia with homocystinuria. Various enzyme defects and/or altered neurotransmission induce hyperhomocysteinaemia, which hypothetically supports onset of dystonia due to its N-methyl-D-aspartate (NMDA) agonistic and mimicking properties. Thus NMDA-antagonists may represent a novel therapeutic principle in subjects with dystonia and severe hyperhomocysteinaemia.

P322
POLYMORPHISMS OF GLUTATHIONE-S-TRANSFERASE IN PARKINSON'S DISEASE. T. Mueller, W. Kuhn, K. Hellwig, S. Peters, H. Przuntek, H.M Bolt, M. Kempkes (Bochum, Münster, D)

Glutathione S-transferases (GSTs) are involved in the detoxification of endogenous or exogenous toxins, which may play a role in the pathogenesis of Parkinson's disease. We genotyped the Glutathione-S-Transferase isoenzymes GSTM1 and GSTT1 by polymerase chain reaction in order to evaluate different gene polymorphisms of these isoenzymes in 149 parkinsonian and 99 control subjects. No differences appeared between both groups regarding the frequencies of the homozygous deletion of GSTM1 (odds ratio 1.021; 95% CI [0.613; 1.699], p< 0.521 Fisher's exact test) and GSTT1 (odds ratio 1.514; 95% CI [0.811; 2.824], p< 0.127). Age of onset of PD did not correlate to GSTM1 and GSTT1 polymorphisms. These results do not support the hypothesis of a possible impact of GSTM1 and GSTT1 detoxification activities in the pathogenesis of Parkinson's disease.

P323
GAIT PARAMETERS AFTER PALLIDOTOMY OR SUBTHALAMIC STIMULATION. F. Valldeoriola, J. L. Molinuevo, F. A. Nobbe, J. Valls-Solé, E. Tolosa, Hospital Clinic (Barcelona, E)

Background and obiective: Functional neurosurgery is widely used as a therapeutic approach in Parkinson's disease (PD) but there is only little information about the effects of such interventions on parkinsonian gait. We have investigated in P13 patients the changes of gait parameters before and after unilateral posteroventral pallidotomy (UPP) or bilateral subthalamic stimulation (STN-DBS).

Methods: We studied 5 patients before and after STN-DBS. Their mean age was 64 (56–67) years, and their mean weight and height was 74 (68–85) kg, and 167 (157–181) cm. We also studied 6 patients before and after UPP. Their mean age was 62 (56–69) years, and their mean weight and height was 59 (50–70) kg and 164 (150–175) cm. Gait analysis was performed using a commercially available device. Patients walked at three different velocities (preferred, fast, and slow). Before surgery, assessments were done while off and on l-dopa in either group. Six months after surgery, while off l-dopa/on-DBS in stimulated patients and off and on l-dopa in UPP patients.

Results STN-DBS (off): at the preferred speed, stride length changed from 60±27 to 108±37 cm, velocity from 34±9 to 66±12 m/mn, and cadence from 116±14 to 127±17 steps/mn. At slow gait, stride raised from 52±16 to 90±20, velocity from 26±6 to 46±10, and rate from 103±17 to 112±15. At fast speed, stride length raised from 69±25 to 124±30, velocity from 69±14 to 86±20, but cadence reduced from 145±22 to 141±20.

Results UPP (off): at the preferred velocity stride length changed from 70±37 to 87±31 cm; velocity raised from 30±15 to 43±10 m/mn; and cadence from 88±20 to 103±14 steps/mn; while slow walking stride length changed from 57±33 to 74±31, velocity from 23±12 to 32±12, and rate from 80±16 to 88±13. Fast walking parameters changed from 81±53 to 96+/45 for stride, from 47±26 to 61±21 for velocity, and from 123±29 to 153±22 for cadence. On-drug comparisons showed no significant differences in either group.

Conclusions: STN-DBS significantly improves off-drug condition gait parameters and amends the altered relationship between the step length and cadence seen in PD with increasing velocities. Its effects are equal to that achieved with l-dopa and more effective than those obtained by UPP, probably because unilateral surgery is not enough to improve gait.

P324
LONG-TERM TREATMENT OF BLEPHAROSPASM AND HEMIFACIAL SPASM WITH BOTULINUM TOXIN. L. G. Gogovska, R.Lj. Ljapcev, Clinic of Neurology – Skopje (Skopje, MAK)

Objective: The aim of the study was to assess the effectiveness of a long-term treatment of Blepharospasm and Hemifacial Spasm with Botulinum Toxin type A (BTX-A)

Background: BTX is accepted as a safe and efficacious modality for the treatment of blepharospasm and hemifacial spasm, in spite of the fact that methodological differences in BTX injections techniques, dose of BTX to be administered and optimal sites of injections have not yet been defined. Furthermore, beyond the problem of antibodies formation, little is known about long-term treatment, such as long-term efficacy, safety and drop-out rate as a measure of patients satisfaction with the treatment.

Method/Design: Ten patients with Blepharospasm and ten patients suffering from Hemifacial Spasm were included in a prospective study. The patients with Blepharospasm received a dose of 7.5–15 Units (U)/per eye of BTX-A (Botox) and the patients with Hemifacial Spasm were treated with a total of 12.5–25 U Botox during the initial treatment session. The local injections of Botox were repeatedly administered every 12–16 weeks as continuous treatment for at least 2 years. By patients with Blepharospasm orbicularis oculi spasm intensity (OOSI) rated on a subjective 0–4 scale and a visual disability category (VDC) before and after treatment was assessed. The optimum result of the injections in patients with hemifacial spasm was no orbicularis muscle spasm, little or no midfacial twitching, and a small degree of spasm at the angle of the mouth.

Results: Eighty percent of patients with Blepharospasm achieved a significant improvement (OOSI rated as 0–1, VDC 5–6) after the initial injection with average duration of maximum benefit of 9.5 weeks. By patients with Hemifacial Spasm we noted significant improvement in almost 90% of patients treated with average 10 weeks duration of relief after the initial treatment session. During the repeated treatment sessions we noted a tendency for dose reduction in almost all patients treated and the duration of maximum benefit was significantly prolonged (12–15 weeks after the third administration of Botox) in both patients with Blepharospasm and Hemifacial Spasm. An unexpected finding in the study were the interindividual differences in response to treatment, despite the absence of differences in the initial degree of disease severity. There were no serious side effects, except for mild transient ptosis in 2 patients lasting for 2 weeks.

Conclusions: Treatment with BTX in patients with Blepharospasm and Hemifacial Spasm can also have long-term effects. Long-term treatment with BTX offers potential advantages by reducing the dose administered, prolonging the duration of treatment effects, reducing side-effects of treatment, preventing of resistance to therapy with BTX and reducing the cost of the treatment.

P325
STUDY ON AMINO ACIDS AND BIOGENIC AMINES IN CEREBROSPINAL FLUID OF PATIENTS WITH PARKINSON'S DISEASE: ARGUMENTS FOR AN IMBALANCE BETWEEN GLUTAMATE AND DOPAMINE NEUROTRANSMITTER SYSTEMS. S. Engelborghs, B. Marescau, R. D'Hooge, P. P. De Deyn, University of Antwerp – Born-Bunge Foundation (Antwerp, B)

Introduction: The hypothesis that an imbalance between glutamate and dopamine neurotransmitter systems contributes to the pathogenesis and progression of Parkinson's disease (PD) is supported by recent publicatfons. Nigrostriatal denervation leads to disinhibition of the nucleus subthalamicus which causes glutamate levels to be increased in both central nervous system (CNS) and cerebrospinal fluid (CSF) of animal models of PD. Experiments with animal models of PD revealed serious evidence of nucleus subthalamicus mediated excitotoxicity causing further neurodegeneration of dopamine (DA) neurons.

Aim of the study: In order to study changes in biogenic amines and its possible influence on amino acid metabolism in PD, we set up a prospective study and analysed all biogenic amines (BA), their main metabolites and 23 different amino acids (AA) in CSF of one single population of PD patients and controls.

Materials and methods: We included 24 patients with PD, 17 controls for AA analysis and 20 controls for BA analysis. CSF was obtained by lumbar puncture. AA and BA analysis was performed by means of high pressure liquid chromatography (HPLC) with colorimetric and electrochemical detection respectively. One way ANOVA with an a posteriori Dunnett's test was used for statistical analysis. Spearman's Rank Order was used for correlation analysis. A probability level of $P < 0.05$ was considered significant.

Results: Concentration of DA was significantly higher in the PD group (1.22 ± 1.81 ng/ml) compared to controls (0.32 ± 0.33 ng/ml) ($P < 0.05$) which was interpreted as an effect of treatment (l-dopa, selegiline). The DA metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) was significantly decreased (7.97 ± 3.87 ng/ml; controls: 13.57 ± 6.73 ng/ml; $P < 0.01$) whereas homovanillic acid (HVA) was unchanged in CSF of PD patients. Although levels of serotonin (5HT) are unchanged, we revealed significantly lower 5-hydroxyindoleacetic acid (5HIAA) levels (14.77 ± 7.49 ng/ml) compared to controls (19.82 ± 5.15 ng/ml) ($P < 0.05$). Significantly decreased 5HIAA/5HT ratios ($P = 0.001$) reflect decreased 5HT catabolism in PD. No changes in (nor)epinephrine were found.

We revealed significantly increased CSF glutamate levels (0.315 ± 0.192 µmol/100 ml; controls: 0.183 ± 0.085 µmol/100 ml; $P = 0.011$) correlating with disease duration and with degree of cognitive deterioration in a subgroup of demented PD patients ($n = 12$). With exception of lower taurine levels, no other AA changes were found. No statistically significant differences in concentrations of BA and AA comparing subgroups of PD with ($n = 12$) and without ($n = 12$) dementia could be revealed.

Discussion: In the present study we revealed significantly increased CSF glutamate levels correlating with disease duration in both l-dopa treated and untreated PD patients. Apparently, l-dopa substitution is not sufficient to reverse the decreased nigrostriatal dopaminergic tonus that induces disinhibition and thus relative hyperactivity of the nucleus subthalamicus. Increased CNS gluta-

mate concentrations might cause excitotoxicity thus leading to further damage to vulnerable DA neurons in both l-dopa treated and untreated patients.

This new insight in the neurochemistry of PD might form the basis for the potential use of glutamate antagonists and glutamate release inhibitors in PD.

P326
A MOLECULAR AND IMMUNOHISTOCHEMICAL STUDY OF ALPHA SYNUCLEIN IN A LARGE SERIES OF CASES OF FAMILIAL PARKINSON'S DISEASE AND MULTIPLE SYSTEM ATROPHY. J.R. Vaughan, S. Dhatta, N. Cairns, P. Cantons, N.P. Quinn, N.W. Wood, S.E. Daniel, Institute of Neurology, Institute of Psychiatry, PDS Brainbank (London, UK)

Introduction: Alpha-synuclein (SNCA) is a presynaptic protein of unknown function which is mutated in some cases of familial Parkinson's disease (FPD). SNCA has since been found to strongly stain brainstem-type and cortical Lewy bodies in idiopathic Parkinson's disease (IPD). Glial cytoplasmic inclusions (GCIs) found in multiple system atrophy (MSA) also stain with SNCA indicating that this protein is regionally up-regulated in these cases.

Methods: An immunohistochemical examination of the substantia nigra in a series of 20 cases of pathologically proven FPD and cortical sections from 10 cases of pathologically proven MSA was performed using SNCA polyclonal antibody. Fifty cases of clinically diagnosed MSA were also screened for the 2 known mutations in the SNCA gene.

Results: Alpha synuclein staining of Lewy bodies was positive in all cases of FPD. The GCIs in all 10 cases of MSA were also positive for SNCA. The two mutations so far described in SNCA were excluded from 50 cases of clinically diagnosed MSA. Four cases of pathologically proven MSA were sequenced and no mutations found in the open reading frame.

Conclusions: This study strongly suggests that SNCA aggregation is a common process in certain neurodegenerative diseases, including PD and MSA but failed to detect any of the known SNCA coding mutations in the series studied. Novel coding mutations in SNCA were excluded in 4 pathologically proven cases of MSA.

P327
[18F] DOPA PET IN EARLY PARKINSON'S DISEASE: REGIONAL INFLUX CONSTANTS IN STRIATUM CORRELATE WITH MOTOR SIGNS. J. Karitzky, A. T. J. Vogg, E. Elitok, G. Glatting, A. Gerhard, C. von Arnim, J. Schwarz, A. Storch, S. N. Reske, A. C. Ludolph, G. B. Landwehrmeyer (Ulm, D)

Objectives: To determine the regional pattern of striatal [18F] dopa metabolism in patients with early Parkinson's disease, to correlate regional influx constants (Ki) with the Unified Parkinson's Disease Rating Scale (UDPRS) motor score, to identify the striatal region displaying the best correlation to the severity of motor signs.

Methods: Fourteen patients with early Parkinson's disease (age 59 ± 7 years [mean ± SD], mean disease duration 19 ± 14 months) were examined with [18F] dopa PET and UDPRS motor scores. For PET analysis individual regions of interest (ROIs) were placed on each caudate and on the ventral and the dorsal half of each putamen. Kis were calculated using a multiple time graphical analysis (MTGA) approach with occipital counts as input function. Correlation between different Kis (caudate, ventral and dorsal half of putamen) and total UDPRS motor score and between Kis and the motor scores for each contralateral limb (summed values for upper and lower extremities) were assessed by Pearson product-moment correlation. To examine to what extent each regional Ki correlated with the severity of motor signs a linear regression was applied to regional Kis and summed limb UDPRS motor scores. The gradient of the regression line was compared for each paired UDPRS motor score/Ki. We assumed that the highest sensitivity to the degree of clinical impairment for the regional Ki is indicated by the highest gradient of the regression line.

Results: Mean Kis of the dorsal putamen were significantly lower than mean Kis of the ventral putamen. This may be in part due to the greater partial volume effect in the smaller dorsal part. There was no significant correlation between any regional Ki and the total UDPRS motor score. The [18F] dopa uptake expressed as Ki in the dorsal putamen showed a significant inverse correlation with the UDPRS motor scores of the contralateral upper extremities ($r = -0.67$, $p = 0.009$ and $r = -0.57$ $p = 0.03$ respectively for both sides). There was no significant correlation between Kis in the ventral putamen and limb UDPRS motor scores or between Kis in the dorsal putamen and motor scores of the contralateral lower extremities. The gradient of the regression line was highest for paired dorsal putamen/UDPRS motor scores of the contralateral upper extremities.

Conclusions: Our data confirmed previous findings using [18F] dopa PET of regional changes with earlier involvement of the dorsal putamen compared to the ventral putamen in Parkinson's disease. The Ki in the dorsal part of the putamen showed the best correlation with the severity of motor impairment.

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EFFECTS OF BILATERAL SUBTHALAMIC NUCLEUS STIMULATION IN PARKINSON'S DISEASE. P Krystkowiak, LJP Defebvre, D Devos, F Cassim, G Touzet, S Blond, JD Guieu, A Destée, Hôpital Salengro CHRU (Lille Cedex, F)

Objective: The aim of the present study was to evaluate the effect of bilateral STN stimulation in patients with PD.

Background: Chronic high frequency stimulation of the subthalamic nucleus (STN) can be proposed for the treatment of severe Parkinson's disease (PD). This technique has been reported to improve the different features of parkinsonism (akinesia, tremor, rigidity and other symptoms such as gait disorders) but also the levodopa-induced dyskinesias (LID).

Patients and Methods: Eight patients underwent bilateral STN stimulation. The Unified Parkinson's Disease Rating Scale (UPDRS), time motor tests from the Core Assessment Program for Intracerebral Transplantations (CAPIT) and LID scale were compared in off and on drug conditions, before surgery and 12 months after surgery.

Results: In off drug condition (12 months after surgery), the motor UPDRS score was improved by 36 % on average. The improvement of other symptoms was: tremor 88 %, akinesia 31 %, rigidity 57 %, gait 17 %, CAPIT 65 % (hand-arm movement between 2 points). In on drug condition, a marked improvement of LID (mean 75 %) was observed. The total levodopa equivalents dose was decreased by 30 %. The following adverse effects were observed: dysarthria (n=3) and mild cognitive impairment (n=1).

Conclusion: This study confirms that chronic STN stimulation is effective on both parkinsonism and LID.

P329
A UNIQUE MANIFESTATION OF VASCULAR PARKINSONISM AND REVIEW OF THE LITERATURE. S. Peters, K. Hellweg, E. Eising, H. Przuntek, T. Müller, Ruhr-University of Bochum, University of Essen (Bochum, Essen, D)

Vascular parkinsonism (VP) is characterized by sudden onset and rapid progression of clinical symptoms, absent or poor response to dopamine substitution therapy, postural instability with shuffling gait and absence of tremor, making it a clinically distinct entity from idiopathic Parkinson's disease (IPD), furthermore displaying certain typical findings in neuroradiological investigations. We report on a patient presenting features of VP associated with an intracerebral lesion not ascribed to VP to date, namely an isolated ischemic focal lesion located in the left cerebral penduncle between the substantia nigra and nucleus ruber as evidenced by MRI. The pathophysiological organic correlate for contralateral extrapyramidal symptoms in this patient may be an interruption of nigro-thalamic projections, interrupting the final subcortical station in the cortico-striato-pallido-nigro-thalamico-cortical loop central to the pathophysiology of Parkinsonian syndromes. Non-response to levodopa therapy could be a consequence of disruption of the cortico-basal ganglia-cortical loop on account of ischemic destruction of subcortico-cortical axons, the underlying pathology, therefore, not being the result of a loss of nigral dopaminergic neurons or striatal dopamine deficiency pathognomic to IPD. To our knowledge this is the first described case of clinically manifest VP with a single lesion in the contralateral cerebral penduncle between the substantia nigra and nucleus ruber, and suggests alternate intracerebral patterns for the distribution of disease-causing lesions in VP, and possibly new pathophysiological explanations for the nature of this disease.

P330
RHYTHMIC PALATAL MYOCLONUS AND PENDULAR NYSTAGMUS AS A MANIFESTATION MULTIPLE SCLEROSIS – A CASE REPORT. C. Klötzsch, M. Dihné, J. Noth (Aachen, D)

We present the case of a 46 year-old male patient who has been suffering for ten years from recurrent rhythmic palatal myoclonus (RPM) and pendular nystagmus associated with intranuclear ophthalmoplegia due to multiple sclerosis.

In 1987 he first presented with intranuclear ophthalmoplegia (INO) and vertigo. Magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis were normal except for weak increase of alpha–2-globulin fraction in CSF. The clinical symptoms disappeared after intravenous cortisone therapy.

10 years later diplopia and vertigo reoccurred and were accompanied by dysarthria and discrete right-sided monoparesis of the right arm. Partial remission occurred after another cortisone therapy and a immunosuppressive therapy was installed with methotrexate which was discontinued in 6/98, when the symptoms relapsed and the patient was admitted to the hospital. This time CSF studies revealed 12 lymphocytes/µl and intrathecal autochtonic IgG production but no oligoclonal bands. Amelioration of the symptoms was achieved after cortisone therapy. However, since this moment the patient has suffered from oscil-

lopsia, dysarthria and gait disturbance in a progressive remitting-relapsing way. An MRI from 9/98 revealed almost symmetric hyperdense lesions in the medulla oblongata rostral from the inferior olives and a small hyperdensity in the pons. There were no more alterations suggestive for demyelination. Repeated lumbar punctures revealed oligoclonal bands in one occasion and was normal in another. Evoked potentials showed normal central conduction time execpt for evoked motor potentials to the legs which was on the limit. Cerebral angiography was normal. Since cortisone provoked only partial or no amelioration in two further relapses other therapeutic strategies were chosen for the treatment of the rhythmic palatal and eye movements, which provoked disabling dysarthria and oscillopsia: Carbamezapine, valproate and primidone were unsuccessful for the treatment of the symptoms. Trihexyphenidyle povoked amelioration of RPM and nystagmus but the gait worsened, so the patient discontinued therapy.

Rhythmic palatal myoclonus (RPM) is a rare movement disorder which may be associated with rhythmic discharge of other cranial muscles. It was subdivided by Deuschl et al. into symptomatic and idiopathic RPM. Pendular nystagmus is a well-known but uncommon manifestation of multiple sclerosis. Palatal myoclonus in definite multiple sclerosis was to our knowledge just once described before. Since the disease course is relapsing-remitting, MRI and CSF findings are compatible with the diagnosis we assume that our patient is suffering from multiple sclerosis with an uncommon clinical presentation and lesion localization. The clinical and radiological findings suggest that the lesions are confined to the brain stem.

P331
INVOLUNTARY MOVEMENTS AND CERVICAL MYELITIS REVEALING SYSTEMIC LUPUS ERYTHEMATOSUS. B. Mastain, H. Zephir, P. Charpentier, L. Defebvre, P. Krystkowiak, A. Destée, Service De Neurologie A (Lille Cedex, F)

Introduction: Central nervous system involvement is not rare in Systemic Lupus Erythematosus (SLE). Abnormal involuntary movements (AIM) and myelitis are both common but relatively rare manifestations, observed respectively in approximately 2 % and 4 %, usually during the course of established SLE. Chorea is the most common AIM. When focal lesions cause it, they are usually found in the basal ganglia region.

We present the first case of painful tonic spasm – a well recognized paroxysmal dystonia usually observed in multiple sclerosis – associated with myelitis caused by SLE.

Case Report: A 36 year-old woman presented with a 3-month history of cervicalgia and paroxystic right cervicobrachial pain attacks. Neurological examination revealed discrete right hemiparesia and hemihypoesthesia, markedly most dominant on the hand, and sparing the face. Aura of tension and cramp-like pain accompanied stereotyped sudden-onset tonic spasms involving the superior and, to a lesser degree, the inferior limb. The attacks were brief, lasting a few minutes, occurring up to several times per hour, often precipitated by voluntary movement. This was characteristic for painful tonic spasms (PTS). Cervical MRI revealed a T2-hypersignal of the right lateral tract of the spinal cord from C1 to C3 levels.

The patient had a 6-year history of thrombocytopenia associated with positive antinuclear and anti-DNA antibodies. Therefore, the involvement of the nervous system affirmed the diagnosis of SLE in accordance with 1982 revised criteria. There was a slight elevation of CSF protein (0.69 g/l) with normal gamma-globulin profile. Laboratory studies for antiphospholipid antibodies – included antibodies to beta2 glycoprotein I and P-ethanolamine – were negative. Brain MRI was normal. Carbamazepine was dramatically effective in controlling the PTS but severe granulopenia led us to stop it. Afterwards, specific treatment for SLE (corticosteroïd then cyclophosphamide) brought a slow disparition of paroxysmal dystonia and regression of the size of the lesion on MRI.

Discussion: Painful tonic spasms are now regarded as a typical symptom of multiple sclerosis. Recent studies suggest that for unilateral PTS the site of lesions is more likely to be at the level of either the contralateral posterior limb of the internal capsule or the cerebral peduncle. In our case, the lesion being unique, we can affirm that PTS may be caused by a spinal cord involvement. Furthermore, the absence of antiphospholipid antibodies and the progressive size decrease of the lesion suggest an inflammatory mechanism. Therefore, PTS may occur in other inflammatory diseases of the central nervous system such as SLE. Dramatic improvement with carbamazepine also suggests a similar pathogenetic mechanism, a transversely spreading ephaptic activation of axons within a partially demyelinated lesion.

P332
CAN DOPAMINERGIC THERAPY LEAD TO REDUCTION OF VISUAL ACUITY? A CASE REPORT. S. Peters, K. Hellweg, G. Schweibold, A. Kuhlmann, H. Przuntek, T. Müller, Ruhr-University of Bochum (Bochum, D)

Visual dysfunction is a well-known feature of Parkinson's disease. Dopamine has been shown to be a functional modulator at many levels of the visual system. We report on a Parkinsonian patient, concurrently suffering from various ophthalmological conditions including glaucoma and cataracts, displaying objectively measureable loss of visual acuity and blurring of vision under medication with a MAO-B inhibitor and multiple ergolene-derived dopamine agonists. Various studies have investigated the effects of different D1- and D2-agonists and -antagonists on visual function, finding that the presynaptic dopaminergic autoreceptor involved in the modulation of dopamine release in the retina displays characteristics of D2-receptors. We conclude that the observed phenomenon represents either an inhibition of dopamine release due to excessive stimulation of presynaptic D2-autoreceptors, leading to an insufficient stimulation of postsynaptic dopaminergic receptors, thus impeding retinal signal conduction, or a heretofore unclear interaction between the patients' ophthalmological pathologies and dopaminergic therapy, possibly due to inadequate stimulation of postsynaptic dopamine receptors, leading to faulty retinal information processing.

P333
HUNTINGTON'S DISEASE–CLINICAL CORRELATION WITH REDOX STATUS PARAMETERS. C. Januário, M. M. Grazina, T. Proença, F. Silva, A. Fernandes, L. Oliveira, L. Cunha, C. Oliveira, University Hospital University of Coimbra, Faculty of Medicine, Center for Neuroscience (Coimbra, P)

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disorder, characterized by the presence of movement disorders, cognition and behaviour disturbances. One of the mechanisms that may contribute to the pathogenesis of this disorder is mitochondrial respiratory chain dysfunction. The observation that mitochondrial activity is affected in neurodegenerative disorders indicates that oxidative damage may contribute to neurodegeneration. We selected 13 patients (7 males, 6 females), with age of onset between 14 and 62 (mean age 45.92 ± 14.02), clinically definite HD, confirmed by DNA·analysis. All the patients, free of medication, were assessed by the Unified Huntington's Disease Rating Scale (UHDRS). They had mild to moderate clinical HD, Mini-Mental State Examination, MMSE * 16. The evaluation included physical examination, chest X-ray film, blood chemistry screen, thyroid function test, electrocardiogram and brain MR scan. Chorea was an early sign in 9 patients while psychiatric manifestations were present in all patients. The severity of cognitive deterioration correlated with duration of disease. We investigated mitochondrial respiratory chain function through the substrate oxidation rate and spectrophotometric evaluation of enzymatic complexes II+III and IV. Up to now, the results show increased glutamate and succinate oxidation in patients (11.08 and 20.33 nmol 02/min/mg protein, respectively), compared with controls (7.71 and 13.33 nmol 02/min/mg protein, respectively), indicating impaired mitochondrial function in these patients. This dysfunction may impair mitochondrial respiratory chain activity and contribute to the neurodegenerative process. Furthermore, a larger sample is being studied and a more detailed correlation with oxidative stress parameters (uric acid, glutathione, vitamin E, MDA, superoxide dismutase and glutathione peroxidase activities) is being performed.

P334
WILSON'S DISEASE – INITIAL NEUROLOGICAL MANIFESTATIONS AND THEIR INFLUENCE ON THE LATER COURSE. B. Eggers, W. Hermann, A. Wagner, University of Leipzig (Leipzig, D)

Background: Wilson's disease is a rare disorder of copper metabolism that is often misjudged, due to its variety of initial manifestations. Early diagnosis and early initiating of therapy are essential for surviving and for a better clinical outcome. Initial indicators of prognosis are still not at hand.

Methods: Retrospective study of 47 patients with a neurological course of Wilson's disease (27 men and 20 women), that we observed for a median time of 17,6 years. We created a neurological score, in which every patient was evaluated once a year. We correlated initial manifestations with later disturbances in order to find out, whether there is an influence on later neurological impairment. We used Chi-Square Test for statistical significance.

Results: The most common initial symptoms are tremor (33 patients) and dysarthria (22 patients) followed by other presentations like abnormal hand writing, bad performance at school, personality changes, ataxia and drooling. Tremor is an initial manifestation, which can easily be controlled at an early onset of therapy. Otherwise dysarthria cannot be easily reversed and, in the fur-

ther course, it is often associated with other neurological manifestations like ataxia, dysdiadochokinesis and disturbances of precision movements despite adequate therapy. This bad prognosis was statistically significant ($p < 0,05$). Other initial manifestations had no significant influence on outcome.

Conclusions: Initial dysarthria is a predictor for a bad course of Wilson's disease. Other initial manifestations like tremor have no significant influence on later neurological outcome under adequate therapy.

P335
UNUSUAL CASE OF AN UNILATERAL EXTRAPYRAMIDAL MOTORIC SYMPTOM OF UNKNOWN ORIGIN. A. Hahn, A. Lück, J. Reess, E. Mauch, Neurological Hospital Dietenbronn (Schwendi, D)

We present the case of a 45-year-old patient with an extrapyramidal motoric syndrome. In December 1998 she felt a pain in the left elbow joint that proceeded upwards to the left shoulder joint and downwards to the hand. She was not able to move the left hand and unable to extend the left arm actively. The position the arm was held in was in flexion with the hand in ulnar deviation and the fingers overextended. In the clinical examination we found an increased, rigid muscle tone. The reflexes of the upper limbs showed to be diminished on the left side in comparison to the right. The NMR image of the brain showed a severe degeneration and gliosis of the right nucleus caudatus and putamen. The extrapyramidal motoric symptoms can be well explained with this finding. A probatory medication of levodopa eased the symptoms so we started a medication with the dopamin agonist alpha-dihydroergocryptinmethansulfonat and amantadin. Under this medication the patient was able to return to her work as a nurse's aid. The neurological examination and the NMR-scan six months after the diagnosis showed no signs of progress.

There is no other case similar to this described in the literature. As a differential diagnosis a Parkinson syndrome of vascular genesis as described by Tison et al. (1993) is most unlikely. In comparison to their case the NMR of our patient showed an intact capsula interna. An early childhood brain insult as described by Giladi et al. (1990) with a delayed-onset of Parkinsonism could not be found in her history. Also there is no similar case or a case of Parkinsonism in our patient's family history.

A case of a unilateral degeneration of the nucleus caudatus and putamen with an unilateral extrapyramidal motoric symptom has not been described previously.

P336
MRI IN WILSON'S DISEASE – IMPORTANCE OF PD SEQUENCE APPLICATION. Kozic, Kostic, Svetel, Sternic, Bogdanovic, Popovic, Semnic, Prvulovic, Institute of Oncology, Institute of Neurology (Sremska Kamenica, Belgrade, YU)

Purpose: The aim of the study was to reveal the sites of abnormalities by brain MRI in patients with Wilson's disease and to estimate the most sensitive sequences for lesion detection.

Methods: Thirty-nine patients with Wilson's disease were examined using fast spin-echo T2-weighted (TR 3300, TE 19/93), T1-weighted (TR 260, TE 6) and gradient-echo (FLASH TR 800, TE 26) sequences with 1.5T magnetic resonance imager.

Results: Putaminal lesions with a pattern of symmetric, bilateral and concentric T2W hyperintensities, indicated to be typical for Wilson's disease, were revealed in 59% of patients. Obvious symmetric deposits with paramagnetic properties (iron or copper) in globus pallidus, substantia nigra and nucleus ruber were detected in 53%, 41% and 25% of patients, respectively. Brain stem involvement with pontine and mesencephalic tegmentum being affected was documented in 44% of patients, while additional central aspects of brain stem displayed signal increase in 28% of patients. Caudate nucleus, thalamus and claustrum were involved in 30%, 20% and 10% of patients, respectively. Supratentorial or cerebellar atrophy was observed in 46% of patients, while lesions of gliosis or dismyelination in cerebellum were noticed in only 3 patients with extremely severe clinical symptoms. Three patients with Wilson's disease displayed no parenchymal lesions and cerebral atrophy. In 50% of patients of the examined group, only PD sequence demonstrated high sensitivity for detection of putaminal involvement, while T2-w sequence was either inconclusive or revealed much smaller zones of gliosis or dismyelination.

Discussion: Application of only T1W and spin-echo or turbo spin-echo T2-W sequence (single echo) without PD-W in order to be "time effective" for adult brain examination is absolutely unacceptable. Gradient-echo sequence is the most sensitive for confirmation of paramagnetic deposition.

P337
PARKINSONISM ASSOCIATED WITH SJOGREN'S SYNDROME. S Hassin-Baer, Y Levi, P Langevitz, M Ehrenfeld, Sheba Medical Center (Tel-Hashomer, IL)

Sjogren's syndrome (SS) is a chronic inflammatory multisystem disorder manifested by dry eyes and dry mouth. The nervous system may be involved in up to 30% of the patients. Central nervous system involvement can manifest as either focal or diffuse disorders, which may affect any part of the brain or spinal cord in a chronic or relapsing fashion. Patients with stroke, migraine, encephalopathy, dementia, aseptic meningitis, seizures, focal cerebral deficits, personality and psychiatric disturbances have been described.

We present 3 patients with SS who have a parkinsonian syndrome. The first is a 58-year-old man that developed late onset migraine with aura and classical symptoms of SS at the age of 53. At the age of 55 fibromyalgia began and at 56 a hemiparkinsonian syndrome with tremor developed. The second is a 69-year-old woman who after a prolonged history of polyarthralgia and 2 year history of dry eyes and dry mouth developed a bilateral parkinsonian syndrome with a prominent axial component. The third is a woman of 78 with a 3-year history of asymmetrical dopa-responsive parkinsonian syndrome and a 10-year history of polyarthritis with progressive complaints of dry eyes and dry mouth.

The clinical, neuroradiological and serological characteristics of these patients are presented and possible pathogenetic mechanisms are discussed.

P338
USEFULNESS OF NEUROPHYSIOLOGIC TECHNIQUES IN STEREOTACTIC SUBTHALAMIC NUCLEUS STIMULATION FOR ADVANCED PARKINSON'S DISEASE. J. L. Molinuevo, F. Valldeoriola, J. Rumià, E. Tolosa, Hospital Clinic i Universitari (Barcelona, E)

Background: Bilateral subthalamic nucleus (STN) stimulation has proved to be an effective therapy for the treatment of advanced Parkinson's disease (PD).

Objective: To determine the impact of neurophysiologic guidance on STN targeting and to assess its safet and efficacy.

Methods: We have compared the initial theoretic anatomic target (TAT) of the STN with the final microrecording guided coordinates in 15 consecutive PD patients with bilateraly implanted electrodes in the STN (30 procedures). The clinical results and adverse effects are also reported. Statistical analysis was carried out by means of the software SPSS-PC Windows 3.1 version. All comparisons were done through a paired Student's t test and Pearson's correlation test.

Results: Neurophysiological guidance modified the target coordinates in 26 of the 30 procedures. The mean correction applied to the TAT in order to place the electrode in its definite location was 0,4 mm (±0,8, range 0–3; p=0,03) in the medial-lateral axis, 1,6 mm (±1,2, range 0–5; p=0,01) in the anterior-posterior plane and 0,8 mm (±0,8, range 0–3;p=0,26) in the vertical axis. The mean number of microrecording tracks employed to localize each STN was 2,8±1,8 tracks. After surgery, total UPDRS motor score, in off medication condition improved by 65.9%; UPDRS-II scores were reduced by 71.8% and Schwab and England scores improved by 45.3%. The degree of clinical improvement was not correlated with the number of microrecording tracks nor with the magnitude of the correction. No intraoperative haemorrhages occurred in this series.

Conclusion: Neurophysiological guidance is a useful tool in order to improve and confirm target localization. The correction applied in these patients resulted in a significant clinical improvement six months after surgery and these data can be obtained safely.

P339
ASSESSMENT OF THE CLINICAL EQUIVALENT DOSE TO SWITCH FROM PERGOLIDE TO ROPINIROLE IN PARKINSON'S DISEASE: AN OPEN LABEL BLINDED PILOT STUDY. J. L. Molinuevo, F. Valldeoriola, A. Cardozo, M. Pilleri, E. Tolosa, Hospital Clinic i Universitari (Barcelona, E)

Background and objective: The clinical equivalent dose to switch between the dopamine agonists pergolide (PRG) and ropinirole (RPN) is not well stablished. To investigate the dose of RPN which is able to produce the same clinical effect to that obtained with PRG.

Methods: An open label pilot trial was conducted in 10 patients with Parkinson's Disease (PD) with motor fluctuations and dyskinesias taking l-dopa and PRG. We switched within 24 hours PRG with RPN with the recommended dose ratio of 1:3 and titrated until the patient subjectively referred to reach a similar clinical status. Patients were assessed in off-drug and on-drug condition one week before the pharmacological change and one month later when the final RPN dose was established. Patients were evaluated by one of the authors, unaware of the patient's treatment, with the Unified Parkinson's Disease Rating Scale (UPDRS), a dyskinesia scale (AIMS) and a Clinical Global Impression

(CGI). Motor fluctuations were analyzed through home diaries. All comparisons were done through a paired Student's t test.

Results: The mean PRG dose before the change was 2.9±0.4. The mean stable RPN dose at the one month evaluation was 15.0±4.0. At this time, no significant changes were observed in the UPDRS and AIMS scores neither in off-drug nor in the on-drug condition. Home diaries analysis also revealed no significant changes. The time spent in on-drug condition with dyskinesias decreased by 4.6%, the time spent in on-drug condition without dyskinesias increased by 3.2% and the time spent in off-drug condition increased by 1.4%. At the one month evaluation, CGI was answered as "no changes" by all the patients except two who referred improvement. No adverse effects were seen after switching agonists. The clinical status with PRG and RPN was not statistically different with the described doses, therefore it may be inferred that the mean clinical equivalent dose ratio was 1: 5.25.

Conclusion: These preliminary data suggest that the clinical equivalent dose of PRG and RPN is higher than that previously recommended.

P340
CORTICAL GENERATORS AND FUNCTIONAL INTEGRITY OF SOMATOSENSORY PATHWAY IN THE HUNTINGTON'S DISEASE PATIENTS. M. Rakowicz, E. Zdzienicka, R. Poniatowska, W. Kuran, D. Hoffman-Zacharska, T. Jakubowska, J. Zaremba, R. Krawczyk, R. Boguslawska, U. Zalewska, Institute Of Psychiatry And Neurology (Warsaw, Warsaw, Pl)

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an unstable expansion of CAG repeats within IT15 gene, localised on chromosome 4 and encodes the protein huntington. The neuronal loss in cerebral cortex, striatum, thalamus and cerebellum is associated with clinical symptoms characterised by emotional and cognitive deterioration, chorea, and rigidity. Thirty-five patients aged 9 to 68 with HD confirmed by DNA analysis, with CAG repeats ranging from 40 to 92 were examined clinically and by somatosensory evoked potentials (SEPs). The aim of our study was to evaluate the functional integrity of somatosensory pathway and cortical generators of SEPs, and correlate these observations with the deterioration of cognitive function and with morphometrical study of brain and spinal cord magnetic resonance images (MRI). Scalp recorded SEPs following stimulation of median and posterior tibial nerves revealed alteration of shape and marked diminution of amplitude in 80% and 56% of patients, respectively. The latency of early cortical components was delayed in 34% of cases. Spinal and/or central conduction times (CCT) were prolonged in 38% of patients with adult onset. MRI showed cortical atrophy, particularly in frontal cortex in 82% of cases. In T2-weighted images an increased signal intensity of putamen was found in 72% of patients, which was more pronounced in juvenile onset group. Ratio of linear dimension of caudates significantly correlated with amplitude of cortical SEPs ($p< 0.01$) as well as with Mini-Mental State Examination scores and different degree of dementia ($p< 0.001$). Alterations of cortical SEPs and atrophy of the brain in MRI were consistent with deterioration of cognitive functions estimated by Wechsler and/or Raven tests. We concluded, that in the HD patients diminution of amplitude of early components of SEPs is probably due to cortical atrophy as well as functional alteration of volley transmission via the thalamus and other basal ganglia. Prolonged spinal conduction time and CCT could be associated with involvement of sensory afferents of spinal cord dorsal columns.

P341
"THALAMIC BLEPHAROSPASM". A CASE REPORT. M. Choisy, A. Améri, M. Vidailhet, J-C. Willer, Centre Hospitalier de Meaux, Hopital Saint Antoine, Hopital de la Salpêtrière (Meaux, Paris, F)

Focal cranial dystonia after thalamic lesion is very unusual. This prompted us to report the following case. A 73-year-old male developed a bilateral thalamic infarction located by a magnetic resonance imagery (MRI) in the paramedian thalamic nuclei. This cerebrovascular accident was followed by some intellectual decline, an emotional indifference, a lack of initiative and an apragmatism. Four years later, the patient presented with repetitive involuntary contractions of the orbicularis oculi and an apraxia of lid opening. In contrast with what is observed in idiopathic blepharospasm, the blink reflex was normal. The patient was moderately improved by injections of botulinium toxin in pretarsal muscles. In the present case, as in most cases reported, blepharospasm was associated with paramedian nuclei lesions. Pathophysiology of "thalamic blepharospasm" is discussed as is its differences with idiopathic blepharospasm.

P342
ACQUIRED HEPATOCEREBRAL DEGENERATION: REGRESSION OF NEUROLOGICAL SYMPTOMS AFTER AN HEPATORENAL TRANSPLANTATION. E. Le Page, J. F. Pinel, A. Guillygomarch, K. Boudjema, M. Messmer, M. Verin, G. Edan, University Hospital Pontchaillou (Rennes, F)

INTRODUCTION: Acquired hepatocerebral degeneration (AHD) is a rare complication of chronic liver disease (less than 1%), with cognitive, extrapyramidal and cerebellar symptoms. The evolution is generally progressive with irreversible neurological deterioration. The mechanism is imprecise.

OBSERVATION: An hepatorenal transplantation was discussed for a patient whith alcoholic cirrhosis and IgA nephropathy. Although he was handicaped by cognitive, extrapyramidal and cerebellar symptoms (tremor, ataxia, dysarthria, dyskinesia and dystonia), the operation was decided. To assess the evolution of this neurologic syndrome after liver transplantation, we compared 1) clinical status (video, neuro-psychological tests), 2) encephalic MRI 3) SPECT and 4) biological measures performed before and after operation. Clinical improvement began one month after the transplantation and was strong at three months, neuro-psychological tests did not show any more frontal disturbance, MRI abnormalities of the white matter in the dentate nuclei and in the temporo-parieto-occipito junctions had decreased, but the lenticular nuclei remained hypointense on T1 and hyperintense on T2-weighted sequences, SPECT revealed that the perfusion was increased in the fronto-temporal region. Serum ammonia was normalized, and the renal function improved.

CONCLUSION: AHD is a neurological syndrome that causes progressively neurological deterioration and incapacity. However, this case shows that it can be reversible and does not refuse the indication of the transplantation.

P343
A KINEMATIC CRITERION FOR THE DIFFERENTIAL DIAGNOSIS BETWEEN PARKINSON DISEASE AND PARKINSON-PLUS SYNDROMES IN APOMORPHINE TEST. B. Legros, M. Manto, S. Dethy, Hôpital Erasme (Bruxelles, B)

Apomorphine test is widely used to assess the dopaminergic response in patients presenting parkinsonian signs. Although this test is accepted as a useful tool for daily practice, kinematic criteria to distinguish Parkinson disease (PD) and Parkinson-plus syndromes (PPS) are lacking. We analysed the kinematic profiles of pointing movements in 13 right-handed patients presenting extrapyramidal features (PD: n = 8; PPS: n = 5) before and after administration of apomorphine (subcutaneous route; mean dose: 3.4 ± 1.1 mg; range: 2–5). The mean age in the PD group was 63.4 ± 10.3 years and the mean age in the PPS group was 59.6 ± 14.4 years. The mean duration of the disease was 9.3 ± 6.1 years and was 4.0 ± 3.5 years in the PD group and in the PPS group, respectively. We tested the hypothesis that the kinematic study of reaching movements could provide informations to distinguish PD and PPS patients. We recorded pointing movements in the upper limb of the most affected side (right side: n = 12 patients, left side: n = 1 patient) towards a fixed target located at 85% of the upper limb's length and at the level of shoulder's height. Repeated movements were recorded during a period of 40 seconds. We computed the ratios of the mean movement time (RMMT) in the basal condition and after apomorphine injection. Using a threshold value of 1.15 for the RMMT, we could differentiate the 2 groups. The mean RMMT was 1.61 ± 0.76 (range: 1.17 to 3.42) in the PD group and was 1.04 ± 0.08 (range: 0.92 to 1.12) in the PPS group ($p = 0.002$). Apomorphine administration had a different effect on the movement time in the two groups (interaction group by apomorphine: $p = 0.004$). In the horizontal axis, the ratio of the mean peak velocity (RMPV) was 0.80 ± 0.17 in the PD group and 1.02 ± 0.3 in the PPS group ($p = 0.22$). In the vertical axis, RMPV was 0.82 ± 0.19 in the PD group and was 0.84 ± 0.11 in the PPS group ($p = 0.76$). After a follow-up of 2 years, the diagnosis remained unchanged in all the patients except one who was misdiagnosed initially as presenting a multiple system atrophy (MSA). Our data suggest that the RMMT is a simple and sound kinematic criterion which could be used to differentiate PD patients and PPS patients. A study including a higher number of patients is warranted to confirm our results.

P344
BILATERAL HEMIFACIAL SPASM CAUSED BY VERTEBRO-BASILAR MALFORMATION – CASE REPORT. D. Fanslau, M. Ziolkowska-Kochan, M. Binek, University School of Medical Sciences (Bydgoszcz, PL)

To our knowledge only four cases of bilateral hemifacial spasm have been described. In this paper authors decided to describe their own experiences.

A right-handed 74-years-old woman (W. K.) was admitted to our Department in October 1998 because of appearance of frequent shock-like contractions of the facial muscles on right side. The first clinical symptoms – left eye twitching occurred on the left side of face in August 1996. Unilateral involun-

tary spasm started with the orbicularis oculi muscle and muscles of frontal part and lower part of left side of face were involved as well. She presented a history of hypertension and coronary heart diseases. She suffered from dizziness, imbalance, hearing disturbances – tinnitus. In June 1997 Computed Tomography scan showed bilateral lesions of the periventricular white matter. There were no cranial nerves lesions on the first neurological examination. The exaggeration of the tendon reflexes was present. Cerebellar deficiency – ataxia occurred in Romberg's test, slight intention tremor and dysmetry in both upper limbs were observed as well. The improvement was carried out by injection of 100 units of Dysport in facial muscles of left side. We observed the slight weakness and wasting of lower facial muscles and slight ptosis. In February 1998 clonic facial spasm appeared on the right side of face. The muscles of the lower part of face were involved. Orbicularis oculi muscle presented spasm as a last one. 50 units of Dysport were administrated with a good result. She didn't present involuntary spasm and side effects. She was admitted to our hospital in October 1998. MRI scan has confirmed multifocal small vascular lesions in hemispheres and brainstem. MR Angiography has showed wider (0,6 cm) and elongated right vertebral artery at the medulla level turned to the left side. There was destruction especially of the left side of brainstem caused by the compression of proximal part of basilar artery. There were two small vessels at the level of facial nerve trunk. We didn't observe normal flow in the left vertebral artery. She was treated with seven injections of Dysport with a good result

P345
A SPORADIC CASE OF ROLANDIC EPILEPSY WITH PAROXYSMAL EXERCISE-INDUCED DYSTONIA AND WRITER'S CRAMP (REPEDWC). Z. Jamrozik, P. Janik, J. Kowalski, H. Kwiecinski, Medical University of Warsaw (Warsaw, PL)

We present a 22-year-old woman with exercise-induced paroxysmal dystonia and sustained writer's cramp. The patient is mentally retarded. During early childhood she developed epileptic seizures, agoraphobia and paroxysmal ataxic gait. Ataxia spontaneously remitted at the age of 7 years. Epilepsy is successfully controlled by valproate and ethosuximide administration. Since the age of 18 she has been sufferring from paroxysmal torticollis with retrocollis and dystonia of axial muscles and persistent writer's cramp. Paroxysmal dystonia is often induced by physical exercise and sometimes by emotional stress. MRI of the brain was normal. In EEG (under medication with valproate) discharge waves with prevalence in temporal and central leads were present. DNA testing excluded known mutation in the calcium channel gene responsible for SCA6 and EA–2. Video record during attack; SPECT during paroxysmal dystonia and between attacks, as well as electroencephalogram will be presented. REPEDWC syndrome with autosomal recessive inheritance was recently described by Guerrini et al. (Ann Neurol 1999, 3, 344). We report the sporadic case of REPEDWC syndrome, which may contribute to the spectrum of symptoms and laboratory abnormalities of this newly recognized syndrome.

P346
ASSESSING THE EFFECT OF PRAMIPEXOLE ON TREMOR AND BRADYKINESIA WITH THE MOTOR PERFORMANCE TEST. K. Wenzel, C. N. Homann, M. Scala, G. Ivanic, K. Suppan, E. Ott, Div. F. Special Neurology (Graz, A)

The evaluation of the effect of antiparkinsonian medication usually relies on more or less subjective scales. To objectively evaluate small changes on motor performance apparative tests are of advantage. The aim of our study was to reduce the L-Dopa dose to a maximum while keeping the motor performance on baseline levels. In order to investigate the effect of the new dopamine-agonist pramipexole we performed the Motor Performance Test, twice on baseline and on each of the ten consecutive visits within a ten weeks period on eleven patients. The Motor Performance Test is a test with parameters for postural tremor and action tremor three parameters for bradykinesia as well. During the study L-Dopa was reduced by an average of more than 50 % at the same time the motor performance was stable. Some patients even showed a tremendous improvement and the mean of all patients regarding action tremor ($p=0,06$) and bradykinesia ($p=0,06$) at the tracing task almost reached significant levels of improvement. The apparative results corresponded well to the UPDRS values. The Motor Performance Test seems therefore to be an objective method to assess the effects of medication on motor performance.

P347
THE INFLUENCE OF AGE, GENDER, EDUCATION AND DEXTERITY ON UPPER LIMB MOTOR PERFORMANCE IN PARKINSONIAN PATIENTS AND HEALTHY CONTROLS. C. N. Homann, K. Wenzel, K. Suppan, K. Petrovic, G. Ivanic, N. Kriechbaum, S. Horner, R. Crevenna, G. Pratl, E. Ott, H. P. Hartung, Div. F. Special Neurology (Graz, A)

Parkinson's disease (PD) is characterized by a variety of motor and non motor deficits. Various apparative tests are in use to objectively evaluate motor dysfunction in PD with finger tapping having gained the most widespread acceptance. Considered to be sensitively responsive to disease intrinsic factors like disease severity and changes in medication this test might react to extrinsic factors like age, gender, education and dexterity as well. In order to determine the influence of these demographic variables on various components of tapping performance we recruited 187 normal subjects without neurological deficits and 200 patients with Parkinsonism. They were assessed by means of the BRAIN TEST©, an apparative tapping test measuring tapping speed, accuracy, arrhythmia and akinesia. We found that in normal subjects right hemispheric dominance correlated significantly with higher tapping frequency ($p< 0.005$). Men tended to tap faster than women, but healthy women were more accurate ($p< 0.05$). Younger age correlated positively with higher tapping scores and lesser degrees of akinesia ($p< 0.001$) but in contrast to elderly parkinsonian patients, elderly healthy controls were less dysmetric and more arrhythmic ($p< 0.001$). Higher education was associated with faster and less akinetic movements in both healthy and parkinsonian probands ($p< 0.005$). Education was also the single most important factor in PD patients when correction for disease severity was applied. Our study therefore suggests that when using an apparative device for evaluating upper limb motor function it might be of importance to control test results not only for dexterity and gender but also for age and education.

P348
THE EVALUATION OF PHYSICAL AND MOTOR PERFORMANCE IN ON AND OFF STAGE IN PARKINSON'S DISEASE'S PATIENTS. K. Armutlu, B. Elibol, Hacettepe University School of Physical Therapy and Rehabilitation (Ankara, TR)

Parkinson's Disease, a progressive and idiopathic disease, needs a good follow up due to the presence of complications related to L-dopa.These follow ups are important for the arrangement of the dosage, planning of surgical interventions and planning of physiotherapentic programs. Objective evaluation methods are needed for determining the effectiveness of those therapeutical schedules. Although at the present, there are many scales, most of them depend on the subjective evaluation of the examiner. In our study, we propose to prepare a test battery which will evaluate the physical and motor performance of the patients in their on and off periods.

METHOD: The study enrolled fifteen patients with the diagnosis of Parkinson's disease in the Neurology Department. All patients were assessed two consecutive days before oral administration of Levodopa during the off period and they were reassessed in two successive days in on period through both motor section of Unified Parkinson's Disease Rating Scale (UPDRS) and Physical and Motor Performance Tests (PMPT)which are functional axial rotation, postural stress test, coming from supine to sitting position time, coming from sitting to supine position time, 360 degree rotation time and cadance,10m walking time, gait analysis (footprint), bradykinesia and hypokinesia assessment of upper extremities.

RESULTS: The assessment of off conditions demonstrated that PMPT such as 360 degree rotation time and 360 degree rotation cadence were found to be statistically important ($p< 0.05$).The other PMPT and UPDRS motor examinations were not shown to have statistically important results ($p> 0.05$).

The assessment of on periods demonstrated that time during coming from supine to sitting position was found to be statistically important ($p< 0.05$). The other physical and motor performance tests and UPDRS motor examinations were not shown to have statistically important results ($p> 0.05$).

On the other hand we found a strong correlation between PMPT and UPDRS total motor examinations scores ($p< 0.05$). However our study showed that PMPT have medium level reliability (Cronbach alfa=0.53).

CONCLUSION: The presence of variation in some steps of PMPT made on two consecutive days makes us propose that PMPT are more sensitive to the motor fluctuations. These tests also provide investigation of some special motor functions that can't be evaluated by UPDRS. In spite of the small number of cases, the presence of medium level reliability in PMPT and presence of correlation in most of the test steps with UPDRS make us think these tests can be additional tools in Parkinson's patients and also for follow up of clinical studies as the effectiveness of therapeutic approaches applied is concerned.

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PRIMARY BRAIN LYMPHOMA PRESENTING AS PARKINSON'S DISEASE. M. Sánchez-Guerra, L. Cerezal, C. Leno, C. Díez, J. Figols, J. Berciano, Univ. Hospital Marques de Valdecilla (Santander, E)

Background. Neoplasm is an uncommon cause of parkinsonian syndrome. Objective: To report a patient with primary brain beta-lymphoma presenting as Parkinson's disease (PD). Case report: A woman aged 64 was attended in June 1997 with one year history of generalised motor slowness and clumsiness. Examination revealed bilateral bradykinesia, plastic rigidity with cogwheeling, rest left hand tremor, impassive face and festinating gait with bilateral absence of arm swing. There was generalised hyperreflexia with flexor plantar responses. She was given a diagnosis of PD. Treatment with levodopa/carbidopa up to 600/150 mg was administered with no response. Two months later CT scan showed non-enhanced bilateral basal ganglia and periventricular hypodensity with no mass effect. There was no antecedent of vascular risk factors. In November 1997 she noticed increasing of motor slowness and clumsiness. A non-enhanced MR imaging corroborated tomodensitometric findings now with involvement of the genu of corpus callosum. No abnormal cells were observed in two cerebrospinal fluid samples. In January 1998 there appeared frequent falls, nausea, vomiting, right trigeminal hypoesthesia and left central facial palsy. A second CT and MRI showed accentuation of basal ganglia lesions, slight hydrocephalus and a mass localised to the middle cerebellar peduncle. Basal ganglia stereotactic biopsy showed high degree beta-lymphoma. She died two weeks later; autopsy was not done.

Conclusion: Despite basal ganglia being frequently involved in brain lymphoma, clinical presentation with typical or atypical parkinsonism is exceptional.

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PALLIDOTOMY EFFECT ON CORTICAL EXCITABILITY IN PARKINSON'S DISEASE. C.-H. Tsai, R. S. Chen, Y. T. Huang, C. S. Lu, Chang Gung Memorial Hospital (Taipei, RC)

Surgical lesions in the medial pallidum have been shown to ameliorate motor deficits in Parkinson's disease (PD). It is believed that interruption of the pallidothalamocortical projections to the motor cortex is required for the satisfactory results. In this report, we adopt cortico-cortical inhibition as the tool to assess the pallidotomy effect on cortical excitability. Interstimulus intervals (ISIs) between 1 and 15 ms were investigated. The average peak-to-peak amplitude was measured and calculated at each delay. Six patients (M:F=1:5) aged 51.6 years (SD=8.79) and 11 controls were recruited for the study. In both patients and controls, a maximal inhibition of 50% of the conditioned trial was noted at the 3 ms delay point. The suppression was gone at and after the 7 ms delay point. Result of repeated measure ANOVA shows a significant difference among the controls, PD patients before and 3 months after pallidotomy ($F=3.72$, $p=0.050$). Post hoc examination revealed a significant difference between the controls and PD patients 3 months after pallidotomy at the 15 ms delay point ($p=0.045$). In addition, a reverse correlation between the 15-ms facilitation and the UPDRS motor score was noted ($r=-0.64$, $p=0.021$). The results suggest that pallidotomy can modulate the cortical excitability and the effect could be causally linked to the improvement of the parkinsonian motor deficits.

P351
AXIAL DYSTONIA, EXERCISE-INDUCED CAMPTOCORMIA, AND 'BELLY DANCER'S DYSKINESIA', IN A MARATHON RUNNER. Qureshi, Nisbet, The Royal Sussex County Hospital (Brighton, UK)

A 56 year old marathon runner presented with a 3 year history of camptocormia and involuntary painless spasms affecting his abdominal wall. Both symptoms were initially only noticeable on running but subsequently progressed to be present on walking, standing and on lying down. Symptoms were least noticeable to the patient when lying down. There was no family history of movement disorders and he was not taking any medication. On examination, while lying supine he had involuntary intermittent rippling movements of his anterior abdominal wall on the right with associated jerks in the right quadriceps muscle. On standing these became more marked and jerky in nature. There were also occasional associated jerks affecting the right pectoralis muscle. On walking or jogging he developed progressive truncal flexion (camptocormia). This posture was slightly asymmetric with a component of right lateral flexion of the trunk and superimposed intermittent jerks of the same abdominal musculature together with associated jerks in the flexors and abductors of the right hip. There was no diaphragmatic or palatal involvement and the movements were not stimulus or startle sensitive. There was no evidence of dystonia elsewhere. Neurological examination was otherwise normal. Routine haematology, biochemistry, liver and thyroid function, ESR, serum electrophoresis and auto-antibody screen were normal. Creatinine kinase was slightly raised at 171 IU/l (55–170) in keeping with increased muscular activity. Serum copper and caeruloplasmin were normal and anti-GAD antibodies were negative. The cerebrospinal fluid was acellular with a normal protein and glucose. Nerve conduction studies were completely normal. Electromyography failed to reveal any evidence of spontaneous motor unit activity of the affected muscles. Magnetic resonance imaging of the brain showed mild cerebral atrophy and an area of prolonged T2 signal in the right occipital region. The area was shown to be partially cystic on FLAIR sequences and there was surrounding loss of volume in the right occipital region consistent with an old infarction, not thought to be relevant to the presenting complaint. Magnetic resonance imaging of the cervical spine demonstrated minor anterior thecal impressions due to minor osteophyte degeneration at C5,6 and C6,7 but no evidence of cord compression. Magnetic resonance imaging of the thoracic spine was normal.

This combination of asymmetrical segmental axial dystonia with a myoclonic component also involving the ipsilateral quadriceps together with abdominal wall movements resembling 'Belly Dancer's dyskinesia' is novel. We distinguish the case from spinal myoclonus, neuromyotonia and stiff person syndrome and discuss the clinical features in relation to pure axial dystonia, occupational dystonia and 'Belly Dancer's dyskinesia'. We conclude that the case is most closely related to pure axial dystonia, but may share some common pathophysiological mechanism with the occupational dystonias.

Neurobiology

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SERUM S 100B A POTENTIAL EARLY PREDICTOR FOR CLINICAL OUTCOME IN ACUTE BRAIN TRAUMA: A PILOT STUDY. A Petzold, AJE Green, Z. Plumb, S. Sairley, J. Watkiss, N. Kitchen, M. Smith, E. Thompson, Institute of Neurology, NHNN (London, UK)

S 100b is a cytosolic low molecular weight calcium binding protein released into the cerebrospinal fluid in cellular disintegration of astrocytes. It crosses the blood brain barrier and is a putative serum marker for diffuse astrocytic damage in the brain. The measurement of serum S 100b might therefore prove useful as an early prognostic marker for survival in patients with brain trauma.

In a pilot study we measured serum S 100b using an in-house ELISA assay in a group of patients with acute brain trauma ($n = 14$, median age = 36.1, male = 13). Patients were classified as survivors or non-survivors. Compared to normal controls, the serum S 100b levels were raised in all patients within the first three days. Initially non-survivors have a threefold higher mean level of serum S 100b than survivors suggestive of severe cellular central nervous system damage. The mean S 100b level during the first 12 hours following the traumatic event is 0.12 ng/mL in non-survivors versus 0.04 ng/mL in survivors. Twenty four hours later the mean serum S 100b level differs by a factor of two (0.12 ng/mL in non-survivors versus 0.06 in survivors), as it does also after 72 hours (0.09 ng/mL in non-survivors versus 0.05 in survivors). The difference in serum S 100b levels between survivors and non-survivors is lost by day four after the traumatic event (0.06 ng/mL in non-survivors versus 0.05 in survivors), however non-survivors tend to maintain slightly higher serum S 100b levels.

We also measured intracranial pressure. Non-survivors had higher intracranial pressure at basics than survivors (24.5 mmHg versus 12.75 mmHg). Serum S 100b levels did not directly correlate with the intracranial pressure values. However, in non-survivors high initial serum S 100b levels tended to forecast higher intracranial pressure values and death.

Measuring the serum level of S 100b as a marker for astrocytic damage may provide an alternative method of assessing diffuse cellular brain damage thereby serving as an early predictor of clinical outcome.

P353
THE EFFECT OF RASAGILINE, SELEGILINE, AND THEIR METABOLITES ON OXYGEN-GLUCOSE DEPRIVATION-INDUCED CELL DEATH IN NGF-DIFFERENTIATED PC12 CULTURES. S. Abu-Raya, E. Blaugrund, V. Trembovler, P. Lazarovici, Faculty of Medicine, Hebrew University, Teva Pharmaceuticals, Ltd. (Jerusalem, Netanya, IL)

Introduction: Rasagiline and selegiline are selective and irreversible monoamine oxidase-B (MAO-B) inhibitors. These compounds exert neuroprotective effects in several neuronal systems independently of MAO-B inhibition. Recently, we showed that rasagiline protects nerve growth factor (NGF)-differentiated PC12 cells against oxygen-glucose deprivation (OGD)-induced cell death and reduces OGD-induced PGE2 release in a dose-dependent manner. The aim of the present study was to examine the effect of selegiline and its major metabolite, L-methamphetamine (L-METH), on OGD-induced cell death in

NGF-differentiated PC12 cells. For comparison, the effect of rasagiline and its major metabolite, 1-R-aminoindan (1-R-AI), was also tested.

Methods: PC12 cells were treated with nerve growth factor (50 ng/ml) for 8–10 days. Ischemic-like conditions were achieved by oxygen and glucose deprivation in a special device. Cell death was measured by LDH leakage into the extracellular medium. PGE2 release was measured by radioimmunoassay.

Results: Selegiline reduces OGD-induced cell death by 30 % both at 0.1 and 1 microM; rasagiline inhibits cell death induced by OGD by 46 % and 56 % at 0.1 and 1 microM, respectively. These findings indicate that rasagiline protects PC12 against OGD-induced cell death to a greater extent than does selegiline. L-METH at 1 microM and 10 microM further enhanced OGD-induced cell death, as well as OGD-induced PGE2 release, as opposed to 1-R-AI, which did not affect cell death or PGE2 release. Conclusions: Our results indicate that under OGD conditions L-METH is a toxic compound in NGF-differentiated PC12 cultures. Therefore, rasagiline may have an advantage over selegiline in its neuroprotective effects which are uncomplicated by the production of potentially toxic metabolites such as amphetamine-like compounds.

P354
NA+, K+-ATPASE ISOFORM LOCALIZING IN RAT CEREBRAL SYNAPTOSOMAL MEMBRANES. H. Homerada, K. Kuroda, Kyorin University (Mitaka, J)

Na+, K+-ATPase, which is often called Sodium pump, is an integral membrane protein responsible for the active transport of Na+ and K+ across the cell membrane using ATP as an energy source. The formed gradient of Na+ is used as a driving force for incorporation of amino acid into neuronal and astroglial cells by the Na+-dependent glutamate transporter in the brain tissue. The alpha-subunit, which is a catalytic subunit of Na+, K+-ATPase, is distinguished to three isoforms, alpha–1, alpha–2 and alpha–3. In the rat, the activity of Na+, K+-ATPase with alpha–1 is low-sensitive to ouabain, a specific inhibitor to the ATPase, whereas the activities of the ATPases with two other isoforms are high-sensitive. Utilizing these characteristics of the ATPase and the specific antibodies raised against the isoforms, we examined to identify the Na+, K+-ATPase isoform coupled with the Na+-dependent glutamate transporter in the rat cerebral synaptosomes. The synaptosomal fraction was prepared using a discontinuous-gradient of Percoll. As reported in this last meeting, the fraction strongly reacted with an antibody raised against GLT–1, which is one of the Na+-dependent glutamate transporters localizing in the brain, GLT–1, EAAC1 and GLAST, but did not react with the glial fibrillary acidic protein, a marker of astroglia. Na+, K+-ATPase activity of the synaptosomal membranes was inhibited to 30 % of the control by ouabain at a low concentration (0.1 mM). This result agreed with that shown by the cultured neurons but not with that shown by the cultured astroglia having only the ouabain-resistant Na+, K+-ATPase isoform (Inoue et al., 1988, J. Biochem., 104:349–354). Therefore, major isoforms localizing in the synaptosomal membranes are alpha–2 and/or alpha–3. Immunoblotting analysis indicated that the synaptosomal fraction strongly reacted with an antibody raised against alpha–3. Because it has been reported that Na+, K+-ATPase of the cultured neurons is transiently activated by the extracellular glutamate, the present findings suggest that an increase in the extracellular glutamate concentration induces an elevation of extracellular Na+ concentration via activating Na+, K+-ATPase with alpha–3, and then the Na±dependent glutamate transporter, probably GLT–1, incorporates the extracellular glutamate into neuronal and astroglial cells.

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EFFECT OF HUMAN ANTIBODIES ISOLATED FROM A PATIENT SUFFERING FROM STIFF-MAN SYNDROME ON INHIBITORY AND EXCITATORY SYNAPTIC TRANSMISSION IN AREA CA1 OF RAT HIPPOCAMPUS. S. Hefft, D. Müller, T. Landis, University of Geneva (Geneva 14, CH)

Glutamate acid decarboxylase (GAD) is the key enzyme responsible for Gamma-amino-butyric acid synthesis (GABA) in a single enzymatic step directly derived from its precursor, the excitatory neurotransmitter glutamate. Several lines of evidence point to an auto-immune mediated defect of GABAergic transmission due to anti-GAD antibodies in stiff-man syndrome: 1) the presence of high titres of auto-antibodies against GAD; 2) the capacity of those antibodies to diminish GABA synthesis by GAD in synaptosomes; 3) the reduction of some GABA mediated inhibitory reflex circuits in the spinal cord; 4) reduced GABA signals on two dimensional MR-spectroscopy of the motor cortex in patients. However the role of GAD in the metabolic regulation of GABAergic synaptic transmission is not yet clear despite recent work on Knock out models. Furthermore the effect of human anti-GAD antibodies derived from stiff-man suffering patients, has not been tested directly on mammalian synaptic transmission, yet. Here we compare the physiological effect of blockage of GAD by the pharmacological agent 3-Mercapto-propionic acid (3-MP), with the effect of human CSF derived from a stiff-man patient and of the isolated polyclonal antibodies. 3-MP (500"m"M) reversibly depressed the GABAergic inhibitory field potential (fIPSP) recorded at 330 in area CA1 by 51.5 %. This was accompanied by a 74.5 ± 1.2 % decrease of paired pulse inhibition. There was only a slight, non-significant decrease of the excitatory postsynaptic field potential (fEPSP) during application of 3-MP (500"m"M), without any change in paired pulse facilitation.

Human CSF from a control applied on hippocampal slices of the rat, had no significant effect, neither on fIPSPs nor on fEPSPs. Similarly, the CSF from the patient did not have any effect during brief application on hippocampal slices, neither on fIPSPs nor on fEPSPs. No effect on synaptic inhibition was found after prolonged application on hippocampal acute slices (20 hours). However, there was a clear decrease of synaptic inhibition (50 %) when long-term hippocampal organotypic cultures were incubated with human IgG fraction derived from the patient, containing the anti-GAD autoantibodies. This is the first direct evidence showing human anti-GAD antibodies to interfere with GABAergic synaptic transmission. Prolonged incubation is needed in order to target the intracellular antigen GAD.

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INCREASED STRIATAL DOPAMIN TRANSPORTER DENSITY IN ATTENTION DEFICIT HYPERACTIVITY DISORDER. K.-H. Krause, S. H. Dresel, J. Krause, K. Tatsch, H. F. Kung, Ludwig-Maximilians-Universität, University of Pennsylvania (München, D; Philadelphia, USA)

Attention deficit hyperactivity disorder (ADHD) is the most common neuropsychiatric disorder of childhood, affecting approximately 5 % of children. Meanwhile it is accepted that the disorder in 1/3 to 2/3 of patients persists into adulthood (1). Treatments of choice are psychostimulants, especially methylphenidate, which are known to influence the dopamine transporter (DAT) system. Involvement of the dopaminergic system in ADHD was confirmed by a recent study showing overexpression of the DAT gene (2). Single photon emission computed tomography (SPECT) with technetium–99m TRODAT–1, an analog of cocaine that selectively binds to the presynaptic DAT, offers the possibility to investigate this specific system in vivo (3). 13 adult patients (8 females, 5 males, aged 22–63 years) with ADHD, not treated with psychostimulants, were injected with 800 MBq [Tc–99m]TRODAT–1. SPECT scans were conducted 2 to 3 hours after injection with a triple-headed gamma camera (Picker Prism 3000 XP). Specific binding was calculated semiquantitatively in the striatum with the cerebellum used as background ([STR-BKG]/BKG). Patients with ADHD had a significantly increased specific binding of [Tc–99m]TRODAT–1 to the DAT of the striatum compared to age-matched controls ([STR-BKG]/BKG 1.45 ± 0.16 vs. 1.23 ± 0.05, $p < 0.05$). Our findings confirm that DAT system is disturbed in patients with ADHD. The results are in accordance with those of Dougharty et al., who investigated 6 patients using SPECT with iodine–123-labelled altropane (4). Tc–99m-labeled ligands seem to have clinical advantages compared to I–123-based compounds: Tc–99m is readily available, relatively inexpensive, and radiation exposure is lower as compared to I–123. SPECT with [Tc–99m]TRODAT–1 may offer interesting possibilities for diagnosis and therapy of ADHD.

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Neurophysiology

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EFFECTS OF OPTOKINETICALLY INDUCED ROLL-VECTION ON GAIT DEVIATION DURING WALKING AT DIFFERENT SPEEDS. K. Jahn, E. Schneider, S. Glasauer, M. Strupp, M. Dieterich, T. Brandt, Ludwig-Maximilians University Klinikum Grosshadern (Munich, D)

We recently observed that vestibular tone imbalance exerts less deviation during running than during slow walking in patients with unilateral vestibular dysfunction and in normal subjects with transient vestibular tone imbalance induced by stopping a rotatory chair or by galvanic stimulation. We hypothesized that vestibular input to spinal and supraspinal locomotion generators is differentially regulated depending on the locomotion speed and pattern used. Multisensory control of balance depends on vestibular, visual, and somato-sensory input. Therefore the aim of this study was to test whether large-field optokinetic stimulation that induces apparent motion (roll-vection) has similar effects on net gait deviation at different step frequencies.

Seven healthy subjects were asked to walk straight ahead to a previously seen target at two different step frequencies (0.5 Hz and 1.5 Hz). They wore a helmet with integrated virtual reality display (80° diagonal visual field) and were deprived of optic or acoustic information from the surroundings. A random pattern of coloured dots rotating around the center of the visual field at 15°/s was presented to both eyes to induce roll vection. A two-camera system and diodes attached to the subjects were used to measure deviation in degree from the intended path.

After 10 s of locomotion mean deviation under control conditions (dots stationary) was 0.95±0.7° at 0.5 Hz and 0.63±0.6° at 1.5 Hz step frequency. During stimulation that induces a counterclockwise roll-vection a deviation to the right was seen in all subjects. Mean deviation was 12.1±0.7° at 0.5 Hz and 4.85±0.4° at 1.5 Hz step frequency (mean±s. e., $p < 0.001$).

Visual motion stimulation inducing roll vection thus has a stronger deviating effect on locomotion at the lower step frequency. We conclude that visual control of locomotion, as has been earlier found for vestibular control, is differentially regulated at different locomotion speeds.

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INTRACORTICAL INHIBITORY EFFECTS AFTER STROKE, A PAIRED TRANSCRANIAL MAGNETIC STIMULATION STUDY. A. Boeger, J. Biesecker, A. Ferbert, Klinikum Kassel (Kassel, D)

We wondered whether apart from pyramidal lesions strokes would alter the excitability of the motorcortex and examined 29 patients with a mild hemiparesis due to a stroke in the MCA-territory with paired transcranial magnetic stimulation (paired-TMS). We applied single and double shocks with an interstimulus-interval (ISI) of 3 and 10 ms separately to the affected and to the unaffected hemisphere. 9 patients were excluded as we could not obtain motor evoked potentials (MEP) on the affected side. In the remaining 20 patients the amplitudes of MEP in small hand muscles to single stimuli were significantly lower when stimulating the affected hemisphere. Conditional stimuli with an ISI of 3 ms showed significant inhibition of the test response, while an ISI of 10 ms led to mild facilitation of the test stimulus on either side. The amount of inhibition was significantly larger when stimulating the affected hemisphere compared to the unaffected side. A subgroup analyses showed that these effects were pronounced in subcortical and elder lesions. We conclude from these results that inhibitory and excitatory structures in the human brain may be affected differentially by vascular lesions. This had not yet been shown in humans although there is some suggestion from animal experiments.

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THE EFFECTS OF EDROPHONIUM AND PYRIDOSTIGMINE ON QUANTITATIVE EEG. E. Kogan, M. Neufeld, O. Hilkevich, J. Chapman, A. D. Korczyn, Dept. of Neurology (Tel-Aviv, IL)

OBJECTIVE: To evaluate the effects of edrophonium and pyridostigmine on quantitative EEG (qEEG) activity.

BACKGROUND: Although initially it was believed that quarternary cholinesterase inhibitors do not cross the blood-brain barrier, lately pyridostigmine has been incriminated in the Gulf War syndrome. QEEG provides a method of estimating subtle effects of drugs on the central nervous system. As yet, there is no available information in the literature regarding the effects of these drugs on the EEG.

DESIGN/METHODS: Twenty-two adult patients with suspected or confirmed myasthenic syndromes were tested. Frequency analysis of awake EEG with eyes closed prior to and immediately following intravenous injection of 10 mg edrophonium or one hour after oral 60 mg tablet of pyridostigmine mesylate were performed in 10 (M/F=3/7, age 52±20 years) and in 12 (M/F=7/5, age 61±14 years) patients accordingly.

RESULTS: Edrophonium injection significantly decreased the absolute and relative theta activity in the frontal ($p=0.02$, $p=0.007$) parietal ($p=0.05$, $p=0.007$) and occipital ($p=0.01$, $p=0.004$) areas. Pyridostigmine administration was followed by decrease in relative delta activity in fronto-centro-temporal areas ($p=0.03$, $p=0.013$, $p=0.03$). CONCLUSIONS: The qEEG shows that pyridostigmine and edrophonium have a central effect as manifested particularly by decreased slow EEG activity.

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BLINK REFLEX CHANGES IN ALZHEIMER DISEASE. D. Iacono, A. Thomas, C. Paci, G. D'Andreamatteo, M. P. Buongarzone, M. Onofrj, Institute of Neurology (Chieti, I)

The electrically elicited Blink Reflex (BR) is an exteroceptive-nociceptive reflex recorded on the orbicularis oculi muscle and composed by three components: R1, evoked only on the stimulated side a pontine reflex; R2, recorded bilaterally with unilateral stimulation; and R3, recorded bilaterally and obtained by activation of small diameter and higher threshold afferent fibres, probably nociceptive ones. Besides in Peripheral Nervous System (PNS) diseases the BR may be useful in affections of the Central Nervous System (CNS) like the Wallenberg's Syndrome (WS), Multiple Sclerosis (MS) and Parkinson's Disease (PD). In PD is present an abnormally short latency of R2 in response to a single maximal stimulus and there is a facilitation of R2 by interneuronal activation (dopaminergic inhibition deficit). We considered also another degenerative disease with a principally cholinergic deficit: the Alzheimer Disease (AD). We studied 20 AD patients (age range 64–84 years;12 females and 8 males) diagnosed in according to DSM IV and NINCDS-ADRDA criteria. We used BR before and after ChE inhibitors drug administration (rivastigmine and donepezil). In particular, we analysed the latency of R2 component. We noted a significant shift towards upper limits of R2 latency in these patients: mean latency 39.2 ms (n. v. < 41 ms) ($P < 0.01$). 6 months after the ChE inhibitors drug administration, AD patients showed significant decrease of R2 latency: mean latency 34.2 ms ($P < 0.01$). We conclude that R2 latency is delayed in AD patients and that ChE inhibitors therapy reduce the R2 latency. We hypothesize that the locus of this phenomenon may be located in mesencephalic structures, in particular at thalamic level.

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QUANTITATIVE ASSESSMENT OF INTRAVENOUS IMMUNOGLOBULIN TREATMENT IN ACQUIRED NEUROMYOTONIA. P. Maddison, K. Mills, A. Vincent, J. Newsom-Davis, University Department of Neurology, Dept. of Clinical Neurophysiology (Radcliffe Infirmary, Oxford, King's College Hospital, London, UK)

Autoimmune neuromyotonia (NMT) is characterised by continuous muscle fibre activity detectable as high frequency motor unit discharges on electromyography (EMG). Anti-voltage-gated potassium channel autoantibodies have been implicated in disease pathogenesis and patients have been shown to improve following plasma exchange. Intravenous immunoglobulin (IVIg) has been used to treat a range of immune-mediated neuromuscular disorders but its effectiveness in NMT is not known. We treated 4 NMT patients in an open trial with a 5 day course of IVIg at a dose of 0.4 g/Kg/day. Surface EMG recordings of 30 minutes' duration were made from muscles with detectable myokymic or neuromyotonic discharges both before and after treatment. Off-line analog-digital processing was used to count the number of spontaneously occurring motor units and visual inspection for the identification of the total number of different motor units recorded. Serial measurements of anti-VGKC antibody titres were made in 2 patients. Following IVIg treatment, 2 patients had significantly more and 1 patient significantly fewer myokymic discharges. The fourth patient had no change in the duration of her post-contraction neuromyotonic bursts following IVIg. In the two patients with more spontaneous discharges, there was a significant increase in the mean NMT burst duration (29.8 ms to 36.3 ms 10 days post IVIg in 1 patient: $P=0.03$, Wilcoxon signed rank test) and a reduction in the mean time between each burst (1.56 s to 0.49 s: $P=4.79 \times 10^{-11}$). In the single patient who improved following IVIg, there was a reduction in the mean burst duration (60.3 ms to 42.7 ms; $P=0.027$) and an increase in the time between each NMT burst (0.38 ms to 0.43 ms; $P=2.5 \times 10^{-5}$). Quantitative recordings showed a return to pre-treatment baseline numbers of discharges after 8 weeks in one patient who improved and one who worsened. The second patient who worsened following IVIg died 2 months later of pneumonia. The change in the number of myokymic discharges recorded following treatment correlated closely with improvement or worsening of the patients' NMT symptoms of muscle cramps and twitching. There was a transient rise in anti-VGKC antibody titre following IVIg in one patient who improved and one who worsened. This open study is the first formal evaluation of IVIg treatment in acquired NMT, and suggests that it may be of only limited benefit. One explanation for the failure to respond in VGKC antibody positive patients could be irreversible effects on the antigenic target.

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Abstract withdrawn

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CORTICAL AND SUBCORTICAL DISTRIBUTION OF A CONTINGENT NEGATIVE VARIATION. M. Bares, I. Rektor, St. Anne's Hospital Masaryk University (Brno, CZ)

The aim of this study was to explore generators of a contingent negative variation (CNV) in cortical and subcortical structures. 27 patients (mean age 28.7±6.9 years) with intractable epilepsy, candidates for epileptosurgery, were explored using intracerebral depth electrodes and subdural strip electrodes. Another three male patients (mean age 69.0±6.2) with drug resistant thalamic pain treated by the stimulation of the contralateral nucleus ventralis posterolateralis (VPL) were investigated as well. All patients underwent several neurophysiological testings including a contingent negative variation (CNV) during the intracerebral electrode implantation. Auditory warning stimulus and visual imperative stimulus in the CNV paradigm were used (audio-visual paradigm). Following the visual imperative stimulus, the patient was instructed to perform distal hand/foot movement (motor task). Various cortical areas – primary motor cortex, supplementary motor area, frontal, parietal, temporal lobes (including amygdala and hippocampus) and postcentral area were explored. Subcortical structures – basal ganglia (putamen, nucleus caudatus and pallidum), posterior thalamus and cingulate gyrus were explored too. The analysis of the CNV was provided off-line pursuing the possible generators. Only the potentials with step amplitude gradient or phase reversal indicating the vicinity of the generating structure were taken in consideration. Results: The generators of the CNV were observed regularly in various cortical sites (primary motor cortex, supplementary motor area, postcentral area). The appearance of the CNV generators in the frontal and parietal cortex and cingulate gyrus was not so regular but significant. No significant appearance of the CNV generators in the temporal cortex, amygdala and hippocampus was observed. There were also generators of the CNV in subcortical structures observed (basal ganglia and posterior thalamus). The results indicate the role of several cortical (paracentral region, supplementary motor area, frontal cortex) and subcortical structures (basal ganglia, thalamus, cingulate gyrus) in the generation of the scalp CNV. We suggest that some cognitive potentials including the CNV are generated parallel in cortical and subcortical structures.

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SAFETY OF FOCAL TRANSCRANIAL MAGNETIC STIMULI IN EPILEPSY PATIENTS. A. Schulze-Bonhage, K. Scheufler, J. Zentner, C. E. Elger (Freiburg, Bonn, D)

Single and repetitive transcranial magnetic stimuli have been reported to induce epileptic seizures. Thus transcranial magnetic stimulation has been regarded as hazardous in epilepsy patients. We have investigated the effects of single and repetitive (paired and quadruple) focal transcranial magnetic stimuli in patients investigated by intracranial EEG recordings. Method: 1–4 focal transcranial magnetic stimuli were applied using a Magstim QuadroPulseR magnetic stimulator over the hand area of the motor cortex ipsilateral to the epileptogenic focus at intensities of 120 and 150 % of motor threshold and additionally as close as possible to the suspected epileptogenic zone at 40–100 % of maximal stimulator. Video telemetry was evaluated regarding the induction of epileptic discharges or clinically manifest seizures as well as regarding effects on interictal activity in 21 patients with intractable epilepsy during invasive presurgical monitoring. All had been implanted with subdural and/or intracerebral depth electrodes positioned in close proximity to the suspected epileptogenic zone, and their anticonvulsant medication had been reduced. Results: Transcranial magnetic stimulation did not induce any complex partial or secondary generalized tonic-clonic seizures. One patient with hippocampal sclerosis experienced an aura associated with rhythmic EEG discharges restricted to the ipsilateral intrahippocampal depth electrode after stimulation over his left temporal lobe. This patient, however, had also frequent spontaneously occurring auras with focal ictal discharges originating from this hippocampus. Interictal discharges were not influenced significantly by single or repetitive magnetic stimuli. Conclusion: From this study there is no evidence that single or serial focal transcranial magnetic stimuli activate epileptogenic foci. At least 4 high-frequency repetitive stimuli of high intensity may thus be applied with a low risk of seizure induction even in patients with low seizure threshold when focal stimulation is used.

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HUMAN BRAIN MAPPING OF MOTOR OUTPUT: A TRANSCRANIAL MAGNETIC STIMULATION STUDY. F. Pauri, P. Pasqualetti, P. M. Rossini, AFaR-CRCCS (Rome, I)

The existence of multiple yet discrete efferent micro- and macrozones from primary motor cortex is now accepted as representative of an essential organisational principle of this area in animal experimental models. Movement can be elicited from selective and direct stimulation of different MI regions, often several millimetres apart, separated by non-responsive districts. Such a large body of evidence challenges the labelled-line hypothesis, which suggests that the control of the primate arm is like in a robotic hand with separate software channels, servo amplifiers and motors for each digit; on the other hand, it supports the view that any movement is controlled by a network of neurons distributed throughout the MI cortex. Previous studies never addressed in a comprehensive way the important problem of multiple representation of excitable areas for individual muscles as well as for different muscle combinations acting. Also, no previous reports dealt with the possible modifications of maps induced by simple changes in posture, like maintaining the forearm-hand supinated or prone. In the present report a detailed mapping of the motor output from more than 100 scalp sites for each hemisphere was carried out in combination with simultaneous MEP records from several hand, forearm, arm and shoulder muscles. Ten healthy volunteers participated in this study. TMS was carried out via a figure-of-eight coil. Subjects were wearing an elastic, transparent cup with 121 in a stimulation grid. Motor Evoked Potentials were recorded from Abductor Digiti Minimi, First Dorsal Interosseous, Abductor Pollicis Brevis, Adductor Pollicis Brevis, Extensor Digitorum Communis, Extensor Indicis Proprius, Extensor Ulnaris Carpi, Extensor Radialis Carpi, Flexor Communis, Biceps, Triceps, Deltoid. For each stimulated scalp position, the median value of the responses has been determined. Database included: 10 subjects x 121 scalp positions = 121 rows, 2 parameters (latencies and amplitudes) x 12 muscles = 24 columns. Inter-subjects variability was taken into account. The homogeneity of the co-activation patterns across hemispheres and across the two hand postures were checked. The similarity of the representation of each muscle on the factorial space and on the stimulation grid was analyzed. Significant differences in muscles activation in some areas were found, whereas the pattern was homogeneous in others. In particular, in area 1 (hot spot for ADM) the muscles of hand and forearm resulted more represented and well distinguished in comparison with the arm muscles. In area 3 (more medial) cortical representation of proximal muscles is still well divided from the representation of distal muscles, but proximal muscles are less present. In area 5 (closer to Cz) muscles are pretty closed, probably because of a major representation of triceps, biceps and deltoid muscles. These results may suggest that the upper limb muscles can be activated by stimulating several cortical points by means of TMS. It is possible to select areas where muscles are clearly separated and areas where cortical activation clearly shows an overlapping of responses of different muscles.

Poster session – 2

Cerebrovascular disorders

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A MAGNETIC RESONANCE IMAGING STUDY OF THE CERVICAL SPINAL CORD OF CADASIL PATIENTS. M. A. Rocca, J. Herzog, M. Dichgans, M. A. Horsfield, T. A. Yousry, M. Filippi, Neuroimaging Research Unit, Klinikum Grosshadern, University of Leicester, Neuroimaging Research Unit Scientific Institute Ospedale San Raffaele (Milan, I; Munich, D; Leicester, UK)

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an hereditary small-artery disease that can present with recurrent transient ischemic attacks, migraine and strokes and can evolve to dementia, depression, pseudobulbar palsy and hemi- or quadriplegia. Several magnetic resonance imaging studies showed the presence of abnormalities in the brain and in the brainstem on T2-weighted images in clinically affected subjects. Post-mortem studies showed abnormalities also within vessels of muscle, skin or nerve biopsies thus demonstrating that the underlying pathology is a generalized vasculopathy. The aims of this study were to assess: a) the presence and extent of macroscopic lesions using conventional sequences and b) the overall disease burden (i.e., microscopic and macroscopic) using magnetization transfer ratio (MTR) histogram analysis, in the cervical cord of CADASIL patients. We studied 25 CADASIL patients and 14 age- and sex-matched normal subjects. The following sequences were acquired: a) sagittal

T2-weighted fast spin-echo, b) sagittal fast short tau inversion recovery (fast-STIR), c) sagittal T1-weighted conventional spin-echo; d) axial 2D gradient-echo (GE) with and without a saturation pulse. A review of all the scans from each subject was performed by two observers. Cervical cord MTR histograms were obtained from all patients and controls. For each histogram, the following measures were derived: the relative peak height, the peak position, the average MTR and the number of segmented pixels. No abnormalities were found in the healthy controls on any of the sequences. No abnormalities were also detected in the cervical spinal cord of CADASIL patients the conventional MR sequences (T2-weighted, fast STIR and T1-weighted). Considering MTR histogram metrics, CADASIL patients had significantly lower peak height than healthy controls (p=0.02), while there were no differences in the other MTR histogram metrics. Our study shows that cervical cord signal abnormalities are not a common finding in CADASIL patients. Even if CADASIL is a systemic arterial disease, it is clinically confined to the central nervous system. MTR histograms analysis showed a lower peak height in CADASIL patients than in healthy controls. This could be due to axonal degeneration secondary to the damage of the brain or to the presence of small abnormalities of the cord vessels.

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STANDARDIZATION OF A POSTAL FOLLOW-UP QUESTIONNAIRE FOR A POST-STROKE GREEK POPULATION. A Stathopoulou, G Gioldasis, NP Lekka, J Ellul, C Paschalis, University Hospital of Patras (Rion-Patras, GR)

Postal post-stroke follow up questionnaires have frequently provided blind and independent assessments of functioning in multicenter studies. The lack of a standardized questionnaire in a Greek post-stroke population has prompted the design of this study, aiming to provide response rates and validation of widely used scales. Methods: 129 stroke discharges (mean age 62.6 ± 11.7, female 28%) were identified during a one-year period from the Neurology Department Registry. A postal follow up questionnaire including disability and depression scales was sent to all patients. A fortnight later, if no reply was received, a postal reminder was sent, and a fortnight later in those who had not replied so far, a phone call was made to encourage them to return the questionnaire. All questionnaires were filled in either by the patient him/herself or by the patient with the help of a carer. Results: Altogether, 97 (75%) patients replied (44% from the first letter, 42% from the postal reminder and 13% from the phone call reminder), 13 (10%) patients had changed address and could not be contacted, and 19 (15%) patients either refused to reply or ignored the letter. Replying to the questionnaire was independent of age, sex, and place of residence (urban, semi-urban or rural). The Oxford Handicap Scale scores were significantly correlated with the estimated total Barthel scores from 3-Barthel items ($r=0.58$, $p< 0.0001$) and with the 3-point scores derived of two questions examining whether the patient had fully recovered from the stroke and whether they needed help for everyday activities during the last two weeks ($r=0.76$, $p< 0.0001$). The Zung Self-rating Depression Scale, which has been previously used in Greek population studies, was correlated with the single question asking whether the patient feels depressed ($r=0.75$, $p< 0.0001$), as well as with the 5-point scores of the smiling faces scale ($r=0.63$, $p< 0.0001$). Conclusion: The results of this study indicate that this postal post-stroke follow up questionnaire can be reliably used in Greek populations with satisfactory response rate. We are currently testing this method in stroke patients who were discharged from General Medical wards.

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IMMUNOHISTOCHEMICAL DISTRIBUTION OF μ-CALPAIN IN EXPERIMENTAL CEREBRAL VENOUS THROMBOSIS. M. Liebetrau, H. K. Martens, E. A. Auerswald, D. Gabrielcic-Geiger, J. Roether, G. F. Hamann, LMU, Friedrich Schiller University (Munich, Jena, D)

Objective: Calpains are intracellular located proteases which are activated by an intracellular calcium concentration increase. Their proteolytic activity is mainly directed against the cytoskeleton and especially against spectrin and the microtubuli. We tested the activation of calpains in an animal model of experimental cerebral venous thrombosis (CVT). Material and methods: In 5 male rats CVT was induced by rostral and caudal ligation of the superior sagittal sinus (SSS) and injection of a thrombogenic cephalin suspension. Each animal had 3 hours of thrombosis. Parenchymal lesions were shown by MRI. The region of interest (ROI) was determined by immunohistochemistry showing a loss of microtubule associated protein-2 (MAP-2). Using a polyclonal antibody against the 80kD subunit of μ-calpain an immunohistochemistry with peroxidase staining was performed. The numbers of μ-calpain positive cells in the ROI's and normal tissue were semi-quantitatively measured using a videoimaging microscopy unit. The magnification power used was 400x. Results: In normal tissue a slight staining of the periplasma of the cells could be detected. In contrast the ROI's showed a more intense staining of the cells including the nucleus. A cell was declared as calpain positive when the nucleus was stained by the μ-calpain antibody. In tissue without a loss of MAP-2 there were 5±2% of calpain positive elements seen. In the ROI's 57 ± 14% of the cells could be detected as calpain positive ($p< 0.01$). Conclusion: The intracellular increase of μ-calpain in CVT is demonstrated by immunohistochemistry. The slight periplasmal staining in normal tissue changed to an intense and nuclear pronounced staining in the tissue damaged by CVT.

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ISCHEMIA OF THE LOWER MEDULLA AND UPPER CERVICAL CORD DUE TO VERTEBRAL DISSECTION — A SYNDROME OF THE POSTERIOR SPINAL ARTERY. G. Lehrieder, H. Molitor, Juliusspital (Würzburg, D)

Chiropractic manipulation of the neck, traumatic hyperextension of the neck and abrupt head turning have been described as causes of dissection of the vertebral artery. Wallenberg's syndrome due to infarcts of the posterior inferior cerebellar artery is a common complication. We report a case of left lateral medullary syndrome with corticospinal and posterior column deficits in a 43 year old man with dissection of the left vertebral artery in the atlanto-axial (V3) segment. Diagnosis was primarily established with colour-coded duplexsonography which showed indirect signs, i.e. high resistance flow pattern and decreased diastolic flow velocity in the extracranial (V1, V2) and poststenotic flow pattern in the intracranial segment (V4). Diagnosis was confirmed by magnetic resonance angiography. CT-scan did not reveal any ischemic area. In MRI we found ischemic damage in the right lateral medulla and in the posterior column in the upper cervical cord, representing the territory of the posterior spinal artery. Patient was treated with anticoagulants, his clinical condition slowly and incompletely improved. We present acute and follow up findings (clinical, radiological, ultrasonographic and neurophysiological data) and demonstrate the arterial blood supply of the lower medulla and upper spinal cord.

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CHOLESTEROL MANAGEMENT AND ISCHEMIC CEREBROVASCULAR DISEASE: APPLICATION OF NATIONAL CHOLESTEROL EDUCATION PROGRAM (NECP) ADULT TREATMENT PANEL II TO A LARGE SERIES OF CONSECUTIVE STROKE PATIENTS. D. Imperiale, P. Cerrato, C. Baima, M. Grasso, P. Fornengo, M. Cassader, G. Pagano, B. Bergamasco, Division of Neurology, Division of Medicine (Torino, I)

Recent studies indicate that cholesterol-lowering drugs, namely HMG-CoA inhibitors, exert a preventive effect on stroke events in CHD patients and on carotid atherosclerosis progression. We applied current guidelines for management of hypercholesterolemia detailed in National Cholesterol Education Program Adult Treatment Panel II (NCEP Panel II) to our population of consecutive patients with ischemic cerebrovascular disease (ICVD). Design. Patients: consecutive patients with ICVD referred to our neurologic department. Appropriate clinical, laboratory and instrumental work-up as well as fasting lipid profile and risk factor assessment were obtained in each patient. According to NECP Panel II guidelines patients with symptomatic precerebral vessel atheromatosis (large vessel disease (LVD) group) and those with CHD and/or peripheral atherosclerotic disease (CHD/PAD group) were considered at highest vascular risk. Rest of stroke patients (nonLVD/CHD/PAD group) were considered at intermediate or low risk according to the amount (two or less) of concomitant risk factors (RF) (sex and age, familiarity, hypertension, smoke habits, diabetes, low HDL levels). Candidates for dietary therapy were identified on basis of LDL levels: above 100 mg/dl for LVD and CHD/PAD patients, between 130 and 160 mg/dl for nonLVD/CHD/PAD patients with at least 2 RF, above 160 mg/dl for nonLVD/CHD/PAD patients with fewer than 2 RF. To simulate the effect of dietary modification on the potential percentage of adults who might require drug therapy, the LDL cholesterol of the candidates for dietary intervention were reduced by 15%. Results. At January 2000, study population consisted of 317 stroke patients (204 males): 115 LVD patients (84 males), 25 CHD/PAD patients (21 males), 94 nonLVD/CHD/PAD patients with at least 2 RF (67 males) and 83 nonLVD/CHD/PAD patients with fewer than 2 RF (32 males). According to LDL levels, an immediate aggressive dietary intervention should be mandatory in 84.3% of LVD patients, 84% of CHD ones, 30.9% and 20.5% of nonLVD/CHD/PAD with respectively at least 2 or fewer than 2 RF: therefore 84.3% of stroke patients with symptomatic atheromatosis and 30% of those without symptomatic atheromatosis should need a dietary intervention. Assuming an LDL reduction of 15% after an appropriate period on dietary therapy, drug therapy should be considered in 41.2% of LVD patients on diet, 38.1% of CHD ones, 34.5% and 5.9% of nonLVD/CHD/PAD ones with respectively at leasat 2 or fewer than 2 RF: therefore in 40.7% of stroke patients

with symptomatic atheromatosis and candidates for dietary intervention and 23.9% of those without symptomatic atheromatosis a drug therapy could be mandatory. Globally 51.7% of our consecutive stroke patients should need an immediate dietary approach; after an appropriate period of observation in 36% of them a drug therapy should be considered.

Conclusions. Application of NCEP Panel II guidelines to our consecutive ICVD highlighted that about half of them should need an aggressive dietary intervention. Besides about one third of those on diet should be considered for a subsequent pharmacological approach.

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LIPID PROFILE IN DIFFERENT STROKE ETIOPATHOGENIC SUBTYPES: A POSSIBLE LINK BETWEEN HIGH LIPOPROTEIN(A) LEVELS AND PRECEREBRAL VESSEL ATHEROMATOSIS? P. Cerrato, D. Imperiale, M. Grasso, C. Baima, M. Cassader, P. Fornengo, P. Cavallo-Perin, B. Bergamasco, Division of Neurology, Division of Medicine (Torino, I)

In spite of the established role of high cholesterol plasma levels in coronary heart disease, large observational studies do not show a clear link between hypercholesterolemia and ischemic cerebrovascular disease (ICVD). Aim. To evaluate lipid profile in patients with ICVD, with particular attention to differences among the various etiopathogenic stroke subtypes. Casuistic and methods. At September 1999, study population consisted of 220 consecutive ICVD patients (123 males). According to clinical, instrumental (cranial CT, extracranial Duplex ultrasonography, echocardiographic studies and, when necessary, brain MRI and cerebral angiography) and laboratory findings patients were classified in four groups: Large Vessel Disease (LVD) (77 patients), Small Vessel Disease (SVD) (49 patients), Cryptogenic (45 patients), Other (including cardioembolism, vasculitis, coagulopathy, dissection) (49 patients). Each patient underwent a complete fasting lipid profile evaluation. For statistical analysis data were corrected for age, sex, hypertension, diabetes and smoke habits. Results. There were no significant differences among the various groups as regards mean values of total cholesterolemia, triglyceridemia, LDL and HDL cholesterolemia. Also Apoprotein A1 and B levels are similar among stroke subtypes. Lipoprotein(a) [Lp(a)] mean levels were significantly higher in LVD group (35.83 mg/dl) than in SVD one (21.14 mg/dl). Conclusions. In the present study no significant differences in classical lipid markers emerged among the various etiopathogenic stroke subtypes: in particular LVD patients and SVD ones presented similar lipid profile despite the different vascular beds involved in their pathogenesis. The evidence of higher levels of Lp(a) in LVD versus SVD is intriguing: Lp(a) is known to modulate placque lipid deposition and fibrinolysis and high levels have been associated to carotid atherosclerosis progression and medio-intimal thickening. Further studies are mandatory to understand the etiopathogenic meaning of high Lp(a) levels in patients with ICVD related to LVD.

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AORTIC ARCH ATHEROSCLEROSIS IN STROKE PATIENT WITHOUT CAROTID STENOSIS: A TRANSESOPHAGEAL ECHOCARDIOGRAPHIC STUDY. P. Cerrato, A. M. Marson, E. Gentile, C. Baima, M. Grasso, M. Giraudo, F. Carrà, M. Morello, B. Bergamasco, Division of Neurology, Division of Cardiology (Torino, I)

Transesophageal echocardiography (TEE) allows an optimal evaluation of aortic arch morphology and atheromatous plaques. We studied the records of consecutive patients referred to our Neurologic ward between January 1994 and February 1999 with a diagnosis of stroke or TIA who underwent TEE. We excluded patients with: (1) high-risk embolic cardiopathies; (2) *50% stenosis of the internal carotid artery; (3) other definite stroke etiopathogenic mechanisms. We included 175 patients (88 males and 87 females; mean [±SD] age, 49.7 [±12] years); only 8% of the patients were aged 65 or older. Case patients were divided into two groups: the lacunar (LAC) and the not lacunar group (N-LAC). The LAC group [66/175 (39.4%); mean age, 48.1 ±10 years] included patients with deep infarct due to perforant artery occlusion while the N-LAC group [106/175 (60.6%), mean age, 50.2 ±13 years)] included patients with cerebral or cerebellar cortical "territorial" infarcts and subcortical ischemic areas *2 cm in diameter. The control group consisted of 78 consecutive patients (40 males and 38 females; mean [±SD] age, 53 [±12] years) referred to the echocardiography laboratory for TEE without history of ICVD and known heart disease. Aortic arch atheromatosis (AAA) was detected in 12% of patients and in 10.2% of controls. The frequency was 9.4% (10/106) in N-LAC and 15.9% (11/69) in LAC. No complicated aortic plaques (plaque thickness > 4 mm; plaque ulceration or mobile-peduncolated thrombi) were detected in stroke patients and controls. Conclusion: in not elderly patients without carotid stenosis AAA is uncommon and searching aortic arch plaques as potential sources of embolism appears to be unnecessary.

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THE COMBINED CEREBROPROTECTIVE EFFECTS OF DEXANABINOL AND THE NITROXIDE FREE RADICAL SCAVENGER TEMPOL IN FOCAL CEREBRAL ISCHEMIA IN THE RAT. R. R. Leker, G. Lavi, A. Teichner, E. Shohami, O. Abramsky, H. Ovadia, Hadassah University Hospital (Jerusalem, IL)

Neuronal death in stroke is triggered by several parallel mechanisms. Therefore, combination of drugs active against individual damaging mechanisms may have synergistic anti-ischemic effects. The synthetic cannabinoid dexanabinol is a potent and safe NMDA antagonist that also has anti-TNF alpha effects. Tempol is a highly potent free radical scavenger and may help minimize the infarct volume further by adding anti-oxidant effect to the anti-ischemic properties of dexanabinol. Methods: Spontaneously hypertensive rats underwent permanent middle cerebral artery occlusion (PMCAO) by craniotomy and electrocoagulation (n=40). Rats were given vehicle, dexanabinol, tempol or a combination of dexanabinol and tempol (n=10 per group) 1 hour after PMCAO. Five of the animals in each group were evaluated with a clinical motor rating scale 24 hours after the infarct and were then sacrificed and the infarct volume was measured. The remaining animals in each group were examined clinically on days 1 to 5, 10, 15, 20 and 30 after PMCAO, and cognitively with a water maze test on days 15 and 20 to 30. The animals were then sacrificed and infarct volumes determined. Results: Clinical motor scores and water maze tests at all time points examined and infarct volumes at days 1 and 30 were significantly reduced in all treatment groups when compared with vehicle. Clinical motor scores and cognitive testing were most prominently reduced in the group that received combination therapy followed by that that received dexanabinol alone or tempol alone. Infarct volumes did not differ significantly between the 3 treatment groups. Conclusions: Combination therapy with dexanabinol and tempol yielded greater neuroprotection than that conferred by each agent alone.

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ORTHOSTATIC CHANGES OF CEREBRAL BLOOD FLOW IN PATIENTS WITH DIABETES MELLITUS AND ORTHOSTATIC HYPOTENSION. B. N. Mankovsky, R. Piolot, O. L. Mankovska, D. Ziegler, Institute of Endocrinology, Diabetes Research Institute, National Medical University, Diabetes Research Institute (Kiev, UKR; Dusseldorf, D)

Orthostatic hypotension is well-known feature of autonomic neuropathy often developing in patients with diabetes mellitus. Moreover, cerebrovascular disorders are 2–3 times more common in those with diabetes and especially in those with autonomic neuropathy. However, the changes of cerebral blood flow during orthostasis in people with diabetes are not investigated. Use of transcranial dopplerography provides an opportunity to monitor cerebrovascular reactivity. Therefore, the aim of the study was to investigate the change of blood flow velocity by middle cerebral artery in response to change of position from lying to standing in patients with long-term diabetes mellitus with and without orthostatic hypotension. We studied 25 patients with diabetes mellitus – 10 subjects with orthostatic hypotension (diagnosed in case of noted drop of systolic blood pressure immediately after standing for more than 28 mm Hg (mean age – 48.7±11.7, duration of disease – 23.5±12.3 years, data are presented everywhere as mean ±SD), 15 patients without orthostatic hypotension (mean age – 46.1±14.6, disease duration–19.3±11.4 years), and 13 control subjects without diabetes (aged – 41.9±9.1 years). The mean blood flow velocity by right middle cerebral artery was recorded using transcranial dopplerography at lying position after 15 minutes of rest and immediately after standing and then monitored for another 8 minutes at standing position. The relative changes of flow velocity after standing were calculated and expressed in percentage of basal lying values. We found that mean systolic velocity at lying was not different in three cohorts of patients – 45.0±10.8; 49.4±18.3, and 50.5±10.7 cm/sec, in those diabetic patients with and without hypotension and control subjects respectively, $p > 0.05$. However, we found that change to standing position was associated with more pronounced decrease of flow velocity in persons with orthostatic hypotension compared to those patients without hypotension and controls – relative changes of mean systolic velocity were 23.7±15.5% in diabetic patients with orthostatic hypotension, 1.4±14.4% in those diabetics without drop of arterial blood pressure, and 10.5±11.2% in control subjects, $p < 0.05$. We may conclude that patients with diabetes suffering from orthostatic hypotension cannot maintain appropriate cerebral blood flow during change of position and these impairments reflect disturbances of cerebrovascular regulation in this cohort of patients. Moreover, these abnormalities may predispose to higher incidence of cerebrovascular disorders in patients with diabetes mellitus and autonomic neuropathy.

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UNILATERAL THALAMIC OEDEMA IN INTERNAL CEREBRAL VENOUS THROMBOSIS: WHY IS IT MOSTLY LEFT? W. Küker, F. Schmidt, S. Friese, F. Block, M. Weller (Tübingen, Aachen, D)

Thrombotic occlusion of the internal cerebral veins is a particularly dangerous form of cerebral venous thrombosis (CVT) as it causes venous infarction of the thalamus. Because both thalamus drain into the vein of Galen and straight sinus, bilateral thalamic involvement is thought to be a hallmark of internal CVT. We report three cases of unilateral thalamic venous congestion resulting from internal CVT and review the literature. Case descriptions: A 49-year-old female patient developed sudden headaches and dysphasia. All laboratory studies were normal. No signs of infection were present. MRI showed left thalamic oedema but no further abnormalities. MR phlebography disclosed complete occlusion of the straight sinus and of all internal cerebral veins as well as the left transverse and sigmoid sinus. Under heparin treatment, recanalization of the internal cerebral veins was achieved and the oedema resolved. A 58-year-old female patient had biopsy-proven cerebellar lymphoma treated with radio-chemotherapy 18 months prior to admission. She now complained about sleepiness, headaches and difficulties to recall words, all of recent onset. MRI disclosed straight sinus thrombosis and occlusion of the left internal cerebral veins with congestive oedema of the left thalamus. Heparinization resulted in recanalization of the left internal cerebral veins and resolution of the thalamic sedema with clinical improvement. A 31-year-old female patient presented with progressive headache, reduced word fluency and attention. CT showed oedema of the left thalamus and medial temporal lobe. Angiography on the next day displayed occlusion of the internal cerebral veins bilaterally and of the straight sinus. Although partial recanalization was achieved by heparinisation, bilateral thalamic oedema developed during the following days. Whereas the initial neurological symptoms abated, the patient developed seizures after 10 months. Conclusions: Unilateral thalamic oedema can occur in internal CVT, even if all internal cerebral veins are occluded. This suggests collateral venous drainage of the thalami, that is commonly insufficient in internal CVT. Patients with unilateral congestion of the thalamus, including 3 patients reported here, had mostly left-sided involvement, indicating that right-sided unilateral thalamic involvement in CVT may be clinically silent.

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ISOLATED ATRIAL SEPTAL ANEURISM: WHICH IS THE CARDIOEMBOLISM RISK?. TRANSCRANIAL DOPPLER EVALUATION. J. J. Muñoz-Torrero, R. Soler, M. Lara, F. Domínguez, J. Oliver, E. Díez-Tejedor, University Hospital La Paz (Madrid, E)

Atrial septal aneurysm (ASA) has been pointed out as a potential source of embolus and could be related to the degree of excursion of the atrial septum. We tested the capacity of ASA to produce embolus, using transcranial doppler (TCD) to detect microembolic signals (MES) and the possible relationship between the degree of excursion of ASA and the number of MES detected. Patients and Methods: Inclusion criteria: Patients with ASA diagnosed by transesophagic echocardiography, without another potential source of embolus, previous cerebral infarction or anticoagulant treatment. Assessment: We used TCD monitoring along 45 minutes on medial cerebral artery with a 2 MHz multidepth probe. Automatic detection of MES mode was adjusted to a 9 dB threshold, gain was reduced to this intensity and evaluation was done by the physician all along the procedure. Results: Out of 12 patients, only 5 met all the criteria, 3 males and 2 females. Age ranged between 25 to 56 years and the degree of excursion of ASA between 10 to 15 mm. MES were not detected in anyone. Conclusion: MES are not detected by TCD monitoring in patients with isolated ASA and without cerebral infarction antecedents. Likely, isolated ASA has a low risk for cardioembolism and maybe must coexist with other superimposed factors (as procoagulant states or other heart abnormalities) to make this entity a potential source of embolus.

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QUANTITATIVE VOLUMETRIC ANALYSIS OF BRAINSTEM INFARCTIONS. S. Fitzek, C. Fitzek, P. P. Urban, P. Stoeter, H. C. Hopf, University of Jena, University of Mainz (Jena, Mainz, D)

Little is known about the natural time course of brainstem infarct volumes using high resolution imaging and DWI, while the clinical course often shows an improvement. Patients and Methods: Brainstem infarctions of 12 Patients were analyzed. We performed three MRI: MR0, MR1 and MR2. MR0 was done in the acute stage of the disease (median 1.5 days after onset of symptoms) using an EPI-DWI and EPI-T2W sequence (TR/TE = 4000/102, thickness 3mm, axial orientation). In MR1 (median 8.5 days after symptom onset) we used T2-TSE (thickness 3 mm, axial orientation) and standard sequences (thickness 6 mm, axial orientation). In the control MR2 (median 4.75 months after symptom onset) we used T2-TSE sequences (thickness 3 mm in axial and sagittal orientation). Volumetric analysis was done semiautomatically using the Picker VoxelQ. The volume of the resulting lesion measured in the axial T2 sequence (MR2) was set to 100%. The measured volumes of the other sequences were set into relation. We performed the Friedman Test over all sequences and compared each sequence with the resulting lesion using the Wilcoxon Test. Results: The brainstem infarctions measured with the five sequences shrink along the time ($p< 0.001$). Comparing T2-TSE (3 mm slice thickness) in the first two weeks after onset of symptoms (MR1) and the resulting infarction volume (MR2, 3mm slice thickness) there was a shrinking between 16% to 76% median 41% ($p < 0.05$). There was no resulting difference between the infarct volume measured in axial or sagittal slice direction in the control MRI (MR2) after months ($p=9.17$). There was no statistical significant difference between the lesion in EPI-DWI and EPI-T2 measured median 1.5 days after infarction (MR0). There was no difference between the total brainstem volume of a patient measured with EPI-DWI (MR0, diffusion gradient in z-Axis) and with T2-TSE (MR1). The areas with restricted diffusion measured in z-axis (MR0) were significantly greater than the resulting lesions between 23% to 80% median 56% ($p < 0.05$), and were greater than the first control within the first two weeks ($p < 0.05$). Discussion: In this study we see a shrinking of the brainstem infarct volume according to the observed clinical improvement of the patients in T2-TSE sequences. Under the hypothesis that lesions of acute brainstem infarctions measured in each T2W sequence (e. g. EPI-T2, T2-TSE, T2-SE) are equal, we see also a shrinking of the infarct volume comparing EPI-DWI and EPI-T2 (MR0) with the resulting infarct volume (MR2) measured with T2-TSE. We therefore conclude that great extension of restricted diffusion measured with EPI-DWI in the early stage of brainstem infarction does not strictly lead to a great infarction.

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THE OXFORDSHIRE COMMUNITY STROKE PROJECT (OCSP) CLASSIFICATION: ROLE IN THE PREDICTION OF EARLY AND LATE OUTCOME AFTER ACUTE ISCHAEMIC STROKE. S.J Pittock, D. Meldrum, O. Hardiman, J.T Moroney, Beaumont Hospital (Dublin, IRL)

The OCSP is a simple and quick method of classifying cases of acute ischaemic stroke into one of four distinct clinical syndromes: total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI), and posterior circulation infarct (PACI). Few studies have investigated the relationship between the OCSP classification and early and late outcome after acute ischaemic stroke.To investigate the relationship among the OCSP classification, complications of stroke, stroke recurrence, stroke-related disability and mortality, we classified 118 patients (mean age 69 ±12.6 years) consecutively hospitalized with acute ischaemic stroke using the OCPS method. Patients were assessed at 48 hours, 2 weeks, and 6 months with neurological and functional examinations, including the Barthel Index (BI), European Stroke Scale (ESS), Orpington Prognostic Scale (OPS), Rankin score, and the Rivermead Motor Assessment (RMA). Complications of stroke including confusion, cardiovascular events, deep venous thromboses (DVT), depression, falls, gastrointestinal bleeding, incontinence, painful shoulder, pressure sores, respiratory tract infection (RTI), seizures, swallowing problems, and urinary tract infection (UTI) were recorded during the first two weeks (early) and from two weeks to six months (late) after the index stroke. We also documented the occurrence of recurrent strokes and transient ischaemic attacks (TIA) at both time points after the index stroke. Of the 118 patients, 31 (26%) were classified as TACI, 24 (20%) as PACI, 48 (41%) as LACI, and 15 (13%) as POCI. TACI was associated with a higher frequency of incontinence (61%, $p< 0.001$), RTI ([33%], $p< 0.001$), seizures (10%, $p< 0.05$), and swallowing problems (28%, $p< 0.001$) compared with the other groups at 2 weeks. Late complications of stroke, including seizures (21%, $p< 0.01$) and UTI (21%, $p< 0.05$) were also more frequent among the TACI group compared with the other groups. In contrast, we found no significant differences in the frequency of complications among the PACI, POCI and LACI groups at 2 weeks or 6 months. Of note, TIA and recurrent stroke were significantly more frequent in the POCI group (42%,$p< 0.001$) compared with the other three groups at 6 months. TACI patients had higher levels of disability as assessed by the BI, ESS, OPS, Rankin, and RMA ($p< 0.001$) a higher mortality (55%, $p< 0.001$) compared with the other groups at 2 weeks and 6 months. Conversely, we found no significant differences in disability or mortality among the PACI, LACI, and POCI groups at 2 weeks and 6 months after the index stroke.The TACI group was associated with a significantly higher frequency of early and late complications of stroke, increased early and late stroke-related disability, and a higher 2-week and 6-month stroke-related mortality in our sample. The rate of stroke-related complications, disability, and mortality among the PACI, LACI, and POCI groups were similar, however, suggesting that recognition of those groups may not be helpful in distinguishing prognostically distinct groups of stroke patients with regard to those outcomes. Interestingly, POCI patients may be at increased risk of recurrent cerebrovascular events, suggesting that clinical recognition of that particular

group may be important to allow the initiation of focused secondary stroke preventive therapies.

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MITRAL ANNULAR CALCIFICATION AND STROKE: SIZE DOES MATTER. I. Henriques, J. Correia, A. Leitão, Hospital Espírito Santo (Évora, P)

In population-based studies, mitral annular calcification (MAC) is associated with a double risk for first ischemic stroke (IS). Although considered a "minor" cardioembolic source, a causal relationship between MAC and cardioembolism is not established. Methods: We designed a hospital-based prospective case-control study including 146 patients and 146 controls. All patients were first IS, observed in the Neurology Department, matched for age and sex, and followed with a protocol that includes at least one CT-scan or MRI. We considered MAC a band of dense high-intensity echoes between mitral valve and the posterior left ventricular wall on 2-dimensional echocardiography. We defined 3 sizes for MAC (small < 1 mm; medium 1–2 mm; large 2 mm). We used the chi-square-test and logistic regression analysis. Results: From 292 patients, aged 30–93 years (median age: 64 years), 170 (58%) were male. MAC was present in 115 patients and associated with IS (p = 0.0000; Odds Ratio: 3.17; 95% Confidence Interval: 1.94–5.19). When considering MAC size, IS was associated with small MAC (p = 0.0000) and large MAC (p = 0.002), but not with moderate sized MAC (p = 0.2312). Conclusion: In this study, ischemic stroke was associated with small and large MAC sizes, but not with moderate. As MAC is a chronic progressive lesion, it might have an initial unstable stage where embolic potential is admitted, followed by a "stable" period. When achieving a larger size, it might cause mechanical or conduction disturbances. This hypothesis may contribute to a new understanding of the complex pathogenesis of stroke in patients with MAC.

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STROKE, HYPERTENSION AND LEFT ATRIAL ENLARGEMENT: OBJECTIVE MEASURES IN STROKE ETIOLOGY RESEARCH. I. Henriques, C. Barata, L. Rebocho, Hospital Espírito Santo (Évora, P)

High blood pressure (HBP) is associated with an increased risk for ischemic stroke, but the importance of HBP in major stroke subtypes is not completely understood. Recent studies found no association between HBP and lacunar infarction (LI). Left atrial enlargement (LAE) and left ventricular hypertrophy (LVH) are related with HBP and considered objective markers of hypertensive disease. We studied the hypothesis that LAE and LVH could be more related with LI than HBP. Methods: We studied 125 consecutive first ever ischemic stroke patients with a protocol that includes at least one CT scan or MRI. We considered the classic lacunar syndromes and HBP was defined according to the V Joint National Committee criteria. LAE and LVH were measured by 2-dimensional transthoracic echocardiography, indexed by body surface area. Statistical methods included logistic regression analysis. Results: From 125 patients aged 32–85 years (median: 60 years), 61% (77) were male. HBP was present in 84 (67%), LAE in 56 (45%) and LVH in 25 (20%). There were 65 LI but no statistical significant association was found between LI and HBP (p=0.3748), LAE (p=0.1207) or LVH (p=0.1673). Conclusion: In this study no association was found between lacunar infarction and HBP, LAE or LVH. The influence of HBP in stroke etiology may differ in recent diagnosed HBP in comparison to patients where objective hypertensive cardiopathy is already present. Objective echocardiographic measures like LAE and LVH may be helpful in clarifying this question.

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UTILITY OF THE OXFORDSHIRE COMMUNITY STROKE PROJECT CLINICAL CLASSIFICATION (OCSP) IN THE PREDICTION OF CRANIAL CT FINDINGS IN PATIENTS WITH ACUTE ISCHAEMIC STROKE. S.J Pittock, D. Meldrum, J. Thornton, P. Brennan, O. Hardiman, J.T Moroney, Beaumont Hospital (Dublin, IRL)

The OCSP is a simple quick method of classifying acute ischaemic stroke into 1 of 4 clinical syndromes: total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI), and posterior circulation infarct (PACI). Few studies have investigated the relationship between the OCSP classification and findings on brain imaging. To investigate the relationship between the OCSP and the site and size of infarction on cranial CT, we classified 118 patients (mean age 69 ± 12.6 years) consecutively hospitalised with acute ischaemic stroke using the OCPS method while blinded to CT findings. A neuroradiologist blinded to the clinical features classified the cranial CT performed within 48 hours of admission and at 2 weeks (initial CT negative) into 4 groups corresponding to the OCSP subgroups: A. > /= $^1/_2$ the cortical territory of the middle (MCA) or anterior cerebral artery (ACA) or large subcortical MCA infarct (TACI); B. < /= $^1/_2$ the cortical territory of the MCA or ACA, large subcortical MCA territory, or border zone infarct (PACI); C. small subcortical infarct in carotid territory (LACI); and D. posterior circulation infarct (POCI). We calculated sensitivity (SN), specificity (SP), and positive predictive value (PPV) for the different OCSP classifications compared with the CT findings for "best-case" scenario (those patients with a negative CT at both time points or those in whom the 48-hour CT was negative and the 2-week CT was not performed were correctly classified) and "worst-case" scenario (those patients with a negative CT at both time points or those in whom the 48-hour CT was negative and the 2-week CT was not performed had infarcts in locations other than those predicted clinically) using cranial CT as the gold standard for each case scenario. We obtained cranial CT in 108 of 118 (91%) patients at 48 hours and in 96 of 106 (92%) patients at two weeks after the index stroke. For "best-case" scenario, TACI had a SN of 0.92 (95% confidence interval [CI] = 0.73–0.99), SP of 0.94 (CI 0.87–0.98), and PPV of 0.81 (CI 0.62–0.94); PACI had a SN of 0.72 (CI 0.56–0.88), SP of 0.93 (CI 0.85–0.97), and PPV of 0.75 (CI 0.53–0.90); LACI had a SN of 0.91 (CI 0.79–0.98), SP of 0.91 (CI 0.82–0.97), and PPV of 0.87 (CI 0.74–0.95); and POCI had a SN of 0.68 (CI 0.43–0.87), SP of 0.98 (CI 0.93–1), and PPV of 0.87 (CI 0.60–0.98) compared with the corresponding neuroradiological classifications. Conversely, for "worst-case" scenario, TACI had a SN of 0.90 (CI 0.68–0.99), SP of 0.90 (CI 0.82–0.95), and PPV of 0.67 (CI 0.46–0.83); PACI had a SN of 0.67 (CI 0.43–0.85), SP of 0.89 (CI 0.81–0.95), and PPV of 0.58 (CI 0.37–0.78); LACI had a SN of 0.47 (CI 0.32–0.62), SP of 0.70 (CI 0.60–0.80), and PPV of 0.45 (CI 0.30–0.60); and POCI had a SN of 0.47 (CI 0.24–0.71), SP of 0.94 (CI 0.87–0.98), and PPV of 0.60 (CI 0.32–0.84) compared with the corresponding neuroradiological classifications. Our results suggest that the OCSP TACI was the most accurate in the prediction of the site and size of cerebral infarction on CT. Accuracy was high for LACI only if a negative cranial CT was considered compatible with lacunar infarction. PACI and POCI performed less well overall in the prediction of cranial CT findings, suggesting that early use of magnetic resonance imaging may be helpful for accurate infarct localisation in those patients.

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ISOLATED PERIPHERAL DEFICIT DUE TO EXTRACRANIAL VERTEBRAL ARTERY DISSECTION. K. Auré, R. Manaï, S. Crozier, M. Obadia, X. Vandamme, Y. Samson, G. Rancurel, Hôpital de la Salpétrière (Paris Cedex 13, F)

Introduction: We report the case of a patient presenting with laterocervical pain, upper limb peripheral motor deficit and amyotrophy due to extracranial vertebral artery dissection.

Case report: A 49-year-old man suddenly developed, after an hyperflexion of the neck a violent left cervical pain regressive in a few hours. Many days later the laterocervical pain reappeared with irradiation in the upper left limb, progressive motor deficit and amyotrophy. Examination showed a weakness of the left supraspinatus, infraspinatus, deltoid and biceps muscles with a mild amyotrophy and abolition of bicipital and styloradial reflex. Cervical MRI demonstrated an hypersignal on T1- and T2-weighted imaging sequences in the left vertebral artery extending from C3 to C6, corresponding to a mural hematoma. Electrophysiological studies confirm the C5-C6 radicular involvement. Angiography of the cervical arteries and cerebral MRI were normal.

Discussion: Few cases of motor peripheral deficit of the upper limb due to extracranial vertebral artery dissection have been described in the literature. In about half of the patients, the diagnosis is easy when the peripheral deficit is associated with a brainstem or cerebral infarction. In the other patients the peripheral syndrome is isolated as in our case, the diagnostic is more difficult. Two mechanisms are evoked: direct compression of the spinal nerves by the enlarged vertebral artery and/or an ischemia of the spinal nerve, the root or the anterior spinal cord.

Conclusion: Extracranial vertebral artery dissection can be revealed by an isolated peripheral motor deficit in the upper limb particularly when associated with a laterocervical pain and torsion of the neck.

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UNUSUAL ASPECTS OF CEREBRAL AMYLOID ANGIOPATHY. H. Gervais, X. Vandamme, S. Crozier, R. Manaï, Y. Samson, G. Rancurel, Hôpital de la Salpétrière (Paris Cedex 13, F)

Our purpose is to describe three unusual aspects of cerebral amyloid angiopathy and to discuss the clinical spectrum of this disease. Case 1: A 59-year-old-man suffered from a one year history of cognitive decline with partial and generalized seizures. Different MRI performed during evolution revealed a left cortical and sub-cortical parieto-occipital lesion, with spontaneous regression in three months, and later on a right parieto-occipital and a left frontal lesion.

Diagnosis of primary angiitis of the central nervous system associated with cerebral amyloid angiopathy was made on a right occipital lobe biopsy. Complete remission and MRI improvement were obtained with corticosteroids alone. Case 2: An 88-year-old-right-handed-man was admitted in our stroke unit for the sudden onset of a left lower and upper limbs sensitivo-motor deficit, with mental confusion and aphasia. He was a still very active and famous painter. Initial cerebral CT-scan revealed a right temporo-parieto-occipital subcortical hypodensity, and a right parasagittal frontal hypodensity. Because of MRI contra-indication, a cerebral venous CT-angiogram was performed and in association with clinical findings, the diagnosis of cerebral venous thrombosis was suspected. Symptomatic and anticoagulant treatments were given, but patient's condition still worsened, and a new cerebral CT-scan performed one week later revealed another lesion (right cerebellar hypodensity with hemorrhagic component). A cerebral biopsy was proposed but declined by patient's family. Symptomatic treatment with corticosteroids was given without clinical response and the patient died after three months of disease course. Post-mortem microscopic examination disclosed a characteristic cerebral amyloid angiopathy. Case 3: A 75 year-old-woman was admitted for the sudden onset of a first left Bravais-Jacksonian's seizure. Physical examination showed cerebellar ataxia, upper limbs myoclonus and cognitive decline of frontal type. Cerebral CT-scan and MRI found a right fronto-parietal meningeal process with contrast enhancement, bilateral white matter non-enhancing areas of increased signal on T2-weighted images and hemosiderin deposits outlining the right fronto-parietal cortex, the brainstem and the cerebellum (gradient-echo MRI). Evolution was marked by a new hospitalization three months later for a confusional state. MRI demonstrated a left temporal lobe hemorrhage. The diagnosis of cerebral amyloid angiopathy with central nervous system superficial siderosis was suspected, but without pathologic confirmation. Our three cases are characterized by heterogeneous and unexpected features of cerebral amyloid angiopathy.

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ISCHEMIC STROKE ASSOCIATED WITH ANTIPHOSPHOLIPID ANTIBODIES: CLINICAL AND NEUROIMAGING ASPECTS. O.Pascal, Medical University (Chisinau, MD)

The purpose of our study was to investigate the antiphospholipid antibodies (aPL) in stroke patients suspected to have the antiphospholipid syndrome (aPLS) and to define the characteristics of neuroimaging features of the aPL-associated stroke.

Patients and methods: a total of 33 patients with ischemic stroke suspected to be manifesting an aPLS have been tested for aPL and studied with either computed tomography or magnetic resonance imaging or both.

We excluded patients with systemic lupus erythematosus according to ARA criteria (1982) and patients over 65 years old. The anticardiolipin antibodies (aCL) of the IgG and IgM class were detected by standard enzyme-linked immunosorbent assay (ELISA). Lupus anticoagulant (LA) was detected by Austen technique in Prudnikova and Saikovskaia modification. Testing for aPL covered all the young patients (under 45 years) with stroke as well as those with the undetermined origin of stroke or with clinical or serological manifestations of aPLS.

OUTCOMES: Elevated titers of aCL have been found in 17 examined patients, in whom LA has been detected in 8 cases. The analysis of neuroimaging findings has demonstrated that small size infarction and multiple infarctions, as well as the combination between infarction and cerebral atrophy, occurred more frequently in patients with an aPL-associated stroke.

CONCLUSION: Certain neuroimaging particularities have been revealed in patients with ischemic stroke associated with elevated titers of aPL. The existence of these neuroimaging features could suggest to a clinician the necessity to perform a testing for aPL as being a possible risk factor of stroke.

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MULTIPLE CEREBRAL ISCHEMIC LESIONS REVEALING COELIAC DISEASE. K. Viala, A. Abdelmoumni, I. Serre, Hôpital Gilles de Corbeil (Paris Cedex 13, Corbeil Essones, F)

Neurological disorders occur in about 8–10 % of patients with coeliac disease (CD), including cerebellar ataxia, epilepsy, myelopathy, dementia, leucoencephalopathy, neuromuscular disease.

We report the case of a 45 year-old woman who suffered from headache and multiple transitory neurological symptoms followed by a left hemiparesis. A T2 weighted MRI showed bilateral hyperintense lesions in the deep periventricular white matter with a selective enhancement in the right putamen. The analysis of CSF demonstrated a mild pleyocytosis. Angiography was normal. The cardiovascular, immunological, hemostasis investigations remained negative. The biological investigation showed a microcytic anemia and a deficiency syndrome. The small bowel biopsy revealed a total villous atrophy with an intraepithelial lymphocytes increase. Ig A antiendomysium antibodies were positive. The course was favorable with aspirin treatment and gluten free diet. The different mechanisms likely to involve ischemic lesions in CD are discussed. Finally, we evoke a vasculitis in the small deep penetrating arteries territory revealing CD. Vasculitis of the central nervous system (CNS) has been exceptionally reported in CD.

Gastrointestinal symptoms and deficiency syndrome should be researched in unexplained cerebral stroke of young adults, because CD, as inflammatory enteropathy, might be associated with ischemic lesions of the CNS.

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D-DIMER LEVELS IN PATIENTS WITH ACUTE ISCHEMIC STROKE AND THE RELATION TO THE STROKE TYPE. T. Rotermund, J. Leclaire, C. Muhl, University of Witten/Herdecke (Wuppertal, D)

Activation of blood coagulation and increased levels of D-dimers in patients with stroke and in patients with atrial fibrillation has previously been detected. The relationship between the d-dimer level and the pathogenesis of stroke was investigated.

We measured the levels of D-dimer, fibrinogen and C-reactive protein in 92 patients with acute stroke within 24 hours after the onset of the first symptoms and in 22 control subjects. All stroke patients were also examined with two CT-scans, a Doppler sonography of the cerebral arteries, a colour coded ultrasound of the carotid and vertebral arteries and a transthoracic echocardiography. In some patients a cerebral angiography, a transesophageal echocardiography and a transcranial colour coded ultrasound was also performed in order to detect the pathogenesis of the stroke.

Significantly higher levels of D-dimer could be detected in that group of patients with stroke (n=92) compared to the control subjects. Those stroke patients with an atrial fibrillation (n=22) showed a higher D-dimer level than stroke patients with sinus rhythm (n=70; $p< 0.05$) and the controls ($p< 0,05$). There was a significant higher level of D-dimer in the group of patients with atrial fibrillation and a detected cardiac thrombus compared to the patients without thrombi ($p< 0.05$). No considerable difference in D-dimer levels was found in patients with lacunar stroke and atherothrombotic stroke compared to the control subjects. The D-dimer level in cases of cardioembolic stroke was significantly higher than in patients with atherothrombotic ischemia ($p< 0.05$).

The D-dimer level seems to be an additional helpful parameter for the identification of the pathogenesis of the stroke. It seems likely that a high concentration of D-dimer can be evidently indicative of the presence of an intracardiac thrombus.

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COAGULATION DISORDERS IN SNEDDON SYNDROME. SA. Blecic, C. Cuvelier, G Hildebrand, Erasme Hospital (Brussels, B)

Objective: (1) To confirm a transient coagulation anomaly is the cause of stroke in patients (pts) with Sneddon Syndrome.

(2) To assess the possible role of oral anticoagulation to prevent stroke recurrence.

Background: Sneddon syndrome (SS) is a non inflammatory arteriopathy characterized by association of livedo racemosa and stroke. In a previous study, we suggested a transient fibrinolysis disorder could contribute to the genesis of stroke in pts with SS. Indeed in 4 pts with SS, tested within the first month after stroke onset, a transient increase in APC resistance in absence of factor V gene mutation, an increase in euglobulin lysis time before venous occlusion and a low level in plasminogen was subsequently found (Blecic et al., Neurology 1997).

Design/Methods: Of 2610 pts admitted to the Stroke Unit, 29 (19 women) met the criteria for SS. All these patients suffered a stroke before being randomized (average time: 5.5 months; range 1 to 11). From February 1996 to September 1997, pts with SS were randomly distributed into two groups. The first included 16 patients (11 women) treated with warfarin to maintain INR between 2.5 to 3. The 13 other pts received aspirin (AAS) 160 mg/d. Before randomization, all had standard blood tests and a coagulation profile. Specific coagulation tests were performed: D-dimers, antithrombin III, plasminogen, Von Willebrand factor, lupus anticoagulant, anticardiolipin antibodies, euglobulin lysis before and after venous occlusion, dosages of protein C, S, t-PA, PAI, determination of APC resistance and of gene mutation for factor V of Leyden. Patients were followed for a period of at least 2 years (max 3.5 years). Conventional stroke work-up and coagulation tests were performed in the case of any vascular event.

Results: Before randomization, all pts had normal coagulation tests. During the 2-year follow-up period, none of the pts treated with warfarin had a recurrent vascular event. In pts treated with AAS, 3 had ischemic stroke, and 1 had myocardial infarction. No other cause of stroke than SS was subsequently found. Compared to the initial results, coagulation test controls carried out within the 2 days following stroke onset disclosed in the 4 pts with a new is-

chemic event and increase in APC resistance in absence of mutation of Leyden's factor V. Euglobulin lysis time before venous occlusion was also statistically increased in all as well as plasminogen levels which were significantly lower in these pts ($p < 0.001$). The pts were retested one month later and results were within normal range.

Conclusions: (1) Despite the small number of patients followed, this second study confirmed a transient coagulation disorder to be the probable cause of stroke in pts with SS. (2) In this study, pts treated with warfarin as secondary prevention for stroke had no recurrence while 4/13 pts treated with AAS had a new vascular event during the 2-year-period, suggesting oral anticoagulation should be recommended in pts with SS to prevent any further vascular event.

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THE VALUE OF EEG AND NEUROIMAGING EXAMINATIONS IN ASSESSMENT OF BRAIN INVOLVEMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS. K. Niedzielska, M. Baranska-Gieruszczak, A. Kuczynska-Zardzewialy, A. Czlonkowska, M. Rzeski, J. Lecka, Institute of Psychiatry and Neurology (Warsaw, PL)

Systemic lupus erythematosus (SLE) is an immunomediated disease of connective tissue that can frequently affect the central nervous system (CNS). The aim of this study was to assess the usefulness of EEG, computed tomography (CT) and magnetic resonance imaging (MRI) in detecting of the brain involvement in SLE patients. We evaluated a group of 47 SLE patients (7 males, 40 females, aged 20–66 years, mean age 47 years) referred to our neurological ward. EEG abnormalities were found in 57.4% patients, in most cases focal slowing and sharp wave activity. CT changes, predominantly cortico-subcortical atrophy, were demonstrated in 14.9% cases. MRI revealed morphological changes in 55%, most frequently multiple microinfarctions in white matter. The clinical manifestation of CNS involvement were observed in 17 (36%) SLE patients. In this group the pathological changes in MRI were found in 90.9%, while in CT scans only in 29.4%; EG abnormalities were seen in 88%, significantly more frequently than in patients with no neurological symptoms ($p < 0.001$). Our results support the observations that MRI is a more precise method than CT for indentifying the organic brain lesions in SLE patients and suggest that EEG examination is a sensitive indicator of CNS involvement in this disease.

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STROKE IN PREGNANCY AND PUERPERIUM. C. Cuvelier, S. Blecic, J. Hildebrand, Erasme Hospital (Brussels, B)

Objective: To assess the causes of stroke in pregnancy and puerperium.

Background: If pregnancy and puerperium could increase the risk of stroke by 13, the causal effect of pregnancy itself remains doubtful. Different causes can be found but their relationships with pregnancy, time distribution and exact etiology are still unresolved.

Design/Methods: From July 1989 to September 1999, out of the 3010 patients (pts) admitted to the Stroke Unit, 9 women (mean age: 31.0 years ± 6.9 years) had a stroke during pregnancy or puerperium. They were either admitted via our obstetric department or referred from other hospitals. In all pts a complete stroke work-up was performed, including in all, urine and blood tests, MRI, MRA, trans-thoracic and trans-oesophageal echographies, transcranial Doppler, and coagulation tests. Lumbar puncture and catheter angiography (only after delivery) were performed in selected cases only. In all pts coagulation tests were checked 3 months after childbirth.

Results: 10 pts had venous stroke and 19 had arterial stroke. In pts with cerebral venous thrombosis (CVT), a coagulation disorder (CD) was found in 4. 2 pts had congenital deficit in protein C and 2 had resistance to activated protein C all with mutation of Leyden's factor V. Two pts suffered migraine + aura. In the remaining 4 pts no other cause than pregnancy itself was found. In pts with arterial stroke, the following causes were found: idiopathic vasoconstriction (IV) in 8. All these women being treated with oxytocin, CD were found in 7 pts in whom 1 pt had Prot S deficiency, 2 had Prot C deficiency, 1 had APC resistance without mutation of Leyden's factor V, 1 had antithrombin III deficiency and 2 had cardiolipin antibodies. Two pts had a cardioembolic (CE) amniotic fluid embolism and 1 had a choriocarcinoma complicating pregnancy, 23/29 pts had stroke during the postpartum period, in which IV occurred exclusively within the first week after delivery while CVT and other causes of stroke were found subsequent to the 15th day after delivery. All pts were treated with anticoagulants. Complete recovery was observed in 7/10 CVT and in 13/19 with arterial stroke, 3 pts died 1 with CVT, 1 with the severe heart failure, and the pt who had a choriocarcinoma. All deaths occurred during the first months of pregnancy.

Conclusions: In our series, stroke in pregnancy remains a rare event, since it has accounted for less than 1% of all admissions. The vast majority is found during the postpartum period. CD is the most frequent cause of stroke since it has been found in 11 pts. In pts with transient arterial vasospasm, the administration of oxytocin could induce vasoconstriction through a V1 vasopressin receptor stimulation. This transient reflex vasospasm could be strengthened by physiological episodes of arterial hypertension due to labour. Complete recovery was found in most pts but in this small series, death occurred in roughly 10% of the cases and occurred always before childbirth

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STROKE IN THE YOUNG: THE PROEMINENT ROLE OF ARTERIOPATHIES. B. Legros, J. Hildebrand, S. Blecic, Erasme Hospital (Brussels, B)

Objective:To assess the causes of stroke in patients (pts) under 50. Background: Except for artery dissections (AD), the place of arteriopathies is unsettled and the fear of cardioembolism (CE) is advocated to propose anticoagulation (AC) in pts under 50. Methods: From 1991 to 1999, 2621 pts were admitted to the Stroke Unit and 354 (13.5%) having under 50. All had a complete stroke work-up. They were distributed into two groups: pts under 35 and pts between 35 and 50 years. Results: In the whole population, a cardiac cause of stroke was identified in 45 pts (13%), 30 had a patent foramen ovale (PFO), only 5 having a source of paradoxical emboli. 10 had atrial fibrillation and 5 had a recent myocardial infarction. Arteriopathy was the cause of stroke in 219 (62%) pts, large artery disease (LAD) being the cause in 122. Non atherosclerotic arteriopathy was found in 64 pts (29%), AD being the cause of stroke in 53, and reversible spastic angiopathies in 11. Atherosclerosis was found in 58, only 3 having heterozygote homocystinuria. Small vessel disease (SAD) was found in 39 pts (18%), migraine in 5 (3.6%) and coagulation disorders (CD) in 29 (16%). In 22 pts no cause was identified. 58 pts had several causes, the most frequent finding being the combination of SAD and LAD. In the 99 pts (27%) under 35 years, LAD was observed in 69 (70%), 44 having AD and 25 atherosclerosis. CE was demonstrated in 10 pts (10%), migraine in 3, CD in 9, the cause remaining unknown in 8. Conclusions: Arteriopathies and mainly LAD were the most frequent cause of stroke. There was no difference between pts under 35 and pts between 35 and 50. CE accounted only for 15%, probably less regarding the controversial role of PFO. This does not favour the early use of AC in young with acute stroke.

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STROKE RECURRENCE IN PATIENTS WITH CRYPTOGENIC STROKE. C. Decock, S. Blecic, J. Hildebrand, Erasme Hospital (Brussels, B)

To determine the evolution and outcome of a population with cryptogenic strokes (CS) compared to a general population (GP) with stroke

CS represents in different series from 4 to 29% of all patients (pts). Little is known about its evolution and mainly if this population can have any vascular recurrence.

From 1991 to 1999, 2621 pts (1351 males) were admitted to the Stroke Unit. Mean age was 66.8 ± 8.7 years. All had a conventional stroke work-up. MRA, trans-oesophageal echography, catheter angiography, extensive coagulation study including homocystenemia level determination, skin biopsy and lumbar puncture were performed in selected cases. All pts with GP and CS were followed twice a year for an average 3 year-period. Pts with CS were rechecked for stroke etiology every year, earlier in cases of new technique availability.

In 41/2621 pts (1.6%), no cause of stroke was found. Mean age of this population was 64.7 ±7.1 years (NS compared to GP). 20 pts had stroke, while 12 had TIA and 9 had hemorrhage. Further work-up allowed to find a possible cause of stroke in 9/41 pts (22%). In 7 a coagulation disorder was eventually demonstrated and in 2 atherosclerosis was found. In 32 patients no cause of stroke could be definitely found. Only 8 were treated with aspirin. Within this 3 year-period, a non-statistical difference was observed for cerebral recurrences between pts with CS and GP, since a new stroke has been found in 4/32pts with CS (12.5%) and in 332/2589 pts of GP (12.8%). Only one pt with CS had a general vascular recurrence, myocardial infarction (MI) for instance, while 474 pts who had a stroke in GP (18.3%) had a new non-cerebral vascular event ($p < 0.001$) which was (MI) in 400/474 (84.4%)

This study demonstrated that pts with CS and GP did not differ by their stroke recurrence rate, both populations having the same evolution at 3 years, but by the occurrence of other vascular events, MI for instance, exclusively encountered in the GP population.

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HOMOCYSTINURIA AS A BRAIN SINUSES THROMBOSIS. E. Toribio, B. Fuentes, A. Miralles, F. Palomo, A. Frank, E. Diez-Tejedor, University Hospital La Paz (Madrid, E)

Background: Homocystinuria is an autosomal recessive inborn error of methionine metabolism due to a deficiency of cistathionine b-synthase in most cases. Its presentation as sinuses thrombosis is very uncommon, specially in adults.

Methods and results: We report the case of a 27-year-old woman with migraine without aura, oral contraceptive use and slight tobacco smoking who presented a progressive clinical picture with headache, partial seizures with secondary generalisation, and right hemiparesis. RM and Angio-RM revealed thrombosis of superior sagittal and right transverse sinuses and bilateral frontal venous infarctions. Laboratory analysis revealed increased levels of homocystine in plasma and urine as well as methionine in plasma, with decreased levels of cystine and cysteine in plasma. Anticoagulant treatment determined a significant clinical improvement. When the diagnostic of homocystinuria was confirmed, pyridoxine and folic acid therapy was started and the homocisteine, cistine and methionine levels returned to the normality. In this patient, without other features of this illness, the association to other cerebral venous thrombosis risk factors (migraine and oral contraceptives) would probably precipitates the sinuses thrombosis.

Conclusion: Although homocystinuria is very uncommon, it should be included in the differential diagnosis of sinus thrombosis at any age, inclusively in patients without other features of this illness and also in patients with other associated risk factors.

P393
ACETYLSALICYLIC ACID MEDICATION PREDICTS THE FREQUENCY OF TRANSCRANIAL DOPPLER DETECTED CEREBRAL MICROEMBOLI IN PATIENTS WITH SYMPTOMATIC ARTERY STENOSIS. S. Krueger, T. Blaser, C.-W. Wallesch, G. Lutze, M. Goertler, Department of Neurology, Institute of Clinical Chemistry (Magdeburg, D)

Background: In patients with symptomatic artery stenosis transcranial Doppler detected cerebral microemboli (ME) ipsilateral to the stenosis are associated with an increased risk of a recurrent ischemic event. Although antithrombotic agents are of proven efficacy in the secondary prevention mainly by reducing cerebral embolism from the stenotic lesion, no impact of an antithrombotic medication on the frequency of ME has yet been demonstrated.

Patient and Methods: 74 patients (24 women, 50 men; mean age 60.1±14 years) from 192 consecutively referred patients with a recently (< =30 days) symptomatic arterial stenosis in the anterior circulation underwent transcranial Doppler monitoring. Patients were excluded in case of insufficient temporal bone windows (n=42) or if Doppler monitoring could not be organised (n=76). With exception of a higher age and a higher frequency of women in patients with insufficient acoustic window, selected and not selected patients did not differ by their clinical characteristics.

Results: The absence of antiplatelet prevention at the time of transcranial Doppler monitoring (OR 7.1, 95%CI 1.6–31.4, p=0.010), an extracranial localisation of the stenosis (OR 7.1, 95%CI 1.6–32.7, p=0.011) and recurrent ischemic events (OR 3.8, 95%CI 1.1–13.3, p=0.038) were independent predictors for ME (multiple linear logistic regression analysis included degree of stenosis and time between ischemia and Doppler monitoring). ME-positive and ME-negative patients did not differ by their age, sex, riskfactors, type of symptoms and CT/MRI findings.

Conclusions: Detection of ME in patients with recently symptomatic artery stenosis is associated with an antiplatelet medication. These findings suggest an influence of antiplatelet drugs on ME of presumed arterial origin.

P394
ACETYLSALICYLIC ACID INDUCED CESSATION OF TRANSIENT ISCHEMIC ATTACKS AND MICROEMBOLIC SIGNALS DETECTED BY TRANSCRANIAL DOPPLER IN A PATIENT WITH ESSENTIAL THROMBOCYTHEMIA. T. Blaser, S. Krueger, R. Kross, G. Lutze, M. Goertler, Department of Neurology, Institute of Clinical Chemistry (Magdeburg, D)

Background: Essential thrombocythemia is associated with neurological symptoms in up to 60% of patients. Platelet thrombi in the arterial microvasculature induced by thrombocytosis and platelet hyperaggregability are considered the underlying pathology. Transcranial Doppler can detect circulating formed element particles.

Patient and Methods: A 69-year-old man presented with recurrent bilateral transient ischemic attacks which completely recovered after 10 to 30 minutes. Medical history detected a moderate hypertension and a nicotine abuse (23 pack years). Cranial computed tomography was normal. Examinations revealed no findings associated with an increased cardioembolic or arterioembolic risk. Transcranial Doppler monitoring detected 18 microemboli (ME)/hour in the middle cerebral arteries. Venous blood samples revealed thrombocytosis (682 x 109/L) with circulating platelet aggregates and mega-platelets. Bone marrow biopsy confirmed the diagnosis of essential thrombocythemia.

Results: Treatment with ASA initiated by an intravenous bolus of 500 mg and continued orally with 300 mg/day abolished further ischemic events corresponding to a cessation of ME and an inhibition of platelet aggregation as early as 30 minutes after ASA injection. Ischemic events and ME reappeared after treatment interruption. Recommencement of therapy stopped both symptoms and ME corresponding to reestablished inhibition in platelet aggregation tests.

Conclusions: Findings in our patient suggest, that ME detected in middle cerebral arteries corresponded to circulating platelet aggregates which were suppressed by ASA and were responsible for cerebral ischemia.

P395
EFFECT OF ANTIPLATELET AGENTS AND HEPARIN ON TRANSCRANIAL DOPPLER DETECTED CEREBRAL MICROEMBOLI OF ARTERIAL ORIGIN. M. Goertler, S. Krueger, T. Blaser, R. Kross, M. Baeumer, C.-W. Wallesch, G. Lutze, Department of Neurology, Institute of Clinical Chemistry (Magdeburg, D)

Background: Anticoagulation with intravenous heparin is considered the therapy of choice immediately after an ischemic event due to high-grade extracranial or intracranial artery stenosis. Reduction of cerebral embolism is the presumed mechanism. Cerebral microemboli (ME) detected by transcranial Doppler in these patients are considered formed element particles originating at the stenotic lesion. Their frequency might reflect the efficacy of an antithrombotic medication.

Patients and Methods: Intravenous heparin (activated partial thromboplastin time 2-fold that of baseline level) was started in 7 patients (2 women, 5 men; mean age 63.6±14 years) with acute symptomatic artery stenosis. Subsequently therapy was switched to antiplatelet agents, i.e. acetylsalicylic acid (300 mg/day), ticlopidine (500 mg/day), or clopidogrel (75 mg/day), or a combination of them. Transcranial Doppler monitoring was performed before and during heparin therapy as well as when the antiplatelet therapy had been started.

Results: Prior to heparin 31.8 ME/hour (mean; range, 4–54) were detected in middle cerebral arteries distal to the symptomatic stenoses. Mean counts did not change during heparin therapy (30.9; range, 5–67). After patients were set on antiplatelet agents, ME only were detected in 2 patients (1 ME/hour each) (p< 0.05). One patient received a recurrent stroke 9 days after an initial transient ischemic attack when he was sufficiently anticoagulated. No recurrent ischemic event occurred during antiplatelet therapy ((> =6 months).

Conclusions: Antiplatelet agents but not intravenous heparin reduce transcranial Doppler detected microemboli of arterial origin. In symptomatic arterial stenosis the effect of antithrombotic agents on microemboli might parallel their efficacy on the prevention of stroke recurrence.

P396
EFFECT OF COMBINED ACETYLSALICYLIC ACID AND TICLOPIDINE OR CLOPIDOGREL THERAPY ON TRANSCRANIAL DOPPLER DETECTED CEREBRAL MICROEMBOLI OF ARTERIAL ORIGIN. T. Blaser, S. Krueger, R. Kross, M. Baeumer, C.-W. Wallesch, G. Lutze, M. Goertler, Department of Neurology, Institute of Clinical Chemistry (Magdeburg, D)

Background: Transcranial Doppler detected cerebral microemboli (ME) in symptomatic artery stenosis are associated with an increased risk of a recurrent ischemic event. In those patients intravenous acetylsalicylic acid (ASA) can rapidly reduce microemboli of arterial origin.

Patients and Methods: Fifteen patients (3 women, 12 men; mean age 62.2±13 years) with recently symptomatic arterial stenosis received ticlopidine (500 mg/d; 10 patients) or clopidogrel (75 mg/d; 5 patients) additional to ASA (100 to 300 mg/day). Seven patients had an amaurosis fugax, a transient ischemic attack or a minor stroke under preexisting ASA. In 8 patients ASA therapy had been started immediately after such an ischemic event.

Results: During ASA therapy 13.1 ME/hour (mean; range, 3–57) were detected in middle cerebral arteries distal to the symptomatic stenoses. In 8 patients without antiplatelet agents at stroke onset ASA reduced ME/hour from 30.1 (mean; range, 9–59) to 16.6 (mean, range, 3–57) (p< 0.05). Already 48 hours after an additional ticlopidine or clopidogrel medication no ME could be detected in 13 of the 15 patients. In 2 patients 2 ME/hour and 3 ME/hour were found (p< 0.05). 2 of the 8 patients in whom ASA was started after the initial stroke had a recurrent ischemia. No recurrent event occurred after patients additionally received ticlopidine or clopidogrel (> =6 months).

Conclusions: Add on therapy with ticlopidine or clopidogrel reduces trans-

cranial Doppler detected microemboli in patients with recently symptomatic artery stenosis and ASA prevention. Efficacy of secondary prevention might be judged by microemboli before recurrent ischemia had occurred.

P397
SIGNIFICANCE OF RISK FACTORS FOR STROKE SEVERITY. T. V. Lepic, Military Medical Academy, Belgrade (Belgrade, YU)

Background and Purpose: Some clinical parameters in acute stroke have prognostic significance for clinical course and outcome. In aim to study significance of relationship between risk factors and stroke severity and fatality we studied presence of risk factors in group of severe stroke patients, comparing with other stroke patients. Severity estimation was based on consciousness level and motor deficit. As severe stroke patients were defined those who were presented with coma or hemiplegia on admission.

Methods and Results: We studied history of risk factors and values of stroke severity score on admission and at the end of hospitalization. Group of 251 patients, 154 men and 97 women, 26–84 (x=60) years old were admitted in neurologic and emergency unit with acute stroke. Following the admission, 68 % of patients were diagnosed as infarction and 31 % as cerebral hemorrhage. Only 11 % of patients were found to be risk free, 19 % reported one risk factor, while the remaining of 70 % of patients had two or more risk factors in the history. There was no statistical difference in the number of risk factors reported between those with ischaemic and hemorrhagic stroke. Greatest majority of the patients (68 %) reported arterial hypertension, heart diseases were reported by 34 %, obesity and smoking by 22.5 %, and family history of cardiovascular disease by 16 % of patients. Previous manifestations of cerebrovascular disease and diabetes mellitus were reported by 15 %, extensive alcohol intake in the past by 13 %, and hyperlipidemia by 9 % of patients. Hypertension, smoking, and family histories of cardiovascular disease were found to be equally distributed in both patients with infarction and cerebral hemorrhage. Heart diseases, diabetes mellitus, previous attacks of cerebrovascular disease and hyperlipidemia were more common in the patients with infarction, while history of alcoholism and obesity in those with hemorrhage. On the basis of neurological score values on admission, severe clinical manifestations were identified in 24 %, moderate in 46 %, and mild in 30 % of patients. At the end of hospitalization, mild severity scores have 46 %, moderate 33 % and severe only 2 % while 19 % of stroke were fatal. Patients with fatal outcome most commonly have more than one risk factor, old age, history of cardiovascular disease and arterial hypertension.

Conclusion: Our results suggest those stroke patients with more than one risk factor, particularly with arterial hypertension, have severe course of illness and higher risk for death in acute phase.

P398
ROTATIONAL VERTEBRAL ARTERY OCCLUSION SYNDROME WITH RECURRENT EPISODES OF VERTIGO DUE TO TRANSIENT LABYRINTHINE EXCITATION. M. Strupp, J. H. Planck, V. Arbusow, H.-J. Steiger, T. Brandt, Ludwig-Maximilians University Klinikum Grosshadern (Munich, D)

The syndrome of rotational vertebral artery occlusion is clinically characterized by recurrent attacks of vertigo, nystagmus, and ataxia. Vertigo – the leading symptom of the vertebral artery occlusion syndrome – is usually attributed to brainstem dysfunction, although the labyrinth is also vulnerable to ischemia. We report on a patient with an angiographically proven rotational vertebral artery occlusion syndrome who had recurrent uniform attacks of vertigo, nystagmus, and tinnitus in the right ear of 3 to 5 seconds duration. These attacks were caused by leftward head rotation and accompanied by a mixed clockwise torsional downbeat nystagmus with a horizontal component toward the right. This case was exceptional in two ways: Detailed analysis of the direction of the eye movements by two-dimensional videonystagmography and assessment of the clinical syndrome allowed us to conclude (1) that the syndrome was most likely induced by a transient ischemia of the right labyrinthine rather than the brainstem and (2) that this labyrinthine ischemia led to a combined transient excitation of the right anterior and horizontal semicircular canals as well as the cochlea. Thus, the nystagmus and tinnitus represented a transient ischemia-induced hyperfunction rather than hypofunction of the labyrinth.

P399
DONEPEZIL AND RIVASTIGMINE IMPROVE P300 LATENCY AND NEUROPSYCHOLOGICAL TEST SCORES IN ALZHEIMER'S DISEASE PATIENTS: ONE YEAR FOLLOW UP COMPARED WITH VIT E TREATED PATIENTS. A. Thomas, C. Paci, G. D'Andreamatteo, D. Iacono, M. P. Buongarzone, M. Onofrj, Institute of Neurology (Chieti, I)

The clinical application of event-related potentials (ERPs) in neurological disease is based on the universal The latency of P300 potentials changes if cholinergic activities of the Central Nervous System are pharmacologically manipulated. The new cholinesterase (ChE) inhibitors Donepezil (DPZ) and Rivastigmine (Riv) may have an effect on P300 of Alzheimer's Disease (AD) patients. Methods: We evaluated 60 patients with mild to moderately severe AD according to NINCS-ADRDA criteria, compared with 40 age matched controls. All subjects underwent P300 recordings and neuropsychological examinations during the 12 months follow-up. 40 patients were randomly assigned to a double blinded trial: DPZ (5–10 mg/day) vs Vit E (2000UI/day) and 20 patients treated in an open trial with Riv (1.5 to 12 mg/day). Results: Patients treated with Vit E show moderate latency increments (6.9+3.5msec). Neuropsychological tests were overlapping to baseline sessions ($p< 0.07$). Patients treated with DPZ, show a significant P300 latency reduction (14.5+2.0msec). Shorter P300 latencies were associated with higher WAIS and MMSE scores and with lower ADAS-cog. scores (R=0.72). Patients treated with Riv show a significant P300 latency reduction (16.5+1.9msec) and neuropsychological correlations comparable with results obtained with DPZ. Conclusions: DPZ and Riv treatment reduce the latencies of P_3 component in AD patients and Neuropsychological improvement was observed. ERPs recordings seem to be a useful tool to evaluate pharmacological responses to ChE inhibitors in AD patients and latency measurements can be correlated with neuropsychological improvements.

P400
P300 IN ALZHEIMER'S DISEASE AND IN PRIMARY PROGRESSIVE APHASIA: A 3 YEAR FOLLOW-UP. C. Paci, A. Thomas, G. D'Andreamatteo, D. Iacono, M. P. Buongarzone, M. Onofrj, Institute of Neurology (Chieti, I)

There is universal agreement that P300 latency is delayed in dementia. Besides latency, morphology and scalp distribution of P300 are also alterated in Alzheimer's disease (AD). Primary progressive aphasia (PPA) is a term introduced by Mesulam to describe a clinical picture of patients with progressive and isolated loss of language functions. Methods: We studied 15 patients (two males and eight females, age range 53–72 years) affected by AD and four patients (two males and two females, age range 54–74 years) affected by PPA, both diagnosed on the basis of clinical and neuropsychological evaluation, CT scan, MRI findings and ERP recordings. Results: P300 was abnormally delayed in four AD patients, topographical distribution was abnormal. P300 latency was normal in PPA patients. During the three years follow-up, the latency of P300 increased in AD by a mean of ± 6 ms each year. In PPA the latency of P3 did not increase in 3 years, while amplitude decreased by 21±8 % on the right hemisphere and by 62±6 % on the left hemisphere. Conclusions: When comparing P300 results with neuropsychological evaluation scores we reached the following conclusions: 1) P3 undergoes completely different patterns of degradation in AD and PPA; 2) reproducible left hemisphere topographical abnormality is specific in PPA; 3) progressive degradation with progressive latency increment is highly specific and sensitive in AD.

P401
HOMOCYSTEINE CONCENTRATION IN CSF IN PATIENTS WITH ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA. M. Barquero Jimenez, E. Varela De Seijas Slocker, F. Mora Teruel, Hospital Clinico (Madrid, E)

There is increasing evidence that risk factors for vascular disease and stroke are associated with cognitive impairment and Alzheimer's disease (AD). Homocysteine (Hcy) may represent a metabolic link in the pathogenesis of atherosclerotic vascular diseases and old-age dementias. Activation of the coagulation system and adverse effects of Hcy on the endothelium and vessel wall are believed to underlie disease pathogenesis. Although Hcy is a potent neurotoxin on culture cortical neurons, this is associated with dual actions of Hcy at N-methyl-D-aspartate (NMDA) receptor. Finally, the pattern of Hcy-like inmunoreactivity in the rat indicates a localization of Hcy mostly in glial elements.

Objective: To examine cerebrospinal fluid (CSF) levels of total Hcy in patients with probable AD and patients with probable vascular dementia (VD). Material and methods: 35 subjects with AD (by criteria of the NINCDS and ADRA) and 25 subjects with VD (by criteria of NINCDS and AIREN) were se-

lected. Subjects were well matched for age, sex, duration of illness, and cognitive function. Total CSF HCY was measured using high performance liquid chromatography (HPLC). Results: Mean total CSF HCY concentration in patients with AD was found to be significantly higher ($p < 0.001$) than that of patients with VD. Conclusion: The elevated Hcy concentration in CSF of patients with AD, compared with patients with VD, suggest the idea that in AD Hcy is involved, at least in part, in other mechanisms than vascular factors and the understanding of Hcy pathophysiology may provide new insights into excitotoxicity neural injury mediaded by NMDA receptors overestimulation and excitatory signaling involving glial elements.

P402
THE EFFECT OF LITERACY ON PROSPECTIVE MEMORY IN EARLY ALZHEIMER DISEASE PATIENTS. M.-C. Pai, S.-H. Chan, C.-Y. Chen, National Cheng Kung University Hospital, National Chung Cheng University (Tainan, Taiwan, RC)

Background: The role of education on the development and onset age of degenerative dementias is still under debate. In order to know the effect of literacy on the performance of prospective memory (PM) in normal elderly and early Alzheimer disease (AD) patients, we designed an everyday memory task to explore this issue.

Participants: Patients with early AD were recruited from a special clinic in a referral, 800-bed National University Medical Center. A behavioral neurologist made a diagnosis of AD according to the criteria of DSM-IV and NINCDS-ADRDA. Severity of the disease was assessed by CDR scale. Normal subjects were encouraged to take part in this study.

Methods: The PM task consists of two parts, PMa performed in the hospital, and PMb after the participants having left the hospital. For PMa, the participant was asked to make a telephone call (PMa1), to buy a copy of newspaper (PMa2), and to ask back their personal belonging (PMa3) on specific occasions, during a 20 minutes walk with a trained examiner. For PMb, the participant was asked to send three letters at different times; one of the last two sent after returned home was with a financial incentive for the normal participants. We finally called their family to ask if they had used memory aids.

Results: A total of 94 participants completed the study, including 48 normal subjects (21 illiterate and 27 literate) and 46 AD patients (18 illiterate and 28 literate). Factorial analyses showed a significant effect of literacy on both PMa ($p=0.003$) and PMb ($p=0.009$), and a significant effect of disease on both PMa ($p=0.000$) and PMb ($p=0.000$). The beneficial effect of literacy on PMa tasks appears in the PMa1 ($p=0.000$) and PMa2 ($p=0.013$), but not in the PMa3 ($p=0.401$), a phenomenon we call "latency effect". Moreover, the literate groups had used more external memory aids to carry out the PMb. The incentive promoted the correct performance of PMb for normal participants.

Conclusions: The procedures of PM tasks are akin to everyday life, which may reflect memory impairment in a more natural setting. The literacy had a beneficial effect on PM performance even in the early stage of AD. In general, early AD patients have a poor PM performance, which can be of value as a discriminator to make an early diagnosis.

P403
DONEPEZIL IN THE TREATMENT OF ALZHEIMER'S DISEASE: RESULTS FROM A POST MARKETING SURVEILLANCE STUDY IN GERMANY. F. M. Berger, C. Goebel, C.A, Sramko, Eisai GmbH, Pfizer Germany (Frankfurt, Karlsruhe, D)

Background: Donepezil, a selective acetylcholinesterase inhibitor, was approved for the symptomatic treatment of mild to moderate Alzheimer's disease (AD) in most European countries in mid 1997. After approval, regulatory authorities often require additional information about products and their routine clinical use. One way to meet this requirement appropriately is to conduct Post Marketing Surveillance (PMS) studies. Objective: To evaluate the efficacy, tolerability and safety of donepezil in patients with AD in the general clinical setting. Methods: From October 97 to May 99, an open-label, observational PMS study was conducted in Germany. Participating centres, mostly office-based specialists in neurology and/or psychiatry, enrolled 2092 patients (60.8% female, mean age 73 years, mean Mini-Mental Status Examination (MMSE) 17.8). Efficacy parameters were MMSE changes from baseline scores and Nurses Observation Scale for Geriatric patients (NOSGER) domain scores. After the suggested observation period of 3 months, efficacy and tolerability were assessed separately by the prescribing physician. A detailed analysis of observed adverse events (AE) was performed. Results: At the end of the observation period, the mean change from baseline MMSE score showed an improvement of + 1.4 points. 63% of patients showed an improved MMSE score compared with baseline. 36% of patients improved by > /=3 points (MMSE). All NOSGER domains – memory, basic and instrumental activities of daily living (ADL), mood, social behaviour, disturbing behaviour – showed an improvement compared with baseline. AD symptoms were judged as "markedly improved" in 11.4% of patients, and "improved" in a further 44.6% of patients. AD symptoms in 9.6% of patients were judged as "worsened" or "markedly worsened". Tolerability of donepezil was judged "very good" or "good" in more than 90% of patients. 12.2% of patients reported at least one AE (most commonly nausea 2.2%, diarrhoea 1.4%, trembling inside 1.4%, vomiting 1.1%). The incidence of AEs recorded in this study was lower than that reported previously in clinical trials. Conclusions: In routine clinical practice, donepezil has been proven to be an effective, well tolerated and safe therapy for patients with mild to moderate AD, confirming results from previous US and multinational Phase III clinical trials.

P404
COGNITIVE PERFORMANCE FOLLOWING CHRONIC SUBTHALAMIC STIMULATION IN PARKINSON'S DISEASE. A. Daniele, L. Romito, A. Bentivoglio, E. Moro, A. Barbier, P. Zinzi, F. Contarino, M. Scerrati, A. Albanese, Catholic University (ROME, I)

Subthalamic nucleus high frequency stimulation is a promising neurosurgical approach in patients with Parkinson's disease who experience disabling motor fluctuations. This procedure has been shown effective in improving motor symptoms managing, while the long-term effects on cognitive performance is still under investigation.

Cognitive functioning was assessed in eleven PD patients before (baseline) and six months after chronic bilateral stimulation of the subthalamic nucleus (STN). At baseline, the mean age of the patients was 57.2 (SD = 7.8), their mean disease duration was 14.4 (SD = 3.7) and their mean Hoehn & Yahr score in off condition was 4.5 (SD = 0.7). Patients were given a battery of neuropsychological tasks, including Mini-Mental State Examination (MMSE), test of episodic verbal memory (Rey's Auditory Verbal Learning Test), abstract reasoning (Raven's Progressive Matrices '47), verbal fluency (letters F, A, S). Patients underwent preoperative neuropsychological assessment while on medication, and postoperative assessment while on medication and with the stimulators turned on. Statistical comparisons between preoperative versus postoperative scores on neuropsychological tests were made by means of the Wilcoxon's signed rank test.

At six months postoperatively a statistically significant improvement ($p = .04$) was observed on the MMSE (mean improvement = + 4.2%), while a statistical trend ($p = .11$) towards an improved performance was detected on the immediate recall task of the Rey's Auditory Verbal Learning Test (mean improvement = + 7%). A nonsignificant postoperative improvement was found on Raven's Progressive Matrices '47 and on the delayed recall task of the Rey's Auditory Verbal Learning Test. A nonsignificant worsening in postoperative performance was observed on the verbal fluency task (mean worsening = – 9%).

These results show that chronic stimulation of the STN does not worsen cognitive functioning in PD patients, suggesting that slight beneficial effects on overall cognitive performance could occur in these patients.

P405
DETECTION OF 14–3–3 ISOFORMS IN THE CEREBROSPINAL FLUID OF PATIENTS WITH CREUTZFELDT-JAKOB DISEASE BY TWO DIMENSIONAL GEL-ELECTROPHORESIS. L. Cepek, M. Otto, P. Steinacker, H. Esselmann, S. Paul, S. Poser, J. Wiltfang, Neurology, Georg-August-University, Psychiatry, Georg-August-University (Göttingen, D)

BACKGROUND: Creutzfeldt-Jakob disease (CJD) belongs to the group of transmissible, spongiform encephalopathies and the diagnosis is based on the combination of clinical symptoms, typical EEG findings and detection of the 14–3–3 proteins by immunoblot. In earlier investigations the diagnosis of CJD was supported by detection of the spots p130 and p131 in the cerebrospinal fluid (CSF) by two-dimensional polyacrylamide gel-electrophoresis (2-D-PAGE). Nowadays these spots are assigned to the 14–3–3 family. By reanalysing the original data the isoelectric point (pI) of the spots in the 2-D-PAGE, the number of detectable spots and the sequenced isoforms seem to differ in the original publication. METHODS: To clarify this statement we established the 2-D-PAGE with an optimized isoelectric focussing and a higher sensitivity for the spot detection. Therefore we changed the sample preparation and checked the results against controls and pI-markers. RESULTS: Our results showed a different pI of the detected spots in contrast to the described ones. By immunostaining of the membranes we reproducibly detect four constant spots and two additional inconstant spots. Because of the spots immunoreactivity against the specific antibody they seem to be members of the 14–3–3 family. The number of spots suggests itself to be caused by the diversity of the isoforms. In the isoform-specific immunostaining the anti-gamma-isoform antibody detects four spots and the anti-eta-isoform antibody detects only one of these. This was reproduced in five different CJD patients. CONCLUSION: For the first time we

showed that there are different 14–3–3 isoforms in cerebrospinal fluid of CJD patients by 2-D-PAGE. These spots differ in their pI, in their immunostaining characteristics and in their ratio. It is necessary to check this ratio in comparison to other diseases, which are positive in the immunostaining for 14–3–3 proteins in the 1-D-PAGE, like epilepsy, herpes-simplex-encephalitis or early ischemic events.

P406
NORMAL PRESSURE HYDROCEPHALUS WITH UNUSUAL PRESENTATION MIMICKING ALZHEIMER'S DISEASE. J. Newman, A. Ashkenazi, Z. Meiner (Jerusalem, IL)

Objective: To describe an elderly woman with normal pressure hydrocephalus (NPH) which clinically mimicked Alzheimer's Disease (AD). Background: The typical manifestation of NPH is a triad of progressive gait disorder, dementia and urinary incontinence. The occurrence of dementia without gait disorder usually suggests other etiologies. Case report: A 82 year old woman presented with slowly progressive cognitive decline of 5 years duration. She could not find her way to familiar places. Her functional status deteriorated significantly. There was neither gait disturbance nor urinary incontinence. She had no history of stroke, head trauma or meningitis. Her mother had also suffered from mental deterioration. On examination, orientation for place and time was severely impaired. Attention was mildly impaired. She had short term memory impairment of the hippocampal type, as well as severe spatial disorientation, constructional apraxia, decreased verbal fluency and dysnomia. Executive functions were also impaired, and perseverations were noted. There were no other focal neurologic signs and gait was normal. Brain CT scan showed markedly enlarged ventricles with no significant cortical atrophy. MRI showed a patent aqueduct of Sylvius. CSF was normal, with an opening pressure of 160 mmH_2O. After LP, significant improvement was noted, mainly in spatial orientation and in praxis. A lumbo-peritoneal shunt was inserted. Cognitive assessment one week later showed a moderate improvement in her attention and in short term memory and a significant improvement in orientation, in visual-spatial function and in problem solving ability. There was also a significant reduction in her perseverative tendency. Conclusions: NPH should be considered in patients with dementia, even when there is no gait disturbance. This case suggests that the clinical spectrum of NPH may be broader than previously appreciated, although we can not rule out the coexistence of NPH and AD in this patient. It also underscores the importance of brain imaging in elderly demented patients.

P407
RISPERIDONE IN THE TREATMENT OF ATTENTION-DEFICIT-HYPERACTIVITY DISORDER. A. Oliveros-Cid, A. Oliveros-Juste, C. Guerrero, M. A. Cid, Clinica Universitaria de Navarra, Hospital Miguel Servet, Center "Los Pueyos", Clinic "Montpellier" (Pamplona, Zaragoza, E)

Attention-deficit-hyperactivity disorder (ADHD) is a common but controversial syndrome characterized by developmentally inappropriate hyperactivity, impulsivity, and inattention; it usually begins in childhood. Its diagnosis is currently established on clinical findings. There are three main subtypes of ADHD: the predominantly hyperactive-impulsive type, the predominantly inattentive type and the combined type. The most widespread routine of treatment is based on a multimodal therapy, but the various components of this therapy are mainly dictated by the needs and the complexity of each individual case. Pharmacological treatment (one of those components) is presently under study, due to its limited efficacy and adverse effects. Risperidone, an atypical antipsychotic drug, has been investigated as a treatment for various severe psychiatric disorders in children and adults. Case report: We present an 8 year-old boy with a history of moderate mental retardation, ADHD and escalating behavior suggestive of mania. This child was suffering from a predominantly hyperactive-impulsive ADHD subtype, according to DSM-IV diagnostic criteria (CIE–10:F90.0), in which hyperactivity, irritability and aggressiveness were the main symptoms. Unable to be managed, always frightened, avoiding social contact, stereotyped movements, null fulfillment at school, tendency to destroy things, impossible to be convinced, tendency to avoid responsibilities... were other remarkable symptoms. Once informed, his parents rejected treatment with stimulant drugs.

Results: Previous findings suggest that risperidone – alone or in combination – may be of value in treating children and adolescents with mood disorders and aggressive behavior. In this case we decided to use a low dose of risperidone, focusing in the leading symptoms and the patient and his parents' preferences. In a few weeks the patient showed great improvement in hyperactivity, aggressiveness, irritability and social behavior, with no remarkable adverse effects. He turned into a person able to attend conversations and orders, quiet and flexible, more sociable. His circadian rhythm became steady. His parents showed to be really astonished for this change "from night to day":

Conclusions: Although limited to a single case, this clinical report suggests that risperidone, an atypical neuroleptic with both serotonin- and dopamine-blocking properties, may be effective in the treatment of predominantly hyperactive-impulsive ADHD disorder.

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THE EFFECT OF EXTRAPYRAMIDAL SIGNS ON THE RATE OF CLINICAL PROGRESSION IN ALZHEIMER'S DISEASE. A Pfeffer, M Golebiowski, K Czyzewski, B Wasiak, E Luczywek, M Styczyñska, M Barcikowska, Neurological Dept. CMDiK PAN/MSWiA, Neurological Dept CMDiK PAN/MSWiA, Neurosurg. Dept CMDiK PAN (Warsaw, PL)

It remains unclear whether extrapyramidal signs (EPS) are simply late signs, or may be predictor of more rapid course of Alzheimer's disease (AD). The aim of this study was to determine whether the presence of EPS can influence the rate of cognitive decline in AD. We examined the sample of 100 patients (64 women and 34 men) with probable AD diagnosed according to NINCDS/ADRDA criteria, who were followed up longitudinally for 12 months. The mean age at onset was 68.9 years average illness duration 3.1 years. Patients were divided into two groups, those with EPS (22 persons) and without EPS (78 persons). We determined the rate of disease progression by using Mini Mental State Examination at the initial disease and 12 months later. Statistically significant difference was observed between these two groups, regarding measures of cognitive decline. The patients with EPS progressed more rapidly (4.6 points per year on MMSE). The rate of decline for patients without EPS was slower, at 2.9 point per year on MMSE. No significant differences were for age at onset, duration of illness and severity of dementia at the initial visit. We suggest that presence of EPS is associated with more rapid course of AD.

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THE VESTIBULAR AUTOROTATION TEST IS THE ROUTINE VESTIBULO-OCULAR TEST. D. Alpini, A. Cesarani, A. Hahn, Scientific Institutes. Maria Nascente Don Gnocchi, University Of Sassari, University Of Prague (Milan, Sassari, Prague)

The function of the vestibulo-ocular reflex (VOR) is to stabilize images on the retina during head movements, thereby ensuring maximal visual acuity. It is possible to obtain reliable and quantitative information on vestibular function using a motorised chair, with the subject's head and body fixed. Such testing of VOR has entailed low-frequency rotation stimuli (0.05 to 0.10 Hz). The frequencies elicited by motorised chairs are below those present in most active and passive head movements in everyday activities, which can reach values up to at least 6 Hz. Therefore one has been looking for tests to measure VOR in the higher frequencies range. A recent development is characterised by both active and passive high-frequency head rotation tests. Active Vestibular Autorotation Test (VAT) consists of recording of eye movements during active rotation of the head at different frequencies.

MATERIAL: 1126 outpatients (737 females and 398 males, aged 21 to 76 yy, mean age 56,7 yy) have been recorded in two years. All of them complained of vertigo, both of peripheral and central origin: 135 unilateral Meniere disease (MD), 365 Benign Paroxismal Positional Vertigo (BPPV),135 clinically defined Multiple Sclerosis (MS), 245 Whiplash Injuries (WI), 132 Bilateral Vestibular Hypofunction (BVH), 114 Central Nervous System Vascular diseases (CNS).

METHOD: Toennies Electro-Oculo-Graphic Equipment recorded eye movements. A rate sensor on a helmet releaves head movements. A dedicated software compared head and eyes movements in order to calculate VOR gain and phase. Patients turned actively their head to-and-fro according to a sound pace-maker from low (0.01) to high (3 Hz) frequencies with Eyes open in the Dark (VAT-ED) and in the light Fixating a Target (VAT-FT); VAT was compared to sinusoidal rotation in the dark provided by a motorised Toennies chair (S-VOR) at 0.10 Hz. Data were considered abnormal when they were up 3 times the standard deviations calculated in a normal group (34 males, 65 females, mean age 42,7 yy). Statistical analysis was limited to 3 VAT frequencies: 0.10, 1 and 3Hz.

RESULTS: In MD S-VOR was abnormal in 51 %, while VAT-ED respectively in 21 % at 0.10 Hz, 26 % at 1 Hz, 31 % at 3 Hz, and VAT-FT in 47,5 %, 63 % and 67 %.

In BPPV S-VOR was alterated in 41 %, VAT-ED in 7, 11, 13 % and VAT-FT in 33,38,48 %.

In MS S-VOR was pathological in 56 %, VAT-ED in 28, 42, 63 %; VAT-FT 63, 71, 78 %.

In WI S-VOR releaved VOR abnormalities in 26 %, VAT-ED in 36,78,82 %; VAT-FT in 31, 83, 89 %.

In BVH S-VOR was abnormal in 58 %, VAT-ED in 11, 16, 37 % and VAT-FT in 67, 86, 93 %.

In CNS S-VOR was alterated in 56%, VAT-ED in 16, 53, 71%; VAT-FT in 46, 78, 85%

CONCLUSIONS: VAT is easy, less expensive than motorised chair (20 times less), well tolerated and results have been promising. S-VOR and VAT-ED at low frequency are quite the same while significative differences are present in all patients at medium (1Hz) and high (3 Hz) frequencies. In WI and BVH, the reduced cervical (WI) or labyrinth (BVH) inputs decrease VOR gain. In MS and CNS the central vestibular structures are not able to compensate head movements. In all cases VAT is more sensible than S-VOR in detecting VOR failure.

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ACUTE Q FEVER RHOMBOENCEPHALITIS IN TWO PATIENTS. G. Castelnovo, A. Sotto, B. Biolsi, A. Barbaud, F. Jambon, P. Labauge, Dpt Of Neurology, Dpt Of Medecine Interne, Dpt Of Neurology Chu Montpellier-Nimes (Nimes, Montpellier, F)

Q Fever is a zoonosis with a worldwide distribution caused by Coxiella burnetii. It can produce an acute and chronic infection. Severe headache is the most common neurological manifestation, instead encephalitis it is a very rare complication of this disease. Objectives: Report of two cases of meningoencephalitis as clinical manifestation of Q fever. Observation: We report patients with neurological manifestations of rhomboencephalitis. Serological findings were consistent with acute Q fever. Lumbar puncture revealed a lymphocytis meningitis. Brain magnetic resonance imaging (MRI) was normal. The patients gradually recovered with tetracycline treatment. Discussion: The neurological features of Q fever are rare and headache is the most common manifestation. The focal neurological deficits suggesting an encephalitis were reported. The analysis of cerebrospinal fluid frequently reveals a lymphocytic meningitis. Brain CT scan and MRI usually are normal. Our reports suggest that rhomboencephalitis is a rare complication of acute Q fever. Prognosis could be considered excellent with antimicrobial therapy. Conclusion: Q fever is likely an underestimated cause of infection of nervous system. It should be considered as a possible diagnosis of lymphocytic meningoencephalitis of unknown etiology, even in non-endemic countries.

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OPTIC NEURITIS AND EPSTEIN-BARR VIRUS INFECTION. C. Iñiguez, P. Larrodé, J. Mauri, F. Morales-Asín, Servicio de Neurología (Zaragoza, E)

There is wide belief that monosymptomatic optic neuritis (ON) in young women is usually a first manifestation of Multiple Sclerosis (MS). ON also may be a manifestation of either a collagen disease, a parainfectious syndrome or viral, bacterial or fungal disease.

Objective: Report the clinical features of 3 patients with ON, all of which had serology evidence of a recent Epstein-Barr virus (EBV) infection. One case had a recurrence of ON following new EBV infection.

Patients: Case 1: A 18-year-old woman complained of obscured vision in the right eye (RE) followed by 1 week a flu-like illness. The neurological examination was normal, except for the RE. Corrected visual acuity was 20/30 RE. The right disk was pale. Cranial MRI and blood test were normal including erythrocyte sedimentation rate, serological tests for syphilis, Lyme disease, herpes and CMV. Thyroid function test, antinuclear antibody, complement levels and Rheumatoid Factor were also normal. Proteins content and numbers of cell in the CSF were normal. No oligoclonal bands were found. Visual evoked potentials(VEP) showed prolonged signal latencies in RE. A serum EBV IgG titer was 3.1 and IgM titer was 1. One month later IgG titer was 4.3 with negative IgM. Intravenous Methylprednisone was given for three days. Over the next month her ophthalmic examination became normal. She has had no further neurologic complaints during 18 months of follow-up.

Case 2: A 27-year-old woman complained of decreased vision in her RE. Visual acuity was 20/200 RE. Her right visual field showed a central scotoma. Neurologic examination was otherwise unremarkable. VEP were abnormal. CSF analysis and MRI were normal. Serologic study for EBV was positive in blood. She was treated with high-dose Methylprednisone and vision gradually improved. However 4 months later she developed a new right ON followed by a flu-like illness. A serum EBV IgM titer was 4.4 and 2 months later was negative. Her vision improved after treatment with high-dose methylprednisone. She has had no neurologic symptoms during 24 months follow-up.

Case 3: A 26-year-old woman developed an ON in RE. MRI, CSF and serum findings including oligoclonal bands were unremarked. Serologic study for EBV was positive in blood. She has had no neurologic symptoms during 4 years follow-up.

Discussion: Neurological complications associated with EBV infection, although well described, are rare. Severe neurological complications occurring in fewer than 0.5%. Our 3 patients had ON and laboratory data suggestive of an EBV infection. Although ON is most often a manifestation of MS and frequently it is the presenting symptom, bacterial and viral infection and post vaccination and post viral disease producing an inflammatory process within the optic nerve are encountered. The laboratory evidence and the clinical course in our patients support an EBV aetiology rather than primary demyelination disease as the cause for the ON. No patients had clinical signs suggestive of MS. The response to corticosteroids suggested oedema and inflammation rather than ischaemia as the mechanism of ON. We concluded that ON may occur as a post infection process following recent EBV infection.

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FREEZING OF GAIT IN MULTIPLE SYSTEM ATROPHY (MSA). T. Gurevich, N. Giladi, Movement Disorders Unit (Tel-Aviv, IL)

Freezing of gait (FOG) is a mysterious symptom, observed in different parkinsonian syndromes. It was considered to be a rare symptom in Multiple System Atrophy (MSA) based on database data and literature review of confirmed cases (Giladi et al., 1997). Objective: To asses the frequency of FOG in patients with MSA. Method: We studied the presence of FOG in 28 patients (17 women, 11 men) with clinical diagnosis of MSA, 22 patients with MSA-Parkinsonism (MSA-P) and 6 with MSA-Cerebellar (MSA-C). 21 patients had probable MSA (15 MSA-P and 6 MSA-C) and 7- possible (MSA-P), according to Quinn's criteria. Mean current age was 66.8 ± 10.2 years, mean disease duration 5.2 ± 3.9 years, and mean Hoehn and Yahr stage 3.8 ± 0.8. Patients' clinical diagnosis was based on neurological examination performed by at least two experienced movement disorders specialists as well as on the results of ancillary examinations and course of the disease. The diagnosis was reconfirmed by recent chart review and clinical examination. FOG was assessed by the FOG questionnaire (FOGQ), consisting of 6 subjective questions concerning FOG, with maximal score of 24. The FOG questionnaire was given to all patients at their last office visit or through the phone. Results: 22 patients (80% of total;16 with MSA-P and 6 with MSA-C) were able to walk at the time of the study, 18 of them (60%) experienced FOG. Among 6 currently bedridden patients, 4 reported presence of FOG in the past. FOG appeared in 81% of patients with MSA-P and in 50% patients with MSA-C. Disease duration was about the same among "freezers" and "non-freezers" in the MSA-P group (6.9 vs 7.5 years, respectively), while among the MSA-C it was 5.0 year for "freezers" and 0.8 for "non-freezers". Mean FOGQ total score for MSA-P patients was 13.6 and for MSA-C 10.2. Conclusion: Freezing of gait is a common and disabling symptom in MSA. In MSA-P, FOG was unrelated to disease duration, while in MSA-C it was associated with longer disease duration.

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ACUTE MYOPATHY ASSOCIATED TO ARSENIC INTOXICATION. J. J. Sevilla, M. Garces, F. Mayordomo, J. J. Vilchez, Hospital Universitari La Fe (Valencia, E)

Arsenic toxicity is a known cause of peripheral neuropathy, however the concomitant appearance of an acute myopathy has seldom been reported and it poses a diagnostic challenge. Objective: To report a case of an acute rhabdomyolysis in the course of arsenic intoxication and to present the morphologic features of muscle and nerve biopsy. Case report: A 47 year-old woman with a history of alcohol addiction and depression was under investigation because of a chronic predominantly sensory neuropathy. She was admitted with an acute picture of myalgia, weakens and worsening of the neuropathic symptoms. Laboratory results showed a serum CK > 20.000 U/L, an abnormal hepatic profile and a severe anaemia. Sural nerve biopsy showed a pronounced loss of myelinated fibers with regenerative features as well as acute axonal degeneration. Muscle biopsy manifested necrotic fibers and reinforcement of the oxidative staining. On electronic microscopy appeared aberrant mitochondria, many of them containing liposfuscine-like debris. The picture was initially attributed to alcohol intoxication, however the presence of basophilic spots in cells of bone marrow biopsy lead to think of a metallic exposition. Arsenic level in hair and nail was increased > 30 times the normal values. Conclusions: An acute myopathy may appear as part of the picture of arsenic intoxication. The mechanism may be an acute metabolic failure due to a derangement of the respiratory chain by the toxic.

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CLINICAL COMPUTING IN NEUROLOGY: A SURVEY OF USER PERFORMANCE AND SATISFACTION. W. Swoboda, S. Krafczyk, University of Munich, Neurology (Munich, D)

Introduction. In the last decade Neurology has become a highly technical and computer oriented area of modern medicine. At the Department of Neurology of the University of Munich 90 computers were used for clinical practise: UNIX-workstations as well as personal computers, e. g. Windows- or Macin-

tosh-systems. To support such systems a substantial effort is invested, moreover, without much feedback from the user regarding performance and satisfaction. A structured survey to evaluate these aspects is described.

Method. A structured questionnaire (BOY/OHMANN) was sent to 148 physicians, nurses and secretaries. The questionnaire interrogates different factors around clinical computing, e. g. demographic parameters, frequency of using computers, but especially user performance and satisfaction. All answers arriving within 8 weeks following the mailing were included into the study. 87 questionnaires (59 %) were returned properly completed. 17.4 % of the sample were younger than 30 years old, 60.5 % between 30 and 39 years, 12.8 % between 40 and 49 years, and 9.3 % older than 49 years. The group of responders consisted of 57 % physicians, 8.1 % secretaries, and 34.9 % nurses and others.

Results. 95.4 % of the participants indicated using computers "very often" or "often" at the time of responding. 39.1 % of the sample would use computers "more often in the future than now", only 11.5 percent "less often than now". 73.5 % of the responders requested a computer-based hospital information system (HIS). About 61.4 % of them would use the HIS-system as an electronic medical record system (EMS), the rest also for clinical decision making. The staff interested in this technology mainly expected an increase of quality ($p< 0.01$), more time for the patients ($p=0.05$), and a decrease of costs ($p=0.015$). Without reporting details, the currently installed system for basic documentation received very poor grades. Only 36 % of the sample was trained in using the installed programs. No differences were found over age or profession between the group of trained and untrained people.

Conclusion. Computers are an essential part of working resources in the field of Neurology. Physicians, nurses and secretaries use computers very often, and in the future even more so. According to the users, hospital information systems should increase quality of care, enable more time for clinical care, and decrease costs. Future systems will be more complex, thus necessitating hospital staff to be well-trained. In this regard, the survey revealed a very desolate situation.

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Acknowledgements. We thank Prof. Ohmann and Dr. Boy of the University of Duesseldorf, Germany, for providing the questionnaire.

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DECREASED TRIGEMINAL SENSITIVITY IN ANOSMIA. T. Hummel, H. Gudziol, M. Schubert, Univ. of Dresden Medical School, Univ. of Jena Medical School (Dresden, Jena, D)

Formic acid is a strong stimulant of the trigeminal system. The present study investigated trigeminal detection threshold in healthy controls (n=95) and patients with anosmia due to head trauma (n=24), naso-sinal disease (n=63), or viral infections (n=8). Anosmic subjects exhibited significantly higher thresholds compared with normosmics. No significant differences were found with regard to the cause of the anosmia. These data indicate that a loss of olfactory sensibility in humans produces a decrease of the perception of trigeminal stimuli. Future studies will focus on the localization of the site where this interaction may take place.

Association of HLA type with nervous system disease in systemic lupus erythamatosus R. Pascal, C. Babiuc, O. Pascal, State Medical University (Chisinau, MD)

Nervous system involvement in systemic lupus erythematosus (SLE) are common (18–70 %) and might be serious. The aim of this study was to determine the prevalence and characteristics of neurological manifestation in SLE patients and evaluate HLA type association with nervous system disease in SLE patients. Clinical features and immunogenetics were assessed in 93 SLE patients attending a rheumatology clinic for periods ranging from six months to ten years (mean five years). Five-year survival was 78,9 per cent. Neurological disorders were seen in 58,76 per cent. Migraine (39,4 per cent), peripheral polineuropathy (23,8 per cent), transient ischemic attack (21,2 per cent) and grand mal convulsions (1,3 per cent) were most common clinical neurological features. A range of serological abnormalities was found, including antinuclear antibodies (97 per cent). Tissue typing confirmed the importance of genetic factors by demonstrating significant increases in A1, B8 in SLE patients. The composite phenotype A1, B8 was present in 22 per cent with a relative risk (RR) of 4.11. We found higher frequency of HLA A1A10 (RR – 3,25), HLA A2B6 (RR – 5,01) in patients with neurolupus.

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ASSOCIATION OF HLA TYPE WITH NERVOUS SYSTEM DISEASE IN SYSTEMIC LUPUS ERYTHEMATOSUS. R. Pascal, C. Babiuc, O. Pascal, State Medical University (Chisinau, MD)

Nervous system involvement in systemic lupus erythematosus (SLE) are common (18–70 %) and might be serious. The aim of this study was to determine the prevalence and characteristics of neurological manifestation in SLE patients and evaluate HLA type association with nervous system disease in SLE patients. Clinical features and immunogenetics were assessed in 93 SLE patients attending a rheumatology clinic for periods ranging from six months to ten years (mean five years). Five-year survival was 78,9 per cent. Neurological disorders were seen in 58,76 per cent. Migraine (39,4 per cent), peripheral polineuropathy (23,8 per cent), transient ischemic attack (21,2 per cent) and grand mal convulsions (1,3 per cent) were most common clinical neurological features. A range of serological abnormalities was found, including antinuclear antibodies (97 per cent). Tissue typing confirmed the importance of genetic factors by demonstrating significant increases in A1, B8 in SLE patients. The composite phenotype A1, B8 was present in 22 per cent with a relative risk (RR) of 4.11. We found higher frequency of HLA A1A10 (RR – 3,25), HLA A2B6 (RR – 5,01) in patients with neurolupus.

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NEUROLEPTIC MALIGNANT SYNDROME AFTER "ATYPICAL" ANTIPSYCHOTIC DRUGS. T. Becker, J. Koester, A. Kopf, A. Schulz, A. Wagner, D. Schneider, University of Leipzig (Leipzig, D)

Background: NMS are rare but serious adverse events during treatment with antipsychotics. The frequency of NMS after clozapine or olanzapine is extremely low and often of non-serious nature.

Case report: A 47 year old female patient suffered from paranoid schizophrenia. During treatment with haloperidol given as intramuscular injection she presented with symptoms of anxiety, ideas of poisoning and sleeplessness. 4 weeks after the last injection and 4 days after starting an oral treatment with clozapine she developed high temperature (39,6°C), loss of consciousness, muscle rigidity, vegetative dysfunction and increase in creatine-phosphokinase and myoglobine. Clozapine was immediately discontinued. She was transferred to an intensive care unit and treated with dantamacrine for 5 days and benzodiazepines. After successful treatment of NMS olanzapine (20 mg per day) for 11 months without abnormalities was administered. 5 weeks after olanzapine was discontinued due to non-compliance patient once more suffered from anxiety and delusional ideas. Again, olanzapine was administered to treat psychotic symptoms. 12 days later worsening of psychotic symptoms, high temperature (40,1°C), loss of consciousness, muscle rigidity, vegetative dysfunction and increase in creatine-phosphokinase and myoglobine (80 fold than normal) were noted. Olanzapine was stopped, transfer to a neuro intensive care unit and treatment with electro convulsive therapy for 9 times.

Conclusions: This is the first published case of a patient, who suffered twice from severe, life- threatening NMS after treatment with atypical antipsychotics.

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BACLOFEN IS EFFECTIVE IN INTRACTABLE HICCUPS INDUCED BY BRAINSTEM LESION, BUT NOT IN HICCUPS OF PSYCHOGENIC ORIGIN. C. Boz, M. Ozmenoglu, Z. Alioglu, I. Bulbul, Karadeniz Technical University, Numune Hospital (Trabzon, TR)

Intractable hiccups is a rare occurence but can be debilitating for the patients. We present four cases of intractable hiccups associated with brainstem infarction demonstrated by MRI and clinical findings, and two patients who had been diagnosed as having a psychogenic cause for their hiccups. All patients were treated with many drugs (chlorpromazine, amitriptyline, carbamazepine), but these drugs had failed to solve their hiccup problems. Therefore, these drugs were discontinued and patients were given 5 mg of baclofen by mouth three times per day. In patients with brainstem lesion, hiccups abated within 48 hours in two patients, and ceased in another two patients. In two patients with psychogenic causes, baclofen was unsuccessful in controling the hiccups, even in doses 45 mg per day.

In patients with brainstem lesion, stopping baclofen therapy after 4–6 weeks without hiccups resulted in a recurrence of symptoms within 48 hours in three patients. In one patient hiccup did not return. Reinstitution of 5 mg baclofen three times per day eliminated hiccups again.

We suggest that baclofen should be considered the drug of choice for treating persistent hiccups induced by brainstem lesion because of its desirable side effects and success rate compared with other drugs used in treatment.

reduced MTR and an attenuated NAA/Cr ratio. In microangiopathic white matter lesions the ADC was increased, MTR unchanged or slightly decreased and spectroscopic spectra without consistent changes. In acute stroke, ADC, MTR, NAA/Cr and Cho/Cr all were reduced. In leukodystrophy, ADC was markedly increased, MTR and NAA/Cr reduced and Cho/Cr unchanged. Conclusion: The combination of calculated ADC and MTR maps together with 1H-spectroscopic information on cerebral metabolites provides differential patterns of brain lesions allowing a better insight into the underlying pathophysiology.

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APOLIPOPROTEIN E GENOTYPES INFLUENCE THE VULNERABILITY OF THE HUMAN BRAIN TO THE EFFECTS OF ALZHEIMER'S AND WILSON'S DISEASE AS WELL AS RELAPSING-REMITTING MULTIPLE SCLEROSIS AND HYPOXIC BRAIN DAMAGE AFTER CARDIAC ARREST. H. Kollegger, M. Schiefermeier, C. Schwarz, B. Kornek, M. Bachner, L. Deecke, University of Vienna (Vienna, A)

Background: Apolipoprotein E (ApoE) is necessary to maintain the physical integrity of biological membranes and is synthesized in three isoforms mainly in the liver but also in astrocytes after central nervous insults. ApoE genotypes may occur as homozygous (e2/2, e3/3, e4/4) or heterozygous (e2/3, e2/4, e3/4) variants. There is evidence that ApoE genotypes alter the risk of patients to develop certain neurological disorders and influence the time course and the severity of their clinical evolution.

Aim: Since it is known that the ApoE allele e4 increases the risk of patients to develop Alzheimer's dementia (AD) we attempted to confirm this hypothesis in 32 Austrian AD patients and investigated whether ApoE genotypes influence the vulnerability of the human brain to the effects of Wilson's disease (WD), multiple sclerosis (MS) and hypoxic brain damage after cardiac arrest (BDCA).

Patients and methods: Three hundred and three patients with AD (32), WD (121), MS (70) and BDCA (80) were investigated clinically, their ApoE genotypes were determined using PCR and the genotype distribution in each group of patients was compared to that in 280 healthy European control subjects. In WD patients, the H1069Q mutation status (most common mutation) was determined and the age at onset of neurological or hepatic symptoms was correlated with the distribution of ApoE genotypes. For statistical analysis, Student's t-test, chi square analysis of contingency tables (nominal variables) or factorial analysis of variance with Tukey's honestly significant difference were used.

Results: The ApoE genotype distribution in patients with AD was found to deviate significantly from that in age-matched healthy controls (the ApoE e4 allele was found in 53% of AD patients but in only 21% of healthy controls; P=0.001).

In WD patients, the ApoE genotype distribution did not deviate from known distributions in control subjects. Within the group of H1069Q-homozygous WD patients (N=40), the onset of neurological and hepatic symptoms was significantly delayed in patients with the ApoE e3/3 genotype (25±6 years) compared to patients with the ApoE e3/4 genotype (20±3 years at presentation).

In MS patients with a relapsing-remitting disease course, the progression index (EDSS score/duration of disease in years) was significantly lower in patients with the ApoE e3/3 genotype (0.29) than in patients with the ApoE e3/4 genotype (0.47; P=0.04). The relapse frequency/year was 0.87 in MS patients with the ApoE e3/3 genotype and 1.38 in patients with the ApoE e3/4 genotype (P=0.021).

In BDCA patients, the mortality rate was 36% in patients with the ApoE e3/3 genotype (67% ApoE non e3/3; P=0.007). A poor neurological outcome 12 months after cardiac arrest was found in 45% of patients with the ApoE e3/3 genotype (73% ApoE non e3/3; P=0.013).

Conclusions: Our results confirm that the ApoE e4 allele is overrepresented in patients with AD and demonstrate that the ApoE genotype e3/3 delays the onset of symptoms in patients with WD, reduces clinical disease progression and relapse frequency in MS patients and reduces the mortality rate and poor neurological outcome in patients after cardiac arrest. The greater antioxidant and membrane stabilizing properties of the ApoE 3 protein in comparison to other ApoE proteins might be responsible for the reduced vulnerability of the human brain to the effects of several neurological disorders.

Multiple sclerosis

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GLOBAL VS. LOCAL DIFFUSION ANISOTROPY IN THE ASSESSMENT OF MS LESIONS. R. Bammer, M. Augustin, T. Seifert, P. Kapeller, S. Strasser-Fuchs, H.-P. Hartung, F. Fazekas, Karl-Franzens University Graz (Graz, A)

INTRODUCTION: Measures of tissue matrix integrity including the preservation of focal fiber tract organization may be markers which better reflect the underlying acute and chronic pathology in Multiple Sclerosis (MS) and can be assessed by Diffusion Tensor Imaging [DTI]. DTI allows to derive the diffusion anisotropy which can be expressed as fractional anisotropy [FA]. So far, FA values of MS plaques have been analyzed in absolute terms only. However, normal regional varieties of FA from density and direction of fiber tracts should strongly influence such measurements, and are likely to limit the usefulness of this approach. Thus, region-related relative FA measurements of different types of MS lesions were compared with results of absolute FA analysis in terms of lesion discrimination. METHODS: DTI was carried out in both volunteers (n=9) and MS patients (10 women and 4 men; 36.2 ± 10.1 years; range 21 to 51 years) with clinically definite MS. All patients suffered from a relapsing-remitting course and had an Expanded Disability Status Scale (EDSS) score ranging from 1.0 to 5.0. Lesion FA was analyzed both in an absolute fashion and relative to adjacent normal-appearing tissue. The lesions were grouped according to their appearance on conventional sequences. We assessed healthy white matter (HWM) (n=273) as well as acute and non-acute focal lesions. Focal non-acute lesions were subdivided according to their intensity on T1-weighted images as T1-isointense (n=48) or T1-hypointense (n=121). Acute lesions were subdivided into densely enhancing lesions (n=15) and ring enhancing lesions (n=8). Ill-defined signal hyperintensity around enhancing lesions, which disappeared on follow-up scans, was considered to be edema (n=6). For statistical analysis the Kruskal-Wallis-ANOVA, and the non-parametric Mann-Whitney U test was employed. RESULTS and DISCUSSION: A similar trend of calculated FA value was found in both types of analysis with a reduction of FA being most pronounced in ring enhancing and T1-hypointense lesions. However, in measurements based on absolute terms there is a markedly greater overlap between lesion types and HWM than for relative FA measurements. Overall, absolute measures of global diffusion anisotropy are compromised by a wide range of normal values of FA and will be less specific for detecting pathologic changes. This was the reason why we related our FA measurements to corresponding values in the supposedly normal vicinity of that particular lesion. This approach largely compensates for the normal variation of diffusion anisotropy due to regional differences in brain architecture and thus allows to increase the sensitivity of measurements for pathologic changes. Employing this method, we found significant differences in FA values for different types of MS lesions, although only subtle absolute FA changes were recorded.

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ABNORMAL UBIQUITINATION OF THE APPARENTLY NORMAL WHITE MATTER IN MULTIPLE SCLEROSIS BRAINS. M. Giordana, P. Richiardi, E. Trevisan, University Of Turin (Turin, I)

The occurrence of axonal changes and loss in the lesions of ms is a recently emphasized event. few is known about the pathological basis of the abnormalities detected by magnetic resonance spectroscopy in the apparently normal white matter. we have investigated the immunoreactivity for ubiquitin (ubq), a sensitive method for detecting axonal dystrophy in six autoptic cases of ms (age 39–66) and six cases of age matched patients. tissue blocks had been fixed in formalin and embedded in paraffin. anti-ubq mab (1:5000, chemicon), anti-phosphorilated neurofilaments mab (smi–31, 1:800, sternberger) have been used. bodian and luxol fast blue (lfb) have been performed. the plaques were subdivided into active and non-active lesions, according to the presence of lfb inclusions in macrophages, indicating ongoing demyelination. bodian and smi–31 showed constantly the presence of axons in the lesions. the axonal network inside the plaques was looser than outside. occasional granular immunoreactivity for ubiquitin was found in actively demyelinating lesions, while no reactivity was present in non-active plaques. in the myelinated white matter surrounding the plaques, dense granular deposits of ubq were found both in proximity and distant from the plaque edge. the immunoelectron microscopic study showed that ubq-deposits were localized in the axonal compartment. no similar staining was found in control brains. ubiquitination is the first step of a non-lysosomal degradation pathway of proteins. the present findings suggest a derangement of this proteolytic pathway in the axons outside the plaques, and confirm that axons inside the plaques are damaged. the spectrum of axonal changes in ms seems to be wider than expected and involves the apparently normal white matter.

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INHIBITION OF LYMPHOCYTE HOMING INTO THE BRAIN PARENCHYMA BY VACCINATION WITH CD44 CDNA: A NEW THERAPEUTIC APPROACH FOR EAE AND MS. D. Karussis, A. Rubinstein, T. Garin, N. Grigoriadis, R. Mizrachi-Koll, O. Abramsky, D. Naor, Hadassah Hospital (Jerusalem, IL)

EAE in an autoimmune model of CNS inflammation and demyelination, which serves as a model of the acute/inflammatory stage of multiple sclerosis (MS). CD44 is a lymphocyte surface molecule which functions as an hyaluronic acid receptor and therefore is implicated in lymphocyte homing and trafficking through the vasculature and extracellular matrix. Variant isoforms of CD44, especially those containing the V6 and the V10 were found to be significantly associated with the metastatic potential of tumor cells and the migration potential of autoimmune cells in experimental models. Inhibition of both CD44 and L-selectin was recently reported to suppress EAE. cDNA vaccination may induce the production of anti-CD44 antibodies and therefore, secondarily suppress EAE.

We examined the effect of CD44 cDNA vaccination on experimental autoimmune encephalomyelitis (EAE). We vaccinated SJL/J mice with cDNA of sCD44 and of vCD44 (standard and variant isoforms) twice, on days –20 and +3. On day 0, EAE was induced with mouse spinal cord homogenate (MSCH) and adjuvant (CFA) together with pertussis injections. Vaccinated animals developed significantly less severe EAE; this suppression was more prominent in mice vaccinated with the CD44 variant cDNA (incidence: 7/11 in vaccinated mice vs 11/13 in the control group; mortality: 1/13 vs 9/13, in two separate experiments). The in vitro proliferations of lymphocytes were only marginally suppressed in the successfully treated animals. Our data indicate that treatment with CD44 cDNA vaccination suppresses EAE and the main mechanism of action involves inhibition of the migration of lymphocytes through the extracellular matrix and less through downregulation of the peripheral activation of lymphocytes.

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BRAIN ATROPHY MEASUREMENTS IN MULTIPLE SCLEROSIS; INTRA- AND INTER-OBSERVER REPRODUCIBILITY OF 2 METHODS. N. Kalkers, E. Bergers, J. Castelijns, C. Polman, F. Barkhof, AZVU (Amsterdam, NL)

Introduction: Due to the poor correlation between the volume of multiple sclerosis (MS) lesions on magnetic resonance imaging (MRI) and clinical parameters, new predictive quantitative measurements are currently studied. One of these new measurements, brain atrophy measurement, shows promising results in correlation with clinical parameters. However, there are several ways to measure brain atrophy. Parenchymal volume and ventricular volume measurements are being used separately, but nowadays the whole brain parenchym- to intracranial volume ratio is more commonly applied. The aim of this study is to give methodological support to brain atrophy measurement by 2 computer programs.

Methods: Axial, 3 mm thick, T1 (600/15/2) and T2 (4500/45–90/1)-weighted MR images, performed at 1.0 T, of 16 patients were analyzed. The volumes of whole brain parenchyma, ventricles and intracranial volume were measured by using a home-developed semi-automated seed growing software (Show Images) and Quanta (De Carli et al. 1992), an automated segmentation computer program which automatically determines an accurate threshold for separation of brain matter and liquor on T1-weighted images. Using the seed-growing method, the ventricular and parenchymal volumes were measured on T1-weighted images and inracranial volume was measured on T2-weighted images. Specified definitions were used for lateral, third and fourth ventricle measurements. All measurements were done twice by one observer (with a two-week interval) and once by another observer to calculate intra- and inter-observer reproducibility.

Results: For the seed-growing method, the different volumes of the ventricles were highly reproducible (correlation coefficient [r] range 0.92–0.99 for intra-observer, 0.84–0.99 for inter- observer). For Quanta the total ventricular volume was also highly reproducible (r= 0.46- 0.95 intra- observer and 0.77–0.99 inter-observer), inspite of the lower correlation of the third and fourth ventricles, due to different interpretations of the definitions of the borders of these ventricles. Measurements of parenchymal volume and intracranial volume were highly reproducible for both methods (for seed-growing intra-observer: 0.97–0.98, inter-observer: 0.84–0.96, for Quanta intra- observer 0.88–0.99 and inter- observer 0.94–0.99). Ratios between brain parenchyma and skull volume were highly reproducible with correlation coefficients ranging from 0.89 to 0.98.

Discussion: In this study we show that two different methods for measuring total ventricular volume, whole brain parenchyma and intracranial volume are highly reproducible. Only the third and fourth ventricle measurements were less reproducible with the Quanta method. Furthermore, due to a long preprocessing time necessary for Quanta, this method is more time consuming than the seed growing method.

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AUTOLOGOUS STEM CELL TRANSPLANTATION IN MULTIPLE SCLEROSIS: EARLY RESULTS IN TWO CASES. C. Gasperini, V. Zoli, S. Galgani, E. Onesti, A. De Laurenzi, G. Piazza, S Camillo-Forlanini Hospital (Rome, I)

The unsatisfactory results obtained with conventional immunosuppressive treatment in Multiple Sclerosis (MS) have been in part explained by the non complete eradication of T and B cells reacting against neural antigens. Myeloblative therapy imports a profound immunosuppression and could potentially lead to the destruction of all autoreactive T and B cells; the reconstitution of a "new" immune system via the hemopoietic stem cell graft may result in a long-lasting or even persistent remission of the disease. Based on animal model and clinical observations autologous stem cell transplantation may be an effective therapy for several autoimmune diseases. Phase II studies with different conditioning regimens have been initiated worldwide to evaluate if autologous stem cell transplantation can halt disease progression in MS patients.

We selected two patients by predefinite criteria: definite MS according to Poser's criteria, an EDSS between 4 and 7, a significant progression of disability in the year prior to inclusion, no response to standard therapy, at least one enhancing lesion on MRI.

In all two patients the transplantation procedure has been completed. All patients suffered from general malaise. Slight liver function disturbance and mucositis were observed. There were no serious infections. Current follow-up is between 1 and 8 months. While the baseline MRI showed respectively 11 and 9 enhancing lesions, on the MRI after transplantation no active lesions were detected. No difference on EDSS was observed.

We conclude that autologous stem cell transplantation for MS can be performed safely with acceptable toxicity. However, for the evaluation of effectiveness, we need a longer follow-up period, comparison of results with other centres and finally randomised studies.

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SERUM CILIARY NEUROTROPHIC FACTOR (S-CNTF) IN MULTIPLE SCLEROSIS (MS). S. Merkelbach, C. Kölmel, M. Klotz, M. Müller, F. Blaes, University Hospital (Homburg / Saar, D)

Background: CNTF, a trophic factor, protects oligodendrocytes and acts as a cell survival factor suggesting a possible role in diseases involving de- and remyelination.

Patients and methods: We measured S-CNTF using an enzyme-linked immuno-sorbent assay in 66 patients with definite MS (mean age 37±8 years) and 35 controls (35±11 years). Basic disease parameters such as Kurtzke-score (EDSS), duration of disease, latency to last relapses, and progression index (PI) were determined.

Results: S-CNTF was significantly increased in MS (11.2±9.1 pg/ml) as compared to controls (5.8±6.3 pg/ml; $p< 0.0001$). In relapsing-remitting MS (n=45), S-CNTF was not correlated to age, EDSS, duration of disease, or latency of last relapses (correlation coefficients ranging from 0.08 to 0.29). However, a significant relationship was found between S-CNTF and PI (r=–0.49; $p< 0.02$).

Conclusion: The results demonstrate, that increased S-CNTF can be found in MS. Our results do not suggest a correlation between S-CNTF and the current clinical condition (expressed as EDSS), but the correlation between S-CNTF and PI might indicate a function of S-CNTF as a marker of disease progression corresponding to repair mechanisms.

P435
COMPARISON OF THE EFFICACY OF TWO THERAPIES IN THE FLU-LIKE SYMPTOMS INDUCED BY INTERFERON BETA 1-A (AVONEX), AT THE WEEKLY DOSE OF 30 µG IM, IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS. C. Belin, V. Sallerin, Avicenne Hospital, BIOGEN (Bobigny, Nanterre Cedex, F)

This multicenter, open, randomized, comparative, 2 parallel arms study assessed the efficacy of paracetamol (1000 mg po t. i. d.), ibuprofen (400 mg/ po t. i. d.) in the flu-like symptoms (FLS) induced by the first injection of Interferon beta 1-a (Avonex) in relapsing remitting multiple sclerosis patients. At screening, patients were administered one first IM injection of 30 µg of Avonex and paracetamol for 48 hours (3000 mg/d po for the first 24 hours, 2000 to 3000 mg/d po for the following 24 hours). Their FLS score (from 0 to 8) was then assessed (fever, chills, malaise, sweats and myalgia). Patients with a FLS score > 2, were treated with Avonex for 3 weeks and randomized in one of the two groups. A third arm (pentoxifylline, 1200 mg/d po) was initially planned, but cancelled by an amendment due to poor recruitment. Overall, 607 patients (73.6% women), aged 38±9 years, were screened, 302 randomized patients

completed the study, 125 in the paracetamol group, 121 in the ibuprofen group (56 had been entered in the pentoxifylline group). After the 1st injection of Avonex at screening, 284 patients (47.9%) responding to paracetamol were not randomised. Efficacy analysis showed no statistical difference between both therapies. The FLS total score (sum of FLS score following 2nd, 3rd and 4th injections) at 3 weeks was 8.68 in the paracetamol group and 8.41 in the ibuprofen group (p = 0,569). There was no difference in the occurrence of any the 5 symptoms assessed in the FLS nor in the emergence of the other symptoms systematically assessed (headaches, asthenia and nausea) in both groups. Patient global discomfort associated to the FLS (measured on a 4 level scale) in both groups at study end-point was moderate to severe in 35.9% of the patients and null to mild in 64.1%. Patients mean global satisfaction (measured on Visual Analog Scale) was higher than 60% for both therapies. Association of both treatments with Avonex was well tolerated, 55/593 of the treated patients (9.3%) experienced light to moderate adverse events, mostly digestive, skin and visual disorders. In conclusion, this study highlights the importance of an early management of the flu-like symptoms as 47.9% of the patients treated by Avonex who received appropriate therapy from the first injection had a low FLS score. No difference in efficacy between paracetamol and ibuprofen in flu-like symptoms management: FLS score, patients global discomfort and global satisfaction were comparable. Flu-like symptoms induced by interferon beta 1-a may be considered as well controlled by first line therapy in more than 60% of the patients.

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EXPRESSIONS AND MODULATION OF SPECIFIC NON-ELR CXC CHEMOKINES IN HUMAN BRAIN ENDOTHELIUM AND ASTROCYTES. M. de Rossi, M. Gelati, A. Dufour, E. Corsini, S. Pagano, E. Ciusani, A. Salmaggi, Ospedale (Milano, I)

Chemokines specific for activated T lymphocytes play a crucial role in the pathogenesis of multiple sclerosis (MS); nevertheless, their cellular source within the brain is still poorly defined. We investigate the gene expression by reverse transcriptase polymerase chain reaction (RT-PCR) and the release by enzyme-linked immunosorbent assay (ELISA) of non-ELR (Glu-Leu-Arg) Cys X-Cys (CXC) chemokines IFN-induced protein of l0kDa (IP–10), monokine induced by IFN gamma (Mig) and IFN-inducible T-cell a-chemoattractant (I-TAC) (only gene expression) by human brain endothelial cells (HBECs), human umbilical vein endothelial cells (HUVECs) and human astrocytes in basal conditions and after stimulation with dexamethasone, IL–1 beta (-'I00U/ml)- IL–10 (50no/ml)- IFN-gamma (200U/ml); TNF-alpha (200U/ml): IFN-gamma (200U/ml) + dexamethasone (20 gg/ml)-, IFN-gamma (200U/ml) + IL–1 beta (200U/ml), IFNgamma (200U/ml) + IL–10 (50ng/ml); IFN-gamma (200U/ml) + TNF-alpha (200U/ml). A Th2type cytokine (IL- 10) and dexamethasone (Dex) were studied, alone or in combination as possible inhibitorv factors. Single inflammatory stimuli induced chemokines in human umbelical vein endothelial cells (HUVECs) and astrocyte more than in HBECs. A strong synergistic effect was detected with the combination of IFN-gamma plus TNF-alpha and IFN-gamma plus IL-I beta in HBECs. RT-PCR and the home-made performed ELISA positively correlated, showing a potential role of HBECs in the recruitment of activated Th–1 cells during inflammation or/and in the presence of pro-inflammatory cytokines. Supernatants from IFN-gamma stimulated HUVECs induced chemotaxis of activated lymphocytes, which was partly antagonised by anti-IP–10 and anti-Mig. Biological activities of IFN-gamma stimulated HUVECs supernatants were investigated in order to check whether HUVECs derived Mig and IP–10 also had a chemotactic activity, indeed HUVECs-derived supernatants, after stimulation for 24 hours with IFN-gamma (500U/ml), induce chemotaxis of T lymphocytes activated for 10 days with IL–2 (200U/ml). The IL–2 treatment allowed the expression of the CXCR-J receptor on the surface of T lymphocytes with a percentage of 62%; T cells were layered over IFN-gamma (200U/ml for 24 hours)-stimulated Havocs stratified over a collagen gel in the presence of medium alone, rabbit anti-IP–1 0 or rabbit anti-Mi, polyclonal antibodies. The adhesion/transmigration experiment was performed according to Pietschmann and celis were stained with CD45 monoclonal antibody and counted. The cheniolactic activity of supernatants of IFN-gamiiia stimulated HUVECs was partly reduced by thenetitralizinu, effect of anti-Mig and anti IP–1 0 antibodies; the inhibition affected both transmigration and adhesion. Concerning the combination of IFN-ganiiiia with inhibitory factors wefound illat IL-] 0 and deämethasone could downregulate the expression of the recently cloned I-TAC only in human astrocytes, even if we provide only preliminary gene expression data as far as 1-TAC is concerned. Overall. our data highlight the possibly active role of HBECs (together with astrocytes) in the release of cytokines/chemokines and support further research aimed at modulating this release in experimental and human diseases.

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THE RELATIONSHIP BETWEEN FOCAL INFLAMMATION AND AXONAL DAMAGE IN EARLY RELAPSING REMITTING MULTIPLE SCLEROSIS: A CROSS-SECTIONAL MAGNETIC RESONANCE SPECTROSCOPIC IMAGING STUDY. D. T. Chard, P. Kapeller, M. A. McLean, C. M. Griffin, A. J. Thompson, D. H. Miller, Institute of Neurology (London, UK)

Proton magnetic resonance spectroscopic imaging (1H-MRSI) provides evidence for axonal damage and loss in both lesions and normal appearing white matter in multiple sclerosis (MS) subjects as shown by lower concentrations of the neuronal marker N-acetyl-aspartate (NAA) compared to normal controls. The relationship of this process to focal inflammation is unclear, and is explored in this cross-sectional study of 18 subjects with early and mild relapsing remitting MS (less than 3 years from symptom onset, EDSS less than 3) and 14 age matched normal controls. Single 1.5cm thick axial 1H-MRSI slices (individual voxel volume 2.34 ml) of volumes of tissue spanning the inter-hemispheric fissure, immediately superior to the lateral ventricles were studied. NAA was quantified using LC Model, producing results for a series of voxels over the volume of tissue under study. This data was combined with tissue segmentation values from a T1 weighted 3D FSPGR image automatically processed through SPM96b, so that for each 1H-MRSI voxel there was an estimate of percentage of white matter (WM), grey matter (GM), and CSF along with NAA concentration. For each subject a mean tissue NAA was calculated (an average of 33 voxels used per subject, mean voxel tissue segmentation values: WM 60%, GM 33%, CSF 5%, unclassified 2%), and a mean WM NAA (by selection of voxels containing less than 20% CSF and greater than 80% WM, yielding an average of 10 voxels per subject, mean voxel tissue segmentation values: mean WM 89%, GM 10%, CSF 0%, unclassified 1%). In subjects with MS, T1 weighted images of the brain were acquired following administration of triple dose gadolinium (Gd), and a count was made of enhancing lesions in order to quantify focal inflammation. The average tissue and WM NAA in normal controls was compared with MS subjects and found to be significantly higher (t-test $p< 0.01$). Subdividing MS subjects into two groups, those with either a single or no Gd enhancing lesions (10 subjects, median 1 lesion), and those with more than 1 (8 subjects, median 3.5 lesions, range 2 to 9), no significant difference was seen. This preliminary data showed no strong relationship between focal inflammation and diffuse axonal damage in early relapsing remitting MS. While this may indicate that these processes develop in part by independent mechanisms, longitudinal studies of a larger cohort will be required to fully clarify the relationship between focal inflammation and axonal damage and loss.

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PATTERNS OF CEREBROSPINAL FLUID CYTOLOGY IN MULTIPLE SCLEROSIS. S. Cepok, M. Jacobsen, S. Schock, B. Tackenberg, R. Gaber, S. Jaekel, W.-H. Oertel, N. Sommer, B. Hemmer (Marburg, D)

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system. Although the cause of MS is unknown, it is believed that the disease is mediated by a dysregulated immune response against brain resident antigens on the basis of a complex genetic trait. However, the clinical course of MS is highly variable indicating that different disease subtypes may exist. Brain histopathology in MS has supported this notion by disclosing different histological subtypes characterized by the patterns of cellular infiltrates, antibody deposition and cellular damage. Since brain tissue can not be accessed in the majority of MS patients, we investigated CSF proteins and cellular compartments to determine whether different patient subgroups can be stratified according to their pattern of CSF pathology. CSF of 80 well characterized MS patients was analyzed by nephelometry for its protein and by four-color flow cytometry for its cellular compartment. Using a variety of immune cell surface markers we found at least three patterns of CSF pathology. The first subtype ("B cell dominant") was characterized by a higher percentage of B cells and plasma cells, intrathecal IgG synthesis and low numbers of monocytes and NK-like T cells. The second subgroup ("monocyte dominant") showed higher numbers of monocytes and NK-like T cells, low numbers of B cells and no intrathecal IgG synthesis. The third group ("intermediate type") was characterized by similar numbers of monocytes and B cells. The patterns were stable over time in individual patients. Preliminary results indicate a lower disease activity with relatively mild progression in MS patients with a "monocyte dominant" CSF pattern compared to those with a "B cell dominant" CSF pattern. Further studies will have to relate those findings to brain pathology, disease course and MRI findings in MS. Our findings suggest that different MS subtypes may not only be reflected by different brain pathology but also specific CSF findings.

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THE POSSIBLE ROLE OF ENDOTHELIUM IN T-CELL APOPTOSIS IN CHRONIC RELAPSING EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS. I. Milonas, N. Grigoriadis, D. Karussis, O. Abramsky, AHEPA Univ Hosp, Hadassah Univ Hosp (Thessaloniki, GR; Jerusalem, IL)

Experimental Allergic Encephalomyelitis (EAE) is an autoimmune demyelinating disorder of the Central Nervous System (CNS) induced in susceptible animals as a model for the human disease multiple sclerosis. Elimination of T-cells by apoptosis appears to play an important role in the down-regulation of acute EAE. Several lines of evidence indicate that, even though apoptotic cells are distributed within the CNS parenchyma, only a limited number is present in the perivascular cuffs.

The distribution of apoptotic inflammatory cells in chronic relapsing EAE (CR-EAE) was studied here. CR-EAE was induced in 15 Lewis rats by inoculation of rat whole spinal cord homogenate and subcutaneous injections of cyclosporine-A (4 mg/Kg body weight) on alternate days until 22 days post in oculation (DPI). Cells undergoing apoptosis were detected by terminal deoxynucleotidyl transferase mediated dUTP nick end-labeling (TUNEL) in longitudinal paraffin embedded spinal cord serial sections. Apoptotic cells were counted, drawn and photographed. Their distributional pattern was evaluated according a grading density scale.

All animals exhibited a first relapse on 14–16 DPI and 5 of them were sacrificed that moment. Seven out of the rest 10 animals presented a second relapse, commencing on 24–26 DPI and were sacrificed during that time. In all the first relapse group animals, apoptotic cells were found to be distributed within the meninges, the white matter and perivascular areas of spinal cord parenchyma. Less apoptotic cells were encountered in animals that presented a second relapse. Yet, few apoptotic cells were additionally found to be attached on the endothelium of some vessels, in 4 animals of this group.

Overall, the above findings suggest that, apart from the established mechanism in which apoptosis is induced after the influx of activated T-cells within CNS parenchyma, and their interaction with reactive brain cells (i. e. astrocytes or microglia), endothelium may play a role in the apoptotic elimination of activated T-cells. The above suggested mechanism applies at least in our chronic EAE model in Lewis rats.

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EFFECTS OF INTERFERON BETA–1A ON GENES EXPRESSION BY USING DNA ARRAYS. B. Weinstock-Guttman, M. Ramanathan, L. Nguyen, L. Jacobs, State University of New York at Buffalo (Buffalo, NY, USA)

Objectives: To identify specific patterns of gene expression changes induced by interferon (IFN)-beta therapy in patients with multiple sclerosis (MS) using DNA array technology.

Background: MS is considered an inflammatory autoimmune disease of the central nervous system. Recombinant IFN beta therapy has been shown to have a significant positive impact on MS disease course. However, IFN beta does not represent the cure for MS and its exact mechanisms of action are incompletely understood. DNA array technology represents a new technique able to provide exhaustive pattern of simultaneous gene expression. In this study we used DNA arrays to examine short-term effects of IFN beta–1a on large-scale gene expression changes in monocyte-depleted peripheral blood mononuclear cells (PBMC) from MS patients.

Methods: Informed consent was obtained for this study from patients with a relapsing remitting definite MS (RRMS) deemed appropriate for interferon therapy. Total RNA was isolated from monocytes-depleted PBMC before and 24 hours after first intramuscular (IM) injection of 30mcg IFN beta–1a (Avonex). The mRNA was reverse transcribed to radiolabeled cDNA and the resultant cDNA was used to probe a DNA array, specifically GeneFilters GF211 (Research Genetics Inc. Huntsville, AL). This DNA array contains over 5000 known human genes. Path files were created to facilitate analysis of genes of interest. The binding of radiolabeled cDNA to probes on the array was measured using a phosphorimager. Statistical analysis using a paired t-test was used to determine the effects of IFN-beta therapy (% of mean change).

Results: Fourteen patients with RRMS (10 females and 4 males) mean age 42.2 yrs (SD 9.23yrs) participated in the study. IFN therapy significantly ($p< 0.05$) upregulated the expression of interleukin–10 (IL–10) receptor (26%), transforming growth factor beta (11%) and colony stimulating factor–3 receptor (CSF, 26%). A significant downregulation was seen for tumor necrosis factor receptor 2 (23%), lymphotoxin alpha (22%), lymphotoxin-beta-receptor precursor (26%). A significant upregulation of certain adhesion molecules (ICAM–1, CD58, integrin beta 3 (CD61), integrin alpha 4b(CD49D), CD 31 antigen, integrin alpha M (CD11b)), and downregulation of other adhesion molecules (CD 1C, integrin beta 1 (CD 29), laminin receptor and integrin beta 2 (CD18) were seen at 24 hours. Significant upregulation changes were also seen on mRNAs for beta–2-microglobulin precursor, immunoglobulin gamma 3 (Gm marker) while T cell surface glycoprotein CD5 precursor, proliferating cell nucleolar antigen p120 and CD81 antigen mRNA were shown to be downregulated after therapy.

Conclusions: Our study showed significant changes in the expression of several cytokines, adhesion molecules and immunological factors 24 hours after IFN beta IM therapy. The capabilities of DNA arrays may prove useful for monitoring the effects of IFN beta on gene expression, thereby helping understand its mechanisms of action and elucidate the nature of differences seen in clinical response to IFN therapy.

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CYTOKINE FLOW CYTOMETRY IN PATIENTS WITH MULTIPLE SCLEROSIS (MS). VARIATIONS WITH BETA INTERFERON TREATMENT. P. de Castro, M. Otano, M. Morel, A. Sanchez Ibarrola, Clínica Universitaria de Navarra (Pamplona, E)

Background: In previous studies we have examined intracellular cytokines in peripheral blood mononuclear cells (PBMC) of MS patients, by using flow cytometry (cytokine flow cytometry). MS patients without treatment showed an increased number of cells producing total interferon gamma (CD4+ and CD8+) in comparison to the controls.

Objective: to find out the production of Interferon gamma is modified by betainterferon treatment.

Patients and method: 40 clinically-definite MS patients. Mean age: 42 years (rank 22–65). Mean EDSS: 2 (rank 0–6). Mean time evolution: 11 years (rank 0,5–22). Twenty with and 20 without treatment. Twenty, age and sex matched, controls. Determination of cells producing Inf-Y and IL4 after activation with phorbol $^1/_2$ myristate 13- acetate and ionomycin.

Results: the amount of cells, CD4+ and CD8+, producing gamma interferon is increased in MS patients, with and without treatment compared to the controls ($P< 0.0001$ and $P< 0,0005$ respectively). There is not any significant difference in CD4+ cells producing gammainterferon, and CD4+ as CD8 producing IL4, between treated and no treated MS patients. The amount of CD8+ cells producing Interferon was decreased in patients treated with Betainterferon ($p< 0,0001$) compared to the treated patients.

Conclusion: The amount of cells CD4 producing gamma interferon is significally increased in MS patients compared to the controls. But the amount of cells producing Gammainterferon CD8+ is decreased in treated patients compared to untreated patients. There is not any significant difference between the production of IL4 in the three groups of patients.

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MTR IN MULTIPLE SCLEROSIS – WHAT TO MEASURE: WHOLE BRAIN TISSUE VERSUS NORMAL APPEARING WHITE MATTER. M. Sailer, N. Bodammer, T. Eckert, C. Tempelmann, H. Hinrichs, H.-J. Heinze, Otto-von-Guericke University (Magdeburg, D)

Calculation of magnetisation transfer ratio (MTR) is an appropriate method to study the integrity of the brain tissue (BT) in patients with multiple sclerosis (MS). However, different methods of analysis were employed including an analysis of regions of interest, calculation of MTR from the whole brain tissue, the measurement of the white matter and the use of different MTR cut of points 1,2,3. In this study we compared the quantitative histogram analysis of the:

whole BT (WBT): (cortex, white matter and lesions)

normal appearing BT (NABT): (cortex and white matter) normal appearing white matter (NAWM): (white matter).

Methods: We investigated 64 subjects (15 normal age-matched controls) and 49 patients with clinical definite MS (20 relapsing remitting RR, 17 secondary progressive SP, and 12 primary progressive PP type of disease). Mean age 41.8 years; mean disease duration and a median EDSS of 3.0. All brain scans were performed on a GE Signa LX 1.5 T. Images and ROI's were co-registered using the AIR Package developed by R. Woods. All histograms were evaluated with a 10 and 30% cut off.

Results: We found a significant difference in the MTR peak height in the NAWM between controls and the MS patient group. The results were robust even when different MTR cut off points (max. 30%) were used. This was not the case for the MTR calculations in WBT and NABT. Significant differences were found only for the MTR mean with a 10% cut off.

Conclusion: The main difference between the WBT or NABT and NAWM is the inclusion of the cortex. That represents a highly variable biological factor (atrophy and cortical thickness) and includes a methodological problem (variable degree of partial volume) that influences the MTR. These factors may confound the assessment and could disguise subtle changes in the "true" NAWM.

1-Filippi et al., Neurology 52, 588–594, 1999, 2-van Buchem et al., MRM 36, 632–636, 1996; 3-Gass et al. Ann Neurol 36, 62–67, 1994

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TGF-ß1 SERUM CONCENTRATION IN PATIENTS WITH MULTIPLE SCLEROSIS TREATED WITH INTERFERON BETA. M. Sailer, D. Rheinhold, K. Schrecke, E. Perlov, S. Ansorge, H.-J. Heinze, Otto-von-Guericke University (Magdeburg, D)

Introduction: TGF-ß is a powerful immunosuppressive cytokine that plays a role in the immunological cascade involved in the inflammation process in multiple sclerosis (MS)1. The objective of this study is to assess whether interferon beta treatment has an impact on the TGFß concentration in vivo. In this study we prospectively monitored the TGFß1 concentration in serum before and after initiation of interferon beta treatment.

Patients and Methods: Blood samples from 23 patients with clinically definite MS were collected prior, 4 weeks and 12 weeks after the initiation of interferon beta treatment. The TGF-ß1 concentration in serum was measured using a specific TGF-ß1-ELISA2. EDSS and adverse events were recorded at same time points.

Results: 16 Patients had a significant increase in the TGF-ß1 serum concentration on week 4 and week 12 while 7 patients did not have a change of TGF-ß1 serum concentration when compared to the baseline measurement. Out of these 7 patients 5 had a deterioration of disability of at least 0.5 points on the EDSS (Expanded Disability Status Scale) within the three months. In contrast only 1 of the 16 patients that responded to the interferon beta treatment with an increase of TGF-ß1 serum concentration had a worsening of the clinical status.

Conclusion: TGF-ß1 can be reliably measured in vivo, in the serum of MS patients undergoing an immunomodulatory treatment. 30% of the patients did not have an increase in TGF-ß1 concentration under active treatment. From in vitro studies there is evidence, that there is a dose dependent effect of interferon beta on the immunomodulatory properties that might mediate the beneficial effect on the course of the disease1. Whether an intensification of the therapy would be appropriate and the monitoring of TGF-ß1 in serum can reliably be correlated with the clinical outcome has to be confirmed in a controlled study design.

1 Ossege et al., Immunopharmacology 1999 Jun;43:39–46; 2 Danielpour et al.; J.Immunol. Meth. 1993;158: 17–25

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CORRELATION OF ADHESION MOLECULES IN BLOOD WITH DISEASE BURDEN IN MULTIPLE SCLEROSIS ASSESSED BY CRANIAL MRI IMAGING. J. Kraus, P. Oschmann, B. Engelhardt, B. S. Kuehne, J. Tofighi, N. Chatzimanolis, R. Bauer, H. Diehl, C. Laske, E. Stolz, C. Schaefer, M. Kaps, H. Traupe, Justus-Liebig-University, Max-Planck-Institute (Giessen, Bad Nauheim, D)

Objective: Adhesion molecules are suggested to play a pivotal role in the regulation of trafficking of mononuclear cells from peripheral blood through the blood-brain barrier into the central nervous system in multiple sclerosis. In a previous study we found a close correlation of soluble and cell bound ICAM–1 and ICAM–3 (s- and c-ICAM–1 and –3) both in CSF and blood with clinical disease activity in patients suffering from MS. This study addressed the question whether there is any correlation of subclinical disease activity determined by cranial MRI scans and levels of soluble and cell bound adhesion molecules.

Methods: We determined concentration levels of s-ICAM–1 and s-VCAM–1 by ELISA in blood samples of 77 patients with relapsing remitting multiple sclerosis. All of them were not treated by any immunosuppressive, immunomodulatory or corticosteroid treatment for at least three months. Additionally, the expression levels of c-ICAM–1 and –3 on CD3+ T cells and CD14+ monocytes/macrophages were measured by two-color FACS analysis. In corresponding cranial MRI scans both the number and the cumulated area from all lesions as well as the number and area of active lesions (Gadolinium enhancement and/or perifocal edema) were determined.

Results: ICAM–1 expression on T cells correlated negatively with the number and cumulated area of all lesions on MRI scans ($p< 0.05$) both for all patients and for the subgroup of patients with active lesions (n= 27), respectively. A negative correlation was also found for ICAM–3 on monocytes and both for the cumulated area of all lesions as well as for the number and the area of active lesions ($p< 0.05$). In the patient group with signs of disease activity on MRI scans, we observed a negative correlation of the expression of c-ICAM–1 on monocytes and the number and area of all lesions ($p< 0.05$). In these patient subgroup a significant correlation of the concentration of s-ICAM–1 and the area of active MS lesions was found ($p< 0.05$). However, regarding the group of patients without activity signs in cranial MRI (n= 50), we could not observe any correlation between cell bound and soluble adhesion molecule levels in serum and number and area of MS lesions.

Conclusion: For the first time we were able to show that there is not only a correlation between the soluble form of ICAM–1 but also for the expression of cell surface ICAM–1 on T cells in peripheral blood and signs of disease activity on cranial MRI scans in MS patients. Furthermore, the expression of c-ICAM–1 and c-ICAM–3 on monocytes could be a useful immunological parameter to observe subclinical disease burden and disease activity.

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LONG TERM EFFECTS OF INTERFERON-BETA–1B-THERAPY ON C-ICAM–1 AND –3. N. Chatzimanolis, R. Bauer, B. Engelhardt, J. Kraus, B. S. Kuehne, J. Tofighi, H. Traupe, P. Oschmann, Justus-Liebig-University, Max-Planck-Institute (Giessen, D)

Introduction: It has been suggested that intercellular adhesion molecules–1 and –3 (ICAM–1 and –3) regulate the transmigration of blood leukocytes through the blood-brain-barrier (BBB) in patients with multiple sclerosis (MS). A short-term induction effect could be found for soluble adhesion molecules (s-ICAM–1 and s-VCAM–1) at the beginning of treatment with interferon beta–1b (IFN beta–1b) in MS patients. The intention of this clinical study has been to investigate the influence of IFN beta–1b treatment on the expression of cell bound forms of ICAM–1 and 3 (c-ICAM–1 and –3).

Material and Methods: 40 patients with relapsing-remitting MS were enrolled in the study. 19 patients (treatment group; 11 female, 8 male) were treated with IFN beta–1b for an observation period of 24 months. 21 patients (control group; 19 female, 2 male) received neither immunomodulatory nor immunosuppressive therapy and were observed for 12 months. The expression of c-ICAM–1 and –3 by peripheral blood mononuclear cells was measured by a two-colour FACS analysis.

Results: Expression of both c-ICAM–1 and c-ICAM–3 was significantly increased on CD3+ T-cells in the treatment group after 3 months of treatment ($M=5.39 \pm 1.84$ vs. $M=4.08 \pm 1.22$; $p< 0.05$). After 12 months, expression of c-ICAM–1 on CD3+ T-cells was reduced compared to the 3-months-level ($M=4.70 \pm 1.57$). After 24 months there was a further decrease of the expression of c-ICAM–1 on CD3+ T-cells in the treatment group ($M=3.13 \pm 0.69$; $p< 0.05$). We also found a significant decrease in the expression of c-ICAM–3 from month 18 on ($p< 0.05$), the decrease being even more significant after 24 months of treatment (6.75 ± 2.59 vs. $M=11.36 \pm 3.15$; $p< 0.0005$). Moreover, a significant decrease of c-ICAM–3 expression on CD19+ B-cells and CD14+ monocytes/macrophages as compared to baseline levels could be observed ($p< 0.05$). Decreases of c-ICAM–1 and –3 expression on T-cells and monocytes could be found as well in the control group after 12 months ($p< 0.05$).

Conclusion: These results suggest a short-term induction effect of IFN-beta–1b on the expression of cell bound adhesion molecules. This could be due either to stabilization of the BBB leading to a pooling of mononuclear cells with enhanced expression levels of adhesion molecules in peripheral blood or a temporary over-activation of cytokines and adhesion molecules induced by interferon-beta–1b.

At the moment we are investigating whether there are differences in the expression of cell bound adhesion molecules between patients responding or not responding to IFN-beta–1b treatment.

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ARE CYTOKINE LEVELS IN SERUM USEFUL PARAMETERS TO DETERMINE DISEASE BURDEN OR ACTIVITY IN MS PATIENTS? J. Kraus, P. Oschmann, B. S. Kuehne, H. Diehl, R. Bauer, N. Chatzimanolis, J. Tofighi, C. Laske, B. Engelhardt, C. Schaefer, M. Kaps, H. Traupe, Justus-Liebig-University, Max-Planck-Institute (Giessen, D)

Introduction: Chronic and acute dysregulation of the cytokine network were seen to be one of the pathway factors for the typical demyelinating inflammatory lesions in the CNS of MS patients. It has been found both upregulation of proinflammatory cytokines like interferon-gamma (IFN-g), tumor necrosis factor-alpha and -beta (TNF-a, -b) and downregulation of antiinflammatory cytokines like transforming growth factor-beta (TGF-ß), interleukin–4 and –10 (IL–4, –10). In contrast, morphological changes of MS can be assessed by cranial MRI scans indicating disease activity and disease progression. This study has been performed to investigate whether changes of cytokines, which are possibly indicating pathway mechanisms are correlating with their effect, seen as morphological changes determined by MRI.

Methods: We included 46 patients into the study. All of them were suffering from relapsing-remitting MS and have not been treated by immunomodulatory or immunosuppressive therapy. In the serum of all the patients we measured the concentrations of TNF-ß, TNF-Receptor–1 and –2, IL–4, IL–10 and IFN-g by ELISA. Cranial MRI scans were performed from all the patients and both the number and cumulated area of all lesions as well as from lesions showing activity signs (Gadolinium enhancement, perifocal edema) were determined and correlated to the cytokine levels in the serum by Spearman-ranking-test. Additionally, the same statistical procedure was performed in the subgroup of patients (n= 21) showing any activity signs in their cranial MRI scans.

Results: Significant ($p< 0.05$) correlation was only found in the subgroup of

patients showing active lesions for the number of both Gadolinium enhancement and perifocal edema and IFN-g levels in serum. We could not observe any further correlation of cytokine levels and MRI parameters.

Conclusion: We only found weak correlation of IFN-g and the number of lesions showing two activity signs in cranial MRI. Our data confirm former published results that there is a delay of time between cytokine changes in serum and the morphological effects of these changes assessed by cranial MRI scans.

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CSF LEVELS OF SOLUBLE ICAM–1 IN CSF CORRELATE WITH DISEASE ACTIVITY IN MULTIPLE SCLEROSIS ASSESSED BY CRANIAL MRI IMAGING. J. Kraus, P. Oschmann, B. Engelhardt, B. S. Kuehne, N. Chatzimanolis, R. Bauer, J. Tofighi, H. Diehl, C. Laske, E. Stolz, C. Schaefer, M. Kaps, H. Traupe, Justus-Liebig-University, Max-Planck-Institute (Giessen, D)

Introduction: Adhesion molecules play a pivotal role in the migration of inflammatory cells from peripheral blood through the blood-brain barrier into the central nervous system in multiple sclerosis. In a previous study we found significantly decreased expression levels of cell surface ICAM–1 (c-ICAM–1) on CD3+ T cells both in cerebrospinal fluid (CSF) and blood as well as a significant decrease of the expression levels of c-ICAM–1 and c-ICAM–3 on CD14+ monocytes/macrophages in MS patients, suffering from an acute relapse as compared to MS patients in remission. In this study we investigated the relationship between subclinical disease activity determined by cranial MRI scans and soluble and cell bound adhesion molecules in CSF.

Methods: In 33 patients c-ICAM–1 and –3 on CD3+ T cells and CD14+ monocytes/macrophages in CSF were determined by two-color flow cytometry. Concentration levels of s-ICAM–1 were measured by ELISA. In corresponding cranial MRI scans both the number and the cumulated area of all MS lesions as well as the number and area of active lesions (Gadolinium enhancement and/or perifocal edema, n= 8) were quantified.

Results: A significant correlation was found ($p< 0.05$) for s-ICAM–1 levels and the number and cumulated area of active lesions, both for the total patient population as well as for the group of patients with signs of active disease on cranial MRI scans. However, no significant correlation was found for the cell bound forms of ICAM–1 and –3 both on T cells and on monocytes.

Conclusion: Soluble ICAM–1 levels in CSF correlate with the number and area of active lesions on cranial MRI. However, no correlation was found for the cell bound adhesion molecules in CSF and signs of disease activity on MRI.

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NEUROLOGIST'S RECORDING AND SELF-ASSESSMENT OF PROGRESSION IN MULTIPLE SCLEROSIS. S. I. Mellgren, G. Hansen, S. A. Grönlie, E. Myrvoll, M. Grönning (TROMSÖ, N)

Mean annual progression on the EDSS (Expanded Disability Status Scale) for multiple sclerosis (MS) has been reported in several publications. We also applied the Cambridge Multiple Sclerosis Basic Score (CAMBS) self reported handicap scale to determine the average yearly progression in comparison with the annual increase in EDSS in initially relapsing-remitting (RR) and primary progressive (PP) MS patients.

125 answered a questionnaire filling in the handicap scale alone or with help. 100 patients were classified as RR and 25 as PP. At the time of investigation none of the patients had been treated with betainterferon.

The average annual increase of EDSS was 0.60 (range 0–3.50) in the patients with relapsing-remitting onset and 0.95 (0.18–3.50) in those with primary progressive course ($p=0.003$, Mann-Whitney U test). Annual increase of CAMBS handicap was 0.45 (0.04–2) in RR and 0.6 (0.10–2.50) in PP patients ($p=0.02$). There was a significant correlation between annual increase of EDSS and CAMBS handicap ($r=0.82$, $p=0.0001$, Spearman correlation coefficient) in the whole patient material and stronger in the PP group ($r=0.84$, $p=0.0001$) than in the RR patients ($r=0.79$, $p=0.0001$).

Not unexpectedly there was a more rapid average progression in the primary progressive MS patients both according to the neurologist' evaluation as well as the patients' themselves. The annual mean increase of EDSS and self reported handicap scores were strongly correlated and most so in those with a primary progressive course.

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ELECTROPHYSIOLOGICAL CORRELATES OF DISABILITY IN MULTIPLE SCLEROSIS. G. B. Groozman, M. Zaretzky, V. E. Drory, J. Chapman, O. Hilkevich, A. D. Korczyn, Tel Aviv University, Tel Aviv University Sackler Faculty of Medicine (Tel Aviv, IL)

Evoked potentials (EP) have been widely used in the diagnosis of multiple sclerosis (MS), in order to detect clinically silent lesions. Though magnetic resonance imaging (MRI) may be more sensitive that EP in the diagnosis of MS, the vast majority of lesions seen on MRI are not associated with symptoms and signs. In contrast, pathologic EP findings may correlate better to clinical deficits, especially in areas poorly visualized by MRI such as the spinal cord, which accounts for much of patient disability.

In the present study we examined 84 patients with clinically probable or definite MS and MRI confirmation. Visual evoked potentials (VEP) were performed stimulating each eye separately. Somatosensory evoked potentials (SSEP) were performed stimulating both median and tibial nerves and recording from the scalp. In each patient the expanded disability status scale (EDSS) score was established at the time of the neurophysiological examination. There was a good positive correlation between EDSS and SSEP latencies from the median ($r=0.62$, $p< 0.001$) and tibial nerves ($r=0.53$, $p< 0.001$) and a weaker correlation between EDSS and VEP latency ($r=0.24$, $p< 0.05$). There was an inverse correlation between EDSS and SSEP amplitudes ($r=-0.28$, $p< 0.05$ and $r=-0.41$, $p< 0.001$, respectively). VEP amplitudes showed a similar trend, but it did not achieve statistical significance.

The results confirm that EP may be useful for the assessment of disability in MS. The advantage of SEP from the upper limbs remains to be validated by longitudinal studies on larger numbers of patients.

P450

USE OF ALTERNATIVE MEDICINE IN MULTIPLE SCLEROSIS. K. Zur, A. D. Korczyn, J. Chapman, University Sackler Faculty of Medicine (Tel Aviv, IL)

There is currently much interest, especially among patients with chronic neurological diseases, regarding the use of alternative medicine. We have recently completed a survey on alternative medicine use among patients with multiple sclerosis (MS).

The study included 37 consecutive patients with clinically definite laboratory supported MS followed up regularly at our Neuroimmunology Clinic. The patients were interviewed with a standard questionnaire that included demographic data, psychosocial data, status of MS and details of patient-physician relationships.

17 of these patients had turned to alternative medicine which included acupuncture (53%), homeopathy (47%), reflexology (50%), naturopathy and herbal remedies (19%), shiatzu (31%), hypnosis (12%), diets (31%), healing (19%), Jewish traditional (6%), hyperbaric oxygen (12%) and others (12%). Most patients had tried more than one modality. The average (±SE) time from diagnosis of MS to initiation of alternative therapy was 84±25 months, the average time on this therapy was 35±13 months and 35% of patients were currently under some form of alternative medicine. 59% had consulted their physician concerning alternative therapy and 82% continued scientifically proven therapies in parallel.

The group of patients turning to alternative medicine were significantly ($p< 0.05$, t-test) different from the others in all 8 measures of patient-physician relationship. They reported that their treating physician failed to adequately explain the disease, discuss planned treatments, involve them in planning management, encourage them, be accessible, be trustworthy, easy to converse with or ready to discuss issues with family members. Interestingly, the alternative medicine practitioner was not reported to be significantly better in any of these measures except for encouragement. In all measures of socioeconomic status and quality of life there was no difference between the two groups. There was a tendency for the alternative medicine group to be slightly more disabled and these patients were receiving significantly more help from parents and other family members.

These findings confirm that it is patient-physician relationship, more than patient status, life style or personality, which influences the choice of alternative medicine. Since turning to alternative medicine is probably a sign of distress, improved physician support is the appropriate response in these cases.

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COMPARISON OF IMMUNOMODULATORY TREATMENT OF RELAPSING REMITTING MULTIPLE SCLEROSIS (RRMS)- A PROSPECTIVE OPEN STUDY IN 498 MS-PATIENTS TREATED WITH INTERFERON BETA (IFNß) 1-B, IFNß 1-A I. M., IFNß 1-A S. C., GLATIRAMERACETAT (COPAXONE) OR IMMUNOGLOBULINE. M. Firzlaff, M. Schröder, M. Schmid, J. Haas, Tembit Software GmbH, Jewish Hospital Berlin Charité Teaching Hospital (Berlin, Berlin, D)

Introduction: In Germany Betaferon, Avonex and Rebif are licensed for exacerbating-remitting MS. Copaxone and Immunoglobulines are available and will be reemboursed in case of contradiction, intolerable side effects and treatment failure of IFNß. In a prospective study we compared the first year of treatment in 498 MS-patients with exacerbating remitting course and an EDSS< =3.5 concerning efficacy and tolerance of the five different immunomodulatory agents. Methods: Baseline data (age (A), sex, Expanded Disability Status Scale (EDSS), exacerbation rate, duration of disease (D), pre-treatment and progression before treatment were documented (database musis). Patients were investigated every three months to assess EDSS, exacerbation rate and side effects. Results: 157 patients (p) (102 female(f), 52 male(m)) were on Betaferon (A 36 years (y), EDSS 2.21, D 5.98 y). 142 p (111 f, 31 m) were on Avonex (A 36y, EDSS 2.25, D 6.9 y). 90 p (61 f, 29 m) were on Rebif 22ug (A 34y, EDSS 2.3, D 5.79y). 123p (96 f, 27 m) were on Copaxone(A 34y, EDSS 1.99, D 6.82). 103p (77 f, 26 m) received 10 g Immunoglobulines monthly. The progression rate was 0.37 for Betaferon, 0.33 for Avonex, 0.40 for Rebif, 0.29 for Copaxone and 0.24 for immunoglobulines. Further evaluation will be done at the completion of observation period after 12 months (up to April 2000) with regard to exacerbation rate, time until first exacerbation, number of exacerbation free patients, number of stabilised patients, progression, reasons for discontinuation and efficacy of consecutive treatment in case of discontinuation. Conclusion: Despite the obvious problems of an open surveillance our evaluation may be helpful to elucidate the benefit of the different immunomodulatory agents in the daily practice. The five treatment groups are comparable concerning baseline data but differ concerning pre-treatment progression rate. A matched pair analysis will be done and the data will be compared with the published study data.

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METHOTREXATE IN CHRONIC PROGRESSIVE MULTIPLE SCLEROSIS. M. Starck, W. Pöllmann, L. P. Erasmus, N. König, Marianne-Strauss-Klinik (Berg, D)

Prophylactic treatment of chronic progressive multiple sclerosis (MS) is still more difficult than that of relapsing remitting MS also in spite of the approvement of Betainterferon 1 b. Low dose oral methotrexate (I\M) once weekly seemed to slow deterioration especially of upper limb functions and to have a positive tendency on the expanded disability status scale (EDSS) as reported by Goodkin and coworkers published in Annals of Neurology 1995; 37: 30–40. During the last years we treated 55 in-patients with clinically definite chronic progressive MS with MTX according to this study. 28 women and 27 men with a mean age of 47 years and a mean duration of disease of 13 years, were examined at least once during a follow-up period of up to 3 years. All patients were routinely scored according to the functional systems (FS) and EDSS of Kurtzke and ambulation index of Hauser. In the pyramidal FS 18 (33 %) patients deteriorated, 10 (18 %) in the cerebellar FS. Regarding the EDSS 24 (44 %) patients worsened, the mean EDSS increased from 6.3 to 6.6. Data were similar for the ambulation index (23 (42 %) patients worsened). 34 (62 %) patients discontinued MTX therapy because of further progression in 17 cases, side effects in 11 and other reasons in 6 patients. In summary there was no convincing effect of MTX on progression of MS in our patients as measured by EDSS and ambulation index.

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Abstract withdrawn

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PROGNOSTIC FACTORS IN MULTIPLE SCLEROSIS: AN MS CLINIC BASED STUDY OF 1243 MULTIPLE SCLEROSIS PATIENTS IN BRITTANY. M. Coustans, F. Le Duff, P. Brunet, O. De Marco, E. Le Page, J. Chaperon, G. Edan, University Hospital Pontchaillou, Public Health Department (Rennes, F)

OBJECTIVE: To assess in multiple sclerosis (MS) population demographic data, clinical manifestations and courses at onset, time to acquire different levels of disability and to evaluate the main prognostic factors which might influence disability in MS.

BACKGROUND: 1243 patients from Brittany were collected using EDMUS. These patients had a clinical onset of the disease between 1947 and 1997; last information was done March 15, 1999.

DESIGN/METHODS: The patients were analysed according to different criteria (sex, age, remitting or progressive course and symptoms at onset, time to reach EDSS 3, number of relapses the first year of the disease). The data were analysed using actuarial methods that account for censored follow-up (endpoint not reached over the follow-up period) to assess time to reach EDSS 3,6 and 8.

RESULTS: 1243 patients entered the study with a median age of 30:7 years. The male female ratio was 0.44; the mean disease duration was 12 years. There were 991 (79.7 %) patients who started with remitting course and 252 (20.3 %) with progressive course. In 13 % the disease began before the age of 20 years, in 4 % after the age of 50 years. The most common symptom at presentation was sensory 43.5 %, handicap at lower limbs (motor or cerebellar) 39.6 % and optic neuritis 26.7 %. The median time to reach EDSS 3, 6 and 8 was respectively for the total population: 6.4, 16 and 37 years, for remitting population it was respectively 8.4, 19 and 37.3 years and for progressive population it was 2.5, 9 and 22.5 years.

The shorter time to reach EDSS 6 was correlate with progressive clinical course, EDSS more than 3 in three years after onset, 2 relapses or more within the 12 months after onset and age more than 40 years at onset. Sex, unifocal or multifocal and clinical symptoms at onset were not significant prognostic factors.

CONCLUSION: The analysis of demographic data and initial symptoms at onset in a population of 1243 patients in Brittany showed bad prognostic factors which influenced the disability in total MS. Beside age at onset and progressive clinical course, we have to note the importance of the number of relapses in the first year and the short interval of years (less than 3 years) to reach EDSS 3.

P455
EFFECT OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) ON SPASTICITY. C. Holzknecht, F.Th. Potrz, S. Halve, D. Poehlau, Sauerlandklinik Hachen, Ruhr-Universität (Sundern, Bochum, D)

Transcranial magnetic stimulation (TMS) is a valuable diagnostic procedure. There is increasing evidence that repetitive TMS (rTMS) may be a therapeutic tool as well. It is currently investigated for the treatment of depression, obsessive-compulsive disorders and epilepsy. We analysed the effect of rTMS on muscle tone and investigated side-effects in severely disabled patients with multiple sclerosis (MS).

39 in-house MS-patients were treated with rTMS (29 females, 10 males; mean age 49.4 years; mean EDSS 7.0). 11 patients had primary progressive, 25 secondary progressive, 3 had relapsing-remitting MS. 81 limbs were treated without change in antispastic medication. The patients received 3 to 5 treatment-sessions per week. Each session comprised 5 to 8 series of 30 stimuli. rTMS was performed with a MagLite™ magnetic stimulator at the DANTEC Keypoint® Workstation using a figure-eight-coil. Stimulation intensities were

70 to 80 % at upper and 80 to 90 % at lower limbs of 1.5 Tesla as possible maximum. Spasticity was measured according to the Ashworth-scale.

31 of 81 (38 %) treated limbs (in 22 patients out of 39) showed a measurable reduction of muscle tone. In 2 limbs (2 patients) muscle tone increased. The mean muscle tone reduction (calculated with all 81 limbs) was 0.4 degrees on the Ashworth-scale ($p< 0.001$). The median of the muscle tone decreased from 3 before the treatment to 2 after the last rTMS-session ($p< 0.001$). EDSS did not change under rTMS. Effects of rTMS occurred rapidly, usually within less than 12 hours. They lasted normally some days. In one case muscle tone reduction is still measurable after more than 10 months. Several patients compared the effect after an rTMS-session with that after Vojta-physiotherapy which also reduces spasticity. Adverse effects like headache and also serious side-effects like seizure or cardiac arrhythmia did not occur. The highest rates of spasticity reduction were found in relapsing-remitting (3/3 patients), the lowest appeared in secondary chronic progressive MS (13/25); primary chronic progressive MS responded with a rate of 6/11 patients. Also high muscle tones improved under rTMS (2/2 limbs from Ashworth 5 to 4; 7/26 limbs with Ashworth 4 were reduced to 3; three limbs were reduced from 4 to 2). The mean duration of MS among the patients with spasticity reduction was 16 years, in the group without profit it was 19 years; the EDSS difference between responders and non-responders was 0.2 (responders with slightly lower mean EDSS).

Repetitive transcranial magnetic stimulation appears as a potentially useful, non-invasive and well-tolerated method for the treatment of spasticity in MS-patients. It should be used complementary to established treatment methods. So far it is not known, by which mechanisms rTMS causes changes in muscle tone. Effects are likely dependent on stimulation parameters like number, frequency and intensity of applied pulses. A randomised, investigator blinded study is necessary and under way.

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EVALUATION OF MITOXANTRONE'S CARDIAC SIDE EFFECTS IN THE TREATMENT OF MULTIPLE SCLEROSIS. V. Kerdoncuff, O. De Marco, M. Laurent, P. Brunet, C. Bossé-Pilon, M. Coustans, G. Edan, University Hospital Pontchaillou (Rennes, F)

INTRODUCTION: Mitoxantrone (Novantrone), an anthracenedione, is one of the immunosuppressive treatments used in multiple sclerosis (MS). Because of structural similarity with other anthracycline drugs, cardiotoxic effects have been reported.

DESIGN/METHODS: Cardiotoxic side effects of mitoxantrone used in MS patients was evaluated in a retrospective study of 106 patients treated with 20 mg of mitoxantrone per month during 6 months (cumulative dose under 160 mg/m^2). Any of the patients had potentially cardiac drug before. They had echocardiography at enrolment, and 6, 24, and 60 months later, using left ventricular ejection fraction (LVEF) as indication of systolic cardiac function.

RESULT: Twenty-two patients had significant decrease of LVEF. We can separate them in three groups. The first one of 13 patients with doubtful results because only one value of LVEF decreased more than 10 % from baseline but remained over 50 %. The second one of 7 patients with possible cardiotoxicity seeing that they had 2 values of LVEF decrease more than 10 % from baseline but remaining over 50 %. And the last of 2 patients only with cardiotoxic effects because one value or more was reduced under 50 %. No patient had clinical sign of heart failure.

CONCLUSION: Cardiac tolerance of Mitoxantrone seems good in MS patients. On 106 patients, only 2 had cardiac side effects resulting in LVEF < 50 %.

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UNSUPERVISED, ADAPTATIVE, 3D SEGMENTATION OF BRAIN TISSUES IN MULTISPECTRAL MRI: APPLICATION TO QUANTIFICATION OF MULTIPLE SCLEROSIS LESIONS. Ch. Pachai, Y. M. Zhu, C. R. G. Guttmann, J. Grimaud, M. Hermier, G. Gimenez, Ch. Confavreux, J.-C. Froment, CREATIS, CNRS UMR 5515, INSA de Lyon, Harvard Medical School, Hôpital Neurologique P.Wertheimer (Lyon, F; Boston, USA)

Aim: automatic processing and analysis of MR volumes for quantification and visualization of brain tissues and MS lesions.

MRI data: Proton density and T2-weighted (2D spin-echo, repetition time/echo time = 3000/14–85 ms, 54 slices 512′512 pixels each, resolution 0.94′0.94′3 mm, acquisition time 9 min and 50 s) or T1-weighted (3D gradient echo, repetition time/echo time = 9,7/4 ms, 170 slices 256′256 pixels each, resolution 1′1′1 mm, acquisition time 8 min and 21 s).

Method: An unsupervised, 3D, adaptative and multichannel algorithm was used. It does not require any particular initialization and classifies the data in gray matter, white matter, cerebrospinal fluid and MS lesions. An objective follow up of MS lesion load and other morphological parameters such as brain and cerebrospinal fluid volumes can be carried out (with possible measurement of brain atrophy over time).

Results: The poster will exhibit 3D visualisation of brain tissues and quantitative results for the follow-up of MS patients with serial MRI studies.

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HEMIAGEUSIA FROM IPSILATERAL MULTIPLE SCLEROSIS PLAQUE AT THE MIDPONTINE TEGMENTUM. O. Combarros, P. Sànches-Juan, C. De Pablos, J. Berciano, Univ. Hospital Marques de Valdecilla (Santander, E)

The exact location of the pontine gustatory pathway has not yet been clarified. Here we report a patient with an isolated hemiageusia and trigeminal sensory neuropathy from a single small pontine lesion. A 46-year-old woman experienced a burning sensation of the tongue on the left side. The next day, she discovered loss of taste on the entire left half of her tongue and numbness on the left face. Neurological examination was normal except for hypaesthesia to pain, touch, and temperature senses in all three divisions of left trigeminal nerve, with decreased left corneal reflex and no weakness of masseters. Taste sensation was markedly diminished in the anterior two-thirds and posterior one-third of the tongue on the left side. CSF analysis showed increased quantitative intrathecal IgG, and oligoclonal bands. Visual evoked potentials following both median and posterior tibial nerve stimulation were normal.The blink reflex was normal upon stimulation on the right, and when stimulating on the left, there was no R1 component and R2 responses were elicited normally. Masseter reflex was absent on the left side. MRI on T2-weighted images demonstrated multiple bilateral hyperintense white matter signals in periventricular distribution, and a hyperintense small lesion in the lateral part of the left midpontine tegmentum that showed enhancement after gadolinium injection. Absence of R1 response of the blink reflex and of the masseter reflex imply ipsilateral brainstem lesions at the trigeminal principal sensory and motor nuclei, respectively. Involvement of the central tegmental tract, which is the anatomic structure adjacent to the sensory and motor trigeminal nuclei at the midpontine tegmentum level, it was probably important in causing taste disturbance in our case.

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NO EVIDENCE FOR CHLAMYDIA PNEUMONIAE INFECTION OF THE CENTRAL NERVOUS SYSTEM IN MULTIPLE SCLEROSIS. E. Pucci, C. Taus, E. Cartechini, M. Morelli, G. Giuliani, M. Clementi, S. Menzo, Torrette, Ospedale di Macerata, University of Trieste, University of Ancona (Ancona, Trieste, I)

Background: Contrasting results were recently published by Sriram et al. (1,2) and Boman et al. (3), about detection of Chlamydia pneumoniae in cerebrospinal fluid (CSF) samples from Multiple Sclerosis (MS) patients.

Objective: To provide further data on the hypothesised relationship between Chlamydia pneumoniae and MS.

Subjects and methods: Antibodies titers (IgM or IgG) in CSF by complement fixation technique and polymerase chain reaction (PCR) in CSF and in peripheral blood mononuclear cells (P13MCs) were carried out in order to detect Chlamydia spp. in 29 subjects with Idiopathic Inflammatory Demyelinating Disease (IIDD) of CNS (19 defined MS, 4 probable MS (4)) and 7 controls.

Results: No Chlamydia spp. DNA was found in CSF samples and in P13MCs from IIDD subjects or controls. All the Chlamydia spp. DNA controls from cell cultures yielded the expected results in PCR. Both subjects and controls displayed < 1:8 antibody titers in CSF.

Conclusion: No apparent active or preceding chlamydial infection was detected in the subjects studied. The role of Chlamydia pneumoniae in the etiology or pathogenesis of demyelination appears improbable.

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TRANSCRIPTIONAL REGULATION OF MATRIX METALLOPROTEINASES IN BRAIN TISSUE AND CSF CELLS IN MULTIPLE SCLEROSIS. R. L. P. Lindberg, C. J. A. De Groot, L. Montagne, P. van der Valk, L. Kappos, D. Leppert, Research and Neurology, Academic Hospital Vrije Universiteit (Basel, CH; Amsterdam, NL)

Matrix metalloproteinases (MMPs) are proteolytic enzymes involved in the degradation and remodelling of the extracellular matrix (ECM) in many pathological processes. There is accumulating evidence for the involvement of MMPs in the pathogenesis of MS based on immunohistochemistry of MS tissue. However, the contribution of individual MMPs and their transcriptional regulation in different stages of plaque formation has not been studied due to the lack of a sensitive methodology. Real-time polymerase chain reaction (RT-PCR) has made it possible to quantitate mRNA expression of target genes with very low copy numbers. In the present study we used this technique to analyze the expression of various MMPs and cytokines in (p)reactive, active, chronic active and chronic inactive ms-plaques (van der Valk P and De Groot CJA, Neuropathol Appl Neurobiol, in press) and corresponding normal appearing white matter (NAWM) samples of secondary progressive multiple sclerosis (spMS) patients. We show that MMP–7 and MMP–9, but not four other MMPs (MMP–2,–3,–8,–12), are transcriptionally up-regulated in all stages of plaques, with peak expression in acute lesions. Moreover, up-regulation of MMP–9 can also be detected in NAWM indicating that inflammatory processes are generalized rather than focal. In contrast, up-regulation of TNFalpha and IL–2, known inducers of MMPs, is restricted to (p)reactive and active plaques, respectively, but was not found in chronic lesions. We assume, that both resident brain cells and blood-derived immune cells contribute to the up-regulation of MMPs. These findings favour the concept of MS as a continuous and generalized, rather than as a focal inflammation. From a therapeutic perspective, the current findings allow to better define the necessary activity profile for MMP-inhibitors as novel tools for MS therapy.

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PROGNOSIS IN MULTIPLE SCLEROSIS – IS EPISTASIS A POTENTIALLY IMPORTANT CONCEPT? S. J. M. Weatherby, A. A. Fryer, C. Mann, M. Boggild, W. Ollier, P. Jones, R. Strange, C. P. Hawkins, North Staffordshire Royal Infirmary, Walton Centre, Epidemiology Centre (Stoke-On-Trent, Liverpool, Manchester, UK)

Introduction. Genetic aspects are considered important in multiple sclerosis (MS). However, in spite of extensive studies, the search for genetic factors influencing outcome and susceptibility has identified relatively few genes of modest effect. Recent reports have emphasised the importance of gene-gene interactions (epistasis) in determining phenotype in complex diseases. Epistasis implies that the influence of a particular gene may be altered when considered together with other candidates. Our previous studies have found that individual polymorphisms of inflammatory cytokines (IL–1 cluster) and of anti-oxidant enzymes (glutathione-S-transferase [GST] supergene family) may be associated with outcome in MS. Patients lacking allele 2 of IL–1 receptor antagonist (IL–1-RN) and patients homozygous for allele 2 of IL–1 beta 511 have been associated with a worse prognosis. The GSTM3 AA allele, and a two-way interaction between possession of GSTP1 AA and GSTM1 null have also been associated with a worse outcome. We report a preliminary investigation into gene-gene interactions between these polymorphisms and relationships with prognosis.

Methods. 449 patients with clinically definite MS were studied. Outcome was measured using the expanded disability status scale (EDSS). Cases were stratified into those with mild/moderate disability (EDSS 0–5.5) and those with severe disability (EDSS 6–10) after a disease duration of 10 years or more. Two and three way interactions between GSTM3 AA, GSTP1 AA, GSTM1 null, IL–1RN and IL–1 beta 511 polymorphisms were studied, and their relationship with outcome assessed. Results were analysed using logistic regression, correcting for independent covariants of age of onset, gender and disease duration. The single genes were also entered as interaction terms to confirm the identification of synergistic interactions.

Results. The following combinations were associated with more severe disability after a disease duration of 10 years or more: –

GSTM1 null, GSTP1 AA and homozygosity for allele 2 of IL–1beta 511 (OR 13.6, P=0.01, 95% CI=1.65–109)

GSTM3 AA, GSTP1 AA and homozygosity for allele 2 of IL–1beta 511 (OR 13.5, P=0.01, 95% CI=1.63–108.40)

GSTM3 AA and non-allele 2 IL–1-RN status (OR 3.8, P=0.02, 95% CI=1.64–8.76)

These interactions also remained the most significant when main effects were analysed as independent covariants. Conclusions. Clearly the analysis of gene-gene interactions is associated with a number of important statistical issues. In addition, it should be noted that the confidence intervals of these results are wide, highlighting the need for large study cohorts and verification of findings in separate populations. Nonetheless, these findings suggest that the relationship between gene-gene interactions and outcome merits further study. Furthermore, if these findings are substantiated in separate large cohorts, and within genetically distinct populations, such interactions might be of clinical use in identifying patients with poor prognosis.

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POLYMORPHISMS OF INTERFERON-GAMMA AND MANGANESE SUPEROXIDE DISMUTASE AND DISABILITY IN MULTIPLE SCLEROSIS. S. J. M. Weatherby, P. Roby, C. Mann, M. Boggild, A. Hajeer, A. A. Fryer, W. Ollier, R. Strange, C. P. Hawkins, North Staffordshire Royal Infirmary, Epidemiology Centre, Walton Centre (Stoke-On-Trent, Manchester, Liverpool, UK)

Introduction. Interferon-gamma (IFNG) has been implicated as an inducer of primary demyelination and of disease exacerbations in Multiple Sclerosis (MS). Increased levels of IFNG precede clinical attacks and interferon-beta significantly reduces INFG production. Antioxidant enzymes such as manganese superoxide dismutase (MnSOD) scavenge free radicals and have been found to reduce the severity of experimental allergic encephalomyelitis. Levels of Mn-SOD are low in oligodendrocytes and axons, and may cause increased vulnerability to oxidative damage. INFG has been shown to alter the expression of MnSOD in cell culture models. A case-control association study was therefore performed to investigate whether genetic variation at these loci is associated with susceptibility or severity in MS.

Methods. Biallelic polymorphisms of both INFG and MnSOD were studied. 362 patients with clinically definite MS were genotyped for the INFG polymorphism and 297 patients for the MnSOD polymorphism. Outcome was measured using the expanded disability status scale (EDSS). Cases were stratified into those with mild/moderate disability (EDSS 0–5.5) and those with severe disability (EDSS 6–10) after a disease duration of at least 10 years. Results were analysed using logistic regression, correcting for independent covariants of age of onset, gender and disease duration. Significance levels were set at $p< 0.05$.

Results. No significant differences in genotype frequency were observed between cases and controls for either of the two polymorphisms. No significant relationship between individual genotype and age of onset, disease subtype or disability was noted for either polymorphism even after examining data according to HLA-DRB1*15 status.

Conclusion. Genetic variation in the polymorphisms of INFG and MnSOD studied individually do not appear to relate to susceptibility or to outcome in MS.

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HUMAN MELANOCYTE STIMULATING HORMONE RECEPTOR VARIANTS AND MULTIPLE SCLEROSIS. S. J. M. Weatherby, A. A. Fryer, C. Mann, M. Boggild, W. Ollier, R. Strange, C. P. Hawkins, North Staffordshire Royal Infirmary, Walton Centre, Epidemiology Centre (Stoke-On-Trent, Liverpool, Manchester, UK)

Introduction. Multiple Sclerosis (MS) occurs most commonly in Caucasians and historically melanocyte stimulating hormone (MSH) has been linked to the regulation of pigmentation. However, it has broader activities including behavioural and anti-inflammatory/immunomodulatory effects. Abnormal alpha-MSH levels have been found in 70% of patients suffering from an MS exacerbation and the possibility that MS may be associated with pineal failure has been considered. Furthermore, MSH has been found to inhibit the production of pro-inflammatory cytokines such as TNF-alpha, and to induce anti-inflammatory cytokines such as IL–10. An association study was therefore performed to investigate whether 3 common polymorphic markers at the MSH receptor locus on chromosome 14 are associated with outcome in MS.

Methods. 430 patients with clinically definite MS were studied (26% males and 74% females). Mean onset age was 31 ± 9 years and mean disease duration was 12.8 ± 8.8 years. DNA was extracted from peripheral blood and polymerase chain reaction (PCR) restriction fragment length polymorphism-based assays were used to identify alleles containing the asp294his, asp151cys and arg160trp variants. Outcome was measured using the expanded disability status scale (EDSS). Cases were stratified into those with mild/moderate disability (EDSS 0–5.5) and those with severe disability (EDSS 6–10) after a disease duration of at least 10 years. Results were analysed using chi-square testing and logistic regression, correcting for independent covariants of age of onset, gender and disease duration. Significance levels were set at $p< 0.05$.

Results. No significant differences in genotype frequency were observed between cases with severe and cases with mild/moderate disability at a disease duration of 10 years. Similarly, no significant relationships were identified using logistic regression after correcting for independent covariants. As disease heterogeneity may be an important issue in MS we explored the possibility of

associations with disability in HLA-DRB1*15 positive and negative patients. No significant relationship between individual genotype and outcome was noted for an individual polymorphism even after examining data according to HLA-DRB1*15 status.

Conclusion. Polymorphic variations at the MSH receptor locus are unlikely, when considered alone, to be associated with prognosis in MS.

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IFNß TREATMENT IN RELAPSING REMITTING MULTIPLE SCLEROSIS – THE EXPERIENCE OF NORTH ITALY MS CENTERS. C. Milanese, Instituto Neurologico C. Besta (Milano, I) and the North Italy MS centers

In order to evalute the efficacy of IFNb 1b (Betaferon) and 1a (Avonex) treatment of Relapsing Remitting Multiple Sclerosis (RR MS), in clinical practice, the data of patients attending MS Centers of North Italy have been collected by an appropriate form. Sixty-six out of 106 Centers participated in the study. On 30 June 99, 962 patients were treated with Betaferon and 715 with Avonex; 128 Betaferon and 68 Avonex treated patients are excluded from the analysis because follow up data were not fully detailed.

In the remaining 834 Betaferon and 647 Avonex patients the mean treatment duration was 21,4 and 12.0 months respectively. Relapse frequency consistently decreased in both treatment groups: from 1.6 to 0.63 and 0.55 in Betaferon, and from 1.45 to 0.65 and 0.65 in Avonex, after 1 and 2 years of treatment. EDSS remained stable in most of the patients, irrespectively of treatment. 41 % of Betaferon and 15 % of Avonex treated patients discontinued treatment during the follow up, more often because of side effects in Betaferon and for in inefficacy in Avonex group. In order to identify which factors will predict treatment response, baseline clinical characteristics and follow-up data will be analyzed separately in drop outs and treated patients, in both treatment groups.

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THE LYMPHOCYTE PROLIFERATIVE RESPONSE TO GLATIRAMER ACETATE IN NORMAL HUMANS IS DEPENDENT ON BOTH MAJOR HISTOCOMPATIBILITY COMPLEX (MHC). S. Ragheb, R. P. Lisak, Wayne State University (Detroit, USA)

Glatiramer acetate (Copolymer–1; Cop–1) has been shown to inhibit the induction of, and be effective in the treatment of experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (MS). It has also been demonstrated to be an effective therapy for patients with relapsing-remitting MS (RRMS). The postulated mechanisms of action in EAE and MS have evolved over the years and have included various combinations of: 1) cross reactivity with myelin basic protein (MBP), one of the central nervous system (CNS) antigens capable of inducing EAE; 2) inhibition of MBP, proteolipid protein (PLP) and myelin oligodendroglial protein (MOG) binding to MHC class II molecules; 3) acting as an altered peptide ligand; and, 4) induction of antigen-specific suppressor cells of the Th2 type, thereby converting a pro-inflammatory Th1 helper response to Cop–1 to an anti-inflammatory Th2/Th3 response. We have postulated additional mechanisms including acting in a superantigen-like fashion with eventual induction of unresponsiveness to Cop–1 in long-term treated patients. Most of these mechanisms involve altering the function of CD4+ T-helper cells which recognize antigen in the context of MHC class II molecules. Th1 cells are currently thought to be the critical immune cell in the pathogenesis of MS lesions. In this study we sought to determine whether the in vitro T-cell response to Cop–1 is dependent on MHC class II exclusively or whether MHC class I molecules play a role. MHC class I molecules are more widely distributed on cells and are involved in interactions with suppressor/cytotoxic CD8+ T-cells. We took advantage of the finding by several groups, including ours, that normal individuals mount a brisk proliferative response to Cop–1 in vitro. Peripheral blood mononuclear cells (PBMC) were cultured in the presence of: 1) Cop–1; 2) Cop–1 + mouse monoclonal antibody (MoAb) to MHC class I or class II; or, 3) Cop–1+ normal mouse IgG. The proliferative response of PBMC to Cop–1 in the presence of MoAb to class I, class II or normal IgG was compared to the response to Cop–1 alone in 9 normal individuals. Mean inhibition by anti-MHC class I was 85 % and by anti-class II was 76 % whereas the control mouse IgG showed an insignificant 18 % stimulation in comparison to Cop–1 alone. Anti-MHC class I inhibited the response to Cop–1 by > 50 % in 9/9, anti-class II in 8/9 and normal mouse IgG in 1/9 cultures. These studies, while preliminary, suggest that Cop–1 may also act on the immune system by interactions with class I histocompatibility antigens and affect cells other than Th1 lymphocytes. Whether such interactions are important in the therapeutic effect of Cop–1 is unknown.

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DOES THE EARLY REDUCTION OF THE APPARENT DIFFUSION COEFFICIENT PREDICT TISSUE NECROSIS? – SERIAL DIFFUSION WEIGHTED MRI OF SYMPTOMATIC WHITE MATTER LESIONS. A. Gass, S. Behrens, J. G. Hirsch, O. Sedlaczek, J. Gaa, M. G. Hennerici, Neurologische Universitätsklinik Klinikum Mannheim (Mannheim, D)

Introduction: In the early phase of experimental models of cerebral ischemia and in stroke patients' diffusion-weighted MR1 demonstrates the ischaemic lesion as an area with a reduced apparent, diffusion coefficient (ADC). It indicates cytotoxic cell swelling and delineates the lesion destined to undergo tissue necrosis. Little is known about the significance of reduced ADC values in white matter lesions. We compared the evolution of lesions with significant ADC reductions in different white matter pathologies with serial MR1. Methods: MR1 data obtained with a 1.5T Siemens Vision unit from (A) 5 acute stroke patients (4m, 1w), (B) 4 MS patients (2m, 2w) and (C) a patient with suspected toxic demyelination were analysed. All patients presented with new clinical deficits and were studied serially using MR1 from the acute phase (at presentation) to a chronic phase (6 months) (4–8 MR1 examinations per patient). Patients underwent a full neurological examination at each MR1 study. MR1: T2-weighted (TSE 2620/14 /85), T1-weighted (SE 530/20), DW in 3 orthogonal planes with 5 b-values (SE-EP TR 4000/TE 144, b=0/160/360/640/1000 s/mm^2), Isotropic ADC-maps were calculated on a pixel-by-pixel basis by a linear least-squares fit after averaging of the direction-dependent DW images. To avoid partial volume contamination the ADC measurement was obtained by ROI analysis (0.2 cm–1.0 cm^2) in the center of the lesion. Results: Lesions with a minimum reduction of 35 % compared to normal appearing white matter (WM ADC = 0.74 ± 0.05 x 10^{-5} CM^2/S) were analysed. Regardless of the underlying pathology, all lesions showed an initial ADC reduction (ADC = 0.45 ± 0.19 x 10^{-5} CM^2/S), which was followed by 'pseudonormalisation' (days after 3–14 days). In the chronic stage patients showed: (A) chronic ADC elevation and tissue atrophy, (B) ADC elevation and some slight residual tissue damage, (C) normalisation of the ADC without overt chronic tissue damage. Conclusion: A reduced ADC delineates symptomatic white matter lesions. It does not necessarily indicate irreversible tissue damage in non-ischaemic pathology.

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ATYPICAL LOCALISATIONS OF MRI LESIONS IN PATIENTS WITH MULTIPLE SCLEROSIS (MS): A RETROSPECTIVE STUDY OF 100 MRI SCANS OF THE BRAIN. F. Mezger, H. Albrecht, B. Mayr, W. Pöllmann, N. König, Marianne-Strauss-Klinik (Berg, D)

MRI scans of the brain of MS patients show typical features with T2-weighted hyperintensities in the cerebral white matter, cerebellum and cerebellar peduncles, brain stem with affection of pons and medulla oblongata, and corpus callosum. In our study we evaluated the localisation of the lesions on T2-weighted MRI scans with special regard on atypically situated hyperintensive lesions (e. g. midbrain, substantia nigra, basal ganglia). Therefore we investigated brain MRI scans of 100 consecutive patients with clinically definite MS according to the Poser criteria and all types of the disease (relapsing-remitting, secondary progressive, primary progressive). The MRI scans have been performed in axial and sagittal slices for better detection of the lesions in the corpus callosum. 83 % of our patients showed lesions in the periventricular white matter, 58 % confluent lesions in this area. Hyperintensive deep white matter lesions occured in 92 %, confluent lesions in 27 % only. In 21 % of the MRI scans the lesions reached subcortical structures. The corpus callosum, known as a typical site of demyelinisation in MS, was affected in 85 % of our patients, 71 % showed brain stem lesions. In the cerebellum we found T2-weighted hyperintensities in 50 % of the investigated MRI scans. In contrast to other reports the most interesting result was the affection of basal ganglia in 56 % as well as midbrain/substantia nigra in 39 % of the cases, although extrapyramidal symptoms are not very common in MS-patients. The second surprising result was the high number of bilateral affection of subcortical structures on MRI scans, which always should lead to an additional cerebrovascular screening for safety reasons.

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TUMOUR-LIKE DEMYELINATING LESIONS IN MULTIPLE SCLEROSIS (MS) IN CHILDHOOD. A CLINICAL AND PARACLINICAL FOLLOW UP STUDY OF TWO CHILDREN. K. Paderova, University Hospital Motol (Prague, CZ)

MS is one of the major neurological problems in adult neurology. The occurrence of MS before the age of 10 years was ignored or neglected for a long time. We distinguish the juvenile MS with an onset between 10 and 15 years of age and the true childhood MS with the beginning before the age of 10 years or before the onset of puberty.The clinical onset at an early age is no reason to exclude the diagnosis of MS.The authors followed up two children with large demyelinating lesions in the brain, which by some of their properties imitated brain tumors. We report our findings in two patients at the age of 8 and 11 years,

who demonstrate the wide spectrum of investigation methods to reach the correct diagnosis. The evaluation and correct interpretation of clinical, radiodiagnostic and possibly also histological findings is essential. Patient 1 is an 8 year-old boy with a probable MS. He had a half-year history of visual impairment and diplopia. MR described T2W hyperintensive lesions with Gd enhancement in parietal and occipital regions of both hemispheres. He was recommended for a suspected brain tumour to the neurosurgical department. Stereotactic biopsy showed perivascular infiltration with lymphocytes. On MR spectroscopy there was low concentration of N-acetylaspartate and incerased lactate and inositol. In the cerebrospinal fluid (CSF) there was normal cytology and no oligoclonal bands (OB). Visual evoked potentials (VEP) were prolonged. We excluded adrenoleukodystrophy. Patient condition improved after steroid treatment. Duration of follow up is 3 years. During this period was observed one exacerbation of visual impairment. Initial improvement of MR after steroids continues to persistent multifocal lesions of white matter. Patient 2 is an 11 year-old girl with a definite MS presenting initially with an acute disseminated encephalomyelopathy (ADEM) with a spontaneous recovery. After 1,5 year she developed acute right hemiplegia. MR showed large demyelinating lesion in the left hemisphere. In the CSF were 3 OB. VEP and other modalities of evoked potentials were normal. She improved after steroid treatment during 10 days. Duration of follow up is 2,5 years, without any relapses in the course of disease. These cases illustrate the fact that demyelinating disease can mimic large tumour in MR imaging. On a contrary we document MR changes in a patient who died due to a multifocal atypical astrocytoma gr. III-IV. In this case MR spectroscopy was the most useful method in a searching for the right diagnosis. Histological examination verified this result. Although our little patients had large lesions in MR, after the therapy with methylprednisolone their state of health is stable and quality of life is satisfying due to a multidisciplinary approach. The prognosis of childhood MS is not necessarily unfavourable.

Muscle disorders

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SELECTINES IN DERMATOMYOSITIS AND POLYMYOSITIS. C. Kayser, S. Probst-Cousin, D. Heuss, B. Neudoerfer, University of Erlangen-Nuernberg (Erlangen, D)

Selectins are members of the group of adhesion molecules. They are responsible for the recruitment of leukocytes from the bloodstream to the sites of inflammation in the tissue. The mechanism includes rolling and adhesion of leukocytes at the endothelium and subsequent migration through the endothelium. We investigated immunohistochemically the expression of E-selectin, L-selectin, and P-selectin on frozen sections in dermatomyositis, polymyositis and normal controls. E-selectin stained positive at the endothelium in both dermatomyositis and polymyositis, but was not expressed by normal controls. P-selectin stained equally positive for dermatomyositis and polymyositis, and to a lesser degree in normal controls. L-selectin was expressed only by perivascular infiltrates in dermatomyositis, but not in polymyositis or normal controls. Therefore L-selectin may not be important for the invasion of inflammatory cells into the muscle fibres in polymyositis. On the other hand dermatomyositis is a vasculopathy with humoral and cellular inflammatory mechanisms. Concerning the cellular mechanisms our results show that L-selectin may be a pathogenic factor for the migration of lymphocytes to sites of inflammation in dermatomyositis.

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NEUROGENIC INVOLVEMENT IN A CASE OF OCULOPHARYNGEAL MUSCULAR DYSTROPHY. Y. Boukriche, T. Maisonobe, C. Masson, Beaujon Hospital, La Salpetrière Hospital (Clichy, Paris, F)

The question of a possible neurogenic involvement in oculopharyngeal muscular dystrophy (OPMD) is still unsettled and only a few proven cases have been reported. We present a patient with OPMD and clinical, electrophysiological and pathological features of chronic axonal neuropathy. Case report: This man, who had no familial history of neurological disease, noticed a progressive bilateral ptosis at age 49. Slight dysphagia and voice change appeared around 53. When he was first seen at age 54, neurological examination showed a bilateral ptosis, dysphagia and a nasal voice. There was neither ophthalmoparesis nor sensorimotor deficit, deep tendon reflexes were present and symmetrical. Two years later, he began to experience proximal weakness in the lower limbs. There was diffuse areflexia, limbs muscles were wasted and weak. Fasciculations were seen throughout his thighs. At age 58, distal sensory loss was noted, hip-girdle muscles were markedly wasted bilaterally. Three years later, there was wasting of the small muscles of both hands, facial and tongue weakness, fasciculations in the upper limbs and limitation of gaze in all directions. An initial EMG showed a pattern of denervation. Cerebro-spinal fluid was acellular with an increased protein level and oligoclonal bands. A neuromuscular biopsy showed evidence for neurogenic muscular atrophy with severe loss of myelinated axons. The diagnosis of chronic axonal polyradiculoneuropathy was suggested and corticosteroids were introduced, without any improvement. A second EMG showed both neuropathic and myopathic changes and a muscular biopsy was then performed in the deltoid muscle. It was consistent with chronic denervation but also revealed excessive centrally located nuclei and rimmed vacuoles. No ragged red fibers were seen. The patient was found to harbor a (GCG)11 mutation in the PABP2 gene, which confirmed the diagnosis of OPMD. Conclusion: This case suggests a possible, although rare, neurogenic involvement in OPMD and raises the possibility of a phenotype variability of this disease.

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RETINAL INVOLVEMENT IN MITOCHONDRIAL ENCEPHALOMYOPATHIES: A NEW METHOD FOR EARLY DETECTION. Ac Turconi, M Robotti, E Spaggiari, P Nicolini, R Salati, G D'angelo, N Bresolin, Irccs Eugenio Medea (Bosisio Parini Lc, I)

In order to detect early involvement of retinal rods, even in the absence of clear signs of retinopathy, we compared the pattern of dark adaptation in 10 patients affected by mitochondrial encephalomyopathy with that of 10 normal controls and 10 patients affected by retinitis pigmentosa. Background: The frequency of retinal involvement in mitochondrial encephalomyopathies reflects the high oxidative phosphorilation demands of this tissue, especially in dark adaptation. In this condition, mild systemic hypoxia causes an overall decrease in ATP production in the inner segment of the rods, due to impairment of mitochondrial enzymes. This causes a slowing of the Na-K pumps, with increase in the standing potential and final elevation of dark-adapted threshold. Thus, mtDNA mutations, reducing mitochondrial function, might lead to an early impairment of dark adaptation. Design/methods: We selected 6 patients with CPEO (chronic progressive external ophthalmoplegia), 2 patients with MERRF (myoclonic epilepsy and ragged-red fibers) and 2 patients with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes), according to clinical and genetic criteria (group 1); 10 normal controls (group 2) and 10 patients with retinitis pigmentosa (group 3). Each subject underwent fundus oculi examination and dark adaptometry. We performed ERG (electroretinography) in groups 1 and 3, too. Results: In group 1, fundus examination showed mild pigmentary changes only in 2 CPEO patients. Mild impairment of the scotopic ERG was detected in 2 CPEO. Compared to normal controls, all patients in this group presented a characteristic pattern of dark adaptometry with increased latency; in 3 patients (1 CPEO, 1 MELAS, 1 MERRF) an elevation of the dark-adapted threshold was detected, too. In group 3, as expected, fundus oculi and ERG were seriously impaired; mean latency was higher than in group 1, while only 2 patients still had a threshold within normal values. Conclusions: This is the first evidence of an early retinal involvement in mitochondrial encephalomyopathies even in the absence of clinical and electrophysiological signs of retinopathy. Although the few available histopathological studies in Kearnes-Sayre syndrome suggest that the mitochondria of the retinal pigment epithelium are primarily affected, we may now speculate that photoreceptors play a crucial role in the genesis of retinal impairment, even in those syndromes (CPEO, MELAS, MERRF) in which retinopathy is not a typical event. For this reason, we consider dark adaptometry a new method to detect retinal involvement in mitochondrial diseases.

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MOLECULAR STUDY IN A LARGE SERIES OF FRENCH PATIENTS WITH MCARDLE'S DISEASE. C. Bruno, S. DiMauro, A. Lombes, R. Aquaron, University of Genova Istituto G. Gaslini, Columbia University, INSERM, Hôpital de la Timone (Genova, New York, Paris, Marseille, F)

McArdle's disease or muscle glycogen phosphorylase deficiency is a common metabolic disorder characterized clinically by exercise intolerance, myalgia, cramps after exercise, and recurrent myoglobinuria. Around fifty percent of patients have a positive family history, and inheritance is autosomal recessive. The diagnosis is based on the clinical phenotype and on the lack of histochemical or biochemical phosphorylase reaction in muscle. The myophosphorylase gene has been cloned, sequenced and assigned to chromosome 11q13. At last count, molecular studies had identified 21 mutations in the myophosphorylase gene in patients from the United States, Europe, and Japan. The most common defect is a nonsense mutation (R49X) in exon 1, which is present in 64% of the alleles in American and in 81% of the alleles in British patients. This mutation also predominates in most European countries, with an apparent north-south gradient of decreasing frequency (81% in the United Kingdom, 56% in Germany, and 32% in Italy and Spain). In addition, in some countries, such as Japan and Finland, the R49X mutation has never been found, while a few private mutations have been identified. To study the frequency of the R49X mutation in the French population, we analyze 25 patients from 22 families. In all subjects, the

diagnosis was based on clinical features and was confirmed by histochemical/biochemical analysis of muscle. The analysis was performed using DNA isolated from leukocytes by PCR/RFLP analysis. We found that 8 patients were homozygous and 12 were heterozygous for the nonsense mutation at codon 49. The other 5 patients did not carry the R49X mutation and were also negative for 3 other less common mutations described in caucasian patients (missense mutations at codon 204, 396 and a splice-site mutation at the 5'-end of intron 14). Therefore, in our population, the frequency of the R49X, is 56% of mutant alleles. Interestingly, this frequency is similar to that reported in Germany, another central European country, confirming the decreasing north-south gradient of the R49X mutation. Ongoing studies are aimed at identifying other known and novel mutations in the French population.

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POLYMYOSITIS MASQUERADING AS MOTOR NEURON DISEASE. A. Ryan, A. M. Nor, D. Costigan, D. Foley-Nolan, M. A. Farrell, O. Hardiman, Neurology Dept., Beaumont Hospital, Neurophys. Dept., Beaumont Hospital, Rheumatology Dept., W. R. H., Neuropath. Dept., Beaumont Hospital (Dublin, Waterford, IRL)

Dysphagia as an isolated symptom is usually due to anterior horn cell disease, disorders of the neuromuscular junction, or focal myopathy such as oculopharyngeal muscular dystrophy. In these conditions, dysphagia is often slowly progressive, although acute presentation may also occur. Acute onset dysphagia has never been reported as the presenting symptom in polymyositis. Case Report: A 75 year old female presented with acute onset dysphagia. Her symptoms had begun 24 hours earlier, when she noticed severe dysphagia for both liquids and solids. She complained of nasal regurgitation, dysphonia and had features of aspiration. Her past history was remarkable for rheumatoid arthritis, which was in remission. Neurological examination revealed nasal dysphonia with relative preservation of tongue and palatal movements. Her gag reflex was absent bilaterally. Manual muscle testing revealed subtle weakness in the limb girdle muscles of the upper extremities, of which the patient had not been aware. Fasciculations were noted in the right deltoid muscle. Deep tendon reflexes were brisk, and the right plantar response was upgoing. The patient also had evidence of an inactive deforming polyarthropathy. A clinical diagnosis of motor neuron disease was entertained. Laboratory investigations revealed a CK of 150iu/l (normal 0–170). Haematological and biochemical tests were normal, with the exception of a positive rheumatoid factor (1:320). AChR antibodies were negative, as was an edrophonium test. X-ray of the cervical spine revealed spondylosis with significant disc space narrowing at C3/4 and C4/5. Barium videofluoroscopy revealed severe oropharyngeal weakness with pooling of secretions and silent aspiration. EMG showed fibrillation potentials, positive sharp waves, complex repetitive discharges, and small short duration polyphasic units with early recruitment, consistent with a myositis. Biopsy of the left deltoid muscle revealed an active polymyositis. Biopsy of the right quadriceps revealed type II fibre atrophy with no evidence of an inflammatory infiltrate. The patient was treated with high dose steroids and azathioprine and has recovered her ability to swallow. Conclusions: Isolated acute dysphagia can be the presenting symptom of polymyositis. Inflammatory myopathies should be included in the differential diagnosis of acute onset dysphagia in the absence of signs referable to the brainstem. Careless or incomplete investigation of such cases could lead to an erroneous diagnosis of motor neuron disease, particularly in patients with concurrent cervical spondylosis. Detailed EMG studies and muscle biopsy of affected regions are required to establish the correct diagnosis.

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APOPTOSIS IN MYOBLAST TRANSPLANTATION. Y. Torrente, G. Fagiolari, A. Gallanti, C. Lamperti, S. Salani, F. Pisati, S. Corti, G. P. Comi, M. Moggio, N. Bresolin, G. Scarlato, Università di Milano (Milano, I)

Myoblast transplantation is a potential treatment for Duchenne muscular dystrophy. One of the reasons possibly responsible for the limited success of clinical trials is the rapid death of the myoblasts after transplantation. To investigate this problem, myoblasts were injected in the tibialis anterior muscles of CD–1 mice. Injection of saline solution was also performed as control. Groups of three mice were killed 1', 3', 5', 10', 15', 20', 30', 40', 50' and 60' after injections. The injected myogenic cells in the frozen muscle sections were assessed by Hematoxylin & Eosin stain and the expression of desmin, Bcl–2, Fas, Caspase 3, CD–8 and MAC–1 was examined by immunohistochemistry. Apoptosis was detected by in situ labelling using the TUNEL method. Apoptotic myonuclei of injected cells peak in treated muscles after 30' from transplantation. Muscles injected with saline solution were negative for the TUNEL reaction. Few of the apoptotic cells were also caspase 3 positive. Some myofibers surrounding the injected myoblasts also showed apoptotic nuclei. 60' after myoblast transplantation no detection of fragmented DNA was found. These data suggest an effective role of the apoptosis in the rapid death of myoblasts after transplantation. Moreover, the pattern of the myoblasts apoptotic pathway seems to be under a time-dependent mechanism and occurs prevalently within 1 hour after transplantation.

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PHENOTYPE AND GENOTYPE IN 92 PATIENTS WITH MITOCHONDRIAL MYOPATHY, CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA AND KEARNS-SAYRE SYNDROME. T. Klopstock, W. Müller-Felber, M. Jaksch, P. Seibel, T. Gasser, K.-D. Gerbitz, H. Reichmann, D. Pongratz, University of Munich, Hospital Muenchen-Schwabing, Technical University Dresden (Munich, Dresden, D)

We studied clinical phenotype, muscle morphology and mitochondrial genetics in 92 patients suffering from mitochondrial myopathy (MiMy, n=6), chronic progressive external ophthalmoplegia (CPEO, n=27), CPEO plus (n=48) or Kearns-Sayre syndrome (KSS, n=11). Mean age at onset was 42.5 (range 21–59) years in MiMy, 32.7 (7–66) years in CPEO, 27.8 (7–60) years in CPEO plus, and 10.7 (0–20) years in KSS. The most frequent presenting symptoms were: muscle weakness in MiMy (80%), and ptosis in CPEO (70%), CPEO plus (83%), and KSS (45%). Four of 6 patients with MiMy showed neurological signs beyond myopathy as hypoacusis, ataxia or sensory symptoms. Ptosis was found in all patients with CPEO, CPEO plus and KSS, while external ophthalmoplegia lacked in 7 of 86 patients. Electromyography showed a myopathic pattern in 66% of all patients, a neuropathic pattern in 11%, and was normal in 23%. Creatine kinase was elevated in 53% of patients with a mean of 200.5 U/l, and normal in 47%. Muscle biopsy showed ragged red fibers in all patients. Molecular genetic analysis of the mitochondrial DNA revealed deletions in 35 patients, a point mutation at position 3243 in 6 patients, and a point mutation at position 5692 in one patient. The distribution of symptoms in this large sample of patients shows that there is a clinical continuum from MiMy to KSS.

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A FAMILY WITH A NOVEL FORM OF MYOTONIC DYSTROPHY. H. von Lindeiner, L. Riedel, S. Noachtar, T. Gasser, T. Klopstock, Klinikum Grosshadern, LMU Muenchen (Munich, D)

We report on a three-generation family with an unusual form of myotonic dystrophy (DM). Affected individuals have clinical features that are similar to chromosome 19-linked DM including myotonia, mild muscle weakness, cataracts, labyrinthine hearing loss, mental changes, cardiac arrhythmias, endocrine dysfunction, and elevated liver enzymes. Genetic analysis, however, did not show the CTG repeat expansion in the DM gene. Although muscle weakness was pronounced proximally in this family, the phenotype was also different from proximal myotonic myopathy (PROMM), since mental changes have not yet been described in this disorder. Linkage analysis for the DM2 locus on chromosome 3q is pending. The syndrome described here is different from DM and PROMM, and may represent a new member of the group of dominant multisystem myotonic myopathies (DOMMOP).

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DIAGNOSIS OF MITOCHONDRIAL DISEASE: RETROSPECTIVE ANALYSIS OF MULTIDISCIPLINARY APPROACH. O. Olivia Droogan, M. Michael A. Farrell, M. Harmey, J. James Murphy, O. Orla Hardiman, Beaumont Hospital, School of Biological Sciences UCD (Dublin, IRL)

Mitochondrial dysfunction is associated with a wide spectrum of clinical disease. In order to establish a definitive diagnosis, a high index of clinical suspicion must be maintained, followed by biochemical, pathological, functional and genetic studies. Abnormalities in one or more of these areas is suggestive but may not be definitively diagnostic of mitochondrial disease. This study describes the multidisciplinary approach to diagnosing mitochondrial dysfunction as practised by our tertiary referral centre. Methods: All patients suspected on clinical grounds of suffering from mitochondrial disease undergo routine clinical, haematological and biochemical studies. Open skeletal muscle biopsy is performed and tissue is analysed morphologically, by enzyme histochemistry, and by functional mitochondrial assessment including enzyme complex activity, oxidative phosphorylation and in organelle protein synthesis. Mitochondrial genomic studies are performed on tissue from patients in whom there is a high index of suspicion of mitochondrial dysfunction on clinical and/or pathological grounds. Results: Data from 80 patients referred to our unit for analysis of skeletal muscle biopsy from June 1996–October 1999 were analysed. Ages ranged from 3 months to 75 years. All had undergone clinical neurological evaluation which has led to a suspicion of mitochondrial dysfunction. Control muscle biopsies were obtained from routine clinical investigation of other neuromuscular diseases. The following abnormalities were observed in skeletal muscle biopsies from patients with suspected mitochondrial disease: ragged red fibres (18); cytochrome oxidase deficient fibres (16); type 2 fibre atrophy (18). Mitochondrial oxidative phosphorylation was successfully performed on 14 of

these samples, an in organelle protein synthesis was accomplished in material from 12 biopsies. Mitochondrial genomic abnormalities have been documented in 10 samples to date. Conclusions: A multidisciplinary approach to the correct diagnosis of mitochondrial dysfunction is essential. Using all of the available, clinical, morphological, functional and genomic tools, the diagnostic yield in establishing clinically significant mitochondrial dysfunction in our population was approximately 20%.

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SOMATIC INSTABILITY OF PREMUTATED ALLELES IN TWO PATIENTS WITH A PREMUTATED AND A FULL-MUTATED ALLELE. Abruzzese C*, Costanzi S*, Monckton DG**, Mariani B* and Giacanelli M*
(*) Dept of Neurosciences, A.O. S. Camillo/Fortanini, Rome – Italy
(**) Div. Molecular genetics, Univ. of Glasgow, UK

Myotonic Dystmphy (DM) is the most common form of neuromuscular disorders with late-onset. DM is caused by the expansion of an unstable CTG trinucleotide repeat localized in the 3' UTR of a gene designed DMPK on chromosome 19q13.3. The expanded CTG triplet repeat in the DMPK gene shows both germline and somatic instability; however the extent of tissue heterogeneity and the mechanisms of the instability are still unknown. We present a DM family with two patients having both a premutated allele and a full mutated allele. Molecular analysis of the CTG triplet repeats in the nuclear family gave the following results: $(CTG)_{18/52}$ for the father, $(CTG)_{14/43}$ for the mother, $(CTG)_{43/500}$ for the daughter, $(CTG)_{14/18}$ for the non affected son and $(CTG)_{43/180}$ for the affected son. Both the affeeted siblings show classical DM clinical signs as myotonia, distal weakness, myotonic facies and cataracts. Moreover the afected son, in spite of the age (28 years) and of the relatively short length of the mutated allele, shows azoospermia. We focalized our study on the stability/instability of premutated alleles in co-presence either with a full-mutated allele or with a normal ranged allele. The behaviour of premutated alleles was analyzed by using the small-pool-PCR (SP-PCR) technique. SP-PCR analysis an DNA from blood leukocytes of the mother shows a somatic instability of the premutated allele of about 30%. As expected, the pattern of the distribution is mostly skewed toward larger alleles, with the maximum addition of 2 triplet repeats. Only the 2% of the alleles shows the maximum deletion of 1 CTG repeat. Conversely, the SP-PCR from PBL's of the affected siblings shows a high rate (about 70%) of somatic instability of the premutated allele. Strikingly, in both patients are present expansions increasing from the premutation range to the pathological range, with the highest addition of 13 repeats and deletions reverting the premutated allele in the normal range (33 CTG repeats). Such a situation has never been found (if not in germ line) in somatic cells (PBL's). The high rate of instability, in terms of frequency (70% v/s 30%) and distribution (addition/deletion) of premutated alleles, is suggestive of a possible influence of the full-mutated allele in trans, as result of interallelic interaction between the unstable expanded and the premutated alleles.

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CONGENITAL MYOPATHY OF FINGERPRINT BODY TYPE: REPORT ON A FAMILY. T. Stojkovic, C. A. Maurage, A. Moerman, J. F. Pellissier, P. Vermersch, Chru de Lille-Hospital Roger Salengro, Chru de la Timone (Lille, Marseille, F)

Objective: To report a family with congenital myopathy characterized by fingerprint inclusions.

Background: Originally described by Engel in 1972, fingerprint body myopathy is a rare condition with only two families published (Fardeau et al., 1976; Curless et al., 1978).

Patients: A 26 year-old patient, referred to our department, is the first child of non-consanguineous caucasian parents. He presented hypotonia during early chilhood and was able to walk at 20 months of age. He had proximal weakness predominantly in pelvic girdle and difficulties in rising from the recumbent position. The first electromyogram (EMG), performed when he was 6-year-old, led to the diagnosis of Kugelberg-Welander disease. During the adolescence, the weakness involved shoulder and pelvic girdle. Moderate facial weakness and mild wasting of shoulder muscles were noticed. Tendon reflexes were all abolished. Fine mouth, high-arched palate, flat feet were also observed. His sister, aged of 16 years, presented a similar phenotype with more pronounced pelvic weakness. She had difficulties in rising from the floor or a chair. These two patients had normal cognitive functions. EMG disclosed a myogenic pattern. Creatine kinase levels were 1000 U/l. Clinical examination of both parents was normal. Muscle biopsy showed a predominance of type I fibers. Several cores were observed on electron microscopy as well as other structural changes such as Z-line streaming. Dense non-reducing inclusions, initially noted under the sarcolemma on histochemical examination, had a lamellar patern at ultrastructural level. These structures showed the typical feature of fingerprint inclusions, which were largely distributed along the fibers.

Conclusion: Fingerprint body myopathy remains controversial, as fingerprint inclusions have been also observed in other myopathies. However, in our case, the numerous and widespread distribution of fingerprint inclusions argues in favour of a true and distinct congenital myopathy.

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CHOREA AS A PRESENTING FEATURE IN MITOCHONDRIAL DISEASE: TWO NEW CASES. K. Viala, T. Maisonobe, R. Levy, F. Chochon, M. Miloudi, C. Jardel, C. Pierrot-Deseilligny, Y. Agid, A. Lombès, Hôpital de la Salpêtrière (Paris Cedex 13, F)

Chorea is unusual in mitochondrial disorders and has only been reported in two cases (Ann Neurol 1995, 37:400–403, Brain 1995, 118: 339–357).

We describe two unrelated patients with generalized chorea revealing a mitochondrial cytopathy. The first patient presented generalized chorea, ataxia, deficit of proprioception, ophthalmoparesis without ptosis, and a mild frontal impairment at the age of 39. The second patient was referred for generalized chorea at 23 years. Eight years later, she developed severe pain in lower limbs, ataxic gait, dysphagia, diplopia and bilateral ptosis. Both patients had no familial antecedent. Huntington's disease and neuroacanthocytosis were excluded.

Investigations showed similar results in both patients. Electrophysiological studies revealed myopathic changes and a predominant sensory neuropathy. Blood lactate was increasing, ragged-red and COX-negative fibers were observed in deltoid muscle. Mitochondrial enzymatic analysis showed a mild defect of the respiratory chain complex IV. Mitochondrial DNA appeared to be of normal size and amount by Southern blot. The search for mutations in mitochondrial tRNA genes is ongoing by Denaturing Gradient Gel Electrophoresis. In conclusion, a mitochondrial etiology should be included in the diagnosis of generalized chorea. The genetic defect of this phenotype remains to be determined.

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INFLUENCE OF SERUM DEPRIVATION ON APOPTOSIS IN MUSCLE CELLS LINE. U. K. Zettl, C. Rehfeldt, G. Nürnberg, S. Dilk, M. Wittstock, T. Böttcher, E. Mix, University of Rostock, Res. Inst. Biol. of Farm Animals (Rostock, Dummerstorf, D)

Susceptibility to apoptosis appears to be a key property in the development of muscle cells under physiological and pathological conditions. Serum deprivation is a strong inductor of apoptosis and therefore suitable for assessment of susceptibility of muscle cells to apoptosis.

Cells of the permanent mouse muscle cell line C2C12 were used to study the influence of serum deprivation on the frequency of apoptosis at different stages of development. The cells were seeded in 35 mm plastic dishes and grown to confluence in Dulbecco's Modified Eagle's medium (DMEM) with 0.02 M glutamine, 100 IU/mL penicillin, 25µg/mL fungizone, and 10% fetal bovine serum (FBS). Serum content was lowered to 1% at day 4 of cultivation when the cultures were confluent and at day 6 when myotubes were apparent. Before serum deprivation (0 h), and at 24 h and 48 h thereafter, samples were collected to determine DNA and protein contents of the monolayers and the frequency of apoptotic cells by terminal transferase ddUTP nick end labeling (TUNEL) and flow cytometric analysis of the cells from monolayers and supernatants. The data of 4 experiments were subjected to analysis of variance.

The responses to serum deprivation appeared different between d 4 and d 6 of development. Serum deprivation at day 4 led to an increase in the percentage of apoptotic cells within 48 h from 6.9 to 12.6% on average ($P < 0.05$). During this time slight increases in DNA (2.7 to 3.7 µg) and protein contents per dish (55.2 to 94.5 µg) were measured ($P < 0.05$), but the values remained below those attained after growth in DMEM with 10% FBS (5.0 and 124.4 µg, resp.). The percentage of apoptotic cells was much higher at day 6 compared to day 4 of cultivation (18.1 vs 6.9% at 0 h). In response to serum deprivation at day 6 of cultivation no changes in the percentage of apoptotic cells were seen when comparing the values of 0 h and 48 h. However, a transient decrease until 24 h was followed by an increase until 48 h. No significant differences in DNA and protein contents were found after day 6 of serum deprivation.

The results suggest that the occurrence of apoptosis in muscle cells in response to serum deprivation depends on the developmental stage of the muscle cells. The proportion of apoptotic cells seems to decrease as differentiation and formation of myotubes proceed.

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PRIMARY BETA-SARCOGLYCANOPATHY MANIFESTING AS RECURRENT MYOGLOBINURIA INDUCED BY MUSCLE EXERCISE. G. Comi, M. Sironi, F. Fortunato, R. Giorda, A. Bardoni, M. Moggio, L. Tancredi, N. Bresolin, University of Milano, IRCCS E. Medea, Ospedale Maggiore Policlinico (Milano, Bosisio Parini, I)

Limb girdle muscular dystrophy (LGMD) type 2E is a genetically heterogeneous group of disorders, characterised clinically by predominantly proximal muscle weakness of variable severity, dystrophic changes on muscle biopsy and variable deficiency of sarcoglycan complex proteins. We report on an unusual presentation of a primary beta-sarcoglycanopathy. A 12 year-old boy came to our attention after four episodes of exercise-induced myoglobinuria. Family history was negative for neuromuscular disorders. CK level after the last episode was 18.460 U. I. and varied from 2.000 to 4.000 in the interval between each episode. EMG showed mild myopathic features at the proximal upper limb muscles. ECG was normal. General examination was also normal. A muscle biopsy showed rare regenerating fibers; the immunohistochemistry was normal for dystrophin, while there was a diffuse pattern of decrease of all the sarcoglycans. Western blot analysis showed relevant decrease of alpha and gamma sarcoglycan and a mild reduction also of dystrophin. Genetic analysis excluded mutations in the gamma- and delta-sarcoglycan genes. Beta-sarcoglycan gene analysis demonstrated that the patient is a compound heterozygous for these mutations: a previously undescribed A-> T base pair substitution at nucleotide 85 in exon 2, changing the codon Arg to a stop codon; a C-> T base pair substitution at nucleotide 272 in exon 3 changing a Arg to a Cys residue.

Exercise-induced myoglobinuria may be the presenting sign of a number of different muscle dystrophic processes, including primary beta-sarcoglycanopathy.

P483
NORMAL INTELLIGENCE AND DECREASED SHIFTING ATTITUDE IN MYOTONIC DYSTROPHY PATIENTS. A. A. Tieleman, J. Hofmeijer, K. P. M. van Spaendonck, B. G. M. van Engelen (Nijmegen, NL)

Myotonic dystropy (MyD) is an autosomal dominant multisystem disease, resulting from an expansion of cytosine-thymidine-guanine (CTG) trinucleotide repeats in the 3'-untranslated sequence of a gene, located at the q13.3 band of chromosome 19. The length of the CTG repeat increases with each generation and is positively related to the severity of the clinical symptoms, consisting predominantly of myotonia, slowly progressive weakness and atrophy. Cognitive impairment is common in MyD and can sometimes be the most disabling component of the disease. The clinical picture is highly variable, but strongly related to age of onset, which has resulted in several subtypes of MyD; congenital, childhood (onset< 10 years), juvenile adult (10–50 years) and minimal (> 50 years) MyD.

Because of this age dependency of signs and symptoms we studied a homogenous group of 21 adult onset MyD patients (11 men, 10 women) mean age 44.6 years, mean duration of disease 21.2 years. In this group we applied an extensive battery of neuropsychological tests, including the Stroop Color Word Test, to characterise mental functioning. In order to avoid the demand of dual task performance – combining cognitive function with speaking fast and aloud – a push-button related computerised Stroop Color Word Test was developed with the aim of exclusion of the motor component of this test.

This study showed a normal intelligence and normal neuropsychological test results which did not differ from normal controls except for a significantly lower score on both simple and complex Stroop Tests. These results contradict the hypothesis that low scores of MyD patients on the Stroop Color Word Test originate from problems of dual task performance, due to dysarthria. They rather suggest that cognitive dysfunction of MyD patients with adult onset is restricted to a deficit in shifting, which correlates with the clinical impression of mental persistence.

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SKELETAL MUSCLE ADAPTATION TO AEROBIC TRAINING IN MITOCHONDRIAL MYOPATHIES. G Siciliano, ML Manca, M. Renna, M. Mancuso, V. Lombardi, A. Rocchi, C. Camaschella, University of Pisa /, University of Turin (Pisa, I)

The pathogenesis of cell damage in mitochondrial diseases suggests that muscle adaptation can occur in some experimental conditions. The data from histological and mitochondrial DNA (mtDNA) analysis of muscle biopsies from 12 patients affected by mitochondrial myopathies (MM) and mtDNA single or multiple deletions were related to metabolic parameters during a constant-workload exercise performed at near lactate threshold (LT), before and after a 10-week course of aerobic training.

All subjects had not been taking medications. The training program consisted of supervised exercise, on electrically braked pedal-rate bicycle ergometer, on the other day, for each patient. The training program included 30 min of exercise for the first 5 weeks and 45 min of exercise, interspaced with 5 min of interval, for the following 5 weeks. In MM patients, mean rest values of lactate decreased after training by 15.5 %; EP by 22.2 % and NEP by 24.2. Lactate peak mean values significantly decreased ($p < 0.05$), as effect of the training, both in MM (–38.6 %) and in controls (–29.5 %). In fact exercise lactate mean increment in MM achieved 314.9 % of the rest value after training compared to 434 % before it (229.8 and 324.8 % respectively in controls, $p < 0.05$). The exercise-induced bout in plasma catecholamines in MM patients was, after the training program, less high compared to controls, with a difference pre-training / post-training of –26 % for EP and –22.1 % for NEP (in controls: –22.5 and –26.7 % respectively). After the aerobic training, lactate/EP area ratio was 1.63 vs. 2.05 (1.20 vs. 1.40 in controls) and lactate/NEP: 1.27 vs. 1.75 (1.19 vs. 1.29 in controls).

No relationship was found between the decrease in lactate / catecholamine peak values and number of ragged red fibers or cytochrome c oxidase negative fibers. On the contrary an inverse trend between the lactate peak decrease and the proportion of deleted mtDNA was observed.

The results show that lactate accumulation during exercise is decreased after aerobic training in mitochondrial myopathy, and that the reduction of exercise lactate increment seems unrelated to cardiovascular and catecholaminergic adaptation to exercise. Furthermore, the level of mutated mtDNA in muscle biopsy could be a useful predictor for the effectiveness of aerobic training program, suggesting some gene shifting mechanisms in mediating muscle adaptation to training.

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A UNIQUE PHYSIOLOGICAL T-CELL INFILTRATE OCCURS IN MUSCLE IN RESPONSE TO EXERCISE INDUCED DAMAGE. J. A. L. Miller, D. Scheel-Toellner, S. J. Curnow, A. Donnelly, H. Roper, M. Salmon, J. B. Winer, University Of Birmingham, University Of Limerick, Heartlands And Solihull Trust (Birmingham, UK; Limerick, Irl)

Muscle biopsies taken from normal subjects after unaccustomed exercise reveal a marked leukocyte infiltrate that is histologically indistinguishable from that found in polymyositis. Unlike polymyositis it resolves within 2–3 weeks after exercise damage. To study the characteristics of the infiltrate, we obtained muscle needle biopsies from the quadriceps of 10 healthy volunteers at 1, 6, 12 and 168 hours after a 10-minute exercise protocol and from 3 resting control subjects.

Elevated serum creatinine kinase levels demonstrated that marked muscle damage of the quadriceps occurred from the exercise protocol. Muscle damage within individual biopsies was assessed by observing for disruption of the sarcolemma, intermediate filaments and metabolic activity of muscle fibres. Cell types were identified using immunofluorescence techniques.

In 4 micron frozen sections, the mean number of T-cells per 1000 muscle fibres increased from 4 (range 3 to 6, n=3) in resting controls to 11 (range 9 to 12, n=2) at 12 hours post-exercise damage. The mean number of macrophages increased from 72 (range 65 to 78, n=3) per 1000 fibres in resting controls to 108 (range 83 to 108, n=2) at 12 hours post-exercise damage. The mononuclear infiltrate was florid at 7 days post-exercise. No neutrophils were observed at any time point.

During muscle regeneration there is a proliferation of fibroblasts and myoblasts. In control biopsies myoblasts were not observed and fibroblasts were restricted to vessel walls and perimysial connective tissue. At 7 days post-exercise damage, myoblasts were located at the periphery of damaged fibres with surrounding fibroblasts. Macrophages were located within damaged fibres (93 %) reflecting their role in phagocytosis whereas T-cells were in contact with the myoblasts and fibroblasts and rarely found within fibres.

In contrast to an acute inflammatory response the marked mononuclear infiltrate after exercise induced damage is not preceded by a neutrophilic infiltrate. Muscle tissue regeneration appears to involve a novel role for T-cells. The physiological infiltrate of T-cells in eccentric exercise may help in understanding the pathological features of chronic inflammation found in polymyositis.

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ADULT-ONSET NEMALINE MYOPATHY REVEALED BY CAMPTOCORMIA. P. Variet, C. Lamy, F. Beuvon, C. Daumas-Duport, M. Zuber, *Department of Pathology-Neurooncology and **Department of Neurology, Hôpital Sainte Anne and Faculté de Médecine Cochin Port-Royal, Paris, France

Nemaline myopathy is a rare congenital muscle disease with 3 clinical subtypes: severe neonatal, slow progressive congenital and adult-onset forms. The latter form is exceptional and its origin remains obscure.

We present an unusual case of a 77 year-old woman with late-onset nemaline myopathy revealed by camptocormia (bent spine syndrome). Her past medical history was unremarkable until the age of 62 when she developed a progressive camptocormia. Neurologic examination confirmed the lumbar reducible kyphosis, a mild bilateral proximal lower muscle weakness without sensory symptoms. Electromyographic findings showed a diffuse myopathic process and CT scan of skeletal muscle showed a low density of paravertebral and posterior crural muscles. Creatinine kinase, thyroid hormone level, HIV

serology, antinuclear factors and serum protein immunoelectrophoresis were all normal.

Open quadriceps muscle biopsy revealed a myopathic pattern with numerous rods occurring in 50% of the fibers without inflammation. Electron microscopy revealed nemaline bodies which are hallmarks of this disorder, in nearly all the atrophic fibers.

Past family history was presumably relevant with sudden cardiac failure of her father, brother and sister at respectively 68, 65 and 63 years. Because of these genealogic characteristics, DNA studies included screening for mutations in human alpha-tropomyosin gene (TPM3) nebulin gene (NEM2) and skeletal muscle alpha actin gene (ACTA1) which to the best of our knowledge, have not been described in late onset nemaline myopathy.

P487
CAP DISEASE – A FAILURE IN THE EMBRYONIC MUSCLE FIBER FORMATION. A. Fidzianska, Neuromusc Unit Med Reser Pol Acad Sci (Warsaw, PL)

Cap disease is one of congenital myopathies clinically defined by muscle hypotonia, weakness, skeletal dysmorphism and respiratory insufficiency since childhood. We observed 4 cases of cap disease presenting two forms fatal and benign.

Morphologically, the muscle biopsy is characterized by peripherally located structures resembling caps. Such structures are characterized by lack of ATP-ase, fast myosin activity and increase in desmin, tropomyosin, alpha-actinin. Cap structures devoid of ATP-ase activity consist of loosely packed myofibrils perpendicularly situated to the long axis of muscle fibers. In addition, the myofibrils forming the cap differed in ultrastructural feature from the normal sarcomere pattern. A specific change in the muscle architecture allowed us to speculate that a failure in the process of muscle fiber formation during myogenesis may occur in cap disease. However the morphological changes in the muscle fibers were identical in all investigated cases, the number of muscle fibers with cap structures was much higher in the fatal form of disease.

Peripheral neuropathy

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BILATERAL FEMORAL COMPRESSION NEUROPATHY SECONDARY TO SPONTANEOUS ILEOPSOAS HEMATOMA DURING HEPARIN THERAPY: A CASE REPORT. A. Jaramillo, L. García, J. Idiáquez, Hospital Naval A. Nef (Viña del Mar, RCH)

A case of femoral neuropathy from ileopsoas muscles hematoma occurring during constant intravenous infusion of heparin for myocardial infarction is reported. Case Report: A 67-year old man with history of arterial hypertension and unstable angina pectoris suffered a subepicardical ischemia during the exercise testing and was treated with Heparin 25.000 IU every day during 5 days, followed by low molecular weight heparin Deltaparin 8400 IU every day during two days. In the third day presented pain in the lumbar region and in both thighs followed by paralysis of the extension of the legs, weakness of flexion of the thighs, decrease of the patellar reflexes and sensory loss over the anterior thigh and the left medial calf. The electrophysiology study confirmed bilateral femoral neuropathy. A computerized tomography of the abdomen and pelvis showed a diffuse enlargement of both ileopsoas muscles and a pelvic ultrasound examination confirmed a distal intramuscular hematoma. The left hematoma was larger than the right and caused a more severe femoral neuropathy. Daily serum analysis revealed that the total creatinine kinase (CK) and CK MB and the activated partial thromboplastin time all were above the therapeutic range at the time when the bleeding started, and before the initial symptoms occurred. After seven days a skin hematoma in lumbar region and both thighs appeared. The hematoma was treated conservatively and the patient had a complete recovery. Discussion: Bilateral ileopsoas muscles hematoma with secundary compression of the femoral nerve is a rare complication of anticoagulation therapy. The early diagnosis is very difficult and it must be suspected in patients receiving anticoagulation therapy who develop pain and weakness in the femoral nerve territory before a skin hematoma appears.

P489
CELL DEATH IN VASCULITIC NEUROPATHY. D. Heuss, S. Probst-Cousin, C. Kayser, B. Neundörfer, University of Erlangen-Nürnberg (Erlangen, D)

Background: Vasculitic neuropathy is characterized by predominantly CD4+ and CD8+ perivascular infiltrates. CD8+ cytotoxic lymphocytes are capable of killing the target cell by different ways. Some mechanisms require the release of molecules like perforin, granzymes and TIA–1 (T cell restricted intracellular antigen), which induce cell death by necrosis and apoptosis. Concerning the latter, a nonsecretory ligand-mediated mechanism has been proposed. This killing mechanism requires the interaction between Fas (expressed on the target cell) and Fas-ligand (expressed on the T cell). We studied these mechanisms in nerve biopsy specimens of vasculitic neuropathy. Material and methods: Open nerve biopsy was performed on the sural nerve. 19 cases of vasculitic neuropathy were compared with 8 controls by light-microscopical investigation employing conventional and immunohistochemical detection procedures. For the detection of DNA fragmentation terminal deoxynucleotidyl transferase (TdT)-mediated nick end labeling (TUNEL) was performed. Results: In neuropathological terms, cases with vasculitis presented with an axonal neuropathy together with epineurial-perivascular and sparse endoneurial inflammatory CD8+ cytotoxic cells. Mononuclear cells predominantly expressed TIA–1, granzyme A, granzyme B, whereas perforin could be detected to a lesser degree. Regarding the ligand-mediated mechanism, we observed Fas and Fas-ligand expressing mononuclear cells in an epineurial-perivascular distribution. Upregulation of the anti-apoptotic molecule bcl–2 was also seen in mononuclear cells. Cells undergoing apoptosis, as demonstrated by TUNEL, represented perivascular mononuclear cells. Target cells lacked features of apoptosis by TUNEL. Conclusions: In vasculitic neuropathy, apoptosis by both a secretory mechanism via TIA–1 and granzymes and by a non-secretory ligand-mediated mechanism (Fas, Fas-ligand) is suspected. However, apoptosis seems to be restricted to inflammatory mononuclear cells, since there is no evidence of apoptotic cell death of target cells. Thus, apoptosis might play a critical role in natural recovery from vasculitic neuropathy. On the other hand, perforin mediated necrosis seems to be a minor pathogenetic factor.

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IS THE FREQUENCY OF NERVE LESIONS ASSOCIATED WITH TOTAL HIP ARTHROPLASTY UNDERESTIMATED? S. Otto, E. Trost, M. Poremba, M. Gabel, H.-W. Springorum, Caritas Krankenhaus (Bad Mergentheim, D)

In the literature, nerve lesions following total hip arthroplasty are described as rare complications with an overall prevalence of about 1%. However, most studies are retrospective or analyze only part of the possibly damaged neuromuscular structures. Methods: In a prospective study 50 patients were examined clinically and with electromyography (EMG) pre- and 14 days postoperatively following a standardized protocol. Preoperatively, none of the patients had signs of neuromuscular lesions. All patients received a cementless total hip arthroplasty (anatomical head, spherical cup) via the transgluteal approach after Bauer (1), which is comparable to the Hardinge (2) approach. EMG analysis was made of the iliopsoas, vastus med., tibialis ant., soleus, biceps fem. (short head), and gluteus med. muscles of the operated extremity. Results: Paresis was found in 38 (76%) patients postoperatively, among them 19 (50%) with mild (Medical Research Council scale for grading muscle strength, level 4), 17 (45%) with moderate (level 2 or 3), and 2 (5%) with severe (level 0 or 1) deficits in one or more muscles. In 27 (54%) branches of the femoral nerve with subsequent palsy of the iliopsoas muscle were involved, in 21 (46%) the superior gluteal nerve with paresis of the gluteus medius muscle, in 5 (10%) the femoral nerve with paresis of the iliopsoas and the vastus med. muscle. Eleven (22%) patients had lesions of the lumbosacral plexus with relating patterns of pareses. Patients with postoperative lesions were examined again 3 to 6 months later, 57% demonstrated complete resolution of their paresis, 37% incomplete recovery, and there was no change in 7%. Conclusions: Clinically and electromyographically proven nerve lesions with paresis occur after standard hip arthroplasty more frequently than generally known. Electrophysiological criteria demonstrated structural axonal damages that might be caused by intraoperative stretching of one or several nerves and/or of parts of the lumbosacral plexus. While in the majority of cases there is satisfactory recovery, some patients continue to suffer from severe paresis. (1) Bauer, R., Kerschbaumer, F., and Poisel, S. The transgluteal approach to the hip joint. Arch. Orthop. Traumat. Surg. 95:47–52, 1979; (2) Hardinge, K. The direct lateral approach to the hip. J. Bone Joint Surg.[Br.] 64:17–19, 1982

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FIRST REPORT OF MULTIFOCAL MOTOR NEUROPATHY AFTER HEPATITIS B VACCINATION. N Duchamp-Vandenberghe, M Debouverie, M Weber, Department of Neurology (Nancy, F)

Since 1994, the hypothesis of a relationship between vaccination against hepatitis B and inflammatory diseases is discussed. Several neurological adverse reactions were reported with hepatitis B vaccination, which are relapses of multiple sclerosis, Guillain-Barré syndrome, polyneuropathy, transverse myelitis, facial nerve palsy, cerebellar ataxia, visual loss, uveitis, sterile meningitis. We

report the case of a 31-year old white man with a multifocal motor neuropathy with conduction blocks. He was previously fit, and presented 60 days after the intramuscular injection of hepatitis B vaccine (GENHEVAC B Pasteur, 0,5 ml), progressive worsening of weakness of left hand and arm with cramps and fasciculations. At physical examination, we found mild wasting of the hyperthenar and hypothenar muscle of the left hand, fasciculations and amyotrophy of the left quadriceps femoris. The patient had not upper motor neuron signs. No routine blood work-up abnormalities were found. There was a high protein content in cerebrospinal fluid (0,60 g/l) with normal cell count. There was no oligoclonal IgG. The nerve-conduction studies showed persistent localised pure motor conduction, proximal blocks of the left cubital nerve and the left peroneal nerve with normal motor and sensory conduction velocities. The further biological results found a high positivity of polyclonal IgM anti-GM1 ganglioside antibodies (ELISA: 1/3200). The neurological weakness worsened during three years. The patient has been treated by immunosuppressive drugs (azathioprine for 6 months, cyclophosphamide for 1 year) and last year with 6-weekly doses of high-dose intravenous immunoglobulin after an initial perfusion of 5 days (0,4 g/kg). Actually, six years later, the patient has a stabilization of his neurological signs, the anti-GM1 IgM antibodies remain positive at a lower level. To the best of our knowledge, this is a first reported case of multifocal motor neuropathy with conduction blocks after hepatitis B vaccination. This illness is a chronic immune-mediated neuropathy and the postulate of the role of anti-GM1 antibodies (generated from peripheral blood lymphocytes) is that they interfere with saltatory conduction, by blocking sodium channels. Standard anti-hepatitis B virus vaccination elicits peripheral blood mononuclear cell proliferative responses, and are mediated by CD4+ T lymphocytes. The potential causal relationship between vaccination and multifocal motor neuropathy is possible.

P492
ULTRASOUND IN THE DIAGNOSIS OF ULNAR NEUROPATHY AT THE ELBOW. B. P. W. Jansen, M. C. Schoemaker, L. H. Visser, Rijnstate Hospital, St. Elisabeth Hospital (Arnhem, Tilburg, NL)

Objective: To investigate the role of ultrasound in ulnar neuropathy at the elbow (UNE), as an additional test to clinical and electrodiagnostic examination. Background: UNE is a frequent cause for neurological consultation. Diagnosis rests on clinical and electrodiagnostic evaluation. Treatment is usually conservative, minority profiting from neurosurgical decompression or transposition of the ulnar nerve. In these cases, reliable localisation of the lesion is necessary. Unfortunately, other conditions (lower cervical radiculopathy, plexopathy, thoracic outlet syndrome) may mimic symptoms and signs of UNE, and nerve conduction studies may be influenced by elbow position, or short segment length of nerve measured across the elbow. Myography often fails to prove an UNE since the ulnar nerve has no motor branches above the elbow, and even with clear UNE forearm muscles may remain intact. Case reports and small series have suggested a role for ultrasound in the diagnosis of compression neuropathies (e. g. carpal tunnel syndrome). It offers an essentially different way of investigating the possible entrapment site, is painless and noninvasive. Method: Eleven patients clinically suspected of UNE were examined; 2 patients had bilateral involvement. All underwent careful clinical examination, and were subjected to EMG, which included sensory and motor nerve conduction velocity over forearm and elbow segments, additional inching over the elbow segment, and needle myography of Flexor Carpi Ulnaris, Flexor Digitorum Profundus (ulnar part), Interosseus Dorsalis I and Abductor Digiti Minimi. Ultrasound investigation of the ulnar nerve at the elbow was performed by an experienced radiologist who was blinded to clinical and electrodiagnostic data. Also 10 healthy controls had ultrasound examination of the ulnar nerve at the elbow (bilaterally). Results: Thirteen ulnar nerves were examined in 11 patients. Electrodiagnostic evaluation was abnormal in 8 arms (7 patients), localising the ulnar nerve lesion at the elbow in 7 of 8 cases. Ultrasound also identified 8 abnormal nerves, 7 of which were consistent with the EMG findings. One patient had abnormal ultrasound with normal EMG, one patient had abnormal EMG but normal ultrasound. In no patient in our (small) group ultrasound influenced treatment decisions. All controls had normal ultrasound evaluations. Conclusions: Ultrasound examination of the ulnar nerve is consistent with clinical and electrodiagnostic results in most patients. We recommend ultrasound if clinical testing and electrodiagnostic studies are inconclusive, and if surgical treatment is planned.

P493
UPREGULATION OF CYCLOOXYGENASE 2 IS DEPENDENT ON TUMOR NECROSIS FACTOR RECEPTOR 1 AND 2 AFTER CHRONIC CONSTRICTION INJURY. M. Marziniak, C. Sommer, Neurologische Universitätsklinik (Würzburg, D)

A frequently used experimental neuropathy causing hyperalgesia and allodynia is produced by tying loosely constrictive ligatures (chronic constriction injury, CCI) around one sciatic nerve. Treatment with antibodies (AB) to tumor necrosis factor-alpha (TNF) or to TNF receptor 1 (TNFR1) can prevent reduction of withdrawal thresholds to thermal and mechanical stimuli in mice with CCI. In previous studies on the pathology of the chronically injured nerve we observed a marked increase in immunoreactivity (IR) for the proinflammatory cytokines, TNF, interleukin 1 beta and interleukin 6. Proinflammatory cytokines are known to induce cyclooxygenase (COX)–2 expression, the inducible isoform of COX. COX upregulation in the nerve would be expected to increase hyperalgesia via elevated prostaglandin levels. The aim of the present study was to investigate, whether COX-IR in the sciatic nerve after CCI is dependent on the presence of TNF, the TNFR1 or the TNF receptor 2 (TNFR2). In the first experiment TNFR1, TNFR2, TNFR1/R2 knockout (ko) mice or wildtype mice (WT) underwent CCI and the nerve was harvested at day 14. In the second experiment CCI was performed in the sciatic nerve and the mice were treated daily by local epineurial administration of sheep IgG, TNF-AB, TNFR1-AB, or TNFR2-AB until day 7. Cryosections of 4–7 mice per group of the nerve segment distal of the ligatures were stained with COX–1-AB and COX–2-AB and morphometric analysis was performed. The endoneurial COX–2-IR was significantly reduced on day 14 in TNFR1 ko (1.71 % ± 0.32 %) and TNFR1/2 ko (2.2 % ± 1.07 %) compared to CCI-operated WT-mice (4.8 % ± 1.25 %), but not in TNFR2 ko (3.02 % ± 0.93 %.). All antibody treated animals showed decreased COX–2-IR: anti-TNF (1.52 % ± 0.92), anti-TNFR1 (1.83 % ± 0.73 %), anti-TNFR2 (1.92 % ± 0.66 %) versus the IgG-treated (3.48 % ± 0.97 %). Contrary to COX–2, the endoneurial COX–1-IR was not significantly different between the groups, e. g. IgG treated (1.73 % ± 0.29) versus anti-TNF treated mice (1.66 % ± 0.25 %). These data suggest that injury-induced upregulation of COX–2 in CCI is mediated via both TNF receptors, with predominance of the TNFR1. We conclude that this pathway may be one possible mechanism not only in acute pain generation but also in the maintenance of the pain-associated behavior in the CCI-model of neuropathic pain.

P494
IMPROVEMENT OF POSTRADIATION LUMBOSACRAL RADICULOPLEXOPATHY AFTER IMMUNE THERAPY. M. Carpo, A. Bersano, A. Di Troia, G. Scarlato, E. Nobile-Orazio, Milan University, IRCCS Ospedale Maggiore Policlinico (Milan, I)

A delayed progressive impairment of peripheral nervous system including brachial and lumbosacral radiculoplexopathy is a well known complication of local radiotherapy. No treatment for this infrequent complication is currently available. Recently, improvement after treatment with high dose immunoglobulin (IVIg) has been reported in some patients suggesting either an immune mediated nerve damage induced by irradiation or a dysimmune neuropathy (CIDP-like) misdiagnosed as postradiation disease. We report on two patients who developed motor lumbosacral radiculoplexopathy several years after local radiotherapy. The first patient (ZA) is a 49-year-old man developing a progressive proximal>distal weakness and hypotrophy of lower limbs, 20 years after radiotherapy of the lumbosacral region for seminoma. Electrophysiological studies showed markedly reduced motor conduction velocities (CV) and prolonged F-waves latencies in lower limb nerves. The second patient (BF) is a 52-year-old woman who developed progressive left brachial plexopathy and distal>proximal weakness and hypotrophy of lower limbs 12 years after a first course of thoracic and lumbar irradiation for Hodgkin lymphoma, followed by a second course of cervicoclavicular irradiation for tumor recurrence 7 years later. Electrophysiological studies showed markedly reduced CMAP amplitudes and proportionally reduced CV in motor nerves. No sensory impairment was detected in both patients. CSF proteins were elevated in both patients while cells were normal. On the assumption of the possible dysimmune origin of the disease, patient ZA underwent high dose intravenous steroid treatment, while patient BF, who had previously deteriorated after steroids, was treated with IVIg. After treatment, patient ZA became able to walk with less waddling, to rise from the floor and climb stairs without support and to run. Improvement was less consistent in patient BF whose right leg strength improved even if she still needed bilateral support to walk. The improvement observed in both patients support the hypothesis that, at least in some patients, an immune mediated mechanism may underlie postradiation radiculoplexopathy.

P495
SECONDARY HYPOKALAEMIC PARALYSIS MIMICKING GUILLAIN-BARRÉ SYNDROME. S. Gierer, M. Hartmann, K. Scheglmann, Neurologische Klinik am Klinikum Darmstadt, Neurologische Klinik am ZK Augsburg (Darmstadt, Augsburg, D)

Secondary hypokaliemia is a rare cause of progressive tetraparesis. We report clinical, laboratory and neurophysiological findings in 3 patients in whom secondary hypokaliemia resulted in a clinical picture mimicking Guillain-Barré syndrome (GBS). Pathophysiological mechanisms of the disease are discussed.

Patients: 3 patients (all female, age 28–76 years) presented with subacute onset of generalized muscle weakness developing over a period of 1–4 weeks. Patient 1 complained also of painful paraesthesias of both feet. On examination, all patients had a moderate to severe proximal tetraparesis. Reflexes were weak and no sensory deficit was found in any of the patients. The pareses recovered completely within days following potassium substitution. Laboratory studies revealed dramatically decreased serum potassium levels (1,3–1,7 mmol/l). Creatine kinase (CK) was raised markedly in patient 2 (971 U/l) and only slightly in patients 1 and 3 (72 U/l and 96 U/l, respectively). Cerebrospinal fluid (CSF) protein was raised in patient 1 (88 mg/dl) and was normal in patients 2 and 3. CSF pleocytosis was not found in any of the patients. Nerve conduction studies disclosed prolonged distal motor latencies in patients 2 and 3 (tibial nerve 6,7 and 9,2 ms) which returned to normal within days. Motor nerve conduction times were slightly reduced and increased by 10–20% after serum potassium normalisation. Electromyography showed pathological spontaneous activity (SPA) in 3 of 5 examined muscles of patient 1. In patient 3, there was no SPA and no voluntary activity at all. Repetitive stimulation of the accessory nerve revealed no decrement of muscle action potential amplitude recorded from the severely paretic trapezius muscle in patient 3 as a possible indicator of dysfunction of the neuromuscular transmission. Discussion: The main cause of hypokalemic paralysis seems to be a functional defect of the muscle membrane, as it has been shown in the literature by Cruz-Martinez and Arpa by in situ studies of the muscle fiber conduction velocity. In our patient 2, there is also a structural defect of the muscle membrane resulting in high levels of the CK. However, an increase of the motor nerve conduction time by 10–20% and prolonged distal motor latencies resolving after normalization of serum potassium levels indicate an additional functional motor neuron defect. Therefore, the disease seems to result from functional defects of muscle and nerve membrane. The latter would explain the fact, that some patients also complain of paresthesias. The nerve conduction studies can imitate the findings in GBS; the main difference is the absence of nerve conduction blocks and the recovery after normalisation of serum potassium levels.

P496
SCREENING THE EARLY GROWTH RESPONSE 2 GENE IN HEREDITARY MOTOR AND SENSORY NEUROPATHY. H. Houlden, M. Lee, M. Groves, J. Jacobs, J. Blake, P. Thomas, N. Wood, M. Reilly, Neurogenetics Laboratory Institute of Neurology, Neuropathology Laboratory, Neurophysiology Laboratory (London, UK)

Hereditary motor and sensory neuropathies (HMSN) reflect a wide clinical spectrum of related disorders with defects in the peripheral nerve axon and myelin. HMSN type I and III are demyelinating whereas patients with HMSN type II display an axonal neuropathy. In HMSN type I the chromosome 17p duplication is the cause of 85% of cases. Connexin 32, P0 and PMP22 mutations account for a proportion but not all of the genetic defects in the remaining cases. PMP 22 and P0 mutations have also been identified in HMSN III. In a number of cases no genetic defects have been identified. Recently point mutations in the Early growth response 2 (EGR2) gene have been identified in a small proportion of HMSN cases. The HMSN phenotype tends to be that of a HMSN type I/III phenotype, with severe disability in childhood and demyelination neurophysiologically. Nerve biopsy in cases with EGR2 mutations commonly show hypomyelination or segmental demyelination with onion bulb formation. To assess the frequency of EGR2 mutations in our HMSN patients, we proceeded to carry out SSCP (nine primer pairs, sequences kindly supplied by Dr. Lupski) of the entire coding region of the gene. We analyzed 30 cases of demyelinating HMSN and 10 cases of HMSN type II that were part of small families or were sporadic HMSN patients, where the chromosome 17 duplication was negative and the PMP, Connexin 32 and P0 genes had been excluded by sequencing. Although a number of non-conforming SSCP bands were seen no EGR2 mutations were identified when these were sequenced. We also carried out SSCP on segments 7 and 8 of the EGR2 gene (the segments where the majority of mutations occur) in a group of 40 patients who had HMSN with onset in childhood and were chromosome 17 duplication negative. Again no mutations were identified. These data suggest that mutations in the EGR2 gene are rare in demyelinating HMSN.

P497
ANTI-GM2 IGM ANTIBODIES INDUCE COMPLEMENT-MEDIATED CYTOTOXICITY IN A HUMAN NEUROBLASTOMA CELL LINE. B. Cavanna, H. Jiang, S. Allaria, G. Scarlato, E. Nobile-Orazio, IRCCS Ospedale Maggiore Policlinico, Detroit University, Milan University (Milan, I; Detroit, USA)

Anti-GM2 IgM antibodies have been reported in some patients with dysimmune neuropathy or lower motor neuron syndrome, often associated with a concomitant reactivity with GM1. In a previous study we showed the presence of high titers of anti-GM2 IgM antibodies in eight patients with dysimmune neuropathies including 2 with multifocal motor neuropathy (MMN), 2 with purely motor demyelinating neuropathy without conduction block (MN) and 4 with Guillain-Barré syndrome (GBS). Serum IgM from all positive patients intensely stained the surface of the SK-N-SH neuroblastoma cell line. To determine if these antibodies are able to mediate complement-dependent cytotoxicity we performed in vitro cytotoxicity assays on neuroblastoma cells with 7 of the 8 positive sera, using normal human serum as a source of complement. As controls we used the sera from 7 patients with other antibody reactivities, the sera from 6 patients with the same type of dysimmune neuropathies and no antibody reactivity, as well as the sera from 8 normal controls. Of the 7 positive sera tested, 5 induced complement-mediated cytotoxicity (2 MN, 1 MMN, 2 GBS), while none of the negative patients or controls had any significant effect on neuroblastoma cells. Incubation with antibody alone or with complement alone did not have any effect either. Pre-incubation of positive serum with purified GM2 removed the cytotoxic activity. Except for one case, the percentage of cell death obtained with positive sera seems to correlate with anti-GM2 antibody titers and with the intensity of immunofluorescence staining on the cells. The two positive sera that do not have cytotoxic activity have in fact very low anti-GM2 antibody titers. These results suggest that complement activation induced by anti-GM2 IgM antibodies and the consequent cell damage might be a possible pathogenetic mechanism in patients with dysimmune neuropathy and high titers of anti-GM2 IgM antibodies.

Poster session – 3

Cerebrovascular disorders

P498
TIME COURSE OF CEREBRAL BLOOD FLOW VELOCITY CHANGES IN NEUROCARDIOGENIC SYNCOPE. S. von Stuckrad-Barre, T. Pfefferkorn, M. Muscholl, W. von Scheidt, G. F. Hamann, Ludwig-Maximilians-Universität Klinikum Großhadern (München, D)

Recent transcranial Doppler (TCD) studies have shown a decline of cerebral mean blood flow velocity (MFV) accompanied by a rise in pulsatility index as a typical finding during Neurocardiogenic Syncope (NCS). In the present study we investigated the time course of flow velocity changes and hemodynamic parameters to further characterize cerebral autoregulation during syncope. Seven Patients (4 women, 3 men; mean age 43 years) with recurrent NCS were evaluated by use of an upright tilt-table test for 35 minutes. TCD was used to assess systolic blood flow velocity (SFV) and diastolic blood flow velocity (DFV) of both middle cerebral arteries. Arterial blood pressure (ABP) and heart rate (HR) were monitored and correlated to SFV and DFV. DFV started to decrease significantly 120–300 sec. prior to syncope and reached values near zero 5 sec. prior to and during syncope. SFV decreased simultaneously, however to a much lesser extent, reaching a minimum of 66.5% of initial during syncope. Cerebral blood flow changes corresponded to decrease in mean arterial blood pressure. As shown previously, DFV showed a significant decrease during NCS. However, SFV was equally found to continuously decrease prior to syncope. In contrast to other results our findings implicate a decrease not only in diastolic velocity but also in systolic velocity prior to and during NCS.

P499
THE EFFECT OF SUBTOXIC DOSES OF 2-DEOXYGLUCOSE ON BICUCULLINE EVOKED SEIZURES AFTER TRANSIENT INCOMPLETE BRAIN ISCHEMIA IN MICE. K. Rejdak, R. Rejdak, M. Sieklucka-Dziuba, Z. Stelmasiak, P. Grieb, Medical University of Lublin, MRC, Polish Academy of Sciences (Lublin, Warsaw, PL)

Background: Recently, it has been found that 2-deoxyglucose (2-DG) administration reduces focal ischemic brain damage and improves postischemic behavioural outcome (Yu and Matson, 1999). This effect is similar to the known phenomenon of chemical preconditioning and the induction of brain tolerance. The aim of the study was to examine the effect of subtoxic doses of 2-DG on seizure activity in mice exposed to transient brain ischemia. Methods: Male Albino Swiss mice were used. Animals were exposed for 30 min to bilateral clamping of the common carotid arteries (BCCA) under pentobarbital anaesthesia. The treatment with 2-DG in a dose of 150 mg/kg i.p was started 6 hours after the re-circulation and continued with single daily injections for 13 days. Treatment groups consisted of: vehicle or 2-DG applied to sham operated and to BCCA animals. Seizures were evoked 14 days after the insult with bicu-

culline injected in a dose of 3.5 mg/kg s.c. The latency to the onset of generalised convulsions as well as the frequency of clonic/tonic seizures and mortality rate were scored. Results: Transient brain ischemia induces protection against bicuculline toxicity which is evident 14 days later. 2-DG administered in sham operated group decreases the mortality rate after bicuculline seizures while in ischemic mice significantly potentiates the anticonvulsant influence of BCCA. Conclusion: Restriction of glucose uptake enhances protection against bicuculline toxicity activated by transient episode of brain ischemia.

P500
THE INFLUENCE OF CYCLOHEXIMIDE ON EPILEPTIC TOLERANCE INDUCED BY TRANSIENT INCOMPLETE BRAIN ISCHEMIA IN MICE. R. Rejdak, K. Rejdak, M. Sieklucka-Dziuba, Z. Stelmasiak, P. Grieb, Medical University of Lublin, MRC, Polish Academy of Sciences (Lublin, Warsaw, PL)

Background: Ischemic tolerance is the phenomenon whereby a proconditioning ischemia of brief duration, inadequate to infarct the brain, protects it from subsequent severe insults (Chen et al., 1996). In our preliminary experiments we have found that transient brain ischemia may induce long-lasting protection against bicuculline toxicity in mice. However, the exact mechanism of the effect remains unclear.

Objective of the study was to examine the influence of a protein synthesis inhibitor, cycloheximide on the induction of the protective effect of transient brain ischemia against bicuculline toxicity.

Methods: Male Albino Swiss mice were used. The animals under pentobarbital anaesthesia were exposed for 30 min to bilateral clamping of the common carotid arteries (BCCA).

Cycloheximide was administered in a dose of 2 mg/kg intraperitoneally in two experimental paradigms: a) peri-insult treatment: three daily injections started 1 hour before clamping of vessels; b) post-insult treatment: three daily injections started 24 hours after re-circulation. Seizures were induced 14 days after the insult with subcutaneous bicuculline injection in a dose of 3.5 mg/kg s.c. equal to CD97. The latency to the onset of generalised seizures as well as the frequency of clonic/tonic convulsions was scored. Additionally, the severity of seizures was evaluated by 5-point rating scale.

Results: Transient brain ischemia evoked by BCCA induced protective effect against bicuculline toxicity as assessed 14 days later. Peri-insult treatment with cycloheximide completely abolished while post-insult treatment only moderately diminished the epileptic tolerance observed after BCCA.

Conclusion: It can be suggested that long-lasting anticonvulsant effect against bicuculline toxicity after BCCA is mediated by protein synthesis.

P501
EARLY PERIPHERAL NERVOUS SYSTEM INVOLVEMENT IN ACUTE HEMIPARESIS. C. Schneider, S. Wunderlich, K. Reiners, University of Würzburg (Würzburg, D)

Objective: To examine the incidence of peripheral nervous system involvement in limb muscles involved in central hemiparesis. Background: Acute hemiparesis may be accompanied by denervation in limb muscles of the hemiparetic side. This has been explained by secondary nerve lesions, e.g. due to shoulder subluxation or by so-called "transsynaptic degeneration". Methods: In 24 patients, 13 males and 11 females, presenting with acute central brachiofacial hemiparesis due to stroke, bleeding or tumour progression electromyography (EMG) of proximal and distal arm muscles involved in hemiparesis was performed. Motor and sensory nerve conduction studies of both median nerves were performed in 20 patients. In addition, in 18 of them, generalized polyneuropathy was excluded by normal nerve conduction studies of the tibial and the sural nerve. First electrophysiological examinations were performed three days after the onset of hemiparesis. Follow-up examinations could be performed within two weeks after the onset of hemiparesis in 20 patients. Results: On EMG positive sharp waves and fibrillation potentials could be detected in 13 of the 24 patients (55%), i.e. in more than half of our patients. Abnormal nerve conduction findings in the affected upper limb were found in 6 patients of the examined 20 patients (35%) only: During the first two weeks after the onset of hemiparesis ipsilateral prolongation of median nerve F-wave latencies and reduced sensory nerve action potentials of the median and/or the ulnar nerve were found in four, prolonged distal motor latencies in two, and inexcitability of median sensory nerve action potentials in two patients. Conclusion: This study confirms the occurrence of coincidental early denervation in affected limbs of hemiparetic patients probably due to upper motor neuron dysfunction. Nerve conduction studies are less frequently pathological than the EMG. Thus, brachial plexopathies due to shoulder subluxation may explain the EMG abnormalities in a few cases only. The diagnosis of coincidental peripheral nervous system involvement has considerable implications for rehabilitation programs, since specific physiotherapeutic strategies are required.

P502
RECURRENT LIMB SHAKING IN RADIATION-INDUCED CAROTID STENOSIS: THE ROLE OF ANTIHYPERTENSIVE MEDICATIONS. F. Chochon, T. Dubard, C. Pierrot-Deseilligny, Hôpital de la Salpêtrière, Clinique Saint André (Paris, Reims, F)

Recurrent limb shaking is a rare and poorly recognized manifestation of occlusive disease. It is defined by episodic rhythmic shaking movements of at least one limb and it generally occurs at standing. Although the precise physiopathological mechanism is a matter of controversy, most authors agree that it reflects a low cerebral perfusion state. Most of previous reported cases were associated with unilateral or bilateral atherosclerotic occlusion. Surgical revascularization procedures are most commonly used to improve these patients. We report two patients who both received cervical radiotherapy for a carcinoma of the epiglottis, and several years later, for a carcinoma of the nasopharynx and of the oesophagus respectively. A few days following the onset of an antihypertensive treatment, both patients presented orthostatic-mediated left-sided limb shaking, spreading to the other limbs for one patient, associated with dizziness. These symptoms ocurred several times a day, lasted 10 to 60 seconds and resolved upon lying down. One patient was found to have orthostatic changes in blood pressure. Both patients had right carotid occlusion and cerebral blood flow study confirmed right cerebral hemispheric tenuous perfusion. Both patients became asymptomatic when antihypertensive treatment was discontinued. We briefly discuss the pressure-related mechanism involved in this hemodynamic ischemic disease. The carotid stenosis in our patients was due to prior cervical irradiation. Carotid arteriopathy is a known complication of this therapy. It is important to suspect carotid disease in any patient with prior irradiation of the neck, who presents limb shaking spells. Before thinking about surgical treatment in such precarious patients, one should optimize blood pressure, by allowing it to be high, or/and by discontinuing antihypertensive drugs. This sole decision may be sufficient to improve symptoms dramatically.

P503
VERTEBRAL ARTERY DISSECTION IN A PATIENT WITH POSSIBLE BEHCET'S DISEASE. V. Caso, L. Parnetti, M. Paciaroni, G. Cardaioli, M. Venti, F. Corea, P. Milia, V. Gallai, Stroke Unit Neurological Clinic (Perugia, I)

Background: Acute cerebrovascular disease has been described in autoimmune disorders. We describe a young patient with vertebral artery dissection and a possible Behcet's syndrome.

Case: A 41-year-old man has been admitted because of acute vertebrobasilar stroke and moderate left frontal-parietal-occipital headache. The patient's history was positive for cigarette smoking and skin lesions like papules on the face some months ago. The clinical examination showed truncal ataxia, nystagmus, vertigo and febricula started ten days before. Duplex-examination showed occlusion of left vertebral artery confirmed by MRA and digital angiography with typical signs of vertebral artery dissection with normal profile of the other blood vessel walls. Cerebral MRI disclosed two small subcortical hyperintense lesions in T2-weighted images without evidence of lesions in brain stem. During the hospitalization oral aphthous ulcers associated with high fever and arthralgias were observed. Laboratory findings showed ESR:111, RCP 16,5 mg/dl, RF 40 UI/ml, the complements factors C3155 mg/dl and C4 52 mg/dl. Pathergy test was negative and there was no genital ulceration and no typical eye lesions. Other parameters of involvement of autoimmunic system were negative and also systemic infections were excluded. Treatment and course: The patient was treated with intravenous heparin and steroids; recanalization of the vertebral artery, regression of systemic symptoms and normalization of the inflammatory parameters was obtained. Conclusion: Behcet's syndrome, classified as a vasculitis, is a multisystemic disease of uncertain pathogenesis without any specific diagnostic feature or laboratory investigation. Neurological signs are not adequately stressed. Vertebral dissection can be the first and serious sign of an autoimmune disorder where a Behcet's syndrome can be hypothesized.

P504
RESTRICTED DISSOCIATED SENSORY SYNDROME IN LATERAL MEDULLARY INFARCTION: CLINICAL-MRI STUDY. P. Cerrato, D. Daniele, M. Bergui, C. Baima, M. Grasso, E. Verdun, D. Imperiale, B. Bergamasco, Division of Neurology (Torino, I)

A 55 year-old was admitted to our neurological ward because of the sudden onset of ataxia with right lateropulsion and vomiting. Besides he reported cold sensation on left hand and numbness on right hand fingers. Neither vertigo nor headache were reported. The only risk factors for cerebrovascular disease were a moderate hypertension and smoke. Neurological examination at the admis-

sion revealed truncal ataxia with right lateropulsion; sensibility to painful and thermic stimulations was decreased on the left hand and forearm, while vibratory sensibility and tactile two-point discrimination was decreased on the right forearm, hand and fingers. No different neurological signs were present, in particular pyramidal, cerebellar or brainstem signs. Symptoms vanished in a few days, with the only exception of a mild left hand thermic hypoestesia and right fingers numbness. CT scan and duplex scanning of epiaortic vessels, obtained at the admission, were normal. Patient was submitted to a MR investigation three days later. MR showed a small lesion on the left medulla oblongata, hyperintense in the T2-weighted sequence, interpreted as a small lacunar infarction of the perforating branches of the left postero-inferior cerebellar or vertebral artery. No other brainstem, cerebellar or brain lesions were present. A careful analysis of the location of the lesion revealed that it was located immediately caudal to the postolivary sulcus, ventral to the inferior cerebellar peduncle in a left paramedian position. The interest of the case is the atypical distribution of the sensory abnormalities. The restricted distribution of the sensory deficits, and the dissociation of spinothalamic (SPT) and lemniscal sensory abnormalities may be explained by an involvement of the SPT tract at the level of the lemniscal decussation. At this level the lateral arciform fibers of the proprioceptive pathway, carrying the arm sensibility, run from the cuneatus nucleus to the lemniscal decussation near to the medial portion of SPT, also carrying the painful and thermic sensibility of the arm. A lesion between the two fibers systems, involving the lateral side of the arciform fibers and the medial side of SPT can explain the symptoms. Rostrally to this level the spinothalamic and the medial lemniscus fibers run together, making impossible the dissociated sensory pattern described above.

P505
COMPLICATIONS OF ELECTIVE PERCUTANEOUS DILATATIONAL TRACHEOSTOMY IN NEUROCRITICAL CARE. B. Eggers, J. Koester, J. Berrouschot, A. Wagner, D. Schneider, University of Leipzig (Leipzig, D)

Background: Elective percutaneous dilatational tracheostomy (PDT) is considered to have fewer complications in comparison to operative tracheostomy. Nevertheless, reports from different authors often cannot be compared, because different complications were not classified. Method: Between 1996 and 1998 112 patients (54 men, 58 women, mean age 57±14 years) underwent elective PDT in a neurocritical care unit under bronchoscopic control. Complications were differentiated in hemorrhage (0=no bleeding, 1=irrelevant bleeding without aspiration, 2=moderate bleeding with aspiration, 3=severe bleeding with complications), damage to the tracheal wall (0=none, 1=irrelevant mucosal, 2=moderate with perforation, 3=severe with complications like pneumothorax or need of surgical intervention), infections and other complications.

Results: We saw 18 patients with irrelevant bleeding (grade 1), 11 patients with moderate bleedings (grade 2), but no severe bleedings with complications. 1 Patient suffered a tracheal perforation (grade 2) and 4 patients a mucosal lesion (grade 1), no one had any complication (grade 3). 1 Patient showed an infection of the tracheostoma, which was treated with antibiotics.

Discussion: In 112 patients in neurocritical care we saw no complications after PDT. Bronchoscopy should be performed in order to detect potentially life threatening complications as early as possible.

P506
PAIN IN STROKE: OCCURRENCE, ORIGIN AND MANAGEMENT. A. Dunac, D. Bandezian, M.-C. Lorenzoni, M.-H Mahagne, M. Lanteri-Minet, M. Chatel, Hôpital Pasteur, Hôpital Saint-Roch (Nice, F)

OBJECTIVE: The aim of this study is to evaluate incidence, location and management of pain in stroke patients. The second objective is to point out patients ratio who do not complain and are still untreated, which may obstruct rehabilitation.

METHODS: Forms concerning pain are registered for each patient in acute phases and during hospitalisation. 100 stroke patients are enrolled during 3 months. We considered onset, incidence and location of pain, as well as duration. Intensity is scaled by patients themselves by analogous visual scale (from 0 to 10). Is considered mild pain when scored from 1 to 3, moderate pain from 4 to 6 and severe pain over 7.

RESULTS: All data are not available yet. We only have informations concerning 40 stroke patients (80 % ischemic and 20 % hemorrhagic). 25/40 were painful: 14 (31 %) had severe or moderate pain, and 11 (24.4 %) had a mild pain. Only 15/25 complained spontaneously, before our questioning. 14/25 had headache, almost in all cases present since acute phases. 6/25 had hemiplegic limb or body pain (thalamic pain or spasticity), and 4/25 were miscellaneous.

Arterial hypertension was causal in 50 % of headache cases. All patients were treated by classical antalgics (paracetamol mostly or anti-inflammatory) with 18/25 (72 %) of success. For the others, morphinic treatments were necessary. When discovered mean delay before treatment is about 2 hours, but relapse of pain took more than 24 hours.

CONCLUSION: Over 50 % of stroke patients have pains. Its treatment is essential for rehabilitation. Classical antalgics are often enough. The most frequently encountered is headache, which is not necessarily related to arterial hypertension. We noticed that only 60 % of patients complain, which requests medical and nurse questioning to emphasize and evaluate the pain, and probably attenuate depression.

P507
INTENSIVE CARE AND MECHANICAL VENTILATION IN ISCHEMIC AND HEMORRHAGIC STROKE: INDICATION, TIMING AND OUTCOME. A. Dunac, M.-H Mahagne, M.-C. Lorenzoni, M. Chatel, Hôpital Pasteur, Hôpital Saint-Roch (Nice, F)

Objective: This study completes results presented in ENS–1999. The goal is to evaluate the interest of mechanical ventilation in ischemic and hemorrhagic stroke patients. This remains controversial, despite poor outcomes previously reported in the literature. Because of the lack of evidence based guidelines, we tried to compare incidence, indications and outcomes to the literature data.

METHODS: A review of ischemic and hemorrhagic stroke patients admitted in the intensive care unit of neurology between January 1st–1998 and December 31–1999, was performed. Age, type, rate of patients timing and indication of mechanical ventilation (MV) as well as status at discharge were analysed.

RESULTS: 230 stroke were admitted, with 72.5 % ischemic (ISC) and 27.5 % hemorrhagic (HEM). After a mean time of 2.5 days, 55 patients went under mechanical ventilation: 20 control patients (non vascular acute neurological diseases) and 35 stroke patients (23 ISC and 12 HEM). The mean age of intubated patients was 61.47 while the whole stroke patients population had a mean age of 68.2 (ISC=67.3 and HEM=69.1). Sex ratio M/F=1.6. All patients required controlled ventilation. Indication was clinical signs of brain herniation or respiratory distress from cerebral origin in all stroke patients.

OUTCOME: We registered fatal evolution in 30/35 (85.71 %) cases of stroke: 19/23 ISC (82.6 %) and 11/12 HEM (91.66 %), whereas all other acute severe neurological diseases registered 7/20 (35 %) of death.

CONCLUSION: These results confirm those previously reported in ENS–1999, with a higher statistical value. They are in accordance with literature data: MV is not likely to improve outcomes in acute stroke patients (ISC or HEM) with brain herniation or respiratory distress from cerebral origin. No neuroprotective effect of MV is found like in cerebral trauma. However, the benefit of early preventive intubation in moderate stroke, still has to be defined.

P508
CRANIAL ARTERITIS (HORTON' DISEASE) WITH INTRACEREBRAL IMPAIRMENT: A CASE TREATED BY ANGIOPLASTY. C Dupel-Pottier, C Belguebli, B Bonnefoi-Kyriacou, D Gayraud, O Levrier, F Viallet, Centre Hospitalier du Pays d'Aix, CHU La Timone (Aix en Provence, Marseille, F)

Horton's disease, well defined histologically as giant cell granulomatous arteritis of extracranial arteries, has been very rarely described on intracranial vessels.

A 68 year-old woman with elevated blood pressure well-treated with beta blockers, was admitted on April 1999 because of a sudden motor deficit of the left lower limb with tinnitus aurium, headache and weight loss for the last three weeks. The initial MRI only showed some periventricular hyperintense zones on T2-weighted imaging whereas the SPECT-HMPAO was considered as normal. Because of an isolated elevated sedimentation rate, a temporal artery biopsy was performed and showed a granulomatous angeitis compatible with Horton's disease.

Clinical outcome was characterized by the fluctuation of the neurological deficit becoming progressively permanent with a left-side sensitivo-motor hemiplegia and homonymous lateral hemianopsia. An increase of the motor disability with depressive state was obvious after seven weeks in spite of the treatment: heparin intravenously (20 000 UI per day) and corticosteroid therapy orally (120 mg per day). A small and subcortical extraterritorial infarction was detected on CTscan in the junctional area between anterior and middle cerebral artery on the right side whereas the SPECT showed an extensive hypometabolism in the same region. The cerebral angiogram showed a severe stenosis on the supraclinoid portion of both internal carotid arteries. Because of the severity of the motor impairment with a poor recovery after informed consent of the patient and her family, an intracranial angioplasty was performed two months after her admission.

Intracerebral ischemic impairment associated with Horton's disease is very rare: strokes occurring concomitantly with Horton's disease have never been reported except for a few cases at the beginning of corticosteroid therapy. The present case was compatible with an hemodynamic disorder due to a very severe

stenosis of the termination of the internal carotid artery on the right side, then producing ischemia and penumbra in the junctional area between anterior and middle cerebral arteries.

Intracranial angioplasty of severe stenosis during inflammatory arteritis have already been performed in a few cases particularly for Takayashu's disease.

P509
THE DISTRIBUTION OF CHLAMYDIA PNEUMONIAE IN ARTERIES FROM THE HEART UP TO THE BRAIN. M. L. J. Wimmer, J. Wohlschläger, D. K. Nägler, R. L. Haberl, S. Weis (Munich, Magdeburg, D)

Background: The role of infectious agents in the pathogenesis of atherosclerosis has been discussed during the last decade. Many papers report an association of the obligatory intracellular, gram-negative pathogen Chlamydia pneumoniae with coronary artery disease (CAD), myocardial infarction (MI) and arteriosclerosis in general. Elevated IgA titers and circulating immune complexes have been found to be an independent risk factor for CAD, MI and stroke. The organism could be demonstrated in various vascular tissues of both surgical and post-mortem specimens (carotid arteries, aorta, coronary arteries) by immunohistochemistry, electron microscopy and polymerase chain reaction (PCR).

Methods and Material: Aim of this study was to determine the frequency of C pneumoniae in postmortem specimens of different arteries including intracerebral vessels. We investigated 114 various samples obtained upon autopsy (coronary (CA) and carotid (ACC) arteries, basilar artery (BA), and middle cerebral arteries (MCA) from both sides) from 19 patients, 5 with ischemic brain infarction and 14 controls, who died of non-cerebral causes (4 males, 15 females, mean age 74.2 years, no statistical difference between cases and controls). PCR was performed to demonstrate specific C pneumoniae-DNA in these specimens.

Results: Atherosclerosis was macroscopically evident in all of the tested vessels. The overall prevalence of C pneumoniae was 32% (6/19). The agent could be detected in all types of analyzed arteries: CA 16% (3/19), ACC 11% (2/19), BA 16% (3/19), and MCA 21% (4/19, both sides in 3 patients). PCR for C pneumoniae was positive in one of the five patients (20%) with a history of stroke and in 5 of 14 (36%) control subjects without a history of cerebrovascular disease (chi^2-test, p=0.48).

Conclusion: This is the first investigation demonstrating C pneumoniae in intracerebral arteries. Despite the reported serological association of C pneumoniae and cerebrovascular disease there is no correlation between positive PCR results and stroke in this preliminary analysis and a causative role for chlamydial infection in stroke cannot be supported by this data. This might be due to the small number of included cases. The results show, however, an association of atherosclerosis and the prevalence of C pneumoniae. We continue to collect prospective material for this ongoing study to achieve a larger amount of cases for further analysis including different stroke subtypes. The evaluation of an association between the grade of atherosclerosis and positive PCR results is pending.

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P510
ISCHEMIC STROKE CAUSED BY SPASMS OF THE CERVICAL INTERNAL CAROTID ARTERY. C. Figge, R. Blessing, P. Rieger, G. Schwendemann, Zentralkrankenhaus Bremen Ost (Bremen, D)

Spontaneously occurring cervical internal carotid artery (ICA) vasospasms are a possible, however, rarely documented cause of cerebral ischemia. In this paper we present colour-coded duplexsonographic (CCDS), arterial digital subtraction angiographic (DSA) and magnet-resonance angiographic (MRA) findings of a patient with bilateral ICA vasospasms leading to cerebral ischemic lesions.

In a woman of 35 with acute left-sided hemiparesis initial CCDS showed distal occlusion of both ICAs. Bilateral dissection was suspected and heparin was given intravenously. 18 hours later CCDS and DSA demonstrated the reappearance of blood flow in the left ICA consistant with a filiform stenosis, the right ICA remaining occluded. 5 hours later CCDS showed blood flow in the left ICA growing further. Follow-up CCDS and MRA 48 hours later revealed occlusion of both carotids again. Now the occluded part of the right ICA had extended downwards, thus it could be demonstrated directly by CCDS. There was narrowing of all of the vessel wall structures, including interna, media and adventitia, which was different to the picture seen in dissection or arteriosclerotic occlusion of the vessel. 48 hours later blood flow in the left ICA could be demonstrated again, the right side remaining occluded.

After stopping nicotine abuse and under treatment with nimodipine and phenprocoumon these findings have been stable during a 6 months follow-up.

The course and the morphologic pattern in this case are consistent with the assumption of spontaneously occurring cervical ICA vasospasms, which lead to a permanent occlusion on one and a long term narrowing on the other side.

P511
ACUTE CEREBRAL ANGIITIS ASSOCIATED WITH ORAL PSEUDOEPHEDRINE INTAKE. A CASE-REPORT AND A REVIEW OF THE LITERATURE. G. Castelnovo, A. Lebayon, L. Bauchet, A. Bonafé, P. Labauge, DPT of Neurology, DPT of Neurosurgery, DPT of Neuroradiology, University Hospital Montpellier-Nîmes (Nîmes, Montpellier, F)

Cerebral angiitis is a rare condition. Clinical and neuroradiological symptoms leading to the diagnosis are heterogeneous. Some of them are secondary to toxic or medications. We report an observation of angiitis occurring in excessive consumption of pseudoephedrine.

CASE-REPORT: A 31-year-old woman, without past medical history, presented severe headache and left hemiplegia after intake of 25 pseudoephedrine tablets (Actifed®) to commit suicide. CT scan and brain magnetic resonance imaging (MRI) showed a diffuse subarachnoid hemorrhage and right frontal lobe hemorrhage. Cerebral angiography was normal. A diagnosis of angiitis was made. Clinical outcome was favourable with decreasing of hemiplegia.

DISCUSSION: Drug-induced angiitis is a rare cause of ischemic or hemorrhagic stroke. One of the main etiologies are toxic intake (i. e. amphetamines, heroin). Only a few observations report ephedrine or pseudoephedrine intake as a cause of angiitis. Neurological symptoms include seizures, strokes and cerebral hemorrhage. Histological findings consist of vasospasm or inflammatory vascular infiltrates. Although frequently suspected, cerebral angiography can miss aspects of angiitis, as in our case report.

CONCLUSION: This report underlines that cerebral hemorrhage can occur in ephedrine abuse. Cerebral angiitis is likely the mechanism of this hemorrhage, even the angiography is negative.

P512
EXPRESSION OF IL-1BETA IN THE HIPPOCAMPUS FOLLOWING FOCAL ISCHEMIA IN THE RAT. M. Nolden-Koch, E. Breuer, F. Block, University Hospital RWTH Aachen (Aachen, D)

Spreading depression induced by occlusion of the middle cerebral artery (MCA-O) is supposed to be the cause of glial reactions and neuronal expression of c-fos and heat-shock protein in the hippocampus. Expression of the cytokine interleukin (IL)-1beta has been described for the ischemic core and penumbra but so far not for remote areas like the hippocampus. Transient (three hours) MCA-O was induced in male Sprague-Dawley rats using the intraluminal suture method. After survival periods of 1, 3, 7 and 14 days the animals were sacrificed and coronal brain sections were processed for immunohistochemistry with antibodies against glial fibrillary protein (GFAP), against OX 42 (a marker for microglia/ macrophages), and against IL-1beta. Reactive microglia and astrocytes were observed in the ipsilateral hippocampus from day 1 to 14, whereas no glial changes appeared in the contralateral hippocampus. Expression of IL-1beta increased on day 3 and remained elevated up to day 14 in the ipsi- and contralateral hippocampus. Due to the shape of IL-1beta-positive cells they seem to be neurons. Treatment with the glutamate receptor antagonist dizocilpine maleate (MK-801) (4 mg/kg) prevented this increase. The present data suggest that the increase in hippocampal IL-1beta expression seems to result from ischemia-induced spreading depression.

P513
ISCHEMIC STROKE IN CHILDREN WITH NON-ATHEROSCLEROTIC VASCULOPATHIES. A. Wilczek, B. Ujma-Czapska, T. Marciniak Hospital (Wroclaw, PL)

Background. Non-atherosclerotic vasculopathies, with the most often location in the cervical carotid artery, are frequent causes of cerebral infarct in children. In our study we focused on determining frequence of vasculopathies occurence in children with ischemic stroke.

Methods and results. We analysed 50 children who had suffered from ischemic stroke (23 boys and 27 girls, aged from 6 months to 16 years). The diagnosis was established on the base of a clinical examination, CT and MRI. In few patients the cause of the stroke was confirmed using angiography and MRI angiography. These diagnostic tests revealed non-atherosclerotic vasculopathies in 22% of patients: fibromuscular dysplasia in 4 patients, Moya/Moya disease in 2 patients, hypoplasia of internal carotid artery in 2 patients, hypoplasia of middle cerebral artery in 4 patients and coils and kinkings of internal carotid artery in 1 patient.

Conclusions. As non-atherosclerotic vasculopathies were the most frequent reason for the ischemic stroke, we suggest performing angiography or MRI an-

giography (especially in the cervical portion of the internal carotid artery) in the diagnosis of ischemic stroke in children.

P514
THE VALUE OF EEG AND NEUROIMAGING EXAMINATIONS IN ASSESSMENT OF BRAIN INVOLVEMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS. K. Niedzielska, M. Baranska-Gieruszczak, A. Kuczynska-Zardzewialy, A. Czlonkowska, M. Rzeski, R. Poniatowska, J. Lecka, Institute of Psychiatry and Neurology (Warsaw, PL)

Systemic lupus erythematosus (SLE) is an immunemediated disease of connective tissue that can frequently affect the central nervous system (CNS). The aim of this study was to assess the usefulness of EEG, computed tomography (CT) and magnetic resonance imaging (MRI) in detecting of the brain involvement in SLE patients. We evaluated a group of 47 SLE patients (7 males, 40 females, aged 20–66 years, mean age 47 years) referred to our neurological ward. EEG abnormalities were found in 57.4 % patients, in most cases focal slowing and sharp wave activity. CT changes, predominantly cortico-subcortical atrophy, were demonstrated in 14.9 % cases. MRI revealed morphological changes in 55 %, most frequently microinfarctions in white matter. The clinical manifestations of CNS involvement were observed in 17 (36 %) SLE patients. In this group the pathological changes in MRI were found in 88 %, significantly more frequently than in patients with no neurological symptoms ($p< 0.001$). Our results support the observations that MRI is a more precise method than CT for identifying the organic brain lesions in SLE patients and suggest that EEG examination is a sensitive indicator of CNS involvement in this disease.

P515
ANTI-CHLAMYDIA PNEUMONIAE ANTIBODIES IN YOUNG PATIENTS WITH ISCHEMIC STROKE. B. Piechowski-Jozwiak, A. Mickielewicz, H. Berent, Z. Gaciong, H. Kwiecinski, The Medical University of Warsaw (Warsaw, PL)

Background: Chlamydia pneumoniae (ChP) has been demonstrated in atherosclerotic lesions of coronary arteries, aorta and carotid arteries. There are no data showing titers of anti-ChP antibodies in different subtypes of ischemic stroke. Materials: We examined serum specimens from a cohort of 5 6 young patients (15–5 5 years of age) diagnosed with acute ischemic stroke and 15 age matched controls. Methods: The patients were divided into groups according to stroke etiology using the TOAST classification: cardioembolism (C), large artery atherosclerosis (L), small artery occlusion (S), other determined etiology (0) and undetermined etiology (U). The serum samples were obtained in maximum two weeks from the onset of stroke and were examined by using ELISA method for the presence of ChP-specific IgG and IgA antibodies. Results: The patients were divided into 5 groups: C (n=4), L (n=8), S (n=7), 0 (n= 10) and U (n=27). Serum IgA levels were significantly higher in the group, 0 compared to, controls ($p=0.02$). The serum levels of IgA and IgG in other groups did not show significant diferences when compared to controls. In the group L IgA levels were 1.5 times higher in comparison to controls ($p=0.16$) and IgG levels were more than two times higher compared to controls ($p=0.05$). Conclusion: Chronic ChP infection may play an important role in the etiology of some subtypes of the young stroke.

P516
POSTPARTUM CEREBRAL ANGIOPATHY IN A YOUNG PATIENT WITH MYASTHENIA GRAVIS. A. Opuchlik, B. Piechowski-Jozwiak, A. Kaminska, H. Kwiecinski, Central Clinic Hospital (Warsaw, PL)

Cerebral angiopathy of the postpartum period is a rare entity characterized by severe headaches, seizures and neurological focal deficits. In most cases symptoms are transient, however sometimes the angiopathy can also lead to cerebral infarction. The diagnosis is usually based on clinical findings and angiography. Fourteen cases of cerebral postpartum angiopathy have already been reported in the literature including 10 cases after bromocriptine administration. We report a new case of cerebral angiopathy in the postpartum period, occurring after bromocriptine administration in a 22-year-old woman affected with generalized myasthenia gravis. The delivery was complicated and cesarean section was performed due to mother respiratory failure and child heart rate abnormalities. After delivery the patient was given 5 mg/day bromocriptine to suppress lactation and 2 days later she experienced moderate mixed aphasia and right-sided spastic paralysis. Laboratory results including coagulation parameters, cerebrospinal fluid, lupus anticoagulant and antinuclear antibodies were normal. CT scan revealed extensive, irregular hypodense area in the left hemisphere. MRI scan revealed the same localization of the changes in the left hemisphere and few small lacunes in the right hemisphere. An angio-MRI revealed hypoperfusion of the left hemisphere with beading and narrowing of cerebral arteries in the carotid territory. The patient was successfully treated with i. v. methylprednisolone and artificially ventilated due to myasthenic crisis. Within 5 weeks neurological deficit almost completely resolved. We conclude that bromocriptine may have triggered the cerebral angiopathy in our young patient with myasthenia gravis.

P517
FACTOR XII DEFICIT AND STROKE. M. Logak, S. Timsit, M. Obadia, A. Ankri, G. Rancurel, Urgences Cerebrovasculaires, Salpêtrière (Paris, F)

The role of coagulation factor XII deficit (FXIID) in ischemic and hemorrhagic strokes is still debated.

Objectives: To detect and describe subjects having a FXIID in a population of patients hospitalized for stroke.

Patients and methods: Retrospective study of patients having a FXIID hospitalized from November 1992 to February 1998 for hemorrhagic, ischemic stroke or transient ischemic attack.

Results: Previously, we studied consecutively and retrospectively 164 young patients under 45 years hospitalized from 1992 to 1995 for an ischemic stroke. Despite extensive hemostasis investigations (85 % of patients), only one patient had a FXIID. In the present study, six patients with FXIID were identified. This FXIID was moderate (20 to 50 %) except for one patient who had mild familial FXIID. Mean age was 42 (±8.5) years. Four patients had one or more vascular risk factor. Two patients had a transient ischemic attack. Three had an ischemic stroke. One had an hemorrhagic stroke. Among patients with ischemia, 2 had an anterior ischemic optic neuropathy (AION). Noticeably, despite an extensive work-up, only 2 patients had a determined cause: bilateral spontaneous dissection of cervical arteries. In four other patients, FXIID was the only identified abnormality.

Discussion: Frequency of FXIID is low as shown by our study in young patients. FXIID is associated with rare clinical presentation (AION) or rare aetiology of stroke (bilateral dissection). In six patients with FXIID, three had hemorrhagic patterns (parietal hematoma or parenchymatous hemorrhage).

Conclusion: Our data suggest that the role of FXIID in patients with ischemic and hemorrhagic stroke should be further evaluated.

P518
PRIMARY MEDULLARY HAEMATOMA DUE TO CAVERNOUS ANGIOMA: RISK OF RECURRENCE AT THREE YEAR FOLLOW-UP. M. Gudin, O. Mateo, B. Legido, P. Bustos, R. Ibàñez, J. Vaamonde, A. Hernàndez, M. Del Real, Ntra Sra de Alarcos (Ciuda Real, E)

Background. Subependymal brainstem haematomas are focal lesions which arise from congenital vascular malformations. In 1988 Mangiardi and Epstein reviewed literature and proposed surgical treatment for such lesions. But conservative vs. surgical treatment is still debated in small brainstem haematomas. These types of lesions may destroy the primary malformation from whence they arise. A case of a medullary hemorrhage due to a cavernous angioma treated with conservative measures is presented in order to disclose outcome.

Case description. A previously well 26 year old man was admitted at hospital because of sudden onset of occipital headache and cramplike sensations in left hand and foot. He was alert and fully conscious with a dysarthric speech. CT scan showed no changes. An MRI showed a small haematoma in the left medial medullary region. Cerebral angiography was normal, but angio-MRI was suggestive of cavernous angioma, and a 1,5 T MRI realized afterwards showed a small cavernoma. Although surgical evaluation was performed this case was treated just with supportive measures. The patient recovered without sequel on a few days.

Follow-up. Six months later the patient developed sudden vertigo, dysphagia, dysarthria and left hemiplegia. On evaluation he had left palatal weakness, left hypoglossal palsy, and left hemiplegia. CT scan and MRI, showed rebleeding of the lesion. The patient was discharged on 15 days with a severe left hemiparesis. He recovered completely without any remaining symptoms. After three years follow up, the patient did not have any other symptomatology. MRI suggested a spontaneous cavernoma occlusion.

Conclusion. This case is an example that medullary haemorrhage due to cavernous haemangioma may show a spontaneous recovery. Conservative measures instead of surgical treatment may be adequate to treat haematoma due to small brainstem cavernomas, because this type of lesions may spontaneously be destroyed by the haemorrhage.

P519
BLOOD PRESSURE AFTER STROKE: AN INFLUENCE OF PATIENT MOBILISATION. M Trošt, E Rumpl, University Medical Centre Ljubljana, Landeskrankenhaus (Ljubljana, SLO; Klagenfurt, A)

Background and purpose: The central nervous system plays an important role in the regulation of cardiovascular functions. Acute stroke causes autonomic dysregulation and consequently blood pressure abnormalities. In this study blood pressure changes during an early mobilisation of acute stroke patients were studied.

Subjects and methods: Sixty-eight acute ischemic stroke patients and 30 age-matched controls were studied using a modified Schellong test. It was modified so that the sequence of orthostatic events was similar to that which occur during mobilisation of stroke patients. Blood pressure was measured during the test automatically every minute. Its changes were studied. Attention was paid to blood pressure "swings", i.e. changes of blood pressure that occurred from one measurement to the next. Special attention was paid to blood pressure swings that occurred during verticalisation of subjects, i.e. when the subjects sat up or stood up from a supine position. The intent was to investigate the association between blood pressure stability and different factors. Two of them were mobilisation time and patients outcome.

Results: Stroke patients had less stable blood pressure compared to control subjects. Different factors, but not the mobilisation time, had an influence on blood pressure stability. Patients with a shorter mobilisation time had a better outcome.

Conclusion: An insight into blood pressure changes during early mobilisation after acute stroke was obtained. Blood pressure is frequently unstable, but the time of mobilisation does not have any influence on blood pressure stability. Patients with more stable blood pressure during early mobilisation have generally a better outcome. A relatively early mobilisation of patients is preferable.

P520
PROGNOSIS OF STROKE PATIENTS WITH MECHANICAL VENTILATION. N. Deligiorgis, A. Terentiou, R. Divari, E. Kouremenos, C. Mandragos, A. Papadimitriou, Red Cross Hospital (Athens, GR)

Stroke patients requiring mechanical ventilation are reported to have a poor outcome, although mortality rates vary. We studied a group of 67 stroke patients (21 with ischemic stroke and 46 with intracerebral hemorrhage) admitted in the Neurological Department during the years 1997–1999, who required mechanical ventilation, in order to determine the mortality rate, the functional outcome in the survivors and the possible factors predictive of outcome. Criteria for intubation were severe hypoxemia or hypercarbia. Age, stroke type, predisposing risk factors and neurological evaluation before intubation were studied in relation to the mortality rate and the final outcome. Results: The overall mortality was 86% and was similar in all types of stroke. The functional outcome in the survivors at three months was poor (median 4.2) according to Rankin Scale. Usual risk factors were of no predictive value. Factors significantly correlated with survival and outcome were the level of consciousness on the time of intubation (median Glasgow Coma Score (GCS) for survivors 6 versus 3, $p< 0{,}0001$), the preservation of the pupillary light reflexes and the indication for intubation (neurological deterioration, respiratory failure, hypoxemia.).

Conclusion: Survival is very poor in stroke patients intubated with low GCS, absent pupillary reflexes and in cases of intubation not for neurological deterioration but for apneic episodes. On the contrary mechanical ventilation is of more benefit in less severe cases. The low survival in our patients in relation to other studies is due to our admission criteria for Intensive Care Units (mainly respiratory failure). It is obvious that the organization of special Stroke Units and the intubation on early stages according to neurological criteria would benefit more stroke patients.

P521
HYPERTENSION – THE MAIN RISK FACTOR OF CEREBRAL INFARCTION: THE INFLUENCE OF BLOOD PRESSURE ON STRESS COPING-MECHANISMS OF STROKE-RISK-PATIENTS. I. Spindler, U. Wranek, G. Ladurner, Christian-Doppler-Klinik (Salzburg, A)

The influence of blood pressure, especially in case of hypertension, on the risk of cerebral infarction, primary intracerebral and subarachnoidal haemorrhage, is proved by many studies in medical science. In fact, the blood pressure is related to lifestyle factors and the way patients are able to cope stress. The purpose of the present study was to find interactions between coping-mechanisms, sex and the rate of blood pressure.

Subjects: The sample consisted of 1260 ambulatory patients who participated stroke-prevention-check. Of these patients, 600 (300 male and 300 female) with a mean age of 60 years suffered from hypertension. The remaining 660 patients (330 male and 330 female) with a mean age of 60 years were normotensive with a blood pressure-rate below 90/160.

Methods: Strategies of coping stress were evaluated with the "stress-coping-test" (SVF) (Janke, W., Erdmann, G., and Boucsein W.).

Results: Multivatiate analyses of variance revealed a significant interaction between hypertension and "bad" stress-coping-mechanisms. Significant differences in coping-strageties were observed between male and female patients not only in the hypertension-group but also in the normotension-group. Male patients prefer isolation and coping by drinking alcohol in case of stress while female patients want to control themselves and to eat sweets. In case of hypertension, those "unhealthy coping-mechanisms" increased.

P522
LEUKOARAIOSIS AND ANTIOXIDANT VITAMINS IN PATIENTS WITH STROKE. M. Revilla, N. Vila, V. Obach, A. Chamorro, Hospital Clinic (Barcelona, E)

Background: To evaluate whether antioxidant vitamins are related with cerebral leukoaraiosis in patients with stroke.

Methods: We measured on blood samples obtained the day after admission plasma levels of vitamin E (alpha-tocopherol, gamma-tocopherol), vitamin C (ascorbat), and vitamin A (alpha-carotene and beta-carotene) in 216 patients with acute stroke. Leukoaraiosis was defined as areas of decreased radiosensity of cerebral white matter on brain CT scan. We also recorded in all subjects age, sex, and vascular risk factors.

Results: Seventy one patients (32.8%) had leukoaraiosis on brain CT scan. Patients with leukoaraiosis were older (73.6 ± 8.5 years vs 67.1 ± 11.7 years; $p< 0.001$) and had a higher rate of hypertension (74.6% vs 56.5%; $p< 0.01$) compared with patients without leukoaraiosis. Levels of alpha-tocopherol (30.2 ± 6.7 µmol/L vs 34.3 ± 7.7 µmol/L; $p< 0.001$) and gamma-tocopherol (2.95 ± 1.86µmol/L vs 3.57 ± 2.2 µmol/L; $p< 0.05$) were significantly lower in patients with leukoaraiosis. However, plasma levels of ascorbat (36.6 ± 14.3 µmol/L vs 38.1 ± 15.5 µmol/L), alpha-carotene (0.5 ± 0.5 µmol/L vs 0.6 ± 0.5 µmol/L) and beta-carotene (0.25 ± 0.17 µmol/L vs 0.28 ± 0.19 µmol/L) were similar between patients with and without leukoaraiosis. On multiple regression analysis age < 65 years (OR:1.9), hypertension (OR:1.4) and alpha-tocopherol levels lower than 27 µmol/L (lower quartile) (OR:1.8) were independently associated with leukoaraiosis.

Conclusions: Vitamin E supplements might be indicated in stroke patients with low alpha-tocopherol levels to prevent leukoaraiosis formation or progression.

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INTRACRANIAL DOLICHOECTASIC ARTERIES AND CEREBRAL ISCHEMIA AN ASSOCIATION WITH SMALL VESSELS DISEASE? L. Coeroli, S. Timsit, G. Rancurel, Hopital Salpêtrière (Paris, F)

Patients and methods: Eighteen consecutive patients with IDA and cerebral ischemia (transient or constituted) were included from November 92 to July 97. Diagnosis of IDA was based on CT scan (100%), NIRI (83%) and angiogram (94%). All had an EKG, an echo-doppler of cervical vessels, a TCD, and an echocardiogram. Results: Mean age was 63 ± 6.8 years, sex ratio was 1/4.5 with a male predominance, 78% had one or more vascular risk factors and 60% an hypertension. Clinically, on admission, 78% had a vertebro-basilar (VB) syndrome, 6% a carotid syndrome and only one had a lacunar syndrome. None had a cardiac source of embolism. Study of the vessels revealed that 39% had an isolated VB IDA, 6% had an isolated carotid system disease and 55% had an involvement of both systems. MRI analyses showed hypersignals in the periventricular white matter, deep nuclei and pons in more than 87% of cases. In 45%, no abnormalities was detected in the vessels corresponding to the involved parenchyrna. Conclusion: IDA predominates in VB and in these cases associates with VB syndrome. However, for patients with carotid IDA, only few had carotid symptoms and signs. The absence of concordance between small deep lesions and visible morphological vessels abnormalities suggests that small vessels disease is associated with IDA.

P524
OUTCOME PREDICTORS FOR ANEURYSMATIC CEREBRAL HAEMORRHAGES. V. A. Golyk, L. A. Dzyak, Dnipropetrovsk State Medical Academy (Dnipropetrovsk, UKR)

Several factors are prognostically specific for cerebral aneurysmal haemorrhages course. Arterial aneurysm (AA) and extravasated blood location serves as important one. We investigated correlations between functional outcomes and primary blood location. Materials & methods: 78 patients composed 3

groups: I – 48 (subarachnoid haemorrhages), II – 10 (intraventricular haemorrhages), III – 20 ("pure" intracerebral haemorrhages). Computerized tomography (CT) & lumbar puncture (if CT was negative) verified diagnosis. All patients were admitted on 0–3rd day of haemorrhage, transcranial dopplerography was performed on the day of admission, day 4, 9, 13, 15, 20 after ictus. All persons underwent angiographic evaluation for AA detection and location followed by operation. Its timing was established according to Hunt-Hess scale. The distribution of locations (general and in groups) was the following: anterior communicating artery (ACoA) –31, anterior cerebral (ACA) –8, internal carotid (ICA) –15, media cerebral (MCA) –20, posterior circulation (PC) – 4 and group I: MCA – 6, ACoA – 24, ACA – 7, ICA – 8, PC – 3; group II: ACoA – 7, MCA – 2, PC – 1; group III: ACA – 1, MCA – 12, ICA – 7. After 2 months Barthel index of daily activities was obtained. Results: Survives included 75 patients (2 die in group I, 1 – group II). Among them Barthel index was the following: group I severe disability was observed in 8, moderate – 11, slight – 29 patients, group II – 2, 5, 3, group III – 8, 10, 2 correspondingly. Ischaemic complications of different severity were observed in 6, 4, 3 patients in all groups accordingly causing fatal outcome in 2 patients (group I). Conclusions: Positive correlation was observed for CMA, ACoA location and worst functional outcome. On the contrary, ICA location was associated with better overall endpoints. The data should be useful for therapy correction and prognosis forming for such patients.

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HYPOXIA MEDIATED EXPRESSION OF MATRIX METALLOPROTEINASES: MMP–2, MT1-MMP AND THE TISSUE INHIBITOR OF MMPS, TIMP–2, IN HUMAN ENDOTHELIAL CELLS. Y. Ben-Bassat, N. Lahat, S. Shapiro, C. Bitterman, A. Miller, Carmel Medical Center (Haifa, IL)

Background and Aims: Tissue injury as a result of ischemia and reperfusion is characterized by inflammation and the extravasation of immune cells through the endothelium to the site of injury. The migration of immune cells requires breakdown of the basement membrane and extracellular matrix (ECM) mediated by a family of zinc-dependent endopeptidases, the MMPs. The activity of these proteases is tightly regulated by many factors including cytokines and endogenous inhibitors, TIMPs. Although hypoxia and reoxygenation comprise a major component of ischemia/ reperfusion processes, little is known regarding their isolated effects on MMPs, including MMP–2. We therefore studied the effect of short and prolonged hypoxia and reoxygenation on endothelial cells and their expression of MMP–2, a molecule relevant to basement membrane breakdown, its physiological activator, membrane type (MT)1-MMP, and its endogenous inhibitor TIMP–2. Methods: Human endothelial cells were examined by northern blot to evaluate the level of MMP–2, TIMP–2 and MT1-MMP mRNA expression, following short (3–6 hr) or prolonged (24 hr) hypoxia (~ 22 mmHg) and reoxygenation (24 hr). Results: Short hypoxia (3 or 6 hr) led to a decrease in the level of MMP–2 mRNA while 24 hr of hypoxia showed a 50% elevation in the expression of this molecule in comparison to normoxic cells. Reoxygenation also led to an elevation in MMP–2 mRNA level (50% above normoxic cells) following prolonged hypoxia. Short hypoxia led to a slight decrease in TIMP–2 mRNA which was further decreased at 24hr. The level of TIMP–2 mRNA was also lower than in normoxic cells following reoxygenation. Hypoxia led to a more pronounced reduction in MT1-MMP mRNA at 24hr. Reoxygenation led to its elevation back to normoxic level (2.8 fold above 24 hr hypoxia level). Conclusions: Prolonged hypoxia may lead to an induction of MMP–2 expression and therefore to the breakdown of the endothelial basement membrane allowing extravasation of immune cells. The reduced level of TIMP–2 may potentially lead to increased MMP–2 activity, which may be further enhanced by elevated MT1-MMP during reoxygenation. Understanding the expression of these proteases and their inhibitors may lead to the development of effective therapies for ischemic-reperfusion injury.

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MICROVASCULAR DAMAGE FOLLOWING SINUS-VEIN THROMBOSIS IN RATS. M. R. Vosko, T. K. Pfefferkorn, C. U.A Kloss, B. Friedl, G. Bueltemeier, M. Hoehn, J. Roether, G. F. Hamann, Klinikum Grosshadern, LMU, Max-Planck-Institute f. Exp. Neurol., Friedrich Schiller Univ. (Muenchen, Koeln, Jena, D)

The pathophysiology of microvascular changes caused by sinus-vein thrombosis (SVT) in patients and experimental animals remains largely unexplained. The aim of this study was to evaluate effects of a standardized occlusion of the superior sagittal sinus (SSS) and its bridging and cortical veins on the extent of microvascular damage. SVT was induced by ligation of the SSS and injection of kaolin-cephalin suspension into the SSS in Wistar rats. Cryoslices of rat brains (n=8) were examined for the presence of infarction and microvascular damage after 3 hours of thrombosis. The infarct size and definition of regions of interest (ROIs) were estimated by magnetic resonance imaging and immunohistochemical staining of microtubuli associated protein–2 (MAP–2). For the estimation of microvessel integrity immunohistochemical staining of collagen type IV was performed. The morphometric analysis of microvessels (amount and area) was done using computerized video imaging analysis software (Optimas, USA).

Results: In contrast to control areas, there was a significant decrease in the amount of vessels of 21,5% (p=0,043, Wilcoxon test) and a significant decrease in the total area of collagen-positive vessels of 20% (p=0,043) in infarct areas. Furthermore, microvessels in ROIs appeared microscopically more damaged and collagen staining showed lower intensity (bleaching effect).

Discussion: This study showed a significant decrease in the total area of collagen positive vessels and reduced microvascular collagen IV expression in infarcted regions after three hours of experimental cerebral SVT. This microvascular damage may contribute to edema and hemorrhagic infarction in SVT.

P527
STROKE ASSOCIATED WITH SYSTEMIC SCLEROSIS. N. Vokatch*, F. Assal, C. Chizzolini, R. Sztajzel, Neurology, Clinical Immunology (Geneva, CH)

Background: Systemic sclerosis (SSc) is a multisystemic disorder affecting the connective tissue in the skin, gastrointestinal tract, lung, heart, kidneys and the peripheral nervous system. The vasculopathy associated with SSc is non inflammatory. Only a few cases have been reported in the literature describing an association of SSc with Takayasu's disease, an inflammatory arteritis of large arterial trunks, but no intracerebral vessels, or giant cell arteritis. However, no ischemic strokes have been observed in these patients.

Case report: Here we present the case of a 37-year-old woman without cardiovascular risk factors, suffering from SSc since age 21, who presented with headache and left sensorymotor signs. The diagnosis of limited SSc was initially based on typical skin lesions, Raynaud's phenomenon, abnormal capillaroscopy and the presence of anticentromere antibodies. On admission Doppler ultrasound, angio-MRI, as well as cerebral arteriography revealed a severe stenotic lesion of the supraclinoid portion of the right internal carotid artery. Laboratory investigations demonstrated a high sedimentation rate, normal renal function and the presence of IgG anticardiolipin antibodies. Anticoagulation therapy was initiated and the patient was discharged from hospital. Two months later the headache reoccurred, warranting investigation for the second time. The angio-MRI showed a circumferential narrowing (80%) of V1 segment of the left vertebral artery, not present at earlier studies, suggestive of a vasculitic process. High dose steroid therapy was installed and resulted in prompt relief of symptoms.

Conclusion: Here we present a patient with the association of limited SSc, anticardiolipin antibodies and a high sedimentation rate, who rapidly developed multiple stenotic lesions of major cerebral arteries. This clinical picture combined with the immunological and vascular status does not fulfil classification criteria for Takayasu's disease or giant cell arteritis, which have been reported in association with SSc. Therefore this is an uncommon presentation of cerebrovascular disease in a young patient, combining SSc with inflammatory vasculitis of large extra-and intracranial arteries.

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STROKE ASSOCIATED WITH PANCREATIC CARCINOMA: REPORT OF FOUR CASES. A. Muellner, N. Goebels, M. Liebetrau, G. F. Hamann, Klinikum Grosshadern (Munich, D)

Cerebrovascular disease is a clinically significant complication in patients with cancer. Second only to metastasis stroke is the most frequent cause of central nervous system (CNS) pathology at autopsy. Factors for ischemic CNS infarcts in cancer patients range from the direct effect of the tumor, associated coagulation disorders, infections, cancer therapies, and conventional stroke mechanisms. We report on four patients, who suffered from ischemic stroke associated with pancreatic carcinomas.

In all four patients (J. S., female, 64 yrs.; W. L., male, 79 yrs.; M. T., female, 65 yrs.; A. H., female, 76 yrs) the diagnosis of a metastasis of carcinoma of the pancreas was established before the occurrence of stroke. Three patients suffered from infarcts of the medial cerebral artery (MCA) (J. S., M.T, A. H.) two of them by occlusion (M.T, A. H.), patient W. L. had a vertebrobasilar stroke.

All four patients had either elevated blood glucose parameters (A. H.) or already established diagnoses of diabetes mellitus (It remained unclear, to what extent the blood glucose disturbances were already the result of the destruction of islet cells by the carcinoma). In none of the 4 patients a significant extracranial stenosis of cerebral blood vessels or a cardiogenic source of embolism was detected. Additional vascular risk factors were arterial

hypertension (patients W. L. and M. T.), signs of systemic infections with significantly elevated C-reactive protein (CRP) (J. S.: CRP 13,6 mg/dl; M. T.: CRP 8,7 mg/dl; A. H.: CRP 6,8 mg/dl) and hypercholesterolemia (patients W. L., M. T.).

In conclusion, we postulate that pancreatic carcinoma may pose an independent risk factor for ischemic cerebrovascular events. As pathomechanism disorders of coagulation, disturbances of the endocrine pancreatic functions and embolism due to mucin from systemic neoplastic disease may be discussed. Further studies will be needed to identify the precise mechanisms of paraneoplastic cerebrovascular ischemia in patients with pancreatic carcinoma.

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FORMATION AND ENLARGEMENT OF BRAIN ANEURYSMS; POSSIBLE PREVENTION OF BOTH. P. S. Slosberg, The Mount Sinai Hospital (New York, USA)

The ultimate therapeutic goal of aneurysm research, medical or surgical, is at least 3-fold. First, and most urgent, hemorrhage, especially recurrent hemorrhage, must be prevented. Second, aneurysmal enlargement has to be curbed. Third, perhaps most elusive (and most desirable) of all, the actual formation of brain aneurysms is to be blocked. Hypotheses as to the etiologic factors involved, especially in the latter 2 phenomena, are reviewed. In a series of patients with proven ruptured intracranial aneurysms, unexpected long-term protection against recurrent hemorrhage, by medical-hypotensive therapy (= blood pressure control) has been demonstrated. That series has included 15 patients followed personally for more than 30 years since the time of hemorrhage, with 2 patients followed more than 40 years, so far. In addition, an apparently fortuitous benefit of that program, in the management of vasospasm/vasculopathy, may have been realized and is discussed. These unexpected results raised the possibility that the same, slightly modified, therapeutic approach, perhaps through the same mechanism(s), might also prevent enlargement of aneurysms and even their formation. This modified approach has already been implemented. The way in which it has been individualized is delineated. It is again noted that the prior work, upon which the current, modified approach is based, dealt with proven ruptured intracranial aneurysms. In contrast, from the present program, illustrative examples of treatment of 3 distinct kinds of unruptured – including incidental – aneurysms are now presented for the sole purpose of demonstrating – anecdotally – ease and safety of application of this method, even after long-term follow-up (24 years, 24 years and 11 years, respectively). Their magnetic resonance imaging scans are shown and will point out the complete absence of any demonstrable change in the radiographic appearance of any of the aneurysms despite the passage of many years. The results are, thus, encouraging but it is emphasized that these are only anecdotal cases. Therefore, on the basis of the previously documented excellent results with long-term follow-up of patients with proven ruptured aneurysms along with the demonstrated ease and safety (and results) of the modified method in these 3 anecdotal cases, a formal study of the possibility of preventing formation and enlargement of brain aneurysms is proposed.

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PREDICTORS FOR ATHEROGENESIS IN PATIENTS WITH SEVERE CAROTID STENOSIS. I. Bova, N. Bornstein, A. Gur, Tel Aviv Medical Center (Tel Aviv, IL)

OBJECTIVE: We conducted a study to evaluate the role of different hematological and immunological parameters in asymptomatic severe carotid stenosis (ACAS).

BACKGROUND: Factors influencing the development of carotid atherosclerosis are still not fully identified.

DESIGN-METHODS: Forty-one asymptomatic patients, assessed by color flow duplex, were divided into 3 groups. Group I – 12 young ACAS patients (> 70% internal carotid artery-sranosis), 9 males, mean age ±SD=58.8±9.0 years. Group II – 18 elderly ACAS patients, 11 males, mean age ±SD=77.8± 4.3 years. Group III – 11 non-stenotic asymptomatic patients, 6 males, mean age ± SD 63.2 ± 15.7 years. The following parameters were studied using SPSS analysis: fibrinogen, plasminogen activator inhibitor–1 (PAI–1), cholesterol, HDL-C, LDL-C, triglycerides (TG), lipoprotein-a [LP(a), blood count (WBCC, Hb, Lymphocytes, mean cell volume). RESULTS: The frequencies of the major vascular risk factors were similar in each group. We found statistically significant elevation of LP(a) in group I compared with group II and in combined of LP(a) in group I and II compared with group III (< 0.00001). TG and fibrinogen were found significantly elevatec in group 1 compared with groups II and III ($p< 0.00001$ for PAL–1, $p< 0.03$ for both TG and fibrinogen). Cholesterol, HDL-C, LDL-C, WBCC, lymphocytes and MCV were not found to be significant factors in any group (p=0.9).

CONCLUSIONS: Severe ACAS patients have unique hematological and immunological features which mostly depend on age. LP(a) and PAI–1 might play an important role in atherogenesis in young patients with asymptomatic severe carotid artery disease.

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DOES ASPIRIN PREVENT CORTICAL OR SUBCORTICAL FIRST-EVER ISCHEMIC STROKE? V. G. Karepov, E. V. Karepov, N. M. Bornstein, Tel Aviv Medical Center (Tel Aviv, IL)

OBJECTIVE: We hypothesized that aspirin (ASA) is more likely to prevent subcortical stroke, due to small vessel disease, but not cortical infarction, due to large vessel disease. We designed this study to test our hypothesis.

BACKGROUND: ASA is the most widely used drug for secondary, but not primary stroke prevention.

DESIGN/METHODS: Out of 861 consecutive patients who were admitted to our hospital from July 1997 to July 1999 with the diagnosis of first-ever ischemic stroke, 75 patients had stroke while they were already on ASA, and these were defined as ASA failure (ASAF). The control group was pair-matched for age (3 years deviation), sex, main vascular risk factors and was selected from 786 patients who had first ischemic stroke, without previous use of ASA. The subtypes of stroke (cortical vs subcortical) were clinically evaluated and supported by CT scans in 89% of the patients. Two kinds of analyses were performed. In the first stage, the number of patients who had subcortical/cortical lesions was compared with patients with subcortical/cortical infarcts among the controls using the chi-square test. In the second stage, the doses of ASA were compared in the ASAF patients between the subgroups (cortical vs subcortical) by Student's Mest.

RESULTS: In the first stage of analysis, subcortical stroke was diagnosed in 49 patients in the ASAF group, and in 44 patients in control group (OR=0.75, C1=0.7–1, NS). Twenty-six patients in the ASAF group had cortical strokes, compared to 31 controls (OR=1.3, Cl=l. 1 –1.5, NS). In the second stage of analysis, the ASA doses in patients admitted with cortical strokes (mean 172±34 mg/d) were not significantly different in patients with subcortical strokes (mean 199±28 mg/d).

CONCLUSION: ASA at any dose does not influence the occurrence of either of the two subtypes of ischemic stroke.

Higher function disorders – Dementia

P533
ALZHEIMER'S AMYLOID PLAQUE FORMATION IS A CONDITION FOR NEURONAL DYSFUNCTION. A. Koudinov, T. Berezov, National Mental Health Research (Moscow, RUS)

Diffuse amyloid deposits, amyloid plaques and vascular amyloid of Alzheimer's and Down syndrome patients are considered to be essential features of these pathologies. Nevertheless, there is no direct evidence that human brain amyloid, composed largely of amyloid beta protein (Abeta), has direct effect on neuronal dysfunction. An attempt to unravel this important issue was made in a recent report (Nature Neurosci.1999,2:271) on transgenic mice (TG) expressing human amyloid precursor protein (APP695) bearing Swedish mutation. These TG developed "dramatically elevated concentrations of Abeta and significant Abeta deposits," and had impaired spatial learning and hippocampal long term potentiation (LTP) (a long-lasting increase in synaptic transmission efficacy, LTP), the cellular model for neuronal plasticity, learning and memory. However, this report (as well as another earlier work (Nature 1997,387:500) on LTP deficit in TG expressing the carboxy-terminal 104 amino acids of APP) did not "determine whether the effects measured resulted from elevated concentrations of soluble Abeta, deposited Abeta or both", and it is still unclear whether the maturation of brain amyloid deposits, particularly the development of congo red positive amyloid plaques, is an essential event leading to neuronal dysfunction.

In our study we further attempted to differentiate separate action of diffuse amyloid deposits and plaque amyloid on hippocampal synaptic plasticity in the model of 25.5 months old TG (n=4), expressing wild type human APP695, and corresponding wild type control (WT) mouse hippocampal slices using extracellular recording of CA1 field excitatory postsynaptic potentials (fEPSPs). The input/output (I/O) relationship, a basic parameter of synaptic physiology, and tetanus induced (t) LTP were expressed as a fEPSP slope change versus stimulus intensity and time, respectively, and the analysis was performed essentially as we described previously (J Neurosci.1999,19:9412–25). Immunohistochemistry of slices (40 micron sections prepared on a microtome from 400 micron slices (from the same preparations used for extracellular recording) and overnight fixed in 4% PFH) with 4G8 and 6E10 antibodies (Senetek, PLC., anti-human/mouse-Abeta17–24 and anti-human-Abeta1–17, respectively) revealed extracellular hippocampal immunoreactivity of mouse Abeta in both TG and WT and confirmed extracellular deposits of human Abeta in the TG hippocampus. We also performed congo red staining of slices and found amyloid birefringence specifically in the TG, suggesting that expression of wild type human Abeta in mice lead to a mature plaque-like amyloid. Electrophysiological analysis revealed that TG (as compared to controls) expressed severe deficit in the tLTP and had lower I/O responses for the same high stimulation intensity.

Our data i) provide evidence that one of the causes of synaptic plasticity deficit and neuronal dysfunction is an Alzheimer's mature senile plaque formation, and ii) suggest amyloidosis prevention as an important therapeutic approach in AD. Our results also iii) imply that in Down syndrome, characterized by diffuse amyloid deposition in early life, the other factors (like oxidative stress condition) may contribute to the neuronal dysfunction.

P534
LONG-TERM EFFICACY OF OLANZAPINE IN THE CONTROL OF PSYCHOTIC AND BEHAVIORAL SYMPTOMS IN PATIENTS WITH ALZHEIMER'S DISEASE. J. S. Street, W. S. Clark, B. E. Juliar, P. D. Feldmann, D. L. Kadam, A. Breier, Eli Lilly&Company, Lilly Corporate Center (Indianapolis, USA)

Objective: A multicenter study was conducted to determine long-term efficacy and safety of olanzapine in treating psychotic symptoms and behavioral disturbances associated with Alzheimer's disease.

Methods: Elderly nursing home patients (mean age: 83.1 years) with dementia (n = 137) who successfully completed a 6-week double-blind study entered an open-label phase of up to 18 weeks during which they received olanzapine (dose range: 5, 10, or 15 mg/day). Mean change in the sum of the Agitation, Delusions, and Hallucinations items of the NPI/NH was used as the primary efficacy measure (Core Total).

Results: Following treatment with olanzapine, patients' scores improved significantly on the Core Total (mean, –7.55; SD=8.53; p< .001), Total (mean, –17.85; SD=23.72; p< .001), and 10 of the 13 individual item scores of the NPI/NH, including Occupational Disruptiveness (mean, –2.84; SD=3.24; p< .001). Barnes Akathisia scores improved significantly from baseline (mean, –0.22; SD=0.80; p=.002). Simpson-Angus and AIMS scores were not significantly changed. No significant changes occurred in patient ECGs, including QTc interval, nor in any other vital sign or in weight. Treatment-emergent symptoms included somnolence (26%), accidental injury (25%), and rash (22%).

Conclusion: These data suggest that olanzapine is an effective, generally safe, and well-tolerated long-term treatment for psychotic symptoms and behavioral disturbances in elderly patients with Alzheimer's dementia.

References: 1. Small et al. JAMA 278:1363–1371, 1997; 2. Levy ML et al. Am J Psychiatry 153:1438–1443, 1996

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OLANZAPINE IN THE PREVENTION OF PSYCHOSIS AMONG NURSING HOME PATIENTS WITH BEHAVIORAL DISTURBANCES ASSOCIATED. W. S. Clark, J. S. Street, T. M. Sanger, P. D. Feldmann, A. Breier, Eli Lilly&Company, Lilly Corporate Center (Indianapolis, USA)

Objectives: A multicenter study was conducted to determine the efficacy and safety of olanzapine in treating psychotic symptoms and behavioral disturbances associated with Alzheimer's disease. This analysis was performed post hoc among nursing home patients who did not yet have delusions or hallucinations to assess the appearance of such psychotic symptoms.

Methods: Onset of psychotic symptoms was determined with the NPI/NH during treatment with either placebo or a fixed dose of 5, 10, or 15 mg/day of olanzapine for up to 6 weeks of therapy.

Results: Among patients entering the study with neither hallucinations nor delusions (n=76), there was a significantly greater increase in development of these psychotic symptoms among placebo patients compared to olanzapine patients (p=.006). For the larger subset of patients without hallucinations at baseline (n=155), significantly fewer olanzapine-treated patients (7.4%) developed hallucinations compared to placebo (21.9%, p=.045). Olanzapine had a favorable safety profile in each symptom-subgroup of patients. Changes in extrapyramidal symptoms, labs, and vital signs were not statistically or clinically significantly different for patients treated with olanzapine compared to placebo.

Conclusion: These results suggest that olanzapine may be a safe and well-tolerated antipsychotic that may benefit patients with Alzheimer's dementia by reducing the appearance of psychotic symptoms.

References: 1. Small et al. JAMA 278:1363–1371, 1997; 2. Levy ML et al. Am J Psychiatry 153:1438–1443, 1996

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REDUCTION OF PSYCHOTIC SYMPTOMS BY OLANZAPINE IN PATIENTS WITH POSSIBLE LEWY BODY DEMENTIA. W. S. Clark, J. S. Street, T. M. Sanger, A. Breier, Eli Lilly&Company, Lilly Corporate Center (Indianapolis, USA)

Objective: A post hoc analysis was performed on the results of a double-blind, 6-week study of nursing home patients (n=206) with dementia to determine the efficacy and safety of olanzapine in reducing psychosis and behavioral disturbances.

Methods: The effects of 5, 10, and 15 mg/day olanzapine were assessed relative to placebo in patients who had possible Lewy body dementia (n=29), determined by a nonzero score on the Simpson-Angus Scale and a nonzero score on the Hallucinations item of the NPI/NH. All data are reported as mean changes.

Results: Patients receiving 5 mg/day of olanzapine improved by 82.9% on the NPI/NH Delusions and Hallucinations combined score, compared to 17.4% for placebo (p=.015). On the Delusions item, olanzapine-treated patients improved by 77.8%, compared to 29% for placebo (p=.012). Olanzapine-treated patients showed 85.7% improvement in Occupational Disruptiveness related to the NPI/NH Delusions and Hallucinations items. Placebo-treated patients showed only 14% improvement (p=.002). Significant improvement (p=.042) was also found on the Mini-Mental State Exam for olanzapine-treated patients (2.4-point improvement), compared to placebo (0.1-point worsening). Changes in EPS were not statistically or clinically significantly different for patients treated with olanzapine.

Conclusions: Compared to placebo, 5 mg/day of olanzapine significantly improved psychotic symptoms and behavioral disturbances in patients with possible DLB. Additional well-controlled studies are needed to confirm these results.

References: McKeith IG et al. Neurology 47:1113–1124, 1996; 2. McKeith et al. Psychol Med 22:911–922, 1992

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ENDOGENOUS NERVE GROWTH FACTOR IN PATIENTS WITH ALZHEIMER'S DISEASE. T. Serrano, M. de los A. Robinson, L. Lorigados, M. E. Gonzalez, A. Dorta, I. Diaz, International Center for Neurological Restoration (Ciudad de la Habana, C)

Nerve Growth Factor (NGF) is the best characterized neurotrophic polypeptide. Initially it was postulated that alterations in the expression of NGF within its production sites may be responsible for the consistent atrophy and loss of cholinergic basal forebrain neurons in dementing illness such as Alzheimer's Disease (AD). AD is the most common form of dementia characterized by clinical symptoms and signs of progressive dementia in combination with certain neuropathological changes. The demonstration that NGF exhibits pharmacological effects on basal forebrain cholinergic neurons both in vitro and in vivo has led to the suggestion that NGF normally serves to maintain these cells and that a decline in NGF could contribute to the loss of basal forebrain neurons in AD. We applied a two-site enzyme immunoassay, slightly modified from that described by Lorigados et al. to determine NGF levels in sera of patients with AD. The ELISA detected NGF immunoreactivity in all studied samples. Student's t-test comparison revealed no significant effects ($p < 0.132$) between control and AD patients. The AD group consisted of 18 males and 30 females. The control group consisted of 22 males and 23 females. Sera from Alzheimer's patients (36 ± 7 pg/ml) showed slight but nonsignificant reduction in NGF levels when compared with age-related controls (66 ± 18 pg/ml). Although the results showed no significant differences, we observed homogeneity of NGF levels in AD patients (0.14 to 251, mean: 36 ± 7 pg/ml) compared with the control subjects showed an extensive dispersion of those values (0.00 to 564 pg/ml, mean: 66 ±18 pg/ml). The NGF concentrations in AD patients and control subjects to the sex. Female AD patients showed a mean of 33.27 ± 10.43 pg/ml versus 57.83 ± 22 pg/ml founded in Female Control the mean value for Male AD patients was 40.87 ± 12.29 pg/ml versus 37.47 ± 12.28 pg/ml for the Male Control. In all the cases studied, no significant differences were observed according to Student t-Test. We conclude, that even when no significant differences were observed between controls and AD patients, the results show a tendency NGF concentration decrease in this illness. Certainly, NGF is produced not only in the forebrain but throughout the body, for this reason, more studies, including the analysis of cerebrospinal fluid would be useful to define the real relationship between NGF concentration changes in serum and AD-related changes in endogenous NGF concentrations, taking into account increasing levels by exogenous NGF administration could still be useful in maintaining the cholinergic neurons.

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DONEPEZIL PROVIDES LONG-TERM CLINICAL BENEFITS FOR PATIENTS WITH ALZHEIMER'S DISEASE. A. Burns, S. Gauthier, C. Perdomo, R. Pratt, Withington Hospital, McGill Centre for Studies in Aging, Eisai Inc. Glenpointe Center West (Manchester, UK; Verdun, CDN; Teaneck, USA)

Information on long-term safety and tolerability of cholinesterase inhibitors in the treatment of Alzheimer's disease (AD) is desirable since these medications will be used for a prolonged period of time. Objective: This multicentre, open-label study evaluated the long-term efficacy and safety of the selective acetylcholinesterase inhibitor donepezil in patients with mild to moderately severe AD. Method: The 579 patients who entered the study had previously completed a 30-week randomized, placebo-controlled study with donepezil (n=818), which consisted of a 24-week randomized, double-blind, placebo-controlled phase, followed by a 6-week, single-blind placebo washout. In this open-label study, patients were treated initially with 5 mg/day donepezil, which could be increased to 10 mg/day between Weeks 6–24. During this period, the dose could also be decreased from 10 mg/day to 5 mg/day. No dose adjustments were allowed after Week 24. Patients attended the clinic for assessments every 6 weeks for the first 12 weeks, then every 12 weeks for up to 152 weeks. Efficacy was assessed using the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), Clinical Dementia Rating-Sum of the Boxes scale (CDR-SB), a modified Interview for Deterioration in Daily living activities in Dementia (IDDD), and a quality of life scale. Results: After 24 weeks (54 weeks from the start of the double-blind study), the mean ADAS-cog score declined by 2.57 points (95 % CL, 2.0, 3.2), after 72 weeks (102 weeks from the start of the double-blind study), the mean ADAS-cog score declined by 10.10 points (95 % CL, 8.0, 11.3), and after 132 weeks (162 weeks from start of double-blind study), the mean score declined by 15.57 points (95 % CL, 12, 19.2). Overall the decline was less than the estimated decline of 6–12 points per year if this cohort had not been treated. The most common (> /= 10 %) adverse events reported included diarrhea (12 %), nausea (11 %), infection (11 %), accidental injury (11 %), and urinary tract infection (10 %), which were generally mild. Conclusion: These data provide further support for the long-term (3 years) safety and cognitive effects of donepezil in AD patients.

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A COMPARATIVE ANALYSIS OF ANOMIC VASCULAR APHASIA AND ANOMIC ALZHEIMER'S DISEASE PATIENTS ON A CONFRONTATION NAMING TASK. L. F. Pascual Millán, T. Fernández Turrado, S. Santos Lasaosa, C. Tejero Juste, E. Mostacero Miguel, F. Morales Asin, Hospital Clinico Universitario (Zaragoza, E)

Anomia is present in Anomic Vascular aphasia and Alzheimer's disease of anomic onset but global severity and number and type of paraphasias can be different. Purpose: To compare the number and type of paraphasias observed on a confrontation naming task in Anomic vascular aphasia and Anomic AD. Method: 4 patients with anomic vascular aphasia and 7 patients with anomic AD were compared on a six item confrontation naming task (a wrist watch; the watch strap and its clasp; the elbow; the shoulder; a buttonhole). The Boston Aphasia severity scale (very severe–0 to very mild–5) and Semantic Verbal Fluency (SVF: animals in 1 minute) were used as a measure of severity language impairment Results: Vascular Aphasia: age 72±4 (68–76); sex 4 males; Boston Severity Scale: 4.7±0.5 (4–5); animals: 6.5±3.8; Total number of items correctly named: 4.5±1,7 (2–6); Total number of paraphasias: 0.75±0.8 (0–2); Clear paraphasia Verbal or literal was observed in three patients (70 %). Anomic AD: age 74±3.6 (72–81), sex: 2 males and 4 females; Boston Severity Scale: 2.8±2.0 (1–5); SVF: 2±1.8 (0–4); Naming 2.3±1.8 (0–4); total number of paraphasias: 0.33±0.25 (0–0.5); Only Verbal paraphasia was observed in 3 patients (50 %). Conclusion: Anomic AD patients show greater severity of language impairment, however paraphasic output was more frequent in the vascular patients.

P540
DETECTION OF 14–3–3 ISOFORMS IN THE CEREBROSPINAL FLUID OF CREUTZFELDT-JAKOB DISEASE BY 2-D-PAGE. L. Cepek, M. Otto, P. Steinacker, H. Esselmann, S. Paul, S. Poser, J. Wiltfang, Neurology, Georg-August-University, Psychiatry, Georg-August-University (Göttingen, D)

Creutzfeldt-Jakob-Disease (CJD) belongs to the group of transmissible, spongiform encephalopathies and the diagnosis is based on the combination of clinical symptoms, typical EEG findings and the detection of the 14–3–3 proteins by the immunoblot. In earlier investigations the diagnosis of CJD was supported by detection of the spots p130 and p131 in the cerebrospinal fluid (CSF) by two-dimensional polyacrylamide gel-electrophoresis (2-D-PAGE). Nowadays these spots are assigned to the 14–3–3 family. By reanalysing the original data the isoelectric point(pI) of the spots in the 2-D-Page, the number of detectable spots and the sequenced isoforms seem to differ in the original publication. METHODS: To clarify this statement we established the 2-D-PAGE with an optimized isoelectric focussing and a higher sensitivity for the spot detection. Therefore we changed the sample preparation and checked the results against controls and pI-markers. RESULTS: Our results showed a different isoelectric point (pI) of the detected spots in contrast to the described ones. By immunostaining of the membranes we reproducibly detect four constant spots and two additional inconstant spots. Because of the spots' immunoreactivity against the specific antibody they seem to be members of the 14–3–3 family. The number of spots suggests itself to be caused by the diversity of the isoforms. In the isoform-specific immunostaining the anti-gamma-isoform antibody detects four spots and anti-eta-isoform antibody detects only one of these. This was reproduced in five different CJD patients. CONCLUSION: For the first time we showed that there are different 14–3–3 isoforms in cerebrospinal fluid of CJD-patients by 2-D-PAGE. These spots differ in their pI, in their immunostaining characteristics and in their ratio. It is necessary to check this ratio in comparison to other diseases, which are positive in the immunostaining for 14–3–3 proteins in the 1-D-PAGE, like epilepsy, herpes-simplex-encephalitis or early ischemic events.

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THE VASCULAR FACTOR IN ALZHEIMER'S DISEASE: A STUDY IN GOLGI AND ELECTRON MICROSCOPY. S. J. Baloyannis, V. Costa, Aristotelian University (Thessaloniki, GR)

Although the aetiopathological background of Alzheimer's disease (AD) is mostly associated with the deposition of B amyloid, the hyperphosphorylation of T protein and the synaptic pathology, the vascular factor may play an additional role in plotting the multi factorial pattern of the disease. We attempted to study the blood capillaries in the hippocampus and the prefrontal area of the cortex in ten early cases of Alzheimer's disease, whose brains were examined under electron microscopy and in silver impregnation techniques. The diagnosis of AD was based on clinical, neuropsychological, SPECT and neuro radiological data. The study of the capillaries in cases of AD revealed that the majority of the vessels showed microaneurysms, fusiform dilatations and rough changes of the pattern of arborization, mi correlation with normal control brains of the same age. The ultrastructural study revealed dilatation of the tight junc-

tions between the endothelial cells in the hippocampus and the cortex, mostly seen around the neuritic plaques. Perivascular microglial proliferation intermixed with reactive astrocytes was also prominent in the hippocampus in the majority of the examined brains. Marked morphological alterations of the organelles of the endothelial cells have also been observed. The ultrastructural alterations of the capillaries in Alzheimer's disease suggest that the vascular factor may participate in the pathogenetic mechanisms of Alzheimer's disease.

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APOLIPOPROTEIN E GENOTYPE AND COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE PATIENTS. B. Jasinska-Myga, G. Opala, S. Ochudlo, K. Janiec, J. Tustanowski, D. Friedek, J. Tyrpa, Silesian Medical Academy (Katowice, PL)

The aim of our study was the assessment of the frequency of dementia in highly selected group of Parkinson's disease (PD) patients and the evaluation of the relationship between apolipoprotein E (APO E) genotype and the clinical and neuropsychological parameters in PD with and without dementia. *30* PD patients *(15* males, *15* females; mean age: *66,9 ± 7.2* years) with good response to L-dop were evaluated. The Unified Parkinson's Disease Rating Scale (UPDRS) was used to quantify the severity of PD. Cognitive function was assessed according to the Mini Mental State Examination (MMSE). The frequency and severity of depression were screened with the Geriatric Depression Scale (GDS) and the MontgomeryAsberg Depression Rating Scale (MADRS). The estimation of the APO E genotype was executed by means of the Polymerase Chain Reaction (PCR). Within the group of PD patients the features of dementia *(23* and less points in MMSE) were recognized in 11 *(36,6%)* patients. APO E allele *F,4* and homozygous *F–4/F,4* condition frequencies were significantly higher in the subgroup of PD patients with dementia. APO E allele *F–4* played a significant role in the risk of dementia in PD in our sample.

Multiple sclerosis

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BIPOLAR DISORDER AS CLINICAL PRESENTATION OF FAMILIAL MULTIPLE SCLEROSIS IN TWO PATIENTS (MOTHER/DAUGHTER). P. J. Modrego, J. Ferrandez, Hospital de Alcaniz (Zaragoza, E)

Multiple sclerosis (MS) may present with neuropsychiatric disturbances even in the absence of physical disabilities but this only accounts for a small proportion of all psychiatric admissions. Some previous reports suggest that MS patients are twice as likely to be afflicted with bipolar disorder as the general population. Although both disorders may occur with a familial pattern, there are few cases presenting with both disorders in the same family. We report two members of a family (mother and daughter) with bipolar disorder as initial manifestation of MS. Class I and class II HLA was typed in both cases. CASE 1–A 15 year old female complained of bilateral manual clumsiness that remitted in two months. A MRI of the brain showed extensive periventricular white matter lesions. After improvement of the initial symptoms acutely exhibited flight of ideas, impulsiveness, social intrusive behaviour, euphoria and delusions, nocturnal agitation, decreased sleep and loss of the insight. The patient was treated with corticosteroids, neuroleptics and lithium with improvement to normalisation. Three years after she presented with another acute bout characterised by the same mental disturbance and paraparesis. The same treatment was applied with favourable outcome. CASE 2–A 42 year old female was seen by a psychiatrist because of depression and phobias of acute onset alternating with phases of mania. She developed hypersensitivity to neuroleptics with rigidity and extreme hypokinesia. The gait was somewhat ataxic. The Computed Tomography of the Brain showed marked atrophy and a MRI revealed periventricular, frontal and cerebellar lesions. The outcome was favourable under treatment with neuroleptics plus lithium, and corticosteroids. These are two unusual cases of MS in the sense of coincident presentation with mental disorders in the same family. The concordance in HLA types suggests a common genetic susceptibility for both illnesses. It is also worth mentioning that the concordance of mother/daughter for MS only occurs in 3 % of multiplex families.

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INTERRELATIONS BETWEEN DISABILITY AND QUALITY OF LIFE IN PATIENTS WITH MULTIPLE SCLEROSIS. A GEOGRAPHYCALLY BASED SURVEY IN SPAIN. P. J. Modrego, M. A. Pina, A. Simon, C. Azuara, Hospital De Alcaniz (Zaragoza, E)

Multiple sclerosis (MS) is one of the most disabling diseases in young people but the interrelation between disability and quality of life has been poorly understood. As individual correlation between disability and the perspective of the patient may be weak in individual subjects, the purpose of our work is to analyse and correlate quality of life with neurological impairment and disability in all patients with MS from the geographical area of the Bajo Aragón, north East of Spain. Methods. A total of 36 patients included in this study fulfilled the criteria of probable or clinically definite MS. The average age was 38.1 years (range:17–66). The majority of them were females (66.6 %) and had relapsing-remitting forms (88.8 %). They received the Minimal Record of disability so as to measure neurological impairment, functional limitations and handicaps. Quality of life was measured by means of the Functional Assessment of Multiple Sclerosis (FAMS) scale. Statistical analysis was performed by means of Kruskal-Wallis non-parametric test and Pearson's coefficient correlation. Results. The mean EDSS of our cohort was 2.56 (range: 0–9). The mean FAMS score was 75.4 (sd:53.7). We found that patients moderately or severely disabled (EDSS > 3) showed a significant decreased satisfaction in comparison with the non-disabled or mildly disabled ones. Disability and handicaps were significantly related with some items of FAMS: mobility, symptoms, and emotional wellbeing but not with the remaining items: general contentment, thinking and fatigue, family and social wellbeing and additional concerns. Conclusions. In comparison with the patients from other population-based surveys, our patients were less disabled and enjoyed better quality of life. The perspective of the patients does not necessarily agree with disability scales. Quality of life should be included in the approach of MS patients if we want to provide a cost-effective health care.

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THE EVALUATION OF BALANCE DISORDERS IN MULTIPLE SCLEROSIS BY MEANS OF TETRAATAXIOMETRY. D. Alpini, D. Caputo, D. Pellegatta, M. Fini, R. Kohen-Ratz, Scientific Institute S.Maria Nascente Don Gnocchi Foundation, Hebrew University (Milan, Jerusalem, I)

Most common human activities require the ability to stabilize the human body in upright stance. To counteract the effects of gravity there is a continuous modulation of motor activity, especially in so-called antigravity muscles. Measurement of body movements during stance in order to maintain balance are measured by posturography. The basic concept depends on measurement of the forces actuated by the feet against the ground, measured with a forceplate. The forceplate consists of force transducers placed to pick up the distribution of forces on the ground. Disorders of balance are common during the course of multiple sclerosis (MS) and posturography is the specific tool to assess stance balance disorders in patients. Tetraataxiometry (by Tetrax, Israel) is the last developed equipment, consisting in four forceplates, that allows simultaneous recording of right/left and tools/heels displacements of body in stance. Setting: Patients were recruited from the MS and Physiotherapic Units of don Gnocchi Foundation, a centre specialized in rehabilitation for patients with neurological disease; they were evaluated at the ENT-Otoneurology Service of the same centre and data were elaborated at the Hebrew University, where the posturographic equipment was developed. Patients: 18 inpatients who fulfilled the criteria with clinically defined MS (12 females and 6 males, aged 31–47 yy, with disease history ranging 1–28 yy). MS cases represented mild to moderate stages of disability (EDDS ranging from 1.5 to 6.5). Methods: Tetraataxiometry was performed with patients quietly standing on forceplates in a quiet room in 8 different conditions: eyes open and closed, standing on a rubber foam with eyes open and closed, head turned right and left, head bent back and forward. 13 parameters were calculated each test condition, related to body sway, weight distribution, right and left synchronization, toes and heels synchronization, sway frequencies bands (ranging from 0.05 to over 3 Hz). Results: Numerous abnormalities were found during the stabilometric examination, in all patients, when comparing the results obtained in MS with those collected ina control group of 78 normal subjects (mean age 37 yy), recorded in the same conditions. A Student t-test has been applied to 104 variables. The t-test significance is generally high. Particularly, the most interesting aspects are: transfer of weight on heels, de-synchronization of toes and an elevated intensity of frequencies ranging from 0.10 to 0.25 Hz in conditions eyes closed on the foam, head turned right, back and forward. Also the simplest condition (eyes open) is characterized by significative decrease of body stability and increase of high frequencies (over 1 Hz) of oscillations when comparing with normals. Conclusions: The results suggest the presence of a MS-specific reorganization of the balance control system. MS leads to pervasive postural disturbances. Tetrataxiometry seems to be specifically able to demonstrate postural involvement in MS in order to follow-up the effects of treatment.

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THE FREQUENCY OF CSF OLIGOCLONAL BANDS AND MRI LESIONS IN MULTIPLE SCLEROSIS BEFORE 16 YEARS. ME Eraksoy, A.KA Kiyat Atamer, G. S.D Saruhan Direskeneli, G. A.D Akman Demir, Z.Y Yapici, R.T Tuncay, Ist Fac Med, Neurology (Istanbul, TR)

Although the diagnosis of multiple sclerosis (MS) is ultimately a clinical decision, Magnetic Resonance Imaging (MRG) and examination of cerebrospinal fluid (CSF) are important guides. The characteristic white matter abnormalities are seen on MRI in 99%, and oligoclonal IgG bands (OCBs) in CSF are detected > 95% of adult patients with clinically definite MS (CDMS). The frequency of CSF OCBs and MRI lesions in MS under 16 yrs is a controversial issue.

The objective of this study was to reveal the frequency of CSF OCBs and MRI lesions in MS below 16 yrs. Consecutive patients who developed MS before 16 yrs and followed in our MS and Child Neurology units between 1990 and December 1999 were included. CSF OCBs (isoelectric focusing) and cranial MRI were obtained before 16 yrs in all patients.

Eighteen (10F, 8M) children with MS were evaluated. Mean age at onset was 10 yrs (ranged from 8 to 15 yrs). The patients fulfil the Poser's Committee Criteria (1983) as follows: Group 1: CDMS (n=14, 77.7%); Group 2: Clinically Probable MS (CPMS) (n=3, 16.6%); Group 3: Laboratory supported definite MS (LSDMS) (n=1, 5.5%). CSF was obtained at the first (n=9, 50%) and second attacks (n=9, 50%). In CDMS group, OCBs in CSF were positive in all patients (n=14, 100%). CSF OCBs were negative in two patients with CPMS and positive in a patient with LSDMS. Cranial MRI was performed in 13 children at the initial episode and five children at the second attack. Cranial MRI findings were compatible with MS in 12 patients (85.7%) in CDMS group. Two of 14 patients with CDMS had large, tumor-like demyelinating lesions on MRI and biopsy specimens showed subacute MS plaque. In CPMS group, MR images were consistent with MS (n=1), neuromyelitis optica (n=1) and Schilder's disease (n=1). A girl with LSDMS had new lesions on repeat MRI which was obtained a year later.

These results suggest that the frequency of cranial MRI lesions and CSF OCBs in MS before 16 yrs are not significantly different from those in adults but larger prospective studies are required to determine the answer.

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A LONGITUDINAL STUDY OF SEXUAL FUNCTION IN MULTIPLE SCLEROSIS. M. Zorzan, R. Zivadirov, L. Monti Bragadin, R. Moretti, R. De Masi, D. Nasuelli, G. Cazzato, Neurological Clinic Trieste (Trieste, I)

Sexual dysfunction severely affects the patients' quality of life, but longitudinal studies of sexual function in multiple sclerosis are lacking. We performed a study on a group of patients with multiple sclerosis to evaluate the change in sexual function and to examine the relationship between sexual dysfunction and other clinical variables over time.

Methods: A 2-year follow-up study on 99 patients with definite multiple sclerosis. Information on sexual and sphincter disturbances have been collected through a face-to-face interview. Disability, independence, cognitive performances and psychological functioning have also been assessed. Multiple logistic regression analysis has been employed to remove the effect of confounding covariates and to test variables interaction.

Results: The proportion of patients with sexual dysfunction remained over 70% and did not change during the 2-year follow-up, but the extent and number of symptoms increased significantly. Significantly more patients than before the study resorted to counseling and discussed with doctors of sexual matter. In multiple logistic regression analysis age ($p< 0.02$), anxiety ($p< 0.02$), fatigue ($p< 0.03$) and bowel dysfunction ($p< 0.05$) were associated with the change in sexual function over time, while bladder dysfunction showed a trend ($p= 0.0509$).

Conclusions: Symptoms of sexual dysfunction increase in significance and number over time in patients with multiple sclerosis. The change of sexual function appears to be independently influenced by age, anxiety, fatigue and bowel dysfunction.

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MAGNETIZATION TRANSFER IMAGING TO MONITOR THE EVOLUTION OF MS: A ONE-YEAR FOLLOW UP STUDY. M. Rovaris, M. Inglese, M. P. Sormani, G. Iannucci, B. Colombo, G. Comi, M. Filippi, Neuroimaging Research Unit, Clinical Trials Unit, IRCCS HSR, Neuroimaging Research Unit Scientific Institute Ospedale San Raffaele (Milan, I)

Aims of this study were: a) To assess the sensitivities of magnetization transfer imaging (MTI)-derived measures in detecting changes over time of macro- and micro-scopic lesion burdens in different multiple sclerosis (MS) clinical phenotypes; b) to compare them with those of T2 and T1 lesion volumes; and c) to calculate the sample sizes needed for detecting various treatment effects with 90% power when using outcomes derived from conventional magnetic resonance imaging (MRI) or MTI.

We studied 96 patients with relapsing-remitting (RR) (n = 39), secondary progressive (SP) (n = 19), primary progressive (PP) (n = 9), or benign (B) (n = 9) MS, 20 patients at presentation with clinically isolated syndromes suggestive of MS (CIS), and 20 healthy subjects. Brain T2, T1 and MTI scans were obtained at baseline and after 12 months. We measured T2 and T1 lesion volumes and average lesion MT ratio (MTR). We also derived MTR histograms from the whole brain tissue (WBT) and from the normal-appearing brain tissue (NABT).

In healthy controls, there was no significant change of any of the MTR histogram parameters. At follow up, in the whole patient group, T2 lesion volume significantly increased and average lesion MTR, WBT- and NABT-MTR, and histogram peak positions significantly decreased. Patients with RRMS and SPMS had significantly higher changes of T2 lesion volume and all the MTI-derived metrics compared to the other subgroups. MTI changes were more prominent (and significantly different) in patients with SPMS than in those with RRMS. Compared to patients with BMS, patients with RRMS had significantly greater changes in T2 lesion volume and MTR metrics of the WBT and NABT. Compared to patients with SPMS, patients with PPMS had significantly lower changes of MTI-derived measures. The estimated sample sizes needed to perform clinical trials with 90% power were much lower when using the percentage change of average WBT-MTR as the outcome measure than when using the percentage change of T2 lesion volume.

MTI-derived measures are sensitive for detecting MS-related changes and might provide valuable outcome measures when assessing treatment effect in clinical trials of patients with MS.

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DIFFUSION TENSOR IMAGING IN MULTIPLE SCLEROSIS. M. Filippi, M. Cercignani, M. Inglese, V. Martinelli, L. Moiola, G. Comi. Neuroimaging Research and *Clinical Trials Units, Department of Neuroscience, Scientific Institute Ospedale San Raffaele, University of Milan, Milan, Italy.

Diffusion tensor imaging (DTI) allows to quantify the mean diffusivity (), a measure of diffusion independent of measurement direction, and the fractional anisotropy (FA), an index of fiber directionality. In this study, we measured and FA of lesions and normal appearing white matter (NAWM) from patients with two different multiple sclerosis (MS) phenotypes to improve our understanding of the nature of the pathologic damage in MS.

We studied 43 MS patients (28 with primary progressive – PP – and 15 with relapsing-remitting – RR – MS) and 21 age- and sex-matched healthy volunteers. Dual-echo turbo spin-echo, spin-echo echo-planar with diffusion weighing along eight directions, and T1-weighted scans were obtained from all subjects. From the diffusion scans, images of $\bar{D}$ and FA were derived. Next, $\bar{D}$ and FA maps were co-registered using T2-weighted scans as a baseline. Average $\bar{D}$ and FA of lesions, identified and outlined on proton density-weighted scans, were then measured. On the same scans, $\bar{D}$ and FA were measured from different NAWM regions for both patients and controls.

Average FA was found to be lower in the NAWM from patients than in white matter from controls ($p=0.001$). This difference was significant also when patients with RRMS ($p=0.009$) or PPMS ($p< 0.001$) were considered separately. T2-visible lesions had a higher $\bar{D}$ ($p< 0.001$) and a lower FA ($p< 0.001$) than the NAWM. Consistent with a more severe loss of tissue organization, T1-hypointense lesions had higher $\bar{D}$ and lower FA values ($p< 0.001$) than T1-isointense lesions. In lesions but not in the NAWM, an inverse correlation between $\bar{D}$ and FA ($r=-0.40$, $p< 0.001$) was found. Significant correlations were also found between T2 lesion load and both average lesion $\bar{D}$ ($r=0.65$, $p< 0.001$) and FA ($r=-0.62$, $p< 0.001$). There was no significant correlation between average $\bar{D}$ of lesions and NAWM, whereas a moderate correlation was found between average FA of lesions and NAWM ($r=0.38$, $p=0.01$).

Our findings are consistent with a diffuse loss of structural barriers to water molecular motion both inside lesions and in the NAWM of patients with different MS phenotypes. This study also suggests that the quantification of tissue damage in the NAWM provides partially independent and complementary data for assessing brain pathology from patients with MS.

P550
EFFECTS OF CORTICOSTEROID TREATMENT ON THE EXPRESSION OF IL–10 MRNA. CORRELATION WITH CHANGES IN SOLUBLE ADHESION MOLECULES IN MULTIPLE SCLEROSIS. C Blanco-Jerez, Ml Villar, MT Frutos, J Masjuan, JF Plaza, LM Orensanz, P Gonzalez-Porque, JC Alvarez-Cermeño, Hospital Ramón Y Cajal (Madrid, E)

Soluble adhesion molecules VCAM–1 and ICAM–1 increase during multiple sclerosis (MS) relapses. IL–10 mRNA levels may change in relation to MS ac-

tivity as well. We have studied the effect of corticosteroid treatment (CST) on serum levels of sVCAM–1 and sICAM–1 and on IL–10 mRNA of peripheral blood mononuclear cells, in patients with a relapse of MS. A possible correlation among them was also assessed.

METHODS: Blood samples were obtained from patients before and after CST during a MS relapse. sICAM–1 and sVCAM–1 levels were determined with a commercial kit for ELISA. IL–10 mRNA was amplified by RT-PCR and quantified using an image analyser. Wilcoxon's test was applied to compare differences between means. Correlations were calculated with Spearman's test.

RESULTS: IL–10 m RNA levels increased after CST ($p< 0.005$). Both sICAM–1 and sVCAM–1 decreased with treatment ($p< 0.001$). A negative correlation was found between the increase of IL–10 mRNA and the decrease of sICAM–1 ($p< 0.05$).

CONCLUSIONS: A decrease in sVCAM–1 and sICAM–1 levels, as well as an increase in IL–10 mRNA are observed after CST in MS relapses. Corticosteroid-induced changes in the expression of soluble adhesion molecules may influence lymphocyte traffic across blood-brain barrier. On the other hand, the increase of IL–10 mRNA may contribute to ameliorate MS activity. These results suggest that CST affects the physiopathology of MS.

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GRADUAL DECLINE OF CEREBROSPINAL FLUID OLIGOCLONAL IMMUNOGLOBULIN G IN A CASE OF MULTIPLE SCLEROSIS. M. Schluep, H. Henry, R. de Haller, F. Vingerhoets, C. Bachmann, J. Bogousslavsky, CHUV, Department of Neurology, CHUV, Clinical Chemistry, CHUV, Department of Neurology (Lausanne, CH)

The presence of oligoclonal bands (OCBs) of immunoglobulin G (IgG) in cerebrospinal fluid (CSF) is an indicator of a humoral immune response within the central nervous system. Intrathecal IgG OCBs synthesis is found in 95 % of patients with clinically definite multiple sclerosis (MS). Some serum IgG OCBs may also be found in MS, and are a sign of the disturbance in systemic immunity occurring in MS. Most MS patients do not change their OCBs patterns during the course of the disease. We report the changes of serum and CSF IgG OCBs patterns observed in sequential samples obtained from a single MS patient over 13 months. Case report: A 20-year old female presenting with an aggressive course of MS developed six relapses over 11 months, all with partial recovery. Initial magnetic resonance imaging (MRI) showed multiple lesions of the brain and brainstem white matter (some with gadolinium enhancement). There was a progressive loss of clinical response to steroid therapy; neurological residual deficits after relapses increased rapidly. Because of the unusual severe course of the disease which was accompanied by infrequent signs and symptoms, MRI and CSF examination were repeated to confirm MS, and to exclude other superimposed pathologies. Interferon-beta 1a (Rebif®, 3x44 µg/week) was introduced early in the clinical course, and plasma exchange was finally attempted. Results: The 1st CSF examination demonstrated 86 leukocytes/µl (mostly lymphocytes), intact blood-brain barrier, and IgG OCBs in CSF but not in serum (method: isoelectric focusing). From the 2nd CSF analysis on, leukocytes were within the normal range (< 5/µl). Although IgG OCBs were first restricted to CSF, at one month interval a few IgG OCBs were also detected in serum (CSF OCBs > > serum OCBs; previous treatment: steroids) whereas the number and intensity of CSF OCBs decreased. Twelve (previous/ongoing treatments: steroids, interferon-beta 1a) and 13 months (additional treatment: plasma exchange) after onset, CSF examination showed disappearance of some IgG OCBs both in serum and in CSF as well as appearance of new IgG OCBs in CSF (CSF OCBs > serum OCBs).

Discussion: The observed changes of IgG OCBs patterns could be attributed either to the effect of the treatments (induction of apoptosis of plasma cell clones) and/or to a change in the natural course of the disease with chronic demyelination and axonal degeneration predominating over the inflammatory process.

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MICROGLIA AND NEURONS IN VITRO: EVIDENCE FOR BOTH NEUROTOXICITY AND NEUROPROTECTION. S. Golde, M. G. Spillantini, D. A. S. Compston (Cambridge, GB)

Axon loss is abundant in chronic as well as acute multiple sclerosis lesions and could be the major reason for inability to repair in the chronic progressive phase of the disease. This loss of neuronal integrity might be secondary to oligodendrocyte injury or result from direct toxicity of inflammatory cells. Microglia are prime candidates for causing inflammatory bystander damage. We used rat primary tissue in different culture paradigms (direct co-culture; co-culture with exchange of soluble factors but no cell contact; and culture with medium conditioned by microglia) to test whether microglia can influence the survival of cortical neurons. Monitoring metabolic activity (MTT metabolism), neurotransmitter-uptake (3H-GABA) and cell death (LDH release) we show that microglia activated with IFNg and LPS induce death of healthy neurons in culture, whereas unstimulated microglia promote neuronal survival and function. These findings were confirmed by immunocytochemistry. The microglial effect is partially mediated by soluble factors, but is most effective when microglia are in close proximity of neurons. The toxic effect can be fully reversed by the iNOS specific inhibitor 1400W, but also partially by L-NNA in a concentration specific for nNOS. Our results argue for a role of microglia both in supporting or injuring neurons depending on their activation state. Differential gene expression in neurons subjected to microglial factors is being used to characterise events which subserve these processes.

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QUANTITATIVE BRAIN MRI IN PATIENTS PRESENTING WITH CLINICALLY ISOLATED SYNDROMES: RESULTS OF THE NEW LONDON COHORT. P. A. Brex, K. A. Miszkiel, J. I. O'Riordan, I. F. Moseley, G. T. Plant, A. J. Thompson, D. H. Miller, Institute of Neurology (London, UK)

High signal lesions have been found in 50–70 % of patients presenting with clinically isolated syndrome (CIS) suggestive of demyelination using T2-weighted magnetic resonance imaging (MRI). The presence of such lesions increases the risk of having a relapse in the future leading to a diagnosis of multiple sclerosis (MS). Since the early studies of such patients 10–15 years ago, technology has improved prompting the study of a new cohort, imaged at higher field strength and with thinner slices. This study describes quantitative MRI findings at presentation using a semi-automated contouring technique to measure lesion volume. Methods: 81 patients (48 women, 33 men), with a mean age of 31 (16–50 years) were imaged a mean of 5 weeks (range 1 –12 weeks) after onset of a CIS (55 optic neuritis, 1 optic tract lesion, 18 brainstem & 7 spinal cord syndrome). All imaging was performed on a 1.5 Tesla GE scanner and included fast spin-echo (FSE) [TR 3200ms, TE 15/95ms, 3mm slice thickness] and T1-weighted spin-echo [TR 600ms, TE 14ms, post 0.1 mmol/kg gadolinium] sequences. 69 % (56/81) T2-weighted images demonstrated one or more clinically silent lesions. The median T2 lesion volume was 0.31cm^3 (mean 1.65cm^3, range 0–13.9cm^3) [median lesion number 4 (range 0–76)] for the group as a whole and 1.7cm^3 (mean 3.2cm^3, range 0.21–13.9cm^3) [median lesion number 22] for the 41 patients with 4 or more lesions. The median T2 lesion size was 0.08cm^3 (mean 0.14cm^3, range 0.01–0.78cm^3).The median T1 lesion volume was 0 (mean 0.34cm^3, range 0–4.49cm^3) [median 0 lesions (range 0–19)]. The mean T1/T2 volume ratio was 14 %.

Conclusion:The quantitative baseline MRI data of this prospectively recruited cohort of CIS cases provides valuable natural history data for comparison with volumes from other studies including clinical trials. The use of thin slices in this study (3mm) probably accounts for the small median lesion size (by detecting more small lesions) and for the substantial T1/T2 volume ratio (improving the detection of hypointensity on T1-weighted images).

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EFFECTS OF CORTICOSTEROID TREATMENT ON THE EXPRESSION OF IL–10 MRNA. CORRELATION WITH CHANGES IN SOLUBLE ADHESION MOLECULES IN MULTIPLE SCLEROSIS. C. Blanco-Jerez, L. M. Villar, T. Frutos, J. Masjuan, J. F. Plaza, L. M. Orensanz, P. Gonzalez-Porque, J. C. Alvarez-Cermeño, Hospital Ramon y Cajal (Madrid, E)

BACKGROUND: Soluble (s) adhesion molecules VCAM–1 and ICAM–1 increase during multiple sclerosis (MS) relapses. IL–10 mRNA levels may change in relation to MS activity as well. We have studied the effect of corticosteroid treatment (CST) on serum levels of sVCAM–1 and sICAM–1 and on IL–10 mRNA of peripheral blood mononuclear cells, in patients with a relapse of MS. A possible correlation among them was also assessed.

METHODS: Blood samples were obtained from patients before and after CST during a MS relapse. sICAM–1 and sVCAM–1 levels were determined with a commercial kit for ELISA. IL–10 mRNA was amplified by RT-PCR and quantified using an image analyser.

Wilcoxon's test was applied to compare differences between means. Correlations were calculated with Spearman's test.

RESULTS: IL–10 mRNA levels increased after CST ($p< 0.005$). Both sICAM–1 and sVCAM–1 decreased with treatment ($p< 0.001$). A negative correlation was found between the increase of IL–10 mRNA and the decrease of sICAM–1 ($p< 0.05$).

CONCLUSIONS: A decrease in sVCAM–1 and sICAM–1 levels as well as an increase in IL–10 mRNA are observed after CST in MS relapses. Corticosteroid-induced changes in the expression of soluble adhesion molecules may influence lymphocyte traffic across blood-brain barrier. On the other hand, the increase of IL–10 mRNA may contribute to ameliorate MS activity. These results suggest that CST affects the physiopathology of MS.

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P555
THE INFLUENCE OF INTERFERON BETA–1B NEUTRALISING ANTIBODIES IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS ON COGNITIVE PERFORMANCE AND QUALITY OF LIFE CONSIDERING GENDER. S. Ritter, U. Wranek, G. Ladurner, Christian-Doppler-Klinik (Salzburg, A)

Interferon beta–1b (IFNB–1b) (Betaferon®, Schering) is an immunomodulatory drug reducing the exacerbation rate and total lesion load on magnetic resonance imaging (MRI) in Multiple Sclerosis (MS).The occurrence of neutralising antibodies (NAB) against INFB–1b is associated with an attenuation of treatment effect. During treatment 35–38 % of the patients develop NABs. Cognitive dysfunction affects 40 to 70 % of all MS patients. However, patients receiving IFNB–1b show cognitive improvement, a finding unlikely to be explained by practice effects or brain lesion area. MS patients experience reduction of quality of life (QoL). QoL research shows that the adverse effects of IFNB–1b are not markedly intrusive and burdensome. The purpose of the present study was to investigate whether NABs effect cognitive performance and Qol in patients with relapsing-remitting MS (RRMS) considering gender.

Subjects: The sample consisted of 23 ambulatory RRMS patients (EDSS < 3) who received IFNB–1b (mean treatment duration, 3 years). Of these patients, 11 were NAB-positive and 12 were NAB-negative. The sample consisted of 10 men and 13 women.

Methods: Cognitive performance was assessed with the Mini Mental State Examination (MMSE), the Wechsler Memory Scale (WMS), the d2 and the Reduced Wechsler Intelligence Scale (WIP). Patients rated their QoL with the WHOQOL-BREF.

Results: Analyses of variance revealed no significant differences between NAB-positive and NAB-negative patients. Concerning the WMS there was a significant interaction for the subtest "information" (p=.008). The most striking result of this study is that despite previous research we found no impairment of cognitive performance and diminished QoL compared with population norms. These findings provide support for the assertion that IFNB–1b improves cognitive performance and QoL in patients with RRMS.

P556
COMPARATIVE CLINIC EFFICIENCY ANALYSIS BETWEEN INTERFERON BETA 1-B AND INTERFERON BETA 1-A. A Miralles, B Fuentes, P Barreiro, E Diez-Tejedor, University Hospital La Paz, University Hospital La Paz Universidad Autónoma de Madrid (Madrid, E)

Interferon beta (IFN-B) constitutes the non-symptomatic treatment of first line in relapsing-remitting multiple sclerosis (RR-MS). Currently there are three types of IFN-B in the market, but due to the fact that the accomplished clinical trials were different, it is difficult to do a valid comparison between them. We propose to accomplish a comparative analysis of clinic efficiency between IFN-B 1-b (Betaseron) and IFN-B 1-a (Avonex).

Patients and method: Open observational study where we select the patients with RR-MS, older than 16 years, with at least two relapses in two previous years to the treatment with IFN-B, with a score in EDSS scale > 1 and < 5.5, that began in a same period of time treatment with Avonex (18 cases, group A) and with Betaseron (15 cases, group B). We analyze the number of relapses during the treatment with IFN-B, those that were treated with steroids, and the final punctuation in EDSS scale.

Results: In the data bases of both groups there was no difference in age, sex, evolution time in months until the beginning of the treatment with IFN-B, number of relapses in two previous years, those which were treated with steroids, score in EDSS scale previous to the treatment, and treatment time in months with IFN-B. The results in the three analyzed variables did not show significant differences: number of relapses during treatment with IFN-B (A: 1.33 ± 1.6; B: 0.86 ± 1.35; p 0.39), those which were treated with steroids (A: 0.88 ± 1.27; B: 0.46 ± 1.06; p 0.31), and final score in EDSS scale (A: 1.91 ± 1.14; B: 2.5 ± 1.75; p 0.25).

Conclusion: Our results show that there is no difference in clinic efficiency between the RR-MS patients treated with Avonex or Betaseron, during the period of time analyzed. These are preliminary data. Further studies to confirm these results necessary are.

P557
A WEEKLY MAGNETIZATION TRANSFER AND DIFFUSION WEIGHTED IMAGING STUDY OF MULTIPLE SCLEROSIS LESIONS AND NAWM. M Filippi, M. A. Rocca, M. Cercignani, G Iannucci, G Comi, Neuroimaging Research Unit, Clinical Trials Unit (Milan, I)

In this study, weekly magnetization transfer (MT) and diffusion weighted (DW) imaging were obtained from multiple sclerosis (MS) patients to evaluate: a) if their values at the time lesions form are predictive of the short-term evolution of intrinsic lesion damage and b) whether subtle changes can be detected in the normal appearing white matter (NAWM) before the appearance of new MS lesions.

Conventional magnetic resonance (MR) imaging (dual-echo and T1-weighted scans without and with gadolinium), DW and MT scans were obtained from five MS patients every week on 12 separate occasions. New lesions were identified, outlined on the coregistered MT and DW images and their MT ratio (MTR) and mean diffusivity (D) measured. We also measured the MTR and D values of: 1) the same regions before the appearance of lesions; 2) different regions of NAWM; 3) chronic (unenhancing) lesions. Lesions were also classified as isointense or hypointense on the corresponding T1-weighted images.

Twenty-seven chronic and 16 enhancing lesions were identified and studied longitudinally. All the lesions had significantly higher D ($p< 0.0001$) and lower MTR values ($p< 0.0001$) than the corresponding values of NAWM measured on the same weekly scans. The MTR and D values measured in the NAWM remained stable during the follow up. Chronic lesions that were hypointense on T1-weighted images had lower MTR values and higher D values than chronic isointense lesions and the values of both the groups remained stable during the follow up. Acute hypointense lesions had lower MTR and higher D values at the time of their first enhancement than on subsequent evaluations. During follow up, four MR patterns of active lesions were assessed: a) initially isointense lesions which remained isointense (MTR and D values did not change significantly); b) initially isointense lesions which became hypointense (significant MTR [$p=0.003$] and D [$p=0.01$] changes). The most significant D change ($p=0.002$) in this group of lesions was seen on the scans obtained the first week after enhancement appearance; c) initially hypointense lesions which became isointense (MTR and D values did not change significantly); d) initially hypointense lesions that remained hypointense (MTR and D values did not change significantly). NAWM areas corresponding to future enhancing lesions showed a significant decrease ($p=0.002$) of the MTR and a significant increase ($p=0.01$) of the D values before enhancement appearance. On average, these areas had also lower MTR ($p=0.002$) and higher D ($p< 0.0001$) than the areas of NAWM that did not show any enhancement during the follow up.

Our study shows that MTI and DW imaging enable the different structural characteristics of MS lesions to be quantified. MTR and D changes predict the short-term evolution of new MS lesions. This study also confirms that subtle NAWM abnormalities can be detected before the appearance of new MS lesions.

P558
ASSOCIATION OF AUTOIMMUNE DISEASES AND MULTIPLE SCLEROSIS. PREVALENCE STUDY IN SARDINIAN PATIENTS. M. Lai, E. Cocco, F. Carboni, M. Marrosu, Multiple Sclerosis Center (Cagliari, I)

There is an increased evidence that autoimmune disease susceptibility is sustained by common and environmental factors. In order to test this hypothesis, we studied the occurrence of insulin-dependent diabetes mellitus (IDDM), rheumatoid arthritis (RA) and autoimmune thyroid diseases (ATD) in Sardinian multiple sclerosis (MS) patients.

MATERIALS AND METHODS. The study has been carried out on 920 MS in and out patients, all followed by the MS Center of Cagliari. Co-association of autoimmune disease was confirmed by specific analysis.

RESULTS: Over 920 MS patients, IDDM was presenting 1,2 % (expected in Sardinians: 0,6 %), RA in 0 % and ATD in 1,8 %.

CONCLUSION: The association of multiple autoimmune disease in the same individual supports the notion that in Sardinians there is a common genetic factor that predisposes to autoimmunity.

P559
OCCURRENCE OF AUTOIMMUNE DISEASE IN SARDINIAN MULTIPLE SCLEROSIS PATIENT'S PARENTS. E. Cocco, M. Lai, F. Carboni, M. Marrosu, Multiple Sclerosis Center (Cagliari, I)

Human autoimmune disease (HAD) are chronic conditions involving approximately 5 % of the population. Genetic studies in both animal models of autoimmune disease and HAD suggests a possible shared among different autoimmune disease. In order to confirm clustering of autoimmunity, we

conducted a prevalence study in families of a hospital-based multiple sclerosis (MS) population from Sardinia, an island characterized by a well defined genetic background and an unusually high rate of MS and insulin dependent diabetes mellitus (IDDM).

MATERIALS AND METHODS. The study has been carried out on 920 MS Sardinian patients, all followed by the MS Center of Cagliari. The prevalence of IDDM, rheumatoid arthritis (RA), autoimmune thyroid disease (ATD) was checked in relatives of MS on the basis of interview and, in some cases, of clinical records.

RESULTS. In our MS patient's parents population an autoimmune disease (except MS) was present in 5 % of mothers and only in 0,98 % of fathers. In particular we found IDDM in 2,15 % of parents, 1,5 of mothers and 0,65 % of fathers (expected in Sardinians 0,6 %). RA was found in 2,1 % of parents, 2 % of mothers and 0,1 % of fathers. ATD was found in 1,3 % of parents, in 1,2 % of mothers and in 0,1 % of fathers.

CONCLUSIONS. This preliminary study, showing an unusually high rate of autoimmune disease in parents of MS patients, suggests a generalized dysregulation of the immune system probably genetically controlled. Our data are in agreement with the concept that HAD are preponderant in female sex, but in our opinion the most interesting datum was the high prevalence of RA in MS patient's mothers rather than IDDM, ATD or the same MS.

P560

LOW DOSE ORAL METHOTREXATE (MTX) IN CHRONIC PROGRESSIVE (CP) MULTIPLE SCLEROSIS (MS). A. Lugaresi, D. Farina, F. Marzoli, C. Iarlori, L. Bonanni, G. De Luca, D. Gambi, University of Chieti (Chieti, I)

Low dose oral MTX has been used to slow progression of CP-MS for periods of up to 2 years with modest effects; it represents, anyway, one of the rare drugs demonstrated to be efficacious and safe enough in patients (pts) who are not candidates for interferon beta (IFNbeta) treatment because of the EDSS or disease course. The very low cost of MTX makes it an orphan-drug and renders impossible a large multicenter trial to better demonstrate its efficacy. In view of the recent approval, in Italy, of IFNbeta–1b for secondary CP-MS, it is even more important to verify safety and efficacy of oral MTX in order to propose to pts the best available therapeutic option. Objective. To verify safety and efficacy of MTX in pts treated at our MS Center since December 1997. Patients and methods. Twenty (16 males, 4 females) CP-MS pts, 4 primary progressive (PP-MS), 16 secondary progressive (SP-MS), who had shown disease progression (increase of the EDSS of 1 below 6.0, of 0.5 over 6.0) in the last year. All pts underwent cerebral MRI, Chest X-ray, EKG, abdominal echography before therapy and yearly thereafter. Blood chemistry (liver and renal function) urinalysis and blood cell count were performed before therapy, weekly for the first month and monthly thereafter. Clinical evaluation was performed before therapy and every three months thereafter and in occasion of clinical relapses. Relapses were treated with steroids under close clinical supervision to prevent serious infective complications. Results. Mean follow-up is 18 months (range 12–25 months). Mean EDSS was 6.3 ± 1.1 before treatment and 6.4 ± 1.1 at 1 year. At 1 year 17/20 pts were still treated, 10 were stable and 7 showed progression. Eight pts have completed 18 months of treatment, 2 are showing progression. Two pts stopped treatment because of side effects: 1 at month 3 (lymphoadenopathy, weight loss), 1 at month 8 because of persistently and markedly abnormal liver function; 2 pts stopped treatment at months 9 and 14 because they did not perceive benefit. Five pts presented transient and mild increases in liver enzymes not requiring treatment interruption. MRI performed before treatment and at 1 year had remained unchanged in responders. Conclusions: low dose oral MTX appears safe in CP-MS, but thorough selection of pts and treatment monitoring are required. To assess efficacy a larger, multicenter study and a longer follow-up are needed.

P561

MCP–1 EXPRESSION AND SECRETION IN ADHERENT MONOCYTE CULTURES FROM MULTIPLE SCLEROSIS PATIENTS TREATED WITH INTERFERON BETA–1B. C. Iarlori, M. Reale, G. De Luca, C. Feliciani, D. Farina, F. Marzoli, L. Bonanni, A. Di Iorio, P. Conti, D. Gambi, A. Lugaresi, University of Chieti (Chieti, I)

The pathogenesis of multiple sclerosis (MS) is characterized by breakdown of the blood-brain barrier accompanied by infiltration of macrophages and T lymphocytes into the central nervous system (CNS). The migration of these cells into the CNS may be partly regulated by chemokines, pro-inflammatory, chemo-attractant cytokines. The monocytes chemo-attractant protein (MCP–1) is a potent beta chemokine. In vitro MCP–1 attracts monocytes, memory-T cells and natural killer cells. Its expression has been documented in disorders characterized by mononuclear cell infiltrates, such as MS, suggesting that it may contribute to pathogenesis. Its role, however, is still controversial. In a preliminary study, we demonstrated that MCP–1 levels are significantly higher in supernatants from adherent mononuclear cells from relapsing-remitting (RR)-MS patients (pts) compared to healthy controls (HC). Interferon beta (IFNb) has beneficial effects on relapse rate and severity as well as on disease progression in RR-MS. Objective. To assess MCP–1 expression and production by adherent monocyte cultures, from RR-MS pts in relapse and remission untreated and treated with IFNb–1b. Patients and methods. Eleven RR-MS pts and 5 HC. Six pts were untreated (4 in relapse, 2 in remission), and 5 treated with IFNb–1b for at least 1 year (2 in relapse and 3 in remission). Antigenic MCP–1 levels were quantified in supernatants from unstimulated and phytohemoagglutinin (PHA)-stimulated cultures using a solid phase sandwich enzyme-linked immunosorbent assay (ELISA). Cell pellets were treated with TRIzol Reagent for mRNA extraction and cDNA synthesis. A semi-quantitative analysis was performed by reverse transcriptase PCR amplification (RT-PCR), comparing the amplified product signals for MCP–1 with the G3PDH signal. Results. In unstimulated cultures MCP–1 signal is higher in RR-MS than in HC especially during relapses independently of treatment. In PHA-stimulated cultures MCP–1 signal is higher and comparable in all groups independently of disease phase, but for IFNb–1b treated pts, who show higher expression. MCP–1 production is higher during relapses independently of treatment and in treated patients independently of disease phase. Conclusions. MCP–1 expression and production correlate with disease status in unstimulated cultures. IFNb–1b appears to augment the response to PHA. The significance of this last finding remains to be clarified. Our data highlight an additional effect of IFNb–1b on the immune response.

P562

SYSTEMATIC THYROID ASSESSMENT IN MS PATIENTS UNDERGOING INTERFERON BETA 1B THERAPY. G. Moscato, F. Lombardo, S. Mosti, C. Fioretti, F. Monzani, N. Caraccio, A. Casolaro, E. Ferrannini, L. Murri, G. Meucci, Department of Neurosciences, Department of Internal Medicine (Pisa, I)

Multiple Sclerosis (MS) is a T-cell mediated demyelinating disease of the central nervous system, associated with an aberrant autoimmune response to myelin and possibly non-myelin self-antigens.

Recombinant interferon beta (IFN-beta), an immunomodulatory therapy for relapsing-remitting MS, has been shown to reduce the frequency and severity of exacerbations and the total lesion load measured by magnetic resonance imaging of the brain.

Aim of the study was to evaluate the incidence of thyroid disease (dysfunction and autoimmunity) and its evolution in MS patients undergoing long-term IFN-beta 1b (Betaferon) treatment.

We studied 31 patients (21 female, 10 male; mean age 34 ± 7 years; range 23–49) with relapsing-remitting MS undergoing a 3 years' treatment with IFN-beta 1b. Systematic thyroid assessment and measurements of serum interleukin–6 (IL–6) levels were performed every three or six months depending on the development of thyroid disease.

We previously reported in the same cohort a 33 % overall incidence of thyroid dysfunction (10 % hyperthyroidism, 23 % hypothyroidism) after one year's treatment. Thyroid autoimmunity developed in 19 % of the subjects, in one case without organ dysfunction. The development of thyroid dysfunction was significantly related to a positive baseline TPO-Ab titer; moreover a female gender and the presence of a diffuse hypoechoic ultrasound thyroid pattern emerged as additional risk factors. Serum IL–6 showed a biphasic pattern, raising 2-fold at 3 months, returning to baseline values at 6 months and thereafter raising at 9 and 12 months up to 2-fold.

After the first year of IFN-beta 1b treatment, no further cases of thyroid disease were observed. Among the patients with early incident subclinical hypothyroidism (n = 6), thyroid dysfunction persisted only in those (n = 2) with baseline autoimmune thyroiditis. Those patients who developed transient hyperthyroidism (n = 3) in the course of the first year's treatment remained euthyroid throughout the following treatment course. Moreover, a positive autoantibody titer was continually detected in 2 out of 5 patients with no autoimmunity evidence at baseline. After the biphasic increment occurring during the first year's therapy, IL–6 returned to baseline values at 18 months, and did not rise thereafter.

In conclusion, the risk of thyroid disease appears to be related to IFN-beta 1b treatment during the first year only. The temporal association of serum IL–6 changes with thyroid disease development and reversibility suggests that IL–6 may play a role in the occurrence of thyroid disorders. We recommend a routine systematic thyroid assessment in all patients during the first year of IFN-beta 1b therapy and thereafter, only in those with incident thyroid disease.

P563
EFFECTS OF MITOXANTRONE ON MULTIPLE SCLEROSIS PATIENT'S LYMPHOCYTE SUBPOPULATIONS, IMMUNOGLOBULINE AND TNF ALPHA PRODUCTION. J. G. Gbadamosi, C. H. Heesen, C. B. Buhmann, A. M. Moench, W. T. Tessmer, F. H. Haag, University Clinic/Dep. of Neurology, University Clinic/Dep. of Immunology (Hamburg, D)

Recent studies indicated that mitoxantrone is a well tolerated and clinically effective substance for treating rapid progressive multiple sclerosis patients. We designed this longitudinal study to clarify which lymphocyte cell subsets or secreted effector substances are mainly affected by the drug and how long these changes persist.

Twelve Patients (7 males, 5 females, 5 primary chronic progressive, 4 secondary chronic progressive, 3 relapsing-progressive, mean age 38 years, mean EDSS 6.0) were initially included in this study with altogether 34 cycles of mitoxantrone covering a longitudinal maximum follow-up of 16 months (respectively 4 cycles, n = 4 patients). Mitoxantrone was administered in 3–4 months intervals with a dose of 12 mg/m^2. Serum blood samples were taken before each treatment interval (X1), one (X2) and two weeks (X3) following the infusions. Baseline values before immunosuppression were available from 9 patients. A first analysis was performed for the summarized data of all cycles comparing the pre-treatment values with the one and two weeks post-treatment data (short-term effects). Preliminary analysis was performed for long-term effects over consecutive treatment cycles.

We found a decrease of leukocytes primarily affecting neutrophils but also lymphocyte subpopulations. Highly significant sustained reduction after 14 days was discovered for the following cell populations: CD19+ (B-lymphocytes, $p< 0.001$), CD3+ (T-lymphocytes, $p< 0.01$), CD4+/CD3+ (T-helper cells, $p=0.01$), CD8+/CD3+ (T-suppressor cells, $p=0.03$), CD16&56+/CD3- (NK-cells, $p=0.005$), whereas CD3+/DR+ (activated T-lymphocytes), CD45RA+/CD4+ (naive CD4-lymphocytes), the CD4/CD8 ratio and serum immunoglobulin levels were not significantly altered. Whole blood stimulated mononuclear cell TNF alpha production showed a significant lower level ($p=0.04$) of basal TNF alpha secretion but no significant changes in the stimulated cells 2 weeks post-treatment. Preliminary data from the longitudinal study in 8 patients disclosed a persistent decrease of T-lymphocytes, mainly due to CD4-cell reduction and to a lesser extent due to CD8-cell and B-lymphocyte reduction without reaching significance. Immunoglobulins and TNF alpha secretion were not altered in the follow-up.

In conclusion we could confirm a selective short-term effect of mitoxantrone therapy with a lowering of most lymphocyte subpopulations (excluding activated and naive T-lymphocytes). These changes did not quantitatively affect the secreted effector substance levels of immunoglobulins and TNF alpha. Especially whole blood stimulated TNF alpha seems not to be a suitable response marker for this therapy. Further studies should clarify if lymphocyte subpopulations and their effector molecules are adequate in monitoring the effects of mitoxantrone therapy. The extension of this study will focus on other cytokine parameters and correlations with the clinical outcome.

P564
A CATEGORICAL DISABILITY TREND ANALYSIS OF THE PRISMS TRIAL OF INTERFERON BETA–1A IN RELAPSING-REMITTING MULTIPLE SCLEROSIS. C. Liu, L. D. Blumhardt, on behalf of the PRISMS Study Group, University of Nottingham (Nottingham, UK)

Treatment benefits of immunomodulatory therapies on disease progression in relapsing-remitting multiple sclerosis (RRMS) are mainly based on 'confirmed progression' endpoints, which may be associated with poor reliability and erroneous classifications. Area under disability/time curves improve the quantification of disability changes, but disease trend analyses are required for the direction of such changes.

Methods: Serial EDSS assessments were obtained from the Phase III PRISMS study of subcutaneous interferon beta–1a (IFNB–1a, Rebif®; Ares Serono) for all patients with complete 2-year data (n=533). EDSS trends and categorical disease course classifications were determined. Subgroup analyses with baseline EDSS stratified at 3.5 were made. Clinical predictors for the disease courses were obtained.

Results: Treatment with IFNB–1a resulted in a favourable shift in disease course distributions compared with placebo ($p=0.01$). This was due to an increase in the proportion of subjects with 'stable' courses (31% vs 20%) and a reduction in 'unfavourable relapsing-remitting' courses (28% vs 38%). Subgroup analyses showed significant treatment benefits for patients with baseline EDSS< =3.5 ($p=0.04$) and trends for both active therapy and dose effects for those with entry EDSS> 3.5 ($p=0.05$–0.06). High baseline disability ($p< 0.01$) and pre-trial relapse rates ($p=0.02$) were significant determinants of a 'progressive' course, while short disease durations predicted a 'stable' course ($p< 0.01$).

Conclusions: Categorical disease trend analyses potentially reduce the interpretative errors associated from 'confirmed progression' endpoints. When applied to the entire PRISMS study cohort, significant treatment effects were found. Subgroup analyses also confirmed the conclusions from the original trial. The benefits of IFNB–1a overall seem to be mainly in 'stabilising' patients to a good outcome by reducing the number of cases with prolonged periods of neurological worsening. These results have implications for targeting immunomodulatory therapies in MS.

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QUANTITATIVE MAGNETIZATION TRANSFER IMAGING IN RELAPSING MULTIPLE SCLEROSIS. S. Ropele, P. Kapeller, S. Strasser-Fuchs, T. Seifert, M. Augustin, HP. Hartung, F. Fazekas, University of Graz (Graz, A)

Magnetization Transfer (MT) Imaging has become an important technique for characterizing lesions and to detect even subtle morphologic damage in patients with multiple sclerosis (MS) (1). So far MT has been quantified by the MT ratio (MTR) which is only a relative and composite measure. We recently have developed a method which allows for a more specific assessment of the major determinants of the MTR such as the magnetization exchange rate and water content (2, 3). We now have measured these variables in different types of MS lesions and investigated their relation to commonly reported MTR values.

Material and Methods: Nine patients (6 women, 3 men) with clinically definite MS and 8 healthy controls (4 women, 4 men) were studied. All patients suffered from a relapsing-remitting course and had an Expanded Disability Status Scale (EDSS) score ranging from 1.0 to 5.0. Conventional MR imaging and quantitative MT imaging were performed on a 1.5T unit. The standard protocol included dual-echo spin echo imaging and precontrast and postcontrast T1-weighted spin echo imaging. Quantitative MT analysis was performed with a FastPACE sequence (2,3). A total of 296 areas in different stages of activity and extent of tissue destruction were analyzed. Comparison was made to normal appearing white matter (NAWM) in MS patients and to healthy white matter (NWM).

Results: While the MTR was significantly reduced in NAWM and dirty WM when compared to NWM, the relative water content was increased in dirty WM only. Focal non-active lesions showed a gradual decline of MTR and exchange rate with greater T1-hypointensity. Inversely, the relative water content was noted to increase with T1-hypointensity. Different and more complex patterns could be observed within active lesions. While the MTR was lowest in ring enhancing lesions and highest in oedema, the relative water content was lowest in densely enhancing lesions and highest in oedema. Overall, the exchange rate correlated very well with the MTR when excluding oedema and dirty WM. However, the exchange rate was more sensitive for tissue changes.

Conclusion: While MTR and the exchange rate provide some redundant information the highest gain in additional information can be obtained from the relative water distribution. This information is particularly of high interest in areas where the interpretation of a pure MTR analysis is ambiguous, i. e. NAWM and acute lesions. Quantitative MT analysis offers a more detailed insight into MT dynamics and therefore could also serve better to monitor specific therapeutic interventions than the MTR.

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P566
CORRELATION BETWEEN GYNECOLOGIC ANAMNESIS AND DISEASE ACTIVITY IN MULTIPLE SCLEROSIS. O. Zapletalova, P. Hradilek, University Hospital Ostrava (Ostrava, CZ)

Objective: To analyse the course of multiple sclerosis (MS) during gynaecologic events – pregnancy, puerperium plus post-partum period (3 months), abortion, hysterectomy and hormonal therapy for infertility.

Background: Women are more susceptible to MS than men and sex related differences in disease course are known. A pathogenic influence of sex hormones on immune and nervous systems and activity in MS has been suggested by clinical evidence. Several studies have shown that the symptoms of MS are more severe during post-partum period and increased risk for relapses is clinically known.

Material and methods: 92 pre-menopausal women at the age of 19 to 51 years with clinically and laboratory supported definite MS entered into the retrospective study. We recorded obstetrical data and describe the course of MS during pregnancies, in the post-partum period, the difficulties after abortion, hysterectomy and hormonal treatment for infertility.

Results: There were 176 pregnancies, 116 of them ended by delivery and 60 by abortion. During pregnancy there were 18 exacerbations (15,5%), 14 with

mild symptoms, 4 relapses were moderate. Post-partum period (to 3 months) brought 29 relapses (25%) which were more severe than those during pregnancies. 26 severe relapses (43,3%) were induced by abortions and the course of MS changed to secondary progressive form in 4 cases. There were 5 hysterectomies and we observed noticeable aggravation in 3 cases (60%). 3 women underwent the hormonal therapy for infertility, one of them with worsening of symptoms.

Conclusions: In our study we found that the number and severity of relapses in women with MS increased especially after abortions (both spontaneous and artificial) and hysterectomies, less in post-partum period and declined during pregnancy.

P567
MULTIPLE SCLEROSIS FOLLOWING HODGKIN'S LYMPHOMA: TWO CASES. B. Carlander, C. Delpirou, E. Legouffe, M. Billiard, Neurology B, Hematology-Oncology (Montpellier, F)

Antecedent medical conditions, such as autoimmune or neoplastic diseases, are uncommon in multiple sclerosis (MS). We present two patients treated for Hodgkin's lymphoma (HL) several years before the onset of definite MS, an association which has been reported only once (Bellian et al., J Emerg Med 1992;10:13–8).

Patient 1: A woman born 1951 was treated for HL in 1989–90 (chemotherapy and radiation therapy). In May, 1993, she had right stepping gait and left lower limb hypoesthesia, subsiding in 6 weeks. Five months later, sensory symptoms in the legs and bladder urgency led to MRI which disclosed 2 cerebral lesions. Three years later, she had a Lhermitte's symptom, upper limbs paresthesiae and right optic neuropathy. Repeat MRI showed multiple supratentorial lesions. CSF disclosed 3 oligoclonal bands. Five methylprednisolone infusions have been given. She has remained asymptomatic since, with an EDSS score 2.

Patient 2: This girl born 1982 was treated in 1988 for stage 3 HL. Brain MRI performed in 1992 because of partial complex seizures was normal. In 1998 MS was diagnosed on the basis of erratic sensory symptoms including Lhermitte's, abnormal visual evoked potentials, 4 oligoclonal bands, and multiple hyperintense lesions in the brain and the cervical spinal cord. She has had only one clinical attack, but new enhancing lesions attest dissemination in time. EDSS remains at 0 and no treatment has been given.

Since incidence of HL is estimated 1–3 per 100,000 and prevalence of MS is 40–60 per 100,000, the probability of a chance association is very low. In our two patients, the delay between the two conditions rules out any confusion between MS and cerebral localisation of HL.

The simultaneous finding of probable B-cell lymphoma and of multiple foci of demyelination has been observed in a single pathological report of a monophasic illness (Gherardi et al., Rev Neurol, 1985;141:456–63). Another biopsy-verified case concerns a patient with long standing MS who developed intracerebral lymphoma (Vrethem et al., Eur J Neurol 1998;5:507–510). An epidemiological link between MS and lymphoma/leukaemia has been studied in Yorkshire (UK), yielding an excess of MS cases in relatives of HL patients (Bernard et al., Br J Haematol 1987;65:122–3). One may hypothesize the involvement of a common virus in both conditions or, alternatively, a peculiar immunogenetically determined response to infectious agents paving the way for both HD and MS. Finally, the long term consequences of HL treatments on immune functions may explain the development of MS in a few subjects.

P568
CELLULAR AND GENOMIC LOCALIZATION OF HUMAN HERPESVIRUS 8 IN THE PLAQUES OF MULTIPLE SCLEROSIS PATIENTS. E. Merelli, P. Sola, R. Bedin, F. Casoni, P. Barozzi, Neurological Department, Department Of Internal Medicine (Modena, I)

DNA sequences of a new human herpes virus, Kaposi's sarcoma (KS) herpes virus (KSHV) or human herpes virus 8 (HHV–8), have been identified in Kaposi's sarcoma tissues from patients with AIDS. HHV–8 sequences have been detected in immunocompromised subjects, in transplant patients, and in lymphoproliferative diseases. Since CD4 T+ cells and CD19+ B cells represent the target of HHV–8 and lymphocyte activation is crucial for the development of multiple sclerosis (MS), we investigated a possible relation between HHV–8 and MS.

Patients and methods: We determined HHV–8 seroprevalence in 66 MS patients, using both IFA and ELISA techniques. The presence of HHV–8 specific sequences was investigated by the polymerase chain reaction (PCR) and n-PCR, in the DNAs from: 1) peripheral blood mononuclear cells (PBMCs) of 63 MS and 20 blood donors, 2) cerebral spinal fluid (CSF) of 34 MS, 3) autopsy brain and spinal cord tissues of 17 MS patients, 1 neuromyelitis optica (NMO), 13 adults dead for traumatic cause, and 7 new-born children.

Results: five out of 66 MS cases were positive for HHV–8 antibody by IFA; ELISA analysis confirmed the presence of antibodies in 5/66 cases with one discordant case.

All the DNAs from PBMCs and CSF of MS and control subjects were devoid of HHV–8 genomic sequences. Five out of 17 MS brain specimens were positive for HHV–8 sequences in the plaques or in the grey matter, or both, while the NMO brain and spinal cord were negative. In the controls, viral sequences were present in 2/7 new-born children and in 3/13 adult brains.

Discussion: the HHV–8 seroprevalence in the MS group does not differ from the general population (7.5% vs 7.3%), according to the absence of HHV–8 sequences in the PBMC DNAs from MS and controls. At variance, the high number of PCR-positive brains in MS, normal adults and stillborn children, argues in favour of a strong neurotropism of HHV–8. The fact that 5/17 MS cases examined were positive for HHV–8 sequence is tantalising. However, PCR was positive also in 3/13 adult normal brains and in 2/7 infant brains. This finding makes it difficult to ascertain whether this virus plays a role in MS development.

The absence of HHV–8 in the PBMCs of all MS cases and the presence of the virus in many brain specimens, may suggest that it may be present mainly in the specific site of the pathological lesion, perhaps in the oligodendrocyte, or that HHV–8 resides latent in different regions of the brain.

Results in progress: To verify if HHV–8 is present in the oligodendrocyte, considered the target cell of demyelination, we decided to use a recent technique named micromanipulation of tissue and single cell PCR. We prepared brain and spinal cord tissue sections from HHV–8 positive MS and control cases. The oligodendrocytes were identified using a specific monoclonal antibody. The HHV–8 PCR will be performed in the harvested single cells.

P569
IMMUNE RESPONSES TO COMMON INHALANT/FOOD ALLERGENS AND RECALL ANTIGENS IN MULTIPLE SCLEROSIS (MS). I. Bernstein, J. Feibel, M. Hickman, I. Mortman, Bernstein Clinical Research Center, Riverhills HealthCare, Retired (Cincinnati, OH, USA)

Organ and non-organ specific autoantibodies have been demonstrated in MS, suggesting generalized immune dysregulation by autoreactive Th1-cells and B cells activated via Th2 cells. The precise interactions between Th1 and Th2-like responses are as yet unknown. Because of widespread anecdotal claims that food derived antigens may be involved in MS onset and progression, we examined the prevalence of atopy determined by 2 or > positive prick/puncture (P/P) skin test responses (3 mm. > - than saline control) and specific IgE to a battery of aeroallergens and foods in 25 well characterized MS patients, as compared to age and sex matched normal subjects. We also compared recall antigenic (histoplasmin, tetanus toxoid, candida, trichophyton, mumps) delayed skin test reactivity in these two groups. Although specific IgE results were equivalent in MS and control groups, the total number of positive P/P tests were significantly reduced ($p=0.01$) in MS patients. Especially noteworthy was that food allergen skin test responses were significantly reduced ($p=0.03$). Recall immunity, as indexed by delayed hypersensitivity skin tests, was significantly reduced ($p=0.02$) in MS patients. These results suggest that immune deviation in MS is not skewed to Th2 driven specific IgE reactions. Although the results also suggest that impaired delayed hypersensitivity may be a component of MS immune dysregulation, larger numbers of MS patients must be studied to confirm this.

P570
TREATMENT OF INTENTION TREMOR IN MULTIPLE SCLEROSIS WITH THE 5-HT3 ANTAGONIST ONDANSETRON (TETRAHYDRO-METHYL-CARBAZOL-HYDROCHLORID-DIHYDRATE). O. Cardinal von Widdern, R. Benecke, U. K. Zettl (Rostock, D)

So far there is no effective treatment of intention tremor caused by multiple sclerosis (MS), which originates from disturbed rubro-cerebellar function. The cerebellum has a serotoninergic innervation (Trouillas et al. 1993). Previous findings suggest a particular role of serotonin in the pathogenesis of cerebellar tremor and its reduction by the selective 5-HT3 antagonist ondansetron (Rice et al. 1997). Therefore we examined whether oral administration of ondansetron can reduce intention tremor in patients with MS.

We investigated 16 patients (10M, 6F; mean age of 38 [31–44] years) with moderate to severe cerebellar tremor due to MS (mean points in Kurtzke Scale EDSS 7.5 [5–9]). 9 patients had secondary progressive MS (mean disease duration 8 [2–12] years), 7 had progressive relapsing MS (mean disease duration 6 [1–15] years). They received 8 mg ondansetron (Zofran [R]) per day orally. The patients were evaluated before as well as 5 and 30 days after beginning of treatment. Tremor was assessed by Clinical Tremor Rating Scale (Tolosa 1988) by the same investigator. In addition, the patients' subjective opinion and the improvement in the activities of daily life (washing, eating, writing) were eval-

uated. Exclusion criteria were simultaneous treatment with clonazepam, isoniacid, carbamacepin, valproat and previous treatment with ondansetron. The results were analysed by Fisher's Randomising Test for two depending sample surveys.

We found that the intention tremor reduction as assessed by the clinical scale was statistically significant (p=0.008, alpha=0.025) after 5 days of treatment with ondansetron. A continued positive treatment effect was observed in all patients evaluated again after 30 days. Patients did not perceive any side effects from the treatment. All patients described a difference in tremor severity. 3 of 16 investigated patients (18.8%) recognized a beneficial effect on the activities of daily life. Temporally omitting of treatment resulted in increased tremor severity in these 3 cases.

Our findings indicate that ondansetron may reduce intention tremor due to MS. To further evaluate the beneficial effect of different administration frequencies placebo controlled double blind cross over studies are warranted.

P571
ARTICULAR MANIFESTATION AS A SIDE EFFECT DURING IFN-BETA-1B TREATMENT IN MULTIPLE SCLEROSIS. A. Altýntaþ, Y. Alýcý, M. Melikoðlu, A. Siva (Ýstanbul, TR)

Several autoimmune events have been reported during interferon beta (IFN-B) therapy in Multiple Sclerosis (MS) and organ-specific or non-organ-specific autoantibodies can be detected. These events occur more frequently than expected which may be related either to the many immunologic abnormalities associated with this disease or as a side effect of the drug. We present clinical and laboratory findings of three MS patients who developed articular manifestations during IFN-B1b treatment.

MATERIALS & METHODS: Of the two women who had secondary progressive and one man with relapsing-remitting MS (28, 42 and 42 years of age, respectively), the first developed acute, severe arthralgia with leucocytosis and swelling in both knees one month after the onset of IFN-B1b treatment. Diagnosis was symmetric seronegative polyarthritis. The second case was on IFN-B1b for more than 2 years when she had to be hospitalized because of severe, acute arthralgia, high erythrocyte sedimentation rate, positive rheumatoid factor and high FANA level. MRI findings were consistent with inflammatory arthritis in both knees. Her diagnosis was symmetric seropositive polyarthritis. The third case who was on IFN-B1b for 28 months, developed severe acute arthralgia after each injection even in lower dosages soon after being treated with high dose methylprednisolone because of a relapse. The return of the articular manifestations following each IFN-B1b injection, and their disappearance after its discontinuation suggest that they are closely associated with this treatment.

CONCLUSION: Our report on the development of arthritis in two cases with MS and severe arthralgia in another patient, closely associated with IFN-B1b treatment extends the spectrum of autoimmune disorders induced by IFN-B1b therapy in MS patients.

P572
ORAL SILDENAFIL IN THE TREATMENT OF ERECTILE DYSFUNCTION OF MULTIPLE SCLEROSIS PATIENTS. A. Ghezzi, S. Baldini, V. Martinelli, G. M. Malvestiti, M. Zaffaroni, Centro Studi SM, Neurol. Dept., Urol. Dept. (Gallarate, Milan, I)

Sildenafil is an effective drug for erectile dysfunction (ED) of varius causes, including neurological diseases. We evaluated the efficacy of sildenafil in an open study of patients affected by multiple sclerosis (MS).

Subjects and methods. We studied 26 patients (mean age 40.5 ys) affected by definite MS (mean disease duration 11.4 ys.) complaining of ED for at least 6 months (mean duration 3.6 ys.). ED was scored by the International Index of Erectile Function-5 (IIEF-5). Patients were excluded from the treatment if they had genital anatomical deformities, abnormal hematological, renal, hepatic, cardiovascular function, major psychiatric disorders, history of retinitis pigmentosa. Sildenafil was given at a fixed dose of 50 mg., taken 1 hour before sexual activity. Results to treatment were evaluated after 8 administrations/after 3 months, asking the patients and their partners if the items of IIEF-5 were unchanged, improved, worsened. Patients were considered improved if the scores of at least 4 questions increased.

Results and comments. 30 patients were enrolled, 4 had no sexual activity in the following 3 months and did not answer to the questionnaire. The mean basal IIEF score was 10.9 (maximum score=25, normal erectile function if > 21), ranging from 6 to 18.

question 1 – ability to get an erection: basal score 1.8, improvement in 85%.

question 2 – erection hard enough for penetration: basal score 2.6, improvement in 85%.

question 3 – ability to maintain erection after penetration: basal score 1.7, improvement in 73%.

question 4 – ability to complete intercourse: basal score 1.9, improvement in 85%.

question 5 – intercourse satisfaction: basal score 2.8, improvement in 61%.

An improvement in at least 4 questions was observed in 22/26 patients (85%) patients. Answers from partners confirmed these results. 3 patients complained of headache, no patient discontinued the treatment because of side effects. Sildenafil was effective in most cases of our MS patients with ED.

P573
DO MULTIPLE SCLEROSIS (MS) PATIENTS WITH A FAMILY HISTORY OF AUTO-IMMUNE DISEASE (AID) HAVE SPECIFIC CLINICAL FEATURES? C. Papeix, O. Heinzlef, S. Alamowitch, L. Nahum-Moscovici, E. Roullet and the GRAID (Paris, F)

OBJECTIVE: To compare the clinical characteristics of MS patients belonging to multiplex families (at least one first degree relative with an AID) to those of patients belonging to MS families (at least 1 patient with MS in first degree relatives), and of sporadic MS patients belonging to simplex families (patients without a family history of MS or AID). BACKGROUND: Previous studies comparing sporadic and familial MS did not show significant differences for demographic and clinical features. As familial association of MS and AIDs occurs in more than 15% of unselected MS patients (Heinzlef O et al., Acta Neurol Scand, 1999; 100:1-5), we designed a study to collect clinical and genetic material in such multiplex families, in order to identify genes that may be common to MS and other AIDs. We now compare the clinical characteristics of MS patients belonging to MS, multiplex or simplex families. DESIGN/METHODS: Index MS patients were interviewed on their family history using a semi-standardized questionnaire designed to detect MS and AIDs. When an AID was suspected in a family member, all first degree relatives were then interviewed. Diagnoses and clinical data were confirmed by medical records. Demographics and main clinical MS features were compared for individual MS patients according to the family subtype (simplex, MS, multiplex). RESULTS: The family histories of 202 MS patients were ascertained; seventy two of these were known by, or referred to us as belonging to MS or multiplex families. Compared to MS patients belonging to simplex families, MS patients in multiplex families were more often women, were older at interview (49,4 ± 12,6 yrs vs. 44 ± 11,7 yrs; p=0.02); they were older at MS onset (34±9 yrs vs. 29±9 yrs, p=0.0014, this difference being significant after adjustment on age) and were more likely to be affected by an AID (15% vs. 3.8%; p=0.001). There was no difference for course of MS, frequency of optic neuritis, or disability. MS patients in MS families had more often a progressive course than patients in simplex families (25% vs. 11%; p=0.021). There was no significant difference for demographics or clinical features between MS patients members of MS or AIDs families. CONCLUSIONS: MS patients with first degree relatives affected by autoimmune diseases differ by some demographic and clinical characteristics from sporadic MS patients. In accordance with previous studies, there was no difference between sporadic and familial MS patients. The clinical heterogeneity, in particular the later onset of MS, may reflect the effect of environmental or genetic factors common to MS and other AIDs. Further investigation may be directed to familial associations of MS and specific AIDs.

P574
FAMILIAL AGGREGATION OF MULTIPLE SCLEROSIS (MS) AND AUTOIMMUNE DISEASES (AIDS): VALIDITY AND EFFECTIVENESS OF A METHOD OF COLLECTION OF CLINICAL MATERIAL IN FAMILIES. C. Papeix, O. Heinzlef, L. Nahum-Moscovici, S. Alamowitch, E. Roullet and the GRAID (Paris, F)

OBJECTIVE: To evaluate the validity and effectiveness of a method of determination of the clinical status of first-degree relatives of MS patients in multiplex families (i. e. families with at least one first-degree relative affected by an AID, or MS+AID families). BACKGROUND: As familial occurrence of MS and AIDs occurs in 15% of unselected MS patients (Heinzlef O et al., Acta Neurol Scand, 1999), we designed a study to collect clinical and genetic material in such families, in order to identify common susceptibility genes. The ascertainment of the clinical status is a crucial but time-consuming issue, due to the large numbers of subjects needed, and the great variety of AIDs. It is important to define the most sensible, specific and feasible process to determine the clinical status of individuals included in such studies. DESIGN/METHODS: Patients. The first degree relatives of 72 consecutive MS patients known by, or referred to our center as belonging to multiplex families were included (n=386). Their individual clinical status was assessed in a three-step process: 1) the index MS patients were interviewed using a semi-standardized questionnaire upon their relatives; 2) whichever the results of this first step, all available first-degree relatives were interviewed using a questionnaire specifically designed for selection of AIDs; 3) the medical records of relatives with suspected AIDs were checked. At the end of each step, the status of the relatives, and that of the fam-

ilies were determined. Validity. We compared the results of steps 1 and 2 to each other, and then the results of steps 1 and 2 using the results of step 3 as the definitive diagnosis. We determined the sensitivity, specificity, positive and negative predictive values (PPV and NPV) and efficiency of the different steps of the process.

RESULTS: Individual status. Comparison of the interviews of the MS index patients and those of their first-degree relatives showed false positive and negative rates of 10.4 % and 0.7 %, respectively. The sensitivity and specificity of the interview of index patients for the determination of the status of first degree relatives were 89 and 99.3 %, respectively. As compared to the definitive clinical status, the interview of the MS index patient alone had a sensitivity of 82 %, a specificity of 98 %, a PPV of 93 %, a NPV of 97 %, and an efficiency of 96 %. Family status. Classification of families as multiplex by the index patient alone was associated with a false negative rate of 18 % and a false positive rate of 1 %, corresponding to a sensitivity and a specificity of 87 and 96 %, respectively.

P575
SPECIFIC PROLIFERATION TOWARDS MYELIN ANTIGENS IN MULTIPLE SCLEROSIS PATIENTS DURING A RELAPSE. I. Saez-Torres, L. Brieva, C. Espejo, M. Barrau, X. Montalban, E. Martinez-Caceres, Hospitals Vall d'Hebron (Barcelona, E)

INTRODUCTION AND OBJECTIVES: Whether autoreactive T cells from multiple sclerosis (MS) patients display a certain autoreactive pattern characteristic for this disease is still a controversial issue. The aim of this study was to evaluate the reactivity towards myelin basic protein (MBP), minor myelin (myelin oligodendrocyte glycoprotein (MOG), aB-crystallin) and non-myelin (S100b) antigens that have been poorly studied, in patients with relapsing-remitting MS (RR-MS) during a relapse, assuming that this is the moment when it is more likely to find autoreactive T cells in the periphery.

PATIENTS AND METHODS: 35 RR-MS patients during a relapse and 16 healthy controls (HC) were studied. We performed proliferation assays towards MBP, MOG, S100b and aB-crystallin from PBMC obtained during the relapse and PBMC from these same patients short and long time after the relapse. In 19 patients and 12 HC proliferation assays with CD4+ enriched PBMC were performed.

RESULTS: Enrichment in CD4+ cells increases the sensitivity of the proliferation assays. In the moment of the relapse 15.8 % of patients reacted to MBP, 38.9 % to MOG, 11.1 % to aB-crystallin and 26.3 % to S100b. On the other hand, 12 % of the HC reacted to MBP, 28 % to MOG, 28 % to aB-crystallin and 19.2 % to S100b. There were changes in the specific proliferation towards the antigens studied in the consecutive samples obtained from either RR-MS patients or HC.

CONCLUSIONS: The reactivity pattern to the antigens studied is similar in RR-MS patients and HC, and it fluctuates over time.

P576
USEFULNESS OF MULTIMODAL EVOKED POTENTIALS IN MONITORING DISEASE BURDEN IN MULTIPLE SCLEROSIS. L. Leocani, M. Rovaris, G. Squintani, F. Martinelli, V. Martinelli, P. Rossi, M. Filippi, G. Comi, Hospital San Raffaele (Milan, I)

Evoked Potentials (EPs) are used in the functional assessment of sensory and motor pathways. The usefulness of multimodal evoked potentials in monitoring the evolution of Multiple Sclerosis has not been yet clarified. The aim of this study was the assessment of the value of multimodal evoked potentials in monitoring the natural evolution of the disease in Multiple Sclerosis. We performed a longitudinal evaluation of 105 patients (55 M, 46 F; mean age 39+9.7 years) (21 PPMS, 28 RRMS, 52 SPMS) with a mean disease duration of 8.6 + 6.6 years and a mean baseline EDSS score of 4.52 + 1.6. Follow-up duration was 27.9 + 8 months. We evaluated EDSS, Kurtzke's Functional Systems (FS), conventional scores of EPs at baseline and at follow-up, and MRI active lesion load was assessed using the conventional Ormerod scale. Cross-sectional analysis showed that the severity of each EP score was significantly correlated with the related FS ($p< 0.017$ for all EPs) and with EDSS ($p< 0.015$ for all but brainstem EPs). Moreover, EDSS was significantly correlated with the severity of a global EP score at baseline ($p=0.0001$) but not at final evaluation. At longitudinal evaluation, only changes in somatosensory EPs were significantly correlated both with sensory FS ($p=0.012$) and with EDSS ($p=0.014$). MRI active lesions score was not associated to EDSS changes nor to global or single EP score changes. These results indicate that EPs are a good marker of nervous damage in MS. However, their value is limited in patients with moderate/severe disability, possibly due to a ceiling effect of neurophysiological markers.

P577
SHORT TERM VENTRICULAR VOLUME CHANGES ON SERIAL MRI IN MULTIPLE SCLEROSIS. I.T Redmond, S. Barbosa, L.D Blumhardt, N. Roberts, Nottingham University, Liverpool University (Nottingham, Liverpool, UK)

The recognition of axonal loss as a critical factor in the irreversible neurological deficits of multiple sclerosis (MS) has led to an interest in atrophy on magnetic resonance imaging (MRI). Atrophy of brain and spinal cord correlate moderately with disability in cross-sectional studies of MS, but quantitative data on ventricles is limited. We estimated ventricular volume change by serial MRI over six months as an indirect measure of short term central white matter loss and investigated the relationship between changes in ventricular size and MRI measures of disease activity.

Methods: Nineteen patients had monthly neurological assessments and cranial MRI (proton density and gadolinium enhanced T1-weighted images). The volumes of the ventricles and enhancing and non-enhancing lesions were estimated using the Cavalieri method of modern design stereology.

Results: At baseline, the largest ventricular volumes were found in PP MS patients (median 20.9 ml, IQR 14.4 to 26.2 ml) and the smallest in RR MS (median 15.1 ml, IQR 13.8 to 17.4 ml). In the six month period, ventricular volumes in the total cohort increased by 0.2 % ($F=2.75$, $p=0.02$) (median increase +0.03 mls, IQR 0.94 to +1.93 mls). Five of the 19 (26 %) patients (four RR, one SP MS) showed significant ventricular enlargement. The increases were greatest in RR MS patients (+2.3 mls, IQR –0.94 to +2.51 mls) with no overall change for PP or SP MS groups. Total and enhancing lesion volumes at baseline were greatest in RR and least in PP MS. There were no significant serial changes in enhancing lesion volume/number overall, although RR MS showed a decreasing volume in this six month period. There was no correlation overall between enhancing lesion volume/change and ventricular enlargement – high volumes of enhancing lesions at baseline were seen with or without subsequent ventricular enlargement and, significant ventricular enlargement was seen even when minimal or zero baseline volumes remained unchanged throughout.

Conclusions: We have demonstrated that significant ventricular enlargement can be detected in a substantial proportion of MS patients over relatively short time periods and is a particular feature of the early stage of the disease (RR MS). On-going short-term loss of central white matter may be a result of immediately preceding inflammatory activity, a delayed post-inflammatory degenerative process, or most likely, a combination of both. Further larger studies are required to clarify the temporal relationship between inflammation, ventricular enlargement and atrophy.

P578
THE IMPACT OF MULTIPLE SCLEROSIS ON COGNITIVE PROCESSING – A CROSS-SECTIONAL STUDY ON EVENT-RELATED POTENTIALS. F. Bethke, T. Ellger, A. Frese, R. Lüttmann, S. Evers, University of Muenster (Münster, D)

Multiple Sclerosis (MS) has a deep impact on motor, sensory, and vegetative functions. However, only little is known about the impairment of cognitive processing in different types and stages of MS. Event-related potentials (ERP), in particular the P3 component, reflect cognitive functions such as short term memory and stimulus evaluation. We aimed to detect differences in cognitive processing of MS patients in different types and stages of MS by ERP measurement.

We performed a cross-sectional study on a consecutive series of unselected patients with definite MS but not in an acute phase. ERP were measured in all patients at the same time of day and in the same setting. A visual oddball-paradigm was used to elicit the P3 component which was measured at centroparietal. The latencies of the P2, N2, and P3 components, the amplitude of the P3 component, and the mean choice reaction time were evaluated. Patients' examinations, ERP measurements, and ERP analyses were performed by different investigators who did not know the other results. Nonparametric tests were used for statistical analysis.

We studied 65 patients (30 male, 35 female; mean age 37 ± 10 years). 37 had a relapsing-remitting type of MS, 28 had a primary or secondary chronic-progressive type. The mean Expanded Disability Status Scale (EDSS) score was 3.9 ± 2.0 in the whole group (2.5 ± 1.7 in the relapsing-remitting type versus 5.5 ± 1.2 in the chronic-progressive type, $p< 0.001$). P3 latency was 469 ± 61 ms. As compared to the laboratory normal values of the P3 latency, 55 % of the MS patients had a pathologically prolonged P3. There was a significant correlation between the EDSS score and the latencies of the different components (e. g., $r= 0,466$ and $p< 0.001$ for the P3 component). Patients with a chronic-progressive type of MS had increased latencies of the ERP components compared to patients with a relapsing-remitting type; for the N2 component, this difference was significant (355 ± 48 ms versus 341 ± 60, $p< 0.042$).

Our data suggest that measuring ERP is a useful tool to evaluate the cognitive impairment of patients with different types of MS. Both the relapsing-re-

mitting type and the chronic-progressive type of MS show prolonged ERP latencies with a strong and significant correlation between the latencies and the EDSS score. Cognitive processing in the chronic-progressive type of MS seems to be impaired more severely. However, it cannot be decided whether this just reflects the higher EDSS score in this group or whether cognitive processing in the different types of MS is affected in different ways.

P579
CLINICAL AND IMMUNOLOGICAL CORRELATIONS IN RR MS PATIENTS TREATED FOR ONE YEAR WITH ßIFN – 1B. M. Gelati, E. Corsini, A. Dufour, M. Zaffaroni, S. Giombini, L. La Mantia, C. Milanese, A. Salmaggi, Instituto Nationale Neurologico, Ospedale di Gallarate (Milano, Gallarate, I)

Istituto Nazionale Neurologico "C. Besta" Milan, ITALY
*Centro Sclerosi Multipla Ospedale di Gallarate

In multiple sclerosis (MS) treatment, evidences show that B-IFN is able to reduce relapse rate; however, the mechanism(s) of action are still incompletely understood. PIFN plays immunomodulatory effects in multistep pathogenesis of brain infiltrates, which includes the adhesion of lymphomonocytes to the brain endothelial monolayer and their transmigration through the Blood Brain Barrier. We previously reported data about the migration of Peripheral Blood Mononuclear Cells (PBMNCs) from 7 Relapsing Remitting (RR) MS patients treated for 6 months with B-IFN – lb through an endothelial monolayer stratified over a collagen gel. We now present the immunological follow-up of the same patients after one year of B-IFN – lb treatment, and its correlation with clinical course. Adhered and transmigrated mononuclear cells were analysed before treatment and after 3, 6 and 12 months; concomitantly, we evaluated MW–9 serum levels, since it has been demonstrated that reduction of transmigration phenomena could be related to MMP–9 release. The same experiments were performed in 7 age and sex-matched healthy controls. As expected, relapse rate decreased during B-IFN – lb treatment: relapse frequency increased only in 2 patients as compared to pre-treatment year, while the other 5 patients showed a reduction in relapse rate. Transmigration of CD45+ cells through a TNFa-stimulated endothelium decreased significantly at T3 and then it raised again, approaching – but not reaching – pre-treatment levels at T 12. The finding is of interest, since the number of transmigrating cells was higher in MS patients before treatment as compared with healthy controls. The amount of MMP–9 decreased during therapy and persisted lower at T 12; interestingly, the 2 patients in whom serum MMP–9 levels showed a steady increase over time were the same that displayed an increase in relapse frequency. Overall, in our model a trend to a reduction of MNCs transmigration through endothelial monolayers persists after one year of treatment with BIFN – lb, as well as the decrease in MMP–9 serum levels. However, we were not able to find a close correlation between transmigration and MW–9 levels and it must be borne in mind that the positive clinico-radiological effect of B-IFN – 1 b in MS does not have its peak at 3 months (as the reduction of transmigration). These data confirm the wide range of immunomodulating effects of PIFN – lb and suggest that other mechanisms of action than activity on transmigration may be at work in a later stage of the treatment.

P580
INCIDENCE AND CHARACTERISTICS OF CHILDHOOD MULTIPLE SCLEROSIS. D. Pohl, I. Hennemuth, F. Hanefeld, University of Göttingen (Göttingen, D)

Background: Childhood multiple sclerosis (MS) is considered to be a rare disease and there are conflicting data concerning its frequency and main characteristics.

Methods: In a prospective nationwide survey from 1997–1999, all new cases of suspected MS or acute disseminated encephalomyelitis (ADEM) in Germany with an onset before the age of 16 were registered regularly and evaluated using a standardized questionnaire.

Results: Over 200 new cases of suspected MS or ADEM were reported during the 3 years. Up to now (January 2000) 173 questionnaires could be collected, including 115 of patients with suspected or definite MS. Although the survey is not yet completed some interesting tendencies in this group of early-onset-MS patients are apparent: Most of the children were 10 yrs or older (about 80%), whereas less than 10% were younger than 6 yrs, the youngest patient being 3 yrs old. Interestingly, there was a nearly balanced gender distribution with a female:male ratio of 1.2:1. The percentage of primary progressive courses was low (< 10%), none of these children was younger than 10 yrs. Initial symptoms were sensory, cerebellar or visual, followed by pyramidal and brain stem symptoms. Primary bladder symptoms occurred in less than 5%. Paraclinical findings included MRI-visible demyelinating lesions of the cerebrum (~90%), cerebellum (~30%) or brain stem / spinal cord (~35%), as well as abnormal evoked potentials (> 60%). A pathological CSF analysis was reported in ~80%, but in only 2/3 of all cases was oligoclonal IgG detected.

Conclusions: Principally, adult and childhood MS are the same disease, but childhood MS shows difference in gender distribution (nearly balanced), course (few primary chronic cases) and CSF-findings (less oligoclonal IgG). With over 50 new cases/yr the incidence of childhood MS in Germany is much higher than previously expected and is probably so in other countries as well. Childhood MS should therefore not be classified as a rare disease.

P581
DNA VACCINATION INDUCES NEONATAL TOLERANCE TO EAE. A. Walczak, C. Kowal, J. Nowicka, C. S. Raine, K. Selmaj, Medical Academy (Lodz, PL)

Immunization with naked DNA can generate protective immunity against infectious diseases, allergy and cancer, and is also potentially applicable to autoimmune diseases. DNA vaccination of adult mice can lead to exacerbation of experimental autoimmune encephalomyelitis [EAE] or prevent the disease depending on the timing of EAE sensitization or targeting of fusion gene product to other immune antigens. The therapeutic effect of vaccination with naked DNA encoding PLP upon the outcome of later sensitization for EAE was tested in 2–5 days old mice. Clinical evaluation, proliferation and cytokine production assay were performed. DNA vaccination induces tolerance rather than immunity in neonatal mice. Neonatally tolerized mice were unable to develop EAE and to mount T cell response when rechallenged with PLP. In conclusions: these findings demonstrate important differences in the nature and specificity of the immune response elicited by DNA vaccination in adult and neonatal age. The results suggest also that DNA vaccination may contribute to the controlling of EAE and hopefully to multiple sclerosis.

P582
MULTIPLE SCLEROSIS: YEAR/PERSON SURVEY FOR MS CENTERS. G. Iuliano, M. Tenuta, A. Esposito, Ospedali Riuniti Di Salerno (Salerno, I)

INTRODUCTION: Years/person approach is often used in the evaluation of little groups. It is the standard method when patients have different observation periods, as in Italian district Multiple Sclerosis Centers. Since 1998 we are performing survey by a simple year/person registry. We report the update of the registry to the end of 1999.

PATIENTS AND METHODS: 29 patients are included in this study (11 males, 18 females, age 25–50, mean 37.1), with complete history of the disease, so to avoid periods with different risk of relapses. We divided them in four groups: 1: patients in therapy with beta interferon 1b (IFN1b); 2: patients with IFN1a (i. m. once a week); 3: patients with azathioprine (AZA); 4: patients with IFN1a (s. c. 3/week); 5: patients without therapy. From these 29 patients we obtained 253 years (patients without therapy=62, groups 1–2–3–4 before therapy=121, IFN1b=15, IFN1a 1/week=13, IFN1a 3/week=3, AZA=37). The patients start therapy, or change drug, when they have at least 1 relapse/year for two years.

RESULTS: Group 5 has significantly lower relapse rate (0.317) and is excluded from further evaluation; on the contrary the rate is similar for the years before treatment in groups 1–2–3–4 (mean 1.033, SD 0.836), so we made a single control group. During therapy, for IFN1b the relapse rate is 0.571 (SD 0.756), for IFNIa once a week 0.385 (SD 0.65); 1.000 for IFN Ia 3/Week (but there are only 3 years/person detected); cumulative relapse rate for all the IFN1as is 0.500 (SD 0.730); for those with AZA the rate was 0.514 (SD 0.701). Overall Kruskal-Wallis test is significant (p=0.000166), and so Neuman-Keuls multiple comparisons ($p < 0.05$) for all the groups among each other, except for subcutaneous IFN1a (data for this drug are only preliminar, for it went into prescription by Italian MS centers only in 1999, and there are only 3 patients with an almost complete year of therapy).

Side effects are also taken into account: 1 patient had allergic reaction to AZA; with IFN1b, 3 patients had protracted fever after injection, one had depression, two had site reactions; with intramuscular IFN1a only one patient had fever. With subcutaneous IFN1a nobody had collateral effects.

The year rate of need to change therapy was 0.286 for IFN1b, 0.077 for IFN1a, 0.189 for AZA; nobody has changed therapy with sc IFN1a.

CONCLUSIONS: This kind of statistical evaluation can be helpful for epidemiological monitoring of Italian experience of district SM centers: they deal with patients differing as to observation periods, previous therapies, and requirement to change therapy, sometimes among different types of beta interferons. It is our aim to update periodically the study and to collect and evaluate data from the other centers of Campania.

P583
THE CO-STIMULATORY MOLECULES CD28, CD40, CD40L, CD80 AND CD86 AS MARKERS OF DISEASE SUBTYPE AND RESPONSE TO INTERFERON-B THERAPY IN RELAPSING AND PROGRESSIVE MULTIPLE SCLEROSIS. Y. Galboiz, S. Shapiro, N. Lahat, A. Kinarty, H. Rawashdeh, A. Miller, Carmel Medical Center (Haifa, IL)

Background: T cell autoreactivity in MS has been suggested to be dependent on combined co-stimulation signals of activation and is effectively suppressed by Interferon (IFN)-ß. The present study characterized the expression of a wide spectrum of co-stimulatory molecules on peripheral blood T cells and monocytes of relapsing-remitting (RR) and primary-progressive (PP) MS patients, prior to and during one year of IFN-ß–1a (REBIF) treatment. Methods: Double staining flow cytometric analysis was used to examine cell surface expression of CD11b, CD54 (ICAM–1), CD40, CD80, CD86 and HLA-DR by peripheral blood monocytes (CD14+), and CD28, CD40L and CTLA4 by peripheral blood T cells (CD3+) from RR (n=34, of which 6 treated) and PP (n=10, of which 6 treated) MS patients as well as healthy controls (n=12). Results: Prior to treatment, CD86 expression was significantly reduced (mean x1.6 fold lower) in the PP group vs control and RR. CD80 expression was elevated in both MS subtypes vs control (mean x3.3 and x3.2 fold higher in RR and PP respectively), although the difference reached significance only in the RR group. CD40 expression was reduced in both subtypes vs control (mean x1.4 and x2.2 fold lower in RR and PP respectively), reaching significance in the PP group. CD28 expression was significantly elevated in the RR group vs control (mean x1.2 fold higher). During IFN-ß treatment, a significant reduction was observed in expression of CD54 and CD80 in both subtypes and in CD28 in the RR group. A significant elevation in CD86 and CD40 expression was observed in the PP group. A trend towards reduction in CD40L expression was observed in both subtypes. Conclusions: The results support a distinct immune mechanism underlying RR and PP MS patients and suggest co-stimulatory molecules as potential targets for immunomodulation and therapy in MS. The results may also partially explain the IFN-ß induced immune-deviation and therapeutic effects in MS patients.

P584
INTERFERON (IFN)-GAMMA AND -ß MEDIATED MODULATION OF MATRIX METALLOPROTEINASES (MMPS) AND THEIR TISSUE INHIBITORS (TIMPS) EXPRESSION IN HUMAN MONOCYTES. Y. Galboiz, S. Shapiro, N. Lahat, A. Miller, Carmel Medical Center (Haifa, IL)

Background: Multiple sclerosis (MS) is considered to be a T cell mediated disorder of the CNS in which the pro-inflammatory cytokines IFNgamma and TNFalpha are considered to contribute to the pathogenesis of disease, while IFN-ß serves as an effective treatment. Recent findings have implicated the activity of matrix metalloproteinases (MMPs), in particular MMP2 and MMP–9, in the pathogenesis of MS including the breakdown of the blood brain barrier and immune cell invasion into the CNS. Moreover, MMPs' inhibitors have been reported to suppress disease activity in experimental animal models of MS. Objective: To evaluate the effects mediated by IFN-gamma and IFN-ß on the mRNA expression of MMP–2, its physiological activator, MT1-MMP and its endogenous inhibitor, TIMP–2, by monocytic cells. Methods: Northern blot analysis was used to evaluate mRNA expression of MMP–2, MT1-MMP and TIMP–2 in the human monocytic cell line U–937, following incubation with IFN-gamma and IFN-ß (either separately or combined) at a dose range of 0–100 U/ml. Results: IFN-gamma induced a prominent dose dependent elevation of MT1-MMP mRNA (up to 1.9 fold at a dose of 100U/ml) and MMP–2 mRNA (up to 1.4 fold at doses above 1U/ml), while having no effect on TIMP–2 mRNA. IFN-ß induced a marked elevation of TIMP–2 mRNA (up to 2.4 fold at a dose of 100U/ml) and MT1-MMP mRNA (up to 2.8 fold, only at a dose of 100U/ml), while having no significant effect on MMP–2 mRNA. Conclusions: The present study points to the significance of IFNs in modulating MMPs and TIMPs expression and supports the possibility that the therapeutic effects of IFN-ß may be in part due to elevation in TIMP–2 leading to an inhibition of MMP–2 proteolytic activity.

P585
HYPOTHERMIA IN MULTIPLE SCLEROSIS: A CLINICORADIOLOGICAL STUDY. E. Koutsouraki, K. Siamoulis, P. Hamlatzis, A. Zafiropoulos, V. Costa, S. J. Baloyannis, Ahepa Hospital (Thessaloniki, GR)

We examined prospectively fifty cases of definite multiple sclerosis (MS) patients, according to the criteria of Poser's et al., and we identified three cases of hypothermia (rectal temperature below 35 C). All the above mentioned patients went through cerebral and cervical magnetic resonance imaging (MRI).

The patients who demonstrated hypothermia were severely disabled (EDSS> 6) showing quadriplegia, brain stem and cerebellar dysfunction. The type and duration of the disease was relapsing/remitting–6months, secondary progressive–10 years, relapsing/remitting–7 years respectively. The onset of hypothermia was acute and the duration was approximately two weeks. When hypothermia showed remission clinical improvement occurred. MRI didn't disclose a lesion in the hypothalamic area but lesions in periventricular area, temporal lobe, brain stem and cervical cord.

These cases illustrate hypothermia in MS, which is an unusual symptom and rovser considerations referring to the mechanisms and anatomical structures implicated in the thermoregulatory system in human beings.

P586
DISSOCIATION BETWEEN RELAPSES AND DISABILITY PROGRESSION IN MULTIPLE SCLEROSIS. S. Vukusic, T. Moreau, P. Adeleine, C. Confavreux, Hôpital Neurologique (Lyon, F)

Background. Licensed disease-modifying treatments in multiple sclerosis have shown reduction in frequency of relapses. Efficacy on progression of disability is less convincing. We studied the influence of relapses on accumulation of residual disability in multiple sclerosis.

Methods. 1844 consecutive patients with multiple sclerosis were examined within the same reference centre since 1957 for following determinations: date of onset of multiple sclerosis; inaugural course of multiple sclerosis, whether exacerbating-remitting or progressive; dates of relapses; dates of entry into residual Kurtzke Disability Status Scale scores; occurrence of a progressive course, either secondary to a relapsing-remitting course or primary. Survival analyses were performed for time to entry into DSS4 (limited walking but without aid), DSS6 (walking with unilateral aid) and DSS7 (wheelchair-bound) scores.

Results. Median time intervals from onset of multiple sclerosis to entry into DSS4, DSS6 and DSS7 were longer in cases with an exacerbating-remitting onset (11.4, 23.1, and 33.1 years) than in cases with a progressive onset (0.0, 7.1, and 13.4 years; $p< 0.0001$ for all comparisons). Transitions from one level of disability to another were similar whatever the inaugural course of the disease ($p=0.74$, 0.70, and 0.48 for DSS4 to DSS6, DSS4 to DSS7, and DSS6 to DSS7 transitions). In patients with a secondary or a primary progressive form of multiple sclerosis, these transitions were either not influenced or delayed by presence of superimposed relapses by comparison to cases without superimposed relapses.

Conclusions. There is a relative dissociation between relapses and progressive accumulation of disability in multiple sclerosis.

P587
APOLIPOPROTEIN (A) POLYMORPHISM IN MULTIPLE SCLEROSIS. A. Sena, R. Pedrosa, M. L. Andrade, V. Ferret-Sena, M. Graça Morais, R. Couderc, Faculty of Medical Sciences, Hospital dos Capuchos, ISCS-Sul, Hôpital Trousseau (Lisbon, P, Paris, F)

Background and Goals: Apolipoprotein (a), (Apo (a)) is a major component of lipoprotein (a) and display a considerable polymorphism. Low molecular mass apo (a) isoforms (Mr < 600.000) compete more strongly with plasminogen for binding to cell membranes, in comparison to larger isoforms, and result in decreased plasmin generation. Plasmin is in turn a major physiological activator of metalloproteinases. These proteinases are implicated in multiple sclerosis (MS).pathogenesis by promoting neuro-inflammation and are probably inhibited by steroids and interferon treatments. Therefore, we decided to analyze apo (a) polymorphism in MS patients.

Methods: 64 Relapsing-remitting and secondary progressive MS patients and 52 normal age-matched controls from both sexes were studied. Apo (a) phenotypes were determined according to the electrophoretic method of Couderc et al. (Clin.Chem.1998:44:1047–50). Allelic frequencies were compared using the c2 test. Apo (a) polymorphism was correlated with clinical data.

Results: The frequency of isoforms of small size (B; S1; S2) was lower in patients in comparison to normal controls (11,7 % vs. 22 % $p< 0.05$). A trend to a decreased disability and progression was observed to be associated with the presence of at least one small isoform.

Conclusion: A decreased prevalence of small apo (a) isoforms may promote plasmin generation and neuro-inflammatory invasion in MS patients. These results suggest a novel genetic risk factor for MS susceptibility and progression of the disease. A larger serial study is required.

P588
CEREBELLAR ATAXIA IN MULTIPLE SCLEROSIS PATIENTS TREATED WITH COMBINED INTERFERON BETA–1A (AVONEX) AND 5-HT-AGONIST (BUSPIRONE): NEURO-OTOLOGICAL EVALUATION. J. Bend-Davin, Y. Galboiz, M. Lunz, H. Duchman, S. Dishon, A. Miller, Carmel Medical Center Division of Neuroimmunology & (Haifa, IL)

Background: Recent reports suggest that serotonin agonists may have promising effects in cerebellar ataxia. Accordingly, Buspirone hydrochloride, member of the novel Azapirone class of psychotropic drugs and a selective 5-hydroxytriptamine1A (5-HT1A)-agonist, has recently been suggested to alleviate cerebellar ataxia in patients suffering from cerebellar atrophy.

Aims: To evaluate the clinical and neuro-otological effect(s) of Buspirone hydrochloride in Multiple sclerosis (MS) patients suffering from cerebellar ataxia.

Methods: 15 MS patients treated with IFN-b and suffering from cerebellar ataxia were evaluated using computerized dynamic posturography (CDP), during a prospective, randomized, double-blind controlled study treatment with Buspirone (30 mg/day) or placebo. Evaluation was preformed prior to and at 3 and 6 months of symptomatic treatment. All CDP criteria of the sensory organization test (SOT) and the motor control test (MCT) were evaluated.

Results: The SOT evaluation demonstrated significant improvement in the visual preference score in the treated group vs placebo (0.78 ± 0.78 vs 0.54 ± 0.05), p=0.05. The MCT evaluation demonstrated significant improvement in the amplitude score in the treated group vs placebo (0.2 ± 0.7 vs 6.5 ± 5.9), p=0.02.

Discussion: In the search of combined immunomodulatory and symptomatic therapy in MS, the present study points to the possibility of using Buspirone as an adjuvant to Interferon (AVONEX) therapy, and as an effective symptomatic treatment of cerebellar ataxia, one of the most disabling symptoms of MS.

Neurophysiology

P589
LOCALISED, TEMPERATURE-SENSITIVE WEAKNESS IN PERIPHERAL MOTOR NEUROPATHY. B. P. Turner, L. Pelosi, L.D Blumhardt, University of Nottingham, QMC (Nottingham, UK)

Transient symptomatic neurological deterioration due to slight increases of body temperature is well recognised in multiple sclerosis (MS), but rare in peripheral demyelination. We report a case with transient, localised exacerbations of weakness associated with a temperature-sensitive conduction block complicating a peripheral motor neuropathy.

History: A 69 year old male presented with a one year history of right hand weakness worse after a hot shower. He had also noted wasting of the right hand muscles and dragging of the left leg. Cranial nerve examination was normal. There was wasting and weakness of the right hand and mild weakness of forearm muscles and flexor muscles in both legs. Upper limb reflexes and knee jerks were normal, but ankle jerks were absent. Sensation was normal throughout. Over the next 12 months he developed difficulty with fine movements in the left hand, reduced mobility, slurred speech, tongue fasciculation, wasting of the right arm with fasciculation and bilateral foot drop. Immunology including antiganglioside antibodies was normal and there was no response to immunoglobulins.

Investigations: Electro-physiology showed an asymmetric, patchy reduction of compound muscle action potentials (CMAPs), prolonged terminal latencies and slowed motor conduction velocities (27–45 m/sec) in the majority of nerves examined. Sensory nerve conduction studies were normal. Left median nerve CMAPs were measured before and after warming the hands and forearms in hot water. An increase of skin temperature from 320 to 360C resulted in a 60% amplitude decrement of CMAPs and increased weakness and clumsiness of hand movements. As the temperature decreased, the symptoms resolved and the CMAP amplitudes gradually recovered.

Conclusions: Reversible conduction block due to small increases of temperature within the physiological range has been demonstrated in chronic demyelinating animal models, but has not been reported to be symptomatic in human peripheral neuropathies. Transient exacerbations of generalised weakness in demyelinating peripheral neuropathies have been described only in the context of high systemic fevers. Our patient complained of transient, localised worsening of motor function associated with objective evidence of a peripheral, temperature-dependent motor conduction block induced by slight changes in surface temperature.

P590
A COMPARATIVE STUDY OF LUMBRICAL AND INTEROSSEI RECORDING WITH CONVENTIONAL METHOD IN DIABETIC NEUROPATHY. Mori I, Hasegawa O, Matsumoto S. Department of Neurology, Yokohama City University School of Medicine, Yokohama, Japan

Lumbrical <L> and interossei <I> recording has been used to diagnose carpal tunnel syndrome. We compared L/I recording with conventional study in 117 patients with diabetic neuropathy and 81 healthy controls. By L/I recording compound muscle action potentials <CMAPs> and sensory nerve action potential <SNAP> from the digital nerve <N> was recorded with the same recording electrode placed on the second lumbrical muscle. Supramaximal median nerve stimulation was given at wrist 9 cm proximal to the recording electrode.

In healthy control, distal latency from abductor pollicis brevis <APB> (3.46±.37 ms) was a little longer than that from L (3.15±.27 ms), and SNAP (r=0.) from N (87.1±.5 μV) was 1.6 times as large as that from index finger <F> (53.4±.4 μV). In diabetic neuropathy mean amplitude of SNAP from N (50.3±.3 μV) was 1.6 times as large as that from F (30.7±.1 μV) and they were correlated significantly (r=0.87). In severe neuropathies CMAPs from L/I was obtainable even after that from APB ceased. Their distal latencies (L : 3.89±.59 ms, APB: 4.34±.7 ms) were correlated strongly (r=0.9). CMAPs from L (3.95±.32 mV) and SNAP from N (r=0.412) were better correlated than CMAPs from APB (12.7±.59 mV) and SNAP from F (r=0.396). Besides, by L/I method CMAPs innervated by both ulnar and median nerves were recordable which enabled us to detect the existence of subclinical carpal tunnel syndrome, often observed in diabetic neuropathy. In terms of sensitivity, L/I recording was comparable with conventional methods and excellent correlation efficient was observed in distal latency and amplitude of nerve action potentials. Moreover, by this simple methods CMAPs and SNAP was well documented with the same placed electrode in evaluating diabetic neuropathy.

P591
DECREASED EMG-INHIBITION ELICITED BY ELECTRICAL STIMULATION OF MUSCLE TENDONS IN MYOPATHIES. C. Cinnante, A. Priori, A. Presenti, A. Cappellari, G. Scarlato, S. Barbieri, IRCCS Ospedale Maggiore (Milano, I)

Electrical stimulation of tendons during muscle contraction normally elicits a phase of EMG inhibition (tendon inhibition = TI1) interposed between two phases of facilitation (tendon excitation = TE1 and TE2). The EMG inhibition is attributed to central motoneuronal dysfacilitation due to group III-induced presynaptic inhibition of Ia-afferents in the spinal cord (Priori et al., Brain 121, 373–380; 1998). To assess whether the muscle dysfunction is associated to changes in the central nervous system (CNS), we tested the EMG-modulation after tendon stimulation in six patients with myopathy.

Patients had different myopathies (inflammatory and myotonic disorders were not included) with a mild force deficit (MRC scale 3,5–4,5). None had clinical or neurophysiological signs of CNS involvement or peripheral neuropathy. Nine healthy age-matched subjects were also studied. The tendon of the extensor carpi radialis was electrically stimulated (0.05ms, 70 mA) at the wrist during voluntary isometric wrist extension at 50% of maximum EMG level. The surface EMG signal was rectified and averaged (100 sweeps). The perceptive threshold for the electrical stimulus was also assessed.

Latencies and durations of TE1, TE2 and TI1were normal. In patients the TE2 was markedly less frequent (controls=100%, patients=50%). The EMG area under TI was increased (i. e. the inhibition was decreased) in patients (TI: controls= 44±9.9%, patients= 81±9,3%, p=0.0004, Mann-Whitney test). The background EMG and the perceptive threshold level did not differ between patients and controls.

The TI1 reduction indicates that muscle dysfunction is associated to a reduction of group III-elicited presynaptic inhibition of Ia-afferents in the spinal cord. A reduced presynaptic inhibition could reflect a central compensation for contractile dysfunction in myopathies.

P592
BLOOD FLOW VELOCITY IN THE ANTERIOR AND MIDDLE CEREBRAL ARTERIES DURING FOOT MOVEMENT. A TRANSCRANIAL DOPPLER STUDY. C. Graewe, A. G. Harders, Klinik Holthausen, Ruhr-University (Hattingen, Bochum, D)

We examined if a defined foot movement can induce an increased blood flow velocity in the cerebral arteries and if transcranial Doppler sonography is suitable to measure this increased flow. According to the localization of the primary motor cortex in the parasagittal part of the precentral gyrus and the localization of the supplementary and premotor cortex we performed a bilateral simultaneous transcranial Doppler study of the anterior cerebral artery and the middle cerebral artery during rest and defined unilateral foot movements. We examined

30 volunteers with no sign of cerebral vascular disease, performing three series of two defined foot movements. During the tasks blood flow velocity changed as well in the contralateral and the ipsilateral anterior and in the contralateral middle cerebral artery. We recorded an increased blood flow velocity in these vessels by 9 %. After an initial maximum at approximately 3 seconds, velocity decreased and increased again. A steady state was reached after approximately 30 seconds. At 5–10 seconds after termination of the task blood flow velocity decreased to the steady state in rest.

According to previous results of other authors who showed increased blood flow in the middle cerebral artery during mental activities and increased cerebral blood flow velocities in the posterior cerebral artery during visual activation our study presents a selective activation in the anterior cerebral artery and middle cerebral artery during leg movement.

We want to resume that blood flow velocity changes were found in both anterior cerebral arteries and the contralateral middle cerebral artery and there was no difference between the corresponding and the ipsilateral hemisphere. We detected a bilateral cerebral activation during monolateral foot movement which is possibly caused by a simultaneous activation of the primary, the supplementary and the premotor cortex.

P593
INFLUENCE OF SUBTHALAMIC NUCLEUS STIMULATION ON GAIT IN PARKINSON'S DISEASE: A STUDY USING THE OPTOELECTRONIC VICON SYSTEM. P Krystkowiak, LJP Defebvre, JL Blatt, JL Bourriez, S Blond, JD Guieu, A Destée, Hôpital Salengro CHRU (Lille Cedex, F)

Objective: To evaluate, by using a video motion analysis system, the influence of bilateral subthalamic nucleus (STN) stimulation on gait in Parkinson's disease (PD).

Background: Chronic STN stimulation allows the control of motor symptoms and Levodopa induced dyskinesias in severe PD. The effect on gait is not clearly established, different results have been reported mostly clinical data.

Design/Methods: Gait kinematic parameters (cadence, velocity, stride and step times, single and double support times, stride and step lengths) were studied in 7 patients with PD, before and 3 months after bilateral STN stimulation using quadripolar electrodes, in two conditions: off drug then on drug.

Results: After bilateral STN stimulation, all the kinematic parameters were improved in off drug condition. In on drug condition, cadence, velocity, double support time, stride and step lengths were also improved, whereas there was no statistically significant change for the stride and step times and for single support time.

Conclusion: This study confirms that bilateral STN stimulation induces beneficial effects on gait disturbances in PD.

P594
SYMPATHETIC SKIN RESPONSE (SSR) AND SENSIBLE NERVE ACTION POTENTIALS UNDER ISCHAEMIC CONDITIONS. I. Blaeser, J. Jörg, Universität Witten/Herdecke Klinikum Wuppertal GmbH (Wuppertal, D)

Introduction: Approximately 30 % of diabetic patients display early signs of polyneuropathy (PNP) when making the diagnosis. Because autonomic neuropathy has a strong influence on life expectancy of these patients, PNP should be detected as early as possible. Conventional EMG/ENG examination displays the disadvantage of only moderate sensitivity for mere sensible PNP and can not detect autonomic neuropathy. It is already known from literature that the registration of SNAP under ischaemic conditions may improve the sensitivity for peripheral nerve affections. Methods: In this pilot study 10 patients with known diabetic polyneuropathy and 10 healthy control subjects were examined. After causing a temporary ischaemia SSR and SNAP were registered simultaneously at intervals of 5 minutes. When both potentials had vanished ischaemia was terminated and both potentials were registered at intervals of 2 minutes in the postischaemic period. Results: Control subjects displayed a loss of SSR at a maximum of 55 minutes and a loss of SNAP at a maximum of 75 minutes. While in accordance with literature PNP patients lost their SNAP later than the control group (45–95 min.) they showed an early loss of SSR (5 –35 min.). There were remarkable interindividual differences considering the tolerance to ischaemia of both potentials with a distinct overlap of the range of values. Conclusion: Because of this considerable overlap of values the time until the vanishing of the potentials may alone not distinguish between both groups. We will discuss that compound parameters may prove more useful in this respect.

P595
IS THE DECREMENTAL MOTOR RESPONSE A USEFUL PARAMETER FOR THE FOLLOW-UP OF AMYOTROPHIC LATERAL SCLEROSIS PATIENTS? F. C. Wang, V. De Pasqua, P. J. Delwaide, CHU LIEGE (LIEGE, B)

Decrement of the thenar compound muscle action potential (CMAP) following repetitive nerve stimulation of the median nerve at 3 Hz was evaluated in 15 patients with amyotrophic lateral sclerosis (ALS) without riluzole therapy. CMAP size and motor unit number estimate (MUNE), using the adapted multiple point stimulation (AMPS) method (Wang and Delwaide, 1995) were also evaluated in these patients before (TO) and after 4 (n=13), 8 (n=13) and 12 (n=10) months of treatment with riluzole.

In 8/15 patients at T0, decrement between the first and the fourth CMAP negative peak area was more than 10 % with a maximum value of 35 %. There was a statistically significant correlation ($p< 0.01$) between decrement (%) and CMAP size reduction per year (%). Moreover, after one year, 5 patients presented a motor unit loss, estimated by AMPS, more than 50 % while the motor unit loss was less than 50 % in 5 others. Mann-Whitney U test indicated a statistically significant ($p < 0.05$) difference between decrement (%) values of both groups including 5 ALS patients.

These data provide evidence that: 1) decrement in ALS is related to the activity of disease and 2) a thenar decrement more than 10 % is probably indicative of a quite severe form of disease with immature collateral sprouting. Thus, we propose the decremental motor response as a useful parameter for the follow-up of ALS patients.

Wang FC, Delwaide PJ. Number and relative size of thenar motor units estimated by an adapted multiple point stimulation method. Muscle Nerve 1995; 18:969–979.

P596
THE LUMBRICAL-INTEROSSEOUS LATENCY AS A USEFUL METHOD FOR DIAGNOSIS OF CARPAL TUNNEL SYNDROME. M. Banach, E. Gryz, Collegium Medicum Jagiellonian University (Krakow, PL)

The aim of study is to evaluate the usefulness of a new electrophysiologic technique in the diagnosis of carpal tunnel syndrome (CTS) based on the interlatency difference (ILD) between the second lumbrical (2L) and second dorsal interosseous (INT).

We examined 160 hands of 100 patients (68 women and 32 men; aged from 20 to 84) with evident symptoms and signs of carpal tunnel syndrome, and 60 control healthy subjects. In each case the standard electrophysiological test contained distal motor latency to abductor pollicis brevis (DML-APB), antidromic sensory latency to digit 2 (SL-D2), difference between median and ulnar sensory latency (D4M-D4U) was performed in each case. New method based on comparison between the median motor distal latency by recording from the second 2L and the ulnar latency recording from the INT. The nerves were stimulated at the wrist using identical distances and compound muscle action potentials from both muscles (2L, INT) were recorded between the midpoint of the second and third metacarpal.

The mean ILD (SD) in the control group was (0,15ms. 0,12). The upper limit of the range was 0,4ms (mean 2SD).

DML-APB was abnormal prolonged or absent in 65 % of tested hands. SL-D2 was in 74 % tested hands and D4M-D4U in 87 % of tested hands. The ILD was abnormal in 89 % of tested hands. The ILD was abnormal and present in each case when standard tests were abnormal. In three cases the ILD was the only abnormal test.

We conclude that ILD is more sensitive than standard tests for damage of median nerve, when standard methods do not allow to obtain sensory and motor response.

P597
QUANTITATIVE EEG ABNORMALITIES IN PATIENTS WITH MIGRAINE. M. Szabo, A. Kondacs, A. Borda, County Hospital Pandy Kalman (Gyula, H)

The aim of our present study was to analyse EEG background activity by means of different quantitative EEG (qEEG) parameters in patients with migraine in the headache interval.

Computer analysis and significance probability mappings were performed on the EEGs of 105 migraine patients (47 with aura (MA), 58 without aura (MW) and a control group of 113 healthy subjects. The patients were classified in accordance with the diagnostic criteria of the IHS ad Hoc Committee (1988), that had no neurological deficits and no abnormalities in computer tomography or magnetic resonance imaging. Following qEEG parameters were studied: absolute and relative power, power and mean frequency asymmetry, entropy (as irregularity index), inter- and intrahemispheric coherence. Different qEEG results were analysed by neurometrics. The qEEG alterations between the two

groups were examined by t-test. Correlation analysis was applied to reveal the effect of the clinical severity on the qEEG. A significant decrease in the alpha power and an increase of theta power were detected mainly in the posterior regions during headache-free period in patients with and without aura. The slowing of the posterior region's activity was revealed in a lesser degree in MW group. In comparison to normal group, a significant increase of alpha entropy was observed in MA and MW groups. Inter- and intrahemispheric alpha coherence showed a significant decrease in both groups. A significant positive correlation was detected between the duration of migraine and the relative theta power in the occipital region, while a significant negative correlation was revealed in the relative alpha power in the same region.

Different qEEG parameters can detect neuronal dysfunction in the patients with migraine in headache free interval. Our findings, especially taking into account the changes of entropy and coherence parameters, may suggest an upper brainstem dysfunction and add further support to the neural hypothesis. Investigating different qEEG parameters in patients with migraine, the duration of the illness must be taken into consideration.

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EXCITABILITY RECOVERY CURVE OF THE SUDOMOTOR SKIN RESPONSE IN PATIENTS WITH ESSENTIAL PALMAR HYPERHIDROSIS. J. Valls-Solé, D. Manca, M. A. Callejas, Hospital Clinic, Hospital of Cagliari (Barcelona, E; Sardignia, I)

Essential palmar hyperhidrosis (EPH) is a condition of unknown pathophysiology causing an important social and laboral handicap. EPH might be related to hyperexcitability of centers regulating emotional sweating. The sudomotor sympathetic skin response (SSR) can be used in the assessment of sweating reflex circuits. The excitability of a reflex circuit can be measured by applying pairs of stimuli. However, the excitability recovery curve of the SSR has not been measured so far. We elicited the palmar SSR in 10 healthy subjects and 18 patients with EPH, using single and paired (conditioning and test) electrical stimuli to the median nerve. Stimulus pairs were separated by interstimuli intervals (ISIs) of 0.5 to 3.5 seconds. Recordings were done with a gain of 200 *V per division and a 20 seconds time window. Responses to the test stimulus were expressed as percentages of responses to the conditioning stimulus. In all control subjects, single stimuli generated SSRs in both hands. With stimulus pairs, the SSR to the stimulus test was always absent up to the interval of 1.5 s, and the median onset of recovery was 2.5 s. In patients, single stimuli generated no SSR in 4, and a response with a double peak in 3. The excitability recovery curve, examined in the remaining patients, was enhanced with respect to the control subjects. Responses to test stimuli were already present in 5 patients at 1.0 s, and the median ISI of initial recovery was 1.5 seconds. The percentage recovery was larger in patients than in control subjects ($p < 0.05$) at ISIs between 1.0 and 3.0 seconds. Patients with EPH have an early excitability recovery of the SSR to paired stimuli, suggesting hyperexcitability of somatosympathetic sweating reflex circuits.

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MULTIMODAL ELECTROPHYSIOLOGICAL STUDY IN THE PATIENTS WITH SPINOCEREBELLAR ATAXIA TYPE 1. M. Rakowicz, M. Niewiadomska, E. Zdzienicka, D. Milewska, D. Hoffman-Zacharska, G. Rejnowski, J. Zaremba, K. Niedzielska, E. Waliniowska, E. Pilkowska, D. Wochnik-Dyjas, R. Boguslawska, E. Inglot, Institute Of Psychiatry And Neurology (Warsaw, Warsaw, Pl)

The autosomal dominant spinocerebellar ataxia type 1 (SCA1) is one of the CAG repeat disorders. The aim of the study was to assess electrophysiological function of the central and peripheral nervous system in 17 patients from 13 families with SCA1 confirmed by DNA analysis. The mean age of the patients was 43.3 ±7.6 years and mean disease duration was 7.7±4.6 years. The median and tibial somatosensory evoked potentials (Mn- and Tn-SEPs), sensory (SCV) and motor (MCV) conduction velocity along median, peroneal, sural, axillar and femoral nerves, visual evoked potentials (VEPs), and brainstem evoked potentials (BAEPs) were examined. The obtained results were compared with age-matched normal control subjects. Peripheral dying-back polyneuropathy was found in 16 patients, with features of demyelination of the longest axons in some of them. Mn- and Tn-SEPs dysfunction was distributed along the peripheral, spinal and central segments of somatosensory pathways in all but one patients. VEPs revealed decreased amplitude of P100 component in 13 patients, while the BAEPs interwaves latency of I – III and I – V components were prolonged in 6 of them. The low voltage background EEG activity was recorded in 16 patients with focal changes in temporal region in 11 cases. Magnetic resonance images (MRI) showed moderate to severe atrophy of ventral pons, cerebellar hemispheres and dilation of fourth ventricle in 14 cases, as well as cervical spinal cord atrophy in 8 patients. This study provided further evidence of the peripheral and central axonopathy in SCA1 patients.

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Abstract withdrawn

P601

ABNORMAL LATE RESPONSES UPON TRANSCRANIAL MAGNETIC STIMULATION IN TWO PATIENTS WITH STIFF-MAN SYNDROME. M. Deschauer, W. Schulter-Mattler, M. Kornhuber, S. Zierz, University Halle-Wittenberg (Halle, D)

Introduction: Stiff Man Syndrome (SMS) is a rare disorder characterized by fluctuating stiffness of axial and proximal limb muscles. Diagnosis is made on clinical signs. Elevated titers of antibodies against glutamic acid decarboxylase (GAD) support the diagnosis. We report on findings of transcranial magnetic stimulation (TMS) in two patients with SMS. Both had typical signs and symptoms of SMS and antibodies against GAD were elevated. Additionally, both had an episode with disturbance of ocular movement so that progressive encephalomyelitis with rigidity, an SMS variant, has to be considered. Methods: Cortex and lumbar plexus were stimulated with a magnetic stimulator. Compound muscle action potentials from anterior tibial muscles were recorded with surface electrodes. Results: Upon TMS, in both patients primary responses were normal, but in both legs were abnormal late responses (LRs) after cortical stimulation with a latency of 69–70 ms in the first patient and 67–69 ms in the second patient. Also after lumbar stimulation in both legs late responses of 82–85 ms in the first patient and 92–94 ms in the second patient were seen. The LRs were independent of an attack of stiffness and did not habituate. In the first patient, treatment with diazepam was clinically effective. The LRs were abolished with treatment and did not recur during the following 2 years. In the second patient, effectiveness of treatment with benzodiazepines was limited. After additional effective treatment with immunoglobulins LRs were abolished in the right leg only. Discussion: The LRs were abnormal because they occurred within the physiologically silent period. The correspondence between the presence of the LRs and the patients' symptoms indicates that the LRs are part of SMS. In contrast to other electrophysiological findings in SMS, such as spasmodic reflex myoclonus, the LRs showed no habituation. TMS may be a simple test for SMS.

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PRE- AND POST OPERATIVE SOMATOSENSORY EVOKED POTENTIALS IN SYRINGOMYELIA: A COMPARATIVE STUDY OF 16 CASES. I. Achiti, N. Andre-Obadia, F. Mauguière, Hôpital Neurologique (Lyon cedex 03, F)

Somatosensory evoked potentials (SEPs) are useful to assess the spinal cord dysfunction in syringomyelia, being of higher sensitivity than clinical examination.

Sixteen patients (6 female, 12 male, age range: 25–60 years) were admitted for syringomyelia documented by MRI. 12 patients had an associated Chiari malformation and 3 had a post traumatic syrinx. Median nerve somatosensory evoked potentials and posterior tibial nerve SEPs were recorded before and after decompressive surgical treatment and correlated with clinical findings.

SEPs abnormalities were not correlated with the duration of symptoms. The N13 potential (generated in the cervical dorsal horn) was abnormal in 74% of upper limbs both before and after surgical treatment. It detected subclinical spinal cord involvement in 57% of upper limbs tested before surgery and in 65% of upper extremities after surgery.The most common electrophysiological finding in lower limbs was an alteration of the P30 potential (generated at the cervico-medullary junction), even without sensory deficit in the tested limb.

The post operative SEPs results showed a correlation with the clinical examination in only 7 of the 16 cases. Three patients showed SEPs deterioration even though their sensory symptoms improved.

Upper limb and lower limb SEPs testing proved to be a valuable supplement in the pre- and post operative diagnostic evaluation of syringomyelia since permitting an objective evaluation of the benefits of surgery on the spinal cord function.

P603
SERIAL RECORDING OF SOMATOSENSORY EVOKED POTENTIALS IN PATIENTS WITH CEREBRAL INFARCTION. K. B. Bozic, J. M. M. Mihaljev-Martinov, G. M. P. Misic-Pavkov, S. G. Gvozdenovic, X. G. Gebauer, I. K. Kovac, S. K. Knezevic, Clinical Center Novi Sad, MC (Novi Sad, YU)

The purpose of the study was to investigate the relationship between somatosensory potentials evoked by stimulation of median nerve (SEPs) and recovery from stroke. Methodology: SEPs were recorded in 40 patients suffering their first supratentorial cerebral infarct. SEP were performed within the first week, the third week and after six weeks from the onset of ischaemic symptoms. SEP results were correlated with clinical findings. Infarct location was confirmed by computerized tomography (CT) and/or by magnetic resonance imaging (MRI) of the brain. Clinical evaluation included assessment of motor (stroke severity score – Canadian Neurology Scale) and sensory deficit (sensibility assessment). Results: A high frequency of SEP abnormality (70%) was found in the acute stage (2,72 ± 0,75 days after stroke onset), which declined to 68,5% at 2–3 weeks (17,7 ± 2,01 days) and to 35% after six weeks follow-up (61,9 ± 5,04 days). Changes in SEP and clinical findings were significant in the follow-up period. Neurophysiological and clinical course showed an improvement with the maximum after six weeks from stroke onset. The normalization of initially abnormal SEP findings corresponded with the statistically significant improvement of deep and cortical sensory impairment. Conclusion: Our results suggest that early and serial SEP studies could be used in monitoring the recovery process in stroke patients especially in quantifying the recovery of lemniscal and parietal dysfunction.

P604
CENTRAL MOTOR CONDUCTION IN DISTAL HEREDITARY MOTOR NEUROPATHY TYPE V (HMN V). M. Auer-Grumbach, H.-P. Hartung, Karl-Franzens University (Graz, A)

Forty-seven members of a single family, spanning three generations, were examined. The presenting clinical feature of 12 of the 18 affected individuals was asymmetrical muscle atrophy in the hands. On detailed examination, pes equinovarus and distal wasting was also observed in the legs. Electrophysiological testing revealed signs of axonal degeneration of motor nerves only. None of the individuals complained about sensory symptoms, and clinical and electrophysiological sensory testing was normal in 17 and 16, respectively. Pyramidal features, increased muscle tone, brisk and clonic deep tendon reflexes, were additionally observed in 11. Based on these findings, hereditary motor neuropathy V was diagnosed.

Transcranial magnetic stimulation was performed in 15 definitely and 15 probably affected subjects and prolonged central motor conduction times (CMCT) were observed in 6/15 probably affected and 9/15 definitely affected (χ2-test, n. s.). However, when comparing upper and lower extremities separately, prolonged CMCT were more frequently observed in the definitely than the probably affected group (Fisher's exact test, $p < 0.05$). Thus, CMCTs were prolonged in 9/29 lower limbs and in 2/30 upper limbs in definitely affected patients while only 5/28 lower and 3/30 upper limbs showed prolonged CMCT in probably affected persons. These findings evidence additional involvement of central motor pathways in HMN V. Interestingly, prolonged central motor conduction has also been reported in several cases of HMSN I, while in spinal muscle atrophy II, III and IV it has been found to be normal.

Peripheral neuropathy

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PERIPHERAL NERVE INVOLVEMENT IN HTLV-I POSITIVE BLOOD DONORS. O. J. M. Nascimento, A. C. Leite, M. R.G De Freitas, A.Q-C Araújo, G. Mendonça, Fed. Fluminense University/HEMORIO, Oswaldo Cruz Foundation (FIOCRUZ), State University of Rio de Janeiro (Rio de Janeiro, BR)

The real frequency of HTLV-I neurologic manifestations is still reason for debate in the literature. In order to evaluate the incidence of signs and symptoms of peripheral nerve system (PNS) involvement in a population of blood donors from the largest blood bank (HEMORIO) from the city of Rio de Janeiro, Brazil we designed the present study. Methods: Between May 1995 to December 1997, 392 blood donors from HEMORIO were selected by a cross sectional study (PhD thesis of Dr. AC Leite). Fifty percent of these individuals were HTLV-I positive. For the present study, neurologically impaired HTLV-I positive individuals were considered "cases" and HTLV-I positive individuals with a normal neurological examination, "controls". "Cases" were classified in symptomatics and asymptomatics, according to the involvement of the PNS. Specific laboratory investigations for PNS compromise were performed. Other causes of neuropathy were ruled out. Results: Neurological disease was found in 71 (36.2%) out of 196 seropositive individuals. Of these "cases", 33 (46%) had symptoms and signs of PNS involvement: 26 (78.7%) a predominant sensory polyneuropathy, 5 (15.1%) a carpal tunnel syndrome, and 2 (6%) a lumbosacral radiculopathy. Nerve conduction studies showed evidences of an axonal damage in the majority of these "cases". A sensory nerve biopsy performed in 6 "cases" disclosed an axonal neuropathy with epineurial microvasculitis in 4. The mean age in this group was 46.3 ± 9.8 years. In the HTLV-I seronegative group 5 individuals (mean age: 41.0 ± 10.6) presented a mild involvement of the PNS. Conclusions: Our data suggest that the exposition to HTLV-I virus was significantly associated to the development of peripheral neuropathy in a higher proportion than what has been published so far in the literature. This observation makes necessary a more detailed epidemiological inquiry among candidates for blood donation, mainly in developing countries.

P606
ACUTE POLYNEUROPATHY IN CHURG-STRAUSS VASCULITIS. MD. Alexander, J. O'Donovan, D. Costigan, M. Farrell, M. Keoghan, O. Hardiman, Beaumont Hospital, Mater Private Hospital (Dublin, IRL)

Churg-Strauss Syndrome (CSS) is characterised by a systemic polyarteritis with peripheral eosinophilia and usually presents with multi-organ involvement and adult-onset asthma. Neurological manifestation of CSS are usually associated with a slowly progressive, painful, asymetric mononeuritis multiplex. We describe a patient whose presenting symptoms of CSS were those of a rapidly ascending painless symmetrical sensory-motor neuropathy.

CASE REPORT A 70 year old woman presented with a 5 day history of a painless peripheral sensory loss, ascending motor weakness and low back pain. She also exhibited features of dysautonomia including orthostatic hypotension and palpitations. She described a prodrome of 'flu-like' illness 3–4 weeks earlier. Examination revealed a falccid weakness in all 4 limbs with areflexia. Biochemical analysis demonstrated severe hyponatraemia of 123 mmol/l (normal values 135–145 mmol/l). A clinical diagnosis of Guillain Barre Syndrome (GBS) was made and the patient was commenced on intravenous gammaglobulin. CSF analysis on admission and on day 8 of presentation was normal. Nerve conduction studies were performed on day 5 of presentation, revealing prominent axonal changes. The patient failed to show any signs of improvement. Repeat nerve conduction studies after 2 weeks confirmed the axonal nature of the condition. Haematological investigations, performed repeatedly during her admission, revealed a persistent eosinophilia, 7–8 times the upper limit of normal, and persistently raised inflammatory markers (ESR and CRP). Her immediate past history was remarkable for a 15 kg weight loss, diaphoresis, and late-onset poorly controlled asthma. Pulmonary function studies demonstrated a mixed picture of severe obstruction with excellent reversibility using Salbutamol, and a restrictive pattern with diminished gas transfer. Renal function studies showed a slightly diminished creatinine clearance with mild proteinuria. Her sural nerve and gastrocnemius were biopsied. Examination of the muscle

biopsy demonstrated a necrotizing vasculitis with fibrinoid necrosis and a mixed histiocytic-eosinophil infiltrate. The sural nerve showed evidence of a moderately severe subacute axonal neuropathy with no evidence of any primary demyelination on electron microscopy. The patient was treated for Churg-Strauss Syndrome, and commenced on prednisolone and cyclophosphamide. She made a significant, though incomplete recovery of her neurological deficit.

CONCLUSIONS Churg-Strauss Syndrome can present as a subacute sensory-motor neuropathy, with features suggestive of Guillain Barre Syndrome. As immunosuppressive treatment can significantly alter the course of CSS, early recognition is essential for optimal management.

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PULSE INTRAVENOUS CYCLOPHOSPHAMIDE THERAPY IN CHRONIC INFLAMMATORY POLYNEUROPATHY WITH ANTIBODIES TO NEURAL ANTIGENS AND RESISTANT TO CONVENTIONAL THERAPIES. S. Simonetti, D. Bianchini, E. O. Ospedali Galliera (Genova, I)

Pulse intravenous cyclophosphamide (IVCY) has been reported to be effective in chronic inflammatory demyelinating polyneuropathies (CIDPs) without monoclonal gammopathy of undetermined significance (MGUS) and, in combination with plasma exchange, in CIDPs with antibodies to myelin-associated glycoprotein (MAG) associated or not to MGUS.

To our knowledge, there are no reports dealing with the effect of the only IVCY in CIDPs with antibodies to neural antigens.

Four patients with CIDP associated with antibodies to neural antigens were treated every 20 days with 7 one-day cycles of IVCY (1 gr/m2). One patient had antisulfatide antibodies and no MGUS, while the other three had anti-MAG antibodies and IgM kappa MGUS. All the four patients had progressive sensory-motor polyneuropathies and previous ineffective treatments with various combinations of intravenous immunoglobulin, plasma exchange and prednisone. Quantitative assessment included Rankin disability score, MRC strength score, four limb sensory score, electrodiagnostic studies and autoantibodies serum concentration.

The three patients with anti-MAG antibodies noted a subjective improvement after 4–6 treatment courses lasting for 6–8 months, but an objective improvement was never observed during the follow up. In the patient with antisulfatide antibodies, a subjective improvement began after the last IVCY course while an objective improvement (one point decrease on the Rankin scale, antibody titer reduction, improvement of MRC score and neurophysiological findings) was observed 4 months later. Improvement lasted for 4 months after which a progressive worsening was noted and other treatments were started.

Considering the potential toxicity, our results suggest that the only pulse IVCY treatment seems of limited value in CIDP with antibodies to neural antigens and resistant to conventional therapies.

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SOLITARY SCHWANNOMA OF THE LOWER LIMB: UNUSUAL PRESENTATION WITH AUTONOMIC DYSFUNCTIONS. V. Agnetti, V. Migaleddu, M. R. Murrighile, R. Ortu, G. P. Sechi, University of Sassari (Sassari, I)

The lower limb corresponds to the less frequent site of the already rare peripheral nerve tumors. Solitary schwannomas of the peripheral nerves usually present as swelling painful to pressure. Neurologic deficits are uncommon and no report of autonomic dysfunction was encountered in the literature. We present two cases in which excessive sweating of the foot anticipated of several months any other sign or symptom of a solitary schwannoma of the sciatic nerve in the thigh and tibial nerve, respectively. In one case further autonomic signs developped which played a fundamental role for the diagnosis.

CASE REPORTS: CASE 1 – A 59-year-old man had been complaining for one year of severe pain in the lateral popliteal aspect of his right leg, exacerbated by local pressure with irradiation to his ankle, foot and lateral three toes. Two months before pain onset he started to feel uneasy for persisting profuse sweating of the right foot, revealed by a single wet sock. In addition, he noticed that the leg was warmer from the distal third of the thigh down and the foot showed a mildly swollen reddish sole. Admitted thrice to an Orthopedic Dpt where he underwent angiography of aorta and leg arteries, CT and MR of the lumbar region and echotomography of right leg, all of which showed normal findings. Provisional diagnoses were S1 sciatalgia, lumbar disc prolapse, and anterior-lateral compartment syndrome of the leg. When he was referred to Neurology Dpt a level in the warmer skin beneath the middle third of the thigh and the exacerbation of pain owing to pressure applied to the back of the thigh pointed to a lesion in that region. A new targeted echotomography revealed a solid nodular lesion on the course of the sciatic nerve, confirmed by MR imaging and surgery. Neuropathology showed typical aspects of schwannoma.

CASE 2 – A 49-year-old man with a ten year history of pressure provoked shooting pain at his left medial calf radiating into the medial malleolus complained of his stocking heel bathed in sweat ever since. Echotomography guided by the palpation of the painful mass revealed a nodular lesion in which Doppler evidenced a blood flow compatible with a schwannoma. The definition of the lesion along the tibial nerve was completed by MR imaging and microsurgery allowed removal of the tumor which was confirmed as schwannoma at the neuropathological examination.

COMMENT: The excesssive sweating in the foot of these two patients reflects the altered function of the sudomotor sympathetic pathway. In the first patient autonomic changes also involved skin temperature and color. Complete remission of pain and autonomic dysfunctions followed the surgical removal of the tumor in both cases. Electrical stimulation of the ventral spinal root in the cat causes sweating in the area of supply and electrical activation of unmyelinated nociceptor afferents in human elicits some regional rubor and skin warming. Spontaneous burning pain, mechanical hyperalgesia and red, hot skin observed in our patient are considered in the ABC syndrome to reflect antidromic neurogenic inflammation mediated by C nociceptor antidromoic stimulation. A mechanical stimulation induced by the tumor could involve either the postganglionic cholinergic sympathetic fibers and the antidromic activation of C nociceptor explaining sudomotor and vasomotor responses.

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AUTONOMIC NERVOUS SYSTEM DISTURBANCES IN CHARCOT-MARIE-TOOTH (CMT) 1B DISEASE. J. De Seze, T. Stojkovic, M. C. Arne-Bes, D. Ferriby, J.C Hache, P. Vermersch, R Salengro Chu de Lille (Lille, F)

BACKGROUND: The Charcot-Marie-Tooth (CMT) disease represents a group of clinically and genetically heterogeneous neuropathies. Autonomic nervous system disturbances have been rarely described in CMT in contrast with amyloidosis or diabetis mellitus.

AIM OF THE STUDY: To describe a CMT family with myelin protein zero (MPZ) gene mutation revealed by severe dysautonomic disorders.

METHODS: We studied 6 patients of a large family from France and Belgium. This family was previously published (De Jonghe et al., 1999) as a CMT1B secondary to Thr124Met mutation in the peripheral MPZ gene. We describe the French arm of this family. We studied the postural adaptation, sympathetic skin reflex (SSR), RR interval and pupillometry.

RESULTS: Clinical and laboratory autonomic nervous system disturbances were found in the 2 affected patients and in none of the unaffected subjects. Clinical signs were urinary dysfunctions, sudoromotor troubles and dizziness after rapid wake up. Laboratory abnormalities were predominant in pupillary examination with a total impairment of the pupillary reflex. None of the other tested members of the family had papillary abnormalities.

DISCUSSION: This study showed that autonomic disturbances do not excluded the diagnosis of CMT and may be associated with CMT1B secondary to MPZ gene mutation. Pupillary reflex is easy to perform and allows discrimination between affected and unaffected subjects. However, it remains unclear, in this demyelinating neuropathy, why autonomic nervous system fibers are involved. Further, studies on the MPZ gene will be necessary to understand the involvement of autonomic nervous system in this form of CMT1B.

P610

MUSCLE CRAMPS AND FASCICULATIONS AS SOLE MANIFESTATIONS OF HMSN TYPE IB. J. H. J. Wokke, G. W. Van Dijk, F. Baas, H. Franssen, UMCU, AMC (Utrecht, Amsterdam, NL)

The clinical manifestations of autosomal dominant demyelinating hereditary motor and sensory neuropathy (HMSN) type Ib tend to be more severe compared with those of HMSN type Ia. In HMSN Ib classical Charcot-Marie-Tooth phenotypes have been observed but infantile patients may mimic spinal muscular atrophy type I. We present a patient with HMSN Ib who had only muscle cramps and fasciculations.

The patient, a 30-year old lawyer and keen sportsman, first noted spontaneous muscle contractions in the calves after a long bike tour. Thereafter these movements occurred more frequently, but mostly after exercise. He also had frequent nocturnal muscle cramps in the calves. There were no other complaints. Neurological examination revealed modest pes cavus and atrophy of both extensor digitorum brevis muscles. Muscle strength and sensation were completely normal. Myotatic reflexes were low, the Achilles reflex being depressed. The family history was negative.

Laboratory analysis revealed normal activity of the muscle enzyme creatine kinase. Concentric needle analysis showed fasciculation potentials, but no signs of denervation or reinnervation in distal muscles. Motor nerve conduction velocities were moderately slowed. Left median and ulnar nerve motor nerve conduction velocities (MNCV) were 40 m/sec, tibial and peroneal MNCV's were 24 –27 m/sec. Distal motor latencies were moderately prolonged, but F-waves were markedly slowed. Sensory nerve conduction was also slowed but with

preservation of action potentials. DNA analysis revealed a point mutation (G-to-A mutation at position 605) in the gene encoding P0 on chromosome 1q21–23. This mutation results in a substitution of glutamin acid by lysin at position 605.

Our observation is important for three reasons. First, the phenotype of HMSN Ib appears to be as diverse as in HMSN type Ib. Second, this can be explained by the occurrence of mild and deleterious mutations in the same gene. A similar phenomenon is observed in other hereditary diseases as for instance X-linked dystrophinopathy and autosomal recessive glycogen storage disease type II. Finally, nerve conduction studies should be performed in the muscle cramps-fasciculations syndrome.

P611
T CELL RECEPTOR V BETA GENE UTILISATION IN SURAL NERVE BIOPSIES OF PATIENTS WITH CIDP AND VASCULITIC NEUROPATHY. W. M. J. Bosboom, L. H. van den Berg, I. Mollee, L. D. Sasker, J. H. J. Wokke, T. Logtenberg, UMCU (Utrecht, NL)

Objective: To investigate the utilisation of T cell receptor (TCR) variable (V) regions in infiltrates of sural nerve biopsies of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) and vasculitic neuropathy.

Background: The presence of infiltrating T lymphocytes in sural nerve biopsies may suggest a T cell-mediated immune mechanism in the pathogenesis of CIDP and vasculitic neuropathy.

Patients and methods: The utilisation of TCR Vbeta regions in sural nerves of 13 patients with CIDP and five patients with vasculitic neuropathy was determined by immunohistochemistry, reverse transcription polymerase chain reaction (PCR) and nucleotide sequence analysis. These techniques were also applied in four patients with chronic idiopathic axonal polyneuropathy (CIAP) who acted as noninflammatory controls and in five autopsy controls.

Results: The Vbeta TCR utilisation of infiltrating T cells in sural nerves of patients with CIDP, vasculitic neuropathy and noninflammatory controls is heterogeneous. A dominant Vbeta TCR utilisation was not found in any of the patients or controls.

Conclusion: There is no evidence for the presence of clonally expanded T cells in sural nerves of patients with CIDP and vasculitic neuropathy.

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CYTOKINES IN SURAL NERVE BIOPSIES. T. Lindenlaub, C. Sommer, Universitätsklinik Würzburg (Würzburg, D)

Proinflammatory cytokines have been shown in the serum, the cerebrospinal fluid (CSF) and in nerve biopsies in different neuropathies. Here we examined the expression of the cytokines Interleukin-1beta (IL-1 beta), Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF) in sural nerve biopsies of patients with vasculitic neuropathy (VN) and chronic inflammatory neuropathies (CIDP) and compared them to chronic axonal neuropathies without inflammation (CAN). Cytokine content was correlated to the content of T-cells and macrophages, to the number of degenerating axons and the duration of symptoms. Paraffin sections of diagnostic sural nerve biopsies were stained with haematoxilin-eosin and the macrophage-marker CD 68, semithin-sections were stained with azur-methylenblue and 40 micron thick cryosections were immunoreacted for T-cells (Leu 4), IL-1beta, IL-6 and TNF. Cytokine content in the endo- and epineurium was determined by optical densitometry of the immunostained cryosections of the nerve and expressed as % of endoneurial or epineurial area. A total of 22 nerves was used for analysis, 9 from patients with VN, 6 with CIDP, 6 with CAN, and one normal control. Cytokine immunoreactivity was higher in the endoneurium than in the epineurium. Patients with VN had a higher endo- and epineurial cytokine content compared to patients with CIDP or CAN. IL-1 beta, standing as a representative for the three cytokines examined, was 3.38 ± 7.76 % in the endoneurium of patients with VN compared to 0.54 ± 0.64 % in CIDP and 0.01 ± 0.01 % in CAN. Epineurial values were 1.16 ± 1.58 % in VN, 0.01 ± 0.01 % in CIDP and 0.28 ± 0.28 % for IL-1 beta. High levels of cytokines were correlated with higher numbers of T-cells, macrophages, degenerating axons and a short history. In conclusion, the proinflammatory cytokines IL-1beta, IL-6 and TNF were upregulated in the endoneurium and epineurium in vasculitic and other inflammatory neuropathies. Since high levels of cytokines were correlated with active axonal degeneration the cytokine pattern may help in judging the activity of vasculitic neuropathy.

P613
A CLINICAL AND ELECTRODIAGNOSTIC PROSPECTIVE STUDY OF PATIENTS WITH CRITICAL ILLNESS POLYNEUROPATHY AND MYOPATHY: THE NATURAL HISTORY. M. de Letter, St. Elisabeth hospital (Tilburg, NL)

Introduction: A prospective study of the natural history of 31 patients suffering from Critical Illness Polyneuropathy and Myopathy (CIPNM) is described. Clinical and electrophysiological features are described and parameters that might influence the course of this disease and the muscle biopsy characteristics are discussed.

Methods: All patients met the clinical and electrophysiological criteria of CIPNM and were evaluated on their clinical (motorscore, sensory disturbances, reflexes and atrophy) and electrophysiological (conduction study, needlemyography and somatosensory evoked potentials) features at least until discharge from the hospital or death. Subgroups based on the outcome and the recovery of motor sumscore were correlated with light microscopical features of the muscle biopsies and clinical parameters (age, sex, duration artificial respiration, Apache-III score, sepsis severity score, presence of systemic inflammatory response syndrome, the amount of vecuronium and steroids used and these two drugs combined) using chi-square test.

Results: We defined three subgroups according to the recovery pattern; 1) classical CIPNM with no subjective motor disability in 20 % (6/31), 2) motor disability group in 48 % (15/31) and 3) a group with the worst motor sumscore in 32 % (10/31). Mortality was 0 %, 47 % and 100 % in group 1,2 and 3 respectively. Patients did not mention sensory disturbances. Overall muscle wasting was present. Recovery of the tendon reflexes was related with improvement of the motor sumscore (p=0.039). The CMAP amplitude of the ulnar nerve revealed a decrease towards the time of diagnosis of CIPNM; afterwards the values gradually increased but only reached normal values for subgroup 1. Sensory measurements did not show such a pattern. Needle myography revealed increased denervation potentials towards time of diagnosis of CIPNM most prominent in the distal muscles. Repetitive stimulation of the ulnar nerve and somato-sensory evoked potentials were normal in all patients. No relations were found for the subgroups of CIPNM and the clinical parameters.

Conclusion: CIPNM is mainly a motor neuromuscular disorder clinically, but electrophysiologically both motor and sensory with an unexpectedly high motor disability in time. This indicates the importance to monitor critical ill patients for neuromuscular problems during and after their stay on the ICU for adequate rehabilitation.

P614
PHENOTYPE-GENOTYPE CORRELATION IN PATIENTS WITH CHARCOT-MARIE-TOOTH TYPE1 AND HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES OF TURKISH ORIGIN. Y. Parman, N. Bissar-Tadmouri, E. Battaloglu, F. Deymeer, P. Serdaroglu, Istanbul University Istanbul Medical Faculty, Bogazici University (Istanbul, TR)

Point mutations in peripheral myelin protein 22 (PMP 22), protein zero (P0), and connexin 32 genes are described in Charcot-Marie-Tooth type 1 (CMT 1), Dejerine-Sottas Disease (DSD) and only in PMP22 in hereditary neuropathy with liability to pressure palsies (HNPP) when no deletion is detected. We have screened patients with CMT 1, DSD, HNPP phenotype from Turkey. We report 4 of them whose clinical, electrophysiological and histopathological features were compatible with CMT. One patient with HNPP phenotype carried a novel two-nucleotide deletion (CC) at position 551 and 552 while another with DSD phenotype had a missense point mutation (Ser72Leu) of the PMP 22 gene. Two point mutations affecting different domains of connexin 32 (Val191Met, Tyr21His) were found in 2 males whose mothers were also affected. The severity of the phenotype seemed to correlate with the impact of the mutation detected in all the patients described.

P615
CHRONIC VENOUS INSUFFICIENCY LEADS TO PERIPHERAL NEUROPATHY. F. M. Reinhardt, G. Schuler, P. von den Driesch, W. Lang, B. Neundörfer, University Hospital, Dept. Neurology, University Hosp., Dept. Dermatology, Univ. Hosp., Dept. Vascular Surgery (Erlangen, D)

Objective: Chronic venous insufficiency (CVI) of the lower legs may cause tissue damage, but involvement of peripheral nerves is not clear to date. In this study we investigated peripheral nerve function in patients with CVI. Methods: 30 patients with CVI were examined and compared to 20 healthy controls. The methods used were motor and sensory nerve conduction studies, vibration- and thermotesting, quantitative sudomotor axon reflex test, and laser Doppler flowmetry. Subjects with possible confounding factors for peripheral neuropathies were excluded. Results: Prolongation of distal motor latency of the peroneal nerve (median 5.4 vs. 4.5, p= 0.02), reduced vibration sense (2.8925

vs. 1.1075, p< 0.008) and increased limits for warm (9.60 vs. 5.20°C, p=0.016) and cold detection (3.45°C vs. 1.55°C, p=0.016) were found. Conclusion: The results demonstrate an impairment of A-alpha fibers, A-beta fibers, A-delta fibers and thermoafferent C-fibers. The mechanisms leading to nervous system impairment are not sufficiently clear, but seem to be a consequence of ischemia due to venous microangiopathy in combination with increased endoneurial pressure.

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CHARACTERIZATION OF THE EPITOPE RECOGNIZED BY ANTI-MAG IGM ANTIBODIES ON THE BASAL LAMINA OF SCHWANN CELLS. M Sollberger, B Erne, S Sansano, A Probst, M Tolnay, N Schaeren-Wiemers, AJ Steck (Basel, CH)

Chronic dysimmune demyelinating paraproteinemic peripheral neuropathies are predominantly sensory-motor neuropathies associated often with anti-myelin associated glycoprotein (MAG) IgM antibodies. These IgM antibodies are found as deposits on and within the myelin sheath of nerve biopsies in association to the characteristic widening of the outer myelin lamellae (Gabriel et al., Acta Neuropathol 1998; Ritz et al., Muscle and Nerve 1999). By confocal microscopy we have shown that these IgM antibody deposits are associated with sites of MAG localization, mainly Schmidt Lantermann incisures and paranodal loops. Additionally we found anti-MAG IgM antibodies on the basal lamina of myelinated nerve fibers. Therefore, we postulate that the basal lamina may represent an early target for the uptake of autoantibodies at the surface of myelinated nerves. The identification of the nature of the antigen, which is recognized by the anti-MAG IgM autoantibodies may help to understand the mechanisms which take place during IgM deposition and penetration into the nerve fiber.

For this purpose, a purification protocol for isolation of basal lamina from human peripheral nerves has been established. The purity grade of basal lamina was tested by Western blot analyses and immunohistochemistry, using basal lamina markers such as collagen IV and laminin and myelin protein markers such as MAG, protein 0 (P0), myelin basic protein (MBP) and the peripheral membrane protein 22 (PMP22). The purification led to an enrichment of the extracellular matrix proteins in contrast to an almost complete loss of the myelin proteins. In particular MAG disappeared completely during the purification procedure. Additionally the histoarchitectural structure of the basal lamina could be preserved.

To investigate the expression pattern of the epitope on the basal lamina for the anti-MAG IgM antibodies, we tested anti-MAG IgM patient-sera on the purified basal lamina from normal peripheral nerves and from an inflammatory peripheral nerve by immunofluorescent microscopy. Thereby, we did not detect any binding on the purified basal lamina. These findings could indicate that the epitope for anti-MAG IgM antibodies is upregulated on the basal lamina only in a disease specific manner, though, we can not exclude that it is lost during the purification procedure.

Our next step will be to test the binding specificity of anti-MAG IgM patient sera on the purified basal lamina of their own nerve biopsies or on the purified basal lamina of nerve biopsies from other anti-MAG IgM paraproteinaemic patients.

P617
CAMPYLOBACTER JEJUNI LIPOPOLYSACCHARIDES FROM GUILLAIN-BARRÉ AND MILLER FISHER PATIENTS INDUCE ANTI-GM1 AND ANTI-GQ1B ANTIBODIES IN RABBITS. C. W. Ang, M. A. De Klerk, B. C. Jacobs, J. D. Laman, F. G. A. Van Der Meche, N. Van Den Braak, H.Ph. Endtz, P. A. Van Doorn, Erasmus University Rotterdam (Rotterdam, NL)

Anti-ganglioside antibodies in patients with Guillain-Barré syndrome (GBS) and Miller Fisher syndrome (MFS) are thought to be induced by molecular mimicry between Campylobacter jejuni lipopolysaccharides (LPS) and gangliosides. We used purified LPS fractions from five Campylobacter strains to induce anti-ganglioside responses in rabbits. Two strains were isolated from GBS patients with anti-GM1 and anti-asialo-GM1 antibodies. Two other strains were isolated from MFS patients with anti-GQ1b antibodies. The Penner O:3 serostrain which lacks ganglioside-like epitopes was used as control. Immunization of New Zealand White rabbits with LPS in complete Freund's adjuvant resulted in high titer IgG anti-LPS and anti-ganglioside antibodies and lower titer IgM antibodies. The animals that received injections with LPS from GBS-associated strains developed anti-GM1 and anti-asialo-GM1 antibodies. Animals that were injected with LPS from MFS patients had anti-GQ1b antibodies. The rabbits that were injected with Pen O:3 LPS had a strong anti-LPS response but no anti-ganglioside reactivity was observed. One animal that was immunized with a GBS associated strain developed clinical symptoms. Our results demonstrate that an immune response against C. jejuni LPS can induce anti-ganglioside antibodies and that the LPS structure determines the specificity of the immune response.

P618
MULTIFOCAL MOTOR NEUROPATHY WITH CONDUCTION BLOCK MIMICKING MOTOR NEURON DISEASE: A STUDY OF 17 PATIENTS. A. Echaniz-Laguna, C. Guiraud-Chaumeil, M. C. Fleury, V. Poindron, C. Tranchant, J. M. Warter, Hôpital Civil (Strasbourg, F)

Background: Multifocal motor neuropathy (MMN) with persistent conduction blocks (CB) is a rare clinical entity that often mimicks motor neuron disease (MND). Until now, few series with large numbers of patients have been described. Patients and methods: We report here the clinical, electrophysiological and biological findings, and response to treatment in 17 patients with MMN. Results: Sex ratio (M/F) was 16/1 and mean age of onset was 57.1 years. Weakness or muscle atrophy of a hand was the most frequent presentation (59 % of patients). Tendon reflexes were often absent or weak. All patients had CB. Median and ulnar nerves were the most affected nerves (82 % and 71 % of patients respectively), with CB mostly at the forearm and at Erb's point-elbow segments. Common peroneal and tibial nerves were frequently affected at their distal segments (65 % of patients). Serum electrophoresis showed monoclonal peaks in 47 % of patients. High anti-GM1 antibody titers were found in 59 % of patients. Response to IV immunoglobulins (IVIg) therapy was observed in 7/13 patients. Patients with pronounced amyotrophy did not respond to IVIg (6/13 patients). Conclusion: Electrophysiological and biological studies allowed us to clearly distinguish MMN from MND in all cases. Careful neurophysiological studies and search for anti-GM1 antibodies are crucial to diagnose this clinical entity.

P619
INCREASED PREVALENCE OF AXONAL POLYNEUROPATHY IN OBSTRUCTIVE SLEEP APNEA. A. Frese, R. Dziewas, S. Happe, P. Sörös, F. Lindemann, K. Bade, A. Okegwo, P. Lüdemann, Westfälische Wilhelms Universität (Münster, D)

Objective: To determine the occurrence of polyneuropathy (PNP) in patients with Obstructive Sleep Apnea (OSA).

Methods: Sixteen consecutive patients with newly diagnosed OSA (apnea-hypopnea-index [AHI] > 10/hour) were screened for polyneuropathy by clinical and neurographical examination. PNP was diagnosed neurographically when conduction velocity or amplitude of action potentials (AP) for the peroneal nerve (motor nerve) or the sural nerve (sensory) were outside the normal laboratory range. Data were compared to 16 controls with polysomnographically excluded OSA (AHI < 5). Patients with known diabetes, hepatic or renal disease were excluded from the study. For all patients sex, age, body-mass-index (BMI), alcohol and nicotine intake, and glycosylated hemoglobin (HbA1c) were determined.

Results: With regard to sex, age, BMI, alcohol and nicotine intake, and HbA1c, the OSA- and the control-group did not differ significantly. Eight of 16 patients (50 %) with OSA had clinical signs of PNP. In 10 of 16 OSA-patients (62,5 %), the amplitude of sural sensory AP was reduced. By contrast, in the control group only one patient had clinical signs of PNP and a reduced amplitude of sural sensory AP. The difference between the groups was significant (p < 0,05).

Discussion: The study shows a high prevalence of sensory axonal PNP in patients with OSA. The higher prevalence of PNP as compared to the control group can not be attributed to an unequal load with other known risk factors. It is similar to the prevalence of PNP in patients with chronic obstructive lung disease. We assume that chronic recurrent hypoxemia is an independent risk factor for axonal damage of peripheral nerves. We conclude that screening for OSA can be a helpful tool in the diagnostic evaluation of axonal PNP.

P620
MOTOR NERVE BIOPSY TO THE ANCONEUS MUSCLE. A USEFUL AND FEASIBLE DIAGNOSTIC APPROACH. S. Jann, U. Valentinotti, M. Bramerio, D. D'urso, C. Defanti, Ospedale Niguarda (Milan, I)

Peripheral nerve biopsy is getting more and more important to detect the aetiology and the pathogenesis of many neuromuscular diseases. The most important characteristics of the nerve biopsy are the size of the specimen, the feasibility of the biopsy, and the lack of important deficits. Of course the nerve should be affected by the disease. The most frequent nerve biopsy is the sural nerve biopsy at the ankle level. Unfortunately this biopsy is not useful in pure or predominant motor neuropathy and in the motor neuron disease. In such neuromuscular disorders other nerve biopsies have been performed. The biopsy of the motor nerve to the gracilis muscle is one of the best known but it is indi-

cated in neuromuscular diseases that affect the thigh adductor musculature. When upper limbs are predominantly affected, nerve biopsies to the anconeus, palmaris longus, flexor sublimus and triceps have been occasionally described.

We recently began to perform the motor nerve biopsy to the anconeus in cases of motor neuropathy affecting predominantly the upper limbs. This biopsy is safe and feasible. None of the patients did experience weakness. The main problem was the size of the specimen that did not permit extensive morphological studies. We performed this motor biopsy in cases of CIDP with normal histopathology of the sural nerve, in cases of vasculitis with sparing of the sural nerve but with involvement of the radial nerve as well as in cases of Charcot-Marie-Tooth Disease with normal genetic analysis and uncertain sural nerve pathology. In all these cases motor nerve biopsy to the anconeus was helpful to reveal important mechanisms of the neuromuscular disease. No patients experienced surgical complications.

P621
DETERIORATION OF MULTIFOCAL MOTOR NEUROPATHY AFTER INTERFERON 2 ALPHA THERAPY. B. Sferrazza, M. Lacerenza, P. Canovaro, V. Golzi, S. Iannaccone, HSAN – Raffaele (Milano, I)

The pathogenesis of Multifocal Motor Neuropathy with Conduction Block (MMNCB) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is unclear but for both an immune mechanism is suspected. However the response to therapy is different: CIDP is often responsive to corticosteroids, Plasma Exchange (PE), Intravenous Immunoglobulin (IVIg) and Interferon-alpha 2a therapy; MMMNCB is unresponsive to corticosteroids and PE but responsive to IVIg and cyclophosfamide therapy.

We report two patients, one affected by CIDP (65 yrs, F) and one affected by MMNCB (54 yrs, F), both unresponsive to corticosteroids and to several cycles of IVIg (0.4 gr/kg for five days). After IFN 2 alpha therapy, at dosage of 3 millions IU subcutaneously three times a week for 6 weeks, the patients affected by CIDP clinically improved at six months follow-up (MRC score before treatment 54; after treatment: 76). The patient affected by MMNCB, submitted to the same therapy clinically worsened at six months follow-up (MRC before treatment 71; after treatment 62). The same patient improved after two cycles of cyclophosphamide at dosage of 400 mg/m^2 iv one day bolus (MRC score before treatment 62, after treatment 75). This observation confirms the different therapeutic response of CIDP and MMNCB to the immune therapies.

Rehabilitation

P622
A NEW COMPUTER DEVICE FOR NEUROREHABILITATION PROGRAM. F. Pauri, P. D'Ambrosio, P. M. Rossini, AFaR-CRCCS (Rome, I)

One of the most astonishing properties of the mammalian brain is its capacity of adaptation for change, commonly referred as neural plasticity. Pioneering studies have repeatedly shown how the brain possesses the capacity to reorganise itself after peripheral deprivation by allowing neighbouring cortical regions to expand into territories normally occupied by input from the deprived sense organs. More recently, a bulk of experimental evidences have been accumulated in support of the hypothesis that neuronal aggregates adjacent to a lesion in the sensorimotor brain areas can be progressively vicarious to the function of the damaged neurones. According the knowledge about brain plasticity, we want to organize a rehabilitation program, both in earlier days and in the weeks and months following a cerebrovascular lesion, helping the reorganisation of the brain and the reestablishment of the lost function using computer facilities. So an "electromyografic attuator" has been realised. It could be controlled by external systems, such as personal computers, biofeedback systems and could be employed in so called "domotic project". This system consists of: a polygraphic recorder with 5 channels for EMG – MYOACT 5000 with automatic calibration. The threshold for the EMG recording activity could be adjusted according the variable requested input force of the patient. The system has two digital outputs, that could be easily connected to the computer. The signal from the muscle goes to the EMG device where it is filtered, rectified and sent to the computer where it could provoke the movement of the mouse on the screen. On the screen you can choose between the trace of the mouse and the patient can see the direction of the movement: right, left, up, down, or you can have such kind of easy video-game where the subject has to hit the mark. In both cases the patient has his on-time feedback about what and how he is doing the task. Myoact 5000 has five channels for recording, so you can choose agonist and antagonist muscles or coactive muscles and so on. For each channel there is a threshold you can adjust: low threshold when the muscle is plegic to capture also minimal signal and you can increase the threshold according the improvement of performances. Working in the opposite manner we can manage spasticity: you invite the patient just to relax the muscle and adjust the threshold starting from the top and going down. We started to utilize this device to improve the performances of plegic or paretic upper limb in patients affected by stroke. Electrodes were positioned on the paretic muscles and the subject was asked to do the appropriate movement related to the muscle chosen, if he could, or just to try to contract the muscle, or to think to move the muscle. Patients nicely accepted this new device and tried to manage it themselves. Some improvements were evident after the first week of treatment.

P623
CORTICAL REORGANISATION AFTER FIRST UNILATERAL STROKE. A FMRI AND TMS STUDY. H. Foltys, T. Krings, A. Loeffler, S. Kemeny, R. Sparing, A. Thron, R. Toepper, Department of Neurology, Department of Neuroradiology (Aachen, D)

Recent functional imaging studies have tried to unravel the functional mechanism of restitution after a unilateral stroke with impaired motor function. Plasticity of cortical areas is held responsible for restitution of motor function. In addition a contribution of the hemisphere ipsilateral to impaired motor function has been suggested. Methods: We studied with functional magnetic resonance imaging (fMRI) the cortical activation pattern in ten patients who experienced nearly complete restitution of motor function in the chronic phase after a subcortical or cortical stroke. A simple handclenching and a complex finger-thumb opposition movement with the affected and non-affected hand was performed. We measured the activation of the ipsilateral and contralateral sensorimotor cortex, the premotor cortex, the SMA and the cerebellum. To investigate corticospinal pathways transcranial magnetic stimulation (TMS) was applied to both hemispheres and the location of the most excitable brain areas and the amplitude of motor evoked potentials were compared. Results: During the handclenching task and the finger-thumb opposition task with the affected and non affected hand primary motor, premotor, supplementary motor and cerebellar areas of the hemisphere contralateral and ipsilateral to the movement were activated. The activation in all investigated brain areas was more pronounced during performance of the tasks with the affected hand. Motor evoked potentials (MEP) could be found after stimulation of the contralateral hemisphere and no MEP ipsilateral to stimulation could be excited. No 'atypical' areas from which MEPs within one hemisphere could be excited were observed. Conclusions: In all patients an increased activation of all areas involved in motor planning and execution was observed when moving the affected hand. No additional cortical areas were observed when patients moved the affected hand. Accordingly TMS also failed to locate additional corticospinal connections of both the affected and non-affected hemisphere. The increased activation of contralateral and ipsilateral motor areas might therefore be the consequence of increased effort needed to perform the motor task.

P624
THE ADMINISTRATION OF BOTULIN TOXIN (DYSPORT) IN SPASTICITY TREATMENT IN "LOCKED-IN" SYNDROME PATIENTS. S. Michalak, D. Lenart-Jankowska, W. Kozubski, Chair and Department of Neurology (Poznan, PL)

One may notice the increasing number of indications for botulin toxin treatment involving focal dystonias, spasmodic dysphonia, cerebral palsy, aesthetic surgery, esophagal achalasia and anal fissure. The target of such a treatment is the spasticity developing in the course of multiple sclerosis and stroke. We undertook the attempt of botulin toxin administration in two locked-in syndrome patients. The first patient was a 25 year old man admitted to Intensive Care Unit after car accident resulting in brain and brain stem contussion, fractures of left femoral, peroneal and tibial bones and shock. The consciousness was evaluated as 10 in GCS. There was need of artificial respiration for 11 days, then it was stopped because of sufficient respiration signs. The initial head CT showed signs of contussion, the control examination after six weeks was normal. Clinically he presented locked-in syndrome, left sided central facial paresis, spastic tetraplegia, elevated tendon reflexes, and both-sided Babiński and Rossolimo signs. On 72nd day after trauma the patient was admitted to the Department of Neurology and improved in awareness, trying to respond in whispered monosyllables. On 79th day after trauma we administered botulin toxin (Dysport, 1000 IU) to the most clinically indicated muscles. During next 10 days we observed reduction in spasticity followed by the improvement in range of passive movements in upper and lower limbs. Twenty three days after treatment the patient was able to sit in a wheel-chair, and next thirty days resulted in ability to walk. The second patient was a 20-year old woman who underwent a traffic accident resulting in brain stem and right frontal lobe contussion, with left forearm traumatic amputation. During her stay in surgery ward, 13 days along, she needed artificial respiration. On 38th day she was tranfered to our department. She presented tetraplegia, spasticity in upper and lower limbs, both-sided

Babinski sign. On 51st day she start to react, after further 41 days she performed some tasks and finally a logical contact was possible on 120th day since trauma. Because of positive prognosis we decided about botulin treatment. The clinically relevant muscles were chosen for injection of total amount of 500 IU botulin toxin (Dysport). After 10 days she could walk because of relapsing spasticity and equinovarus deformity of the right feet.

These two cases suggest another possibility of locked-in patient treatment and new clinical sign to be treated with botulin toxin.

P625
IMPROVEMENT OF POSTURAL IMBALANCE FOLLOWING PRISM ADAPTATION IN LEFT HEMIPARETIC PATIENTS. G. Rode, C. Tilikete, Y. Rossetti, J. Pichon, D. Boisson, Hôpital Henry Gabrielle – Hospices Civils de Lyon (Saint Genis Laval, F)

Postural disturbances are common in patients with hemiplegia of vascular origin, mainly as a shift of body weight toward the non-paretic limb. This postural imbalance predominates in left hemiparetic patients, as compared to right hemiparetic patients, regardless of sensory or motor deficit. This predominance could be due to a distorsion of a 'spatial postural representation' (Rode et al., Scan J Rehabil Med 1997; 29: 11–6). Distorsions of spatial representations, as pathological shift of the subjective midline or mental imagery, can be improved by prism adaptation in left brain damaged patients with neglect (Rossetti et al., Nature 1998; 395: 166–9). the purpose of this study was to investigate the effects of prism adaptation on the postural sway characteristics of left hemiparetic patients.

Ten left hemiparetic patients were selected for the study. Five patients were exposed to an optical 10° shift of the visual field to the right and were compared to five controls. The exposure period consisted in making 50 pointing responses to visual targets presented 10 deg to the right or to the left of the objective body midline. Control patients performed the same pointing task without goggles. Posturographic evaluation was performed on a statokinesimetric platform prior to prism exposure (Pre-test), on prism removal (Post-test) and 2 hours later (Late-test).

The main results showed that a short adaptation period to a prismatic shift of the visual field to the right significantly improves the postural imbalance in left hemiparetic patients, suggesting that the process of prism adaptation could activate brain functions related to multisensory integration and spatial representations, used for the adjustment of posture. These findings thus could be useful in posture rehabilitation of hemiparetic patients.

P626
MOBILITY STATUS AT ONE-YEAR FOLLOW-UP IN STROKE PATIENTS DISCHARGED FROM REHABILITATION HOSPITAL. S. Paolucci, M. G. Grasso, G. Antonucci, M. Bragoni, E. Troisi, D. Morelli, P. Coiro, D. Angelis, F. Rizzi, Fondazione S. Lucia IRCCS (Rome, I)

This study was designed to evaluate mobility status at a one-year follow-up in consecutive first stroke patients after discharge from rehabilitation hospital and to identify reliable prognostic factors associated with changes in their abilities.

Mobility evaluation was made of consecutive patients one year after discharge to their own homes. Two multiple logistic regressions (forward stepwise) were performed using both improvement and worsening of Rivermead Mobility Index score between discharge and follow-up as dependent variables. Independent variables were medical, demographic and social factors.

The final sample included 141 out of 155 patients. During the follow-up, 11 patients (7.1 %) died because of new vascular event, 2 patients had new strokes and 1 fractured their paretic legs. Functionally, 37.6 % of the patients maintained mobility level achieved during inpatient rehabilitation treatment, 19.9 % improved and the remaining 42.6 % worsened. Patients with global aphasia, with hemineglect and aged > 75 years had a higher probability of mobility worsening (Odds Ratio [OR] = 5.66, 95 % Confidence Interval [CI] =1.50–21.33; OR=3.01, 95 % CI =1.21–7.50 and OR=5.77, 95 % CI =1.42–23.34, respectively). Post-discharge rehabilitation (performed by 51.5 % of the final sample) was significantly and positively associated with mobility improvement (OR=5.86, 95 % CI =2.02–17), and its absence with mobility worsening (OR=3.73, 95 % CI =1.73–8.04).

In conclusion, in nearly half of the cases mobility status was still not stabilised at time of discharge from rehabilitation hospital. Post-discharge outpatient treatment was useful for preventing worsening of mobility ability achieved during inpatient treatment and increased the possibility of further mobility improvement. Age > 75 years, global aphasia and hemineglect were predictors of mobility worsening at follow-up.

P627
THE EFFECTS OF COMBINATION OF PROPRIOCEPTIVE NEUROMUSCULAR FACILITATION AND JOHNSTONE PRESSURE SPLINTS IN THE TREATMENT OF MULTIPLE SCLEROSIS PATIENTS. K. Armutlu, S. Aksu, A. Guclu, R. Karabudak, Hacettepe University School of Physical Therapy and Rehabilitation (Ankara, TR)

Background: Recently, neurophysiological approaches have been used in physical therapy which are based on the facilitation of physiological responses with the stimulation of neural structures. Proprioceptive Neuromuscular Facilitation (PNF) techniques and Johnstone Pressure Splints are neurophysiologic approaches. These approaches appear to be the most adaptable to the various sensory-motor problems of patients with Multiple Sclerosis (MS). This study was planned because there is no study in the literature using these approaches with statistical results.

Material and Method: Forty MS patients, referred to Hacettepe University Physical Therapy and Rehabilitation School between 1997–1999 were studied. Expanded Disability Status Scale (EDSS) and Ambulation Index scores, muscle strength, normal range of motion, muscle shortness, skin sense and proprioception, spasticity, balance and coordination were evaluated before and after the combined treatment. And the data were analyzed with correlation of MS type, medical treatment, onset of the disease and the duration of physical therapy.

Results: As a result there was a statistically significant difference in EDSS and Ambulation Index scores, muscle strength, normal range of motion, muscle shortness, spasticity, skin sense, balance and coordination ($p< 0.05$), but no difference in proprioception ($p> 0.05$). There was significant correlation between post treatment data and medical treatment and duration physical therapy ($p< 0.05$).

Conclusion: According to the findings, PNF and the Johnstone Pressure Splints approaches with medical treatment are effective methods in the treatment of MS patients. Because there is a significant correlation between the effectiveness of this treatment and duration physical therapy, it does not end with the discharge from a rehabilitation center or going home after a regular out-patient treatment. Therapy must be continued by the patient himself/herself outside of the special treatment setting. Regular home training and controlled sporting activities can give excellent support in this task.

P628
BENEFICIAL EFFECTS OF FLUOXETINE TREATMENT AS AN ADJUNCT TO NEUROREHABILITATIVE EFFORTS IN CHILDREN WITH SPASTIC DIPLEGIA. O. Bolukbasi, E. Cullu, G. Aslan, Adnan Menderes University (Aydin, TR)

Spasticity, behavioral abnormalities like self mutilation and educational problems with cognitive defects are common in children with cerebral palsy. These factors impair the effective neurorehabilitation and education regarding cognitive skills. Fluoxetine is a selective serotonin reuptake inhibitor with little if any effect on other neurotransmitters. Between January and September 1999, an open label pharmacological treatment with fluoxetine ranging from 20 to 40 mgs. daily were given to twelve spastic diplegic children for at least four months trial period. Mean ages for children were 4 to 9 (mean 5.3). Another twelve matched for age and sex spastic diplegic children were arranged as a control group. No medical or surgical intervention other than lioresal and neurorehabilitation was allowed other than fluoxetine in trial group. Only regular neurorehabilitation, antiepileptic drug(s) if any, and lioresal if necessary were allowed to give to controls. All patients were evaluated neurologically and with Ashworth scale for spasticity, Kenny self care evaluation and agitated behaviour scale at the first meeting and every other weeks of the trial period. Examinations were done in the out-patient setting of the Center for Spastic Child. At the end of the fourth trial month, overall rates for Ashworth scales for spasticity, agitated behaviour scales in the fluoxetine group were improved in a comparison with controls in a statistical significance. In some patients (n=4), decrease in the spasticity was observed even in the first month. Improvements in spasticity and cognition were identified as the mostly observed changings during the overall treatment. It should be noted that these factors are easy to detect. Benefici effect on self-mutilation was observed also in two of five children. No significant side effect to stop the treatment was encountered. It is concluded that Kenny self care evaluation is not suitable for these patients and a new and practical test tool is necessary to test both cognition and self care in this particular disorder group of children. Fluoxetine can be administered to spastic diplegic children with large safety profile to improve cognition, spasticity and behavioral problems that interfere with the neurorehabilitative efforts.

P629
VENLAFAXINE MAY BE EFFECTIVE IN DECREASED LIBIDO. H. Gemalmaz, O. Bolukbasis, O. Oge, Adnan Menderes University (Aydin, TR)

Venlafaxine is a serotonin and noradrenaline reuptake inhibitor. It has a negligible affinity for other neurotransmitter receptor sites and so lacks sedative and anticholinergic effects. Beneficial sexual side effects of it has been reported recently (Michael 1997, and Bolukbasi 1999). We determined to test these proposed beneficial side effects on an open label case-controlled study. During June to November 1999, five male patients with a complaint of decreased libido (ranges for age were 33 to 47) were selected in a tertiary care out-patient setting. Selection criteria were defined as patients with a complaint of libido decrease but without erectile dysfunction. To evaluate this selection criteria, patients underwent detailed physical, urological, neurological and laboratory investigations. Blood levels of sexual hormones, index of international erectile function (IIEF), papaverine test (40 mgs. intravenously), stamp test, Beck's depression inventory for primary care, skin sympathetic responses, bulbocavernosus reflex latencies, dorsal nerve of penis stimulation were also assessed. With the help of these investigations, systemic, medicamentous or psychiatric causes of decreased libido were eliminated and were not included in the study. After a wash-out period of ten days for any other drug for decreased libido, venlafaxine, 75 mgs. daily in an extended release form were given to study patients for at least three months. During this period, only venlafaxine was allowed to take by the patients without any other medication. Weekly out-patient controls for libido level, drug compliance and any possible side effect were done. Changings in libido level were assessed on a visual anolog scale. At the end of the first month, in four of the five patients on venlafaxine, increase in libido level was observed and this finding was maintained during the treatment period. It was concluded that the benificial sexual side effects of antidepressants like venlafaxine are independent from their mood altering effect and increase in libido can be seen even in the second week of the treatment.

P630
RESULTS OF A MULTICENTRE RANDOMIZED DOUBLE-BLIND TRIAL TO COMPARE THE EFFICACY OF LOW DOSE STEROIDS AND PLACEBO ON A 3 MONTHS PERIOD ON FLU-LIKE SYMPTOMS OF PATIENT STARTING A TREATMENT WITH INTERFERON-BETA1A. M. Debouverie, N. Duchamp-Vandenberghe, S. Pittion-Vouyouvitchi, R. Anxionnat, B. Doucet, E. Godet, M. Weber (Nancy, Metz, F)

Background: Flu-like symptoms are the most frequent side effects at the initiation of treatment by interferon (IFN)-beta1a and the most frequent cause of early discontinuation of medication. Steroids are anti-inflammatory drugs that could reduce pro-inflammatory cytokine production at onset of IFN therapy and therefore could controle flu-like symptoms. Steroids are efficient for decrease of frequency and intensity of flu-like symptoms at the initiation of treatment by interferon-beta1b. Objective: Compare the efficacy of a 3 month steroid treatment (20 mg oral once-a-day) to a placebo on frequency, intensity and duration of flu-like symptoms. 60 patients with relapsing-remitting MS are treated with EDSS=(0–5.5). Inclusion and exclusion criteria are those of French sanitary authorities. Study description: Four visits are performed by patients at baseline and inclusion study, at one, two and three months after starting interferon-beta1a (AVONEX). Steroids or placebo are initiated 5 days before starting Avonex. Paracetamol will be systematically taken by patients in both groups at each injection time (500 mg) and 4 hours after intramuscular injection (500 mg). EDSS scoring is performed at baseline and at the end of the study. A flu-like symptom intensity score is evaluated by the patients following each injection taking into account the presence of fever, cephalgia, myalgia, sweeting and chills. This study is approved by the Ethical Commitee and Ministry of Health

Poster session 4

Higher function disorders and dementia

P631
A FAMILY WITH INTERMEDIATE SCA3 REPEAT LENGTHS: REFINING THE GENOTYPE – PHENOTYPE CORRELATION. N. van Alfen, M. W. I. M. Horstink, University Hospital Nijmegen (Nijmegen, NL)

Machado Joseph disease (MJD) or spinocerebellar ataxia type 3 (SCA3) is a disorder caused by CAG trinucleotide expansions in the MJD/SCA3 gene on chromosome 14q. Clinical features include cerebellar ataxia, pyramidal and extrapyramidal signs and sometimes polyneuropathy. There is an association between MJD and the restless legs syndrome (RLS), which is reported as a frequent cause of sleep disturbance in MJD. The clinical picture of MJD is influenced by the CAG repeat length. A normal allele contains 12–44 repeats, whereas an affected allele contains 61 to over 85 repeats. There are no reports of intermediate repeats in healthy subjects, and only two patients are known, both with different symptomatology. One suffers from a polyneuropathy and the other from an autonomic neuropathy with ataxia. Hence, the phenotype of intermediate MJD/SCA3 repeats remains uncertain. We describe a family with five members with an intermediate repeat length of 53 or 54 repeats. The proband suffers from a clinical syndrome compatible with late onset MJD. They all suffer from restless legs syndrome and fasciculations, except the youngest one, and two of them also have central neurological signs. We conclude that an intermediate repeat length (of at least 53) is pathologic, and can cause both central and peripheral nervous system dysfunction, which may present with restless legs syndrome and fasciculations only.

P632
EVALUATION OF THE ASSISTENTIAL BURDEN IN PATIENTS WITH DEMENTIA BY MEANS OF CASE-MIX SYSTEM. J. M. Perez Trullen, P. J. Modrego, Hospital de Alcaniz (Zaragoza, E)

Dementia is one of the most frequent causes of admission in old age nursing homes and constitutes an important challenge for any health care system. Whilst the requirements of physical and social care are increasing in industrialised countries, the economic resources are limited. Therefore we need to know the real assistential necessities and costs to assign adequate funding and to implement planning policies. Objective. To provide a systematic and standardised method that measures the care requirements and economic burden of resident demented people in long-term care facilities in order to achieve a better management of economic and human resources. Patients and methods. By Case-Mix is meant the distribution of residents by classification indicators and categories in relation to the care they need to receive. We applied the case-mix system to 67 demented patients, 47 of them fulfilling the NINCDS-ADRDA criteria of probable Alzheimer's disease, 10 meeting the DSM-III ® for vascular dementia and ten more with other dementing processes. The average age of the patients was 84 years. The total population residing in the centre was 220 with a mean age of 82 years. The main parameters taken into account were; daily living activities, daily living behaviour and necessity of continuing care. The combination of the different areas results in 7 assistential categories that range from A (minimum assistential necessity) to G (maximum). We calculated the case-mix score for demented and non-demented patients as well as for the overall population of the centre and analysed the differences in between. Results. The global case mix for the centre was 75.27 points, for demented patients it was 99.65 and for non-demented patients it was 60.3. The case-mix index (case mix for demented patients/case-mix for the centre) was 1.32. Conclusion. The nursing care requirements for demented patients are significantly higher than those for the global geriatric population. The funding of public centres should be based on case-mix assignations but not on equal assignation per patient or centre. The case-mix method is easy to apply and clinically useful.

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CONTRIBUTION OF HEADERS AND SOCCER RELATED CONCUSSIONS TO COGNITIVE IMPAIRMENT IN PROFESSIONAL SOCCER PLAYERS. J. T. Matser Msc, A. G. H. Kessels MD, M. D. Lezak PhD, J. Troost MD, Erasmus University Rotterdam, St. Anna Hospital Geldrop, Oregon Health Sciences University, University Hospital of Maastricht (Geldrop, NL; Portland, USA)

Objective: To determine the effect of headers and soccer related concussions to cognitive impairment in professional soccer players. Methods: Eighty-four active professional soccer players from several professional Dutch premier league soccer clubs underwent neuropsychological evaluation. The number of headers in one professional soccer season and the number of soccer related concussions was investigated regarding cognitive functioning. Results: Soccer related concussions were inversely related to results of tests measuring sustained attention, planning and visuo-perception. The number of headers in one season was inversely related to results of tests measuring focused attention and visual/verbal memory. Conclusion: It seems that concussions produce a more diffuse profile of brain injury whereas headers seem to deteriorate fronto-temporal functions.

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IS IMPAIRED CEREBRAL VASOMOTOR REACTIVITY PREDICTIVE OF DEMENTIA AFTER ISCHEMIC STROKE? ISRAELI-TURKISH COLLABORATIVE STUDY. A. Y. Gur, D. Gücüyener, N. Uzuner, G. Özdemir, A. D. Korczyn, N. M. Bornstein, Tel Aviv Medical Center, Osmangazi University (Tel Aviv, IL; Eskisehir, TR)

Vascular dementia (VD) is one of the common devastating sequels after stroke. The role of the cerebral hemodynamic status in the occurrence and progression of VD is still uncertain. The aim of our study was to determine the value of cerebral vasomotor reactivity (VMR) as a parameter to predict cognitive decline in patients after ischemic stroke (IS). Methods: We assessed VMR in patients after IS using transcranial Doppler and the Diamox test (1 g acetazolamide i. v.). The percent difference between blood flow velocities in both middle cerebral arteries before and after the Diamox test was defined as VMR%. All patients underwent carotid Doppler to exclude severe carotid occlusive disease as a factor which might affect VMR. Bilateral, multiple lacunar infarcts were confirmed by CT and/or MRI in all patients. The patients were divided into those with dementia based on DSM-IV criteria and the MMSE scale (Group 1) and those without dementia (Group 2). The VMR% values of both groups were compared using the ANOVA test. Results: Group 1 (n=10, 7 men, mean age 70.3±18.5 years) and group 2 (n=10, 7 men, mean age 64.2±19.5 years) were comparable in terms of common vascular risk factors and timing after IS (3–36 months). The mean VMR% was 33.3±21.5 % for group 1 and 43.7±29.8 % for group 2. There was no statistically significant difference between the VMR% of the two groups (P=0.2). Conclusion: Our data suggest a non significant trend to worse VMR in VD. Larger studies are needed to further evaluate the influence of intracerebral hemodynamics on this type of dementia.

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MAGNETIC RESONANCE IMAGING (MRI) OF CORTICAL VEIN THROMBOSIS WITHOUT DURAL SINUS INVOLVEMENT: A STUDY OF THREE CASES. I. Declercq, T. Duprez, I. Capron, V. Van Parijs, C. Grandin, A. Depre, F. Pieret, Clinique Sainte-Elisabeth, Cliniques Universitaires St-Luc, UCL (Brussels, B)

Isolated cortical vein thrombosis (ICVT) is an uncommon condition which until now was only diagnosed at surgery or by repeated conventional angiography. The following MRI features were observed in three female patients presenting with partial epileptic seizures and led to a definite or high probability diagnosis of ICVT: (1) focal meningo-cortical oedema due to venous congestión (all 3 cases), with or without parenchymal (1 case), subarachnoid (1 case?), or subdural (1 case) hemorrhage; (2) early recruitment of an abnormal collateral drainage (2 cases); (3) ischemic lesion in a nonarterial territory (1 case); and ultimately (4) direct visualisation of the acute cortical vein thrombus in one case. MRAngiography showed patent cerebral dural sinuses and deep cerebral veins in the three cases. Conventional angiography was not performed as a sufficient degree of diagnostic accuracy was considered to have been obtained using MRI and as the true diagnostic performance of this invasive technique is not established. Thorough workup revealed a heterozygotic factor II mutation in one patient, but failed to detect any aetiologic factor in the others. Anticoagulant therapy with low molecular-weight heparin had to be discontinuated early in two cases because of hemorrhagic complications. Anti-epileptic therapy controlled epilepsy in all cases. Clinical recovery was complete in two patients. The third suffered from persistent frontal behavioural dysfunction. These cases highlight the ability of MRI to reach high probability for the diagnosis of ICVT, avoiding the need for arterial catheterisation.

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METRIFONATES BENEFITS ARE SUSTAINED DURING A 1-YEAR, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL. T. Bernhardt, H. Woelk, Bayer Vital GMBH & CoKG, Psychiatrisches Krankenhaus (Leverkusen, Giessen, D)

The purpose of this study was to evaluate the efficacy and safety of Metrifonate to treat the symptoms of mild to moderate Alzheimer's disease (AD) in a placebo-controlled trial over a 12 month period. This multi-centre, multi-national randomised, double-blind, trial enrolled 291 patients who received Metrifonate at 50 mg/day and 141 who received placebo. The study was designed with particular care so that patient diagnosis and scoring was assessed by external raters in a consistent, blinded fashion. This rater team consisted of physicians and psychologists, who, being completely independent from the treating physician/investigator, travelled to the study centres, and did the patient assessments. The patients were randomised after a four-week screening period. Patients were required to have a baseline Mini-Mental State Examination (MMSE) score of 8 to 25 and an Ischaemic Score (Rosen Modification) of less than 4. ADAS-Cog and CIBIC-Plus were defined as primary efficacy parameters. Primary efficacy analysis was the Valid for Efficacy analysis with a Last Valid Observation Carried Forward. Primary analyses resulted in statistically significant differences in favor of the Metrifonate treatment group: for ADAS-cog, the treatment difference between Metrifonate and placebo group was 2.47 (p=0.01) and for CIBIC-plus the treatment benefit was 0.26 (p=0.02). The ADAS-cog showed a sustained benefit over the 12 months of the trial. Secondary efficacy parameters of NPI, DAD, and Abridged Relative Stress Scale all showed a treatment difference that favored metrifonate although not all parameters reached significant differences. The tolerability and safety of Metrifonate was good. Adverse events typical of acetylcholinesterase inhibitors (AChEI) were nausea (3.4 %), bradycardia (3.4 %) and muscle cramps (2.1 %). Dropout rates due to all adverse events were low for a 12 month study and were very similar for the Metrifonate (17 %) and placebo (16 %) groups. No muscle weakness occurred. Deaths were equally distributed. This study confirms the efficacy of Metrifonate at 50 mg/day, previously shown in 3 studies with a treatment duration of 6 months. Interestingly, it was found that the benefit for the patient was accruing over time, which suggests a delay of progression from Metrifonate.

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AN ANALYSIS OF THE ATTENTIONALS COMPLAINTS OF PATIENTS, RELATIVES AND PROFESSIONALS FOLLOWING TRAUMATIC BRAIN INJURY AND STROKE. M. Leclercq, G. Deloche, M. Rousseaux, Centre Lennox, Inserm U472, CHRU Hôpital Swynghedauw (Ottignies, B; Reims, Lille, F)

Traumatic brain injury (TBI) and cerebro-vascular accidents (CVA) are often associated with attention disorders. The auto and the hetero-evaluations of complaints have been investigated by few authors. The aim of this study was to perform a direct comparison of the patients', close relatives', and professionals' perception of attention disorders, and to confront this perception with the effective patients' performance. Ninety one patients presenting with TBI (49) or CVA (42) were recruited. Both groups did not differ according to sex ratio, education level, mean post-injury interval (22 months). A modified version of the Ponsford and Kinsella attention questionnaire was presented to the patients (auto-evaluation), close relatives and close therapists (hetero-evaluations), and to 91 normal control subjects. This questionnaire is composed of 16 questions about the actual attention disorders in daily life and one other about the difference between the actual and the premorbid situations. We also assessed the main attention disorders using the computerised TAP Battery (Zimmermann; phasic alertness, divided attention, Go-Nogo, visual vigilance), and the dysexecutive syndrome (instrumental and behavioural). Results. We fist compared (ANOVA; $p < .05$) the auto-evaluation in patients and controls. The subjective severity of attention disorders was more severe in stroke than TBI patients and controls, in that order. However, for the hetero-evaluation, the severity was more important following TBI than stroke, and the difference was more severe for the therapists' than the relatives' evaluations. Furthermore, TBI patients estimated their actual attention deterioration in comparison with the premorbid level less severely than stroke patients, when the reverse was reported by relatives and therapists. Correlations between the auto-evaluation and the instrumental assessments of attention disorders were not significant in TBI patients, when they were frequently so in stroke patients. Furthermore, correlations between the hetero-evaluations and the attention performances were much more significant, and especially when they came from therapists. We also found significant correlations between the hetero-evaluation but not the auto-evaluation and the dysexecutive syndrome. Discussion. Both patients groups presented with a significant increase in attention disorders. However these were underestimated by patients with TBI but not by patients with stroke. The hetero-evaluation is better correlated with the objective deficits of attention and dysexecutive syndrome than the auto-evaluation. The underestimation of the severity of attention deficits by TBI patients is probably the result of impaired awareness and anosognosia, which is a consequence of their frontal lesions.

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INHERITED PRION DISEASES IN THE BASQUE COUNTRY (SPAIN) EIGHT FAMILIES WITH THE D178N POINT MUTATION IN THE PRION PROTEIN GENE. J. J. Zarranz, A. Digon, B. Atarés, I. Fernández-Manchola, N. Saracibar, L. Galdós, M. Urtasun, A. Ibáñez, E. Lezcano, M. M. Mendibe, F. Velasco, C. Fernandez, Hospital de Cruces (Baracaldo, E)

The Basque Country is an Autonomous Community in the North of Spain (2.100.000 inhab.). In 1993, the Basque Health Department set up a Prion Disease Registry in accord with the European Community recommendations. All neurologists have been encouraged repeatedly to declare their suspected cases to the registry. A reference Neuropathological Unit has been appointed to perform the autopsies. Patients: 27 Patients with all types of prion disease have been declared between January 1993 and December 1999. Of these, 9 cases are hereditary. A further 10 secondary cases have been observed in their families. The diagnosis is probable in 7 patients and definite in 12 (5 through DNA analysis, 2 by neuropathology, 5 with both studies). Results: An autosomal mode of transmission is observed in all the families. Presenting symptoms were psychological changes (8), gait ataxia (7), vision disorders (2) and cognitive im-

pairment (2). Insomnia was observed in 9 patients (7 early in the course of the disease). Other symptoms and signs observed in more than two patients were: dementia, myoclonus, abnormal eye movements, pyramidal signs, tremor and dysautonomia. Polysomnographic recordings showed a progressive disorganization and loss of sleep rhythms. A selective degeneration of medial thalamic nuclei and inferior olive was observed in 3 cases; additional mild cortical, basal ganglia and cerebellar involvement were observed in 2 patients; an extensive spongiform degeneration of the neocortex basal ganglia and cerebellum was present in 1 case. All patients harbored the D178N mutation and all but one were 129MM. Conclusion. Better ascertainment and the provision of diagnostic facilities have enabled the detection in a small community of eight families with the fatal familial insomnia mutation to add to the other 26 pedigrees reported so far in the literature.

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APOPTOSIS AND LIPOPEROXIDATION STIMULATION BY TNF-ALPHA AND IL–6 IN ALZHEIMER'S DISEASE. A Frank, A Hernanz, E Fernandez-Vivancos, E. Toribio, E. Diez-Tejedor, P Barreiro, University Hospital La Paz Universidad Autónoma de Madrid (Madrid, E)

Cytokines like tumor necrosis factor (TNF-alpha), Interleukine–6 (IL–6), soluble FAS receptor, and Maloldialdehid acid (MDA) are markers of oxygen free radicals which can alter neuron lipid membranes leading to apoptosis and necrosis. Neurotrophic growth factor (NGF) protects neurons against TNF-alpha effect. Objectives: To determine concentrations of TNF-alpha, IL–6, soluble FAS receptor and MDA and NGF in cerebral spinal fluid (CSF) samples from Alzheimer's disease (AD) patients. Patients and methods: We studied two groups of people: 17 patients had a diagnosis of "Probable AD" (NINCDS-ADRDA criteria) and 15 persons without any disease affecting central nervous system (CNS) constituted a control group. Age and gender proportion were similar in both groups. CSF was obtained after verbal consent, aliquoted and maintained at –75°C until all quantifications were made. TNF-alpha (R&D Systems), IL–6 (R&D), FAS (R&D) and NGF (Promega) were measured by EIA with commercial kits and MDA by a R&D colorimetric kit. For statistics were used Student's t (parametric data) and Mann-Whitney U test (non-parametric data). Results: CSF cytokine concentrations TNF-alpha ($6,2 \pm 1,4$ vs $1,7 \pm 0,3$ pg / ml, $p < 0,01$) and IL–6 ($1,4 \pm 0,2$ vs $0,7 \pm 0,2$ pg / ml, $p < 0,05$) were much higher in AD patients than in control subjects. No statistical differences for NGF (32 ± 5 vs 37 ± 7 pg / ml) were found. On the other hand, soluble FAS receptor (413 ± 64 vs 287 ± 25 pg / ml, $p < 0,001$) as well as MDA (135 ± 10 vs 105 ± 5 ng / ml, $p < 0,05$) were significatively increased in AD patients. Conclusions: Our results show in CSF of AD patients increased concentrations of cytokines TNF-alpha and IL–6. They could be responsible for apoptosis, as the increase of FAS and MDA indicates. It also indicates an increase of lipoperoxidation in CNS of AD patients. More studies with larger series are necessary to assess these preliminary results.

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IMPACT OF THE INTRODUCTION OF 14–3–3 PROTEIN ASSAY IN THE SURVEILLANCE SYSTEM FOR CREUTZFELDT-JAKOB DISEASE (CJD) IN CATALONIA. R. Sanchez-Valle, A. Saiz, C. Nos, J. Yagüe, T. Ribalta, A. Dominguez, E. Tolosa, F. Graus, Clinic (Barcelona, E)

The 14–3–3 protein assay in CSF has a high positive predictive value for the diagnosis of sporadic CJD, but its influence in CJD surveillance systems is not known. As part of the surveillance a genetic analysis would be indicated to identify genetic cases without known family history. Objective: To compare sporadic CJD frequency in Catalonia, before and after the introduction of 14–3–3 protein assay. To evaluate the use of genetic studies in cases of "apparent" sporadic CJD. Material/Methods: A specific surveillance system for CJD was established in Catalonia in July 1997. The 14–3–3 protein assay in CSF was made in an unique reference laboratory. Cases were classified using Masters' criteria. Genetic study was performed after informed consent. Frequency of sporadic CJD in the study period, August 1997–September 1999 was compared with that notified to the National Register for CJD in the period 1993–1996. Results: From August 1997 to September 1999, 103 CSF were studied. Twenty-five cases of "sporadic" CJD were diagnosed (14 definite, 3 probable, 8 possible) as compared with the 13 cases in the period 93–96. However, genetic analysis done in 21 of 25 cases, identified 2 genetic CJD associated with the E200K mutation in absence of positive familiar history. Thus, the annual incidence rate was 1.75 per million as compared with 0.54 in the previous period. The annual mortality rate (only definite and probable cases) was 1.15 per million as compared with 0.46 ($p< 0.00001$). Conclusions: The 14–3–3 protein assay is a very helpful tool in epidemiological surveillance systems of CJD. Genetic study identifies familial cases presented as sporadic, and it should be performed in any suspected case of prion disease.

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MAJOR HISTOCOMPATIBILITY COMPLEX AND ALZHEIMER'S DISEASE. N.P Patte, B.D Défontaines, M.C Chauffert, F.C Chédan, J. P. B Blériot, C. F. D Degos, Fondation Hôpital Saint-Joseph (Paris, F)

Early clinical diagnosis of late-onset Alzheimer's disease (AD) is not currently possible. So far no specific biological markers of the disease have been identified and the only certain diagnosis is based on anatomical findings. There is a growing body of evidence suggesting that inflammation plays a role in the pathogenesis of AD and that the major histocompatibility complex is involved in this mechanism. Is there a relationship between HLA genotype and AD and, if so, can this contribute to the early diagnosis of AD? Methods: This was a retrospective study of 135 patients: 55 patients with late-onset AD (A), 42 patients with another form of dementia (C) and 39 controls (B). All patients underwent a neurological history and examination, a standardized neuropsychological battery and laboratory tests including ApoE and HLA DQ A1 and B1 genotyping. Results: We found, as in previous studies, that the E4 allele was associated with an increased risk for AD. There was a significantly greater frequency of the HLA DQ A1301 allele in group A compared to group B ($p=0.006$) and also to group C, although the latter was not significant ($p=0.33$). There was also a significantly greater frequency of the HLA DQ B1302 allele in group A compared to groups B ($p=0.011$) and C ($p=0.035$). Discussion: The strong association between HLA DQ B1302 and AD suggests an immunological pathogenesis for AD. HLA DQ B1302 appears to be a sensitive, but not specific, marker for AD. This is another argument supporting the role of inflammation in AD, as found in most previous studies. This raises the question of whether the presence of HLA DQ B1302 predisposes to the disease. Conclusion: The demonstration of a strong association between HLA DQ B1302 and AD offers new avenues of investigation into the pathogenesis, diagnosis and treatment of AD.

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CEREBRAL BLOOD FLOW VOLUME MEASUREMENTS IN DEMENTED PATIENTS WITH ARTERIOSCLEROTIC SUBCORTICAL LEUKOENCEPHALOPATHY AND IN PATIENTS WITH ALZHEIMER'S DISEASE. T. Arida, N. Artemis, C. Papadimitiou, G. Rafou, I. Milonas (Thessaloniki, GR)

Color duplex flowmetry is a reliable method with high reproducibility that permits bedside estimation and monitoring of global cerebral blood flow volume (GCBFV). Recent studies with PET have shown a decrease of regional cerebral blood flow in demented patients. This study was performed in order to estimate GCBFV in demented patients with arteriosclerotic subcortical leukoencephalopathy (ASL) and in patients with Alzheimer's disease (AD). Subjects and methods: GCBFV was measured in 15 patients with ASL and in 15 patients with probable AD, by using a 7.5 MHz linear array transducer. Intravascular flow volume was calculated by multiplying the angle-corrected time-averaged flow velocity by the vessel cross-sectional area. GCBFV was assessed as the sum of flow volumes in both internal carotid and vertebral arteries. The results were compared with a group of 15 age matched healthy subjects. Results: A significant reduction of GCBFV was observed in patients with ASL compared to controls and patients with AD (427 ± 107.4 versus 637 ± 89.8, $p< 0.01$ and 575 ± 72 ml/min, $p< 0,01$). Although patients with AD were found to have lower GCBFV than controls, this difference was not statistically significant ($p> 0,1$). Conclusions: In our study a significant reduction of GCBFV was observed in demented patients with arteriosclerotic subcortical leukoencephalopathy, which was not found in patients with Alzheimer's disease. Although more studies are required to confirm these results, color duplex flowmetry could be a promising additional new tool in differential diagnosis in demented patients.

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TRI-AL STUDY. A SPANISH EXPERIENCE OF DETECTION OF NEW CASES OF DEMENTIA AND ALZHEIMER DISEASE IN A PRIMARY CARE SETTING. F. Bermejo, J. Peña, R. Blesa, M. Madrigal, Hospital U. "Doce de Octobre", Hospital del Mar, Hospital Clinic, Dpt Medicine. Pfizer (Madrid, Barcelona, E)

Mild cases of dementia and Alzheimer disease (AD) may be underdiagnosed in primary care (PC). A failure to obtain an early diagnosis of AD may cause unnecessary distress and potentially complicated situations. The main objective of the TRI-AL study was to promote the diagnosis of AD and to detect new mild and moderate cases of AD in PC jointly with specialists. The secondary objective was to analyse the sociodemographic data of patients with dementia and AD in this setting. Population and Methods: A two step cross-sectional study was designed. The first phase was performed by PC physicians who screened the patients with clinical cognitive decline without previous diagnosis of dementia, aged 65 years and over, and accompanied by a proxy during their visit

to a PC center. PC physicians performed to these patients a screening protocol (Spanish version of Foltein's MMSE, clock drawing test (CDT), FAQ scale of Pfeffer) and a sociodemographic questionnaire. The positive cases after this screening (patients who obtained < 27 points in MMSE, 0–6 points in CDT and > 5 in the FAQ) were reviewed in the second phase by neurologists who did the syndromic and etiologic diagnosis of dementia and AD, according to standardised international criteria (mainly DSM-IV and NINCDS-ADRDA criteria). Results: 267 family physicians screened 1,718 patients and 51 related neurologists performed the final diagnoses. Of the 1,718 screened subjects, 891 were positive in the first phase and and 636 were diagnosed as demented by neurologists. 560 patients had AD (NINCDS-ADRDA criteria) and 76 suffered from others types of dementia. A substantial proportion of positive cases, 255, had another diagnosis or they did not fit with the inclusion and exclusion criteria of the study.

Discussion: TRI-AL study demonstrated that the most common cause of dementia in primary care setting in Spain is AD. The study also pointed out that the collaboration between specialists and primary care physicians could facilitate the detection of new AD and dementia cases in a primary care setting. The TRI-AL Study was sponsored by Pfizer Spain

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POSTERIOR TRUNCAL TACTILE EXTINCTION IN ANTERIORLY FLEXED PARKINSONIAN (PD) PATIENTS. E. Linetsky, A. Reches, K. M. Heilman, E. Wertman, Hadassah University Hospital Ein-Kerem, University of Florida, Ezrat-Nashim Hospital (Jerusalem, IL; Gainesville FL, USA)

Objective: To learn if there is anterior versus posterior attentional bias in PD patients with flexed posture. Background: A sensory attentional bias can be associated with motor-intentional bias and vice versa. For example, patients with motor-intentional biases such as a left lateral gaze paresis often have associated attentional biases, such as left-sided extinction to simultaneous stimuli. In addition, hemispatial attentional deficit (e. g. in neglect) associated with postural deviation away from neglected hemispace. In this study we wanted to learn if PD patients with flexed posture have an anterior attentional bias. Patients and Methods: 10 flexed PD patients (mean age 67.5 years, SD 4.7, 9 males and 1 female, disease duration 12.0 years, SD 3.91, UPDRS mean 71, SD 18.72), were compared to 10 non flexed PD patients (mean age 65.5 years, SD 7,57, 9 males and 1 female, disease duration 10.4 years, SD 1.77, UPDRS mean 49.9, SD 10.75) and to 10 non flexed control patients without any neurological diseases (mean age 66.3 years, SD 5.57, 9 males and 1 female). Subjects were seated with eyes closed and were presented with 8 anterior, 8 posterior single stimulations and 8 double simultaneous stimuli (DSS) in a randomized order. All stimuli were soft tactile, delivered by the examiner's finger at the midsagittal plain anteriorly – in the region of manubrium sterni and posteriorly at the level of T3. Results: Subjects in all 3 groups identified all the single stimuli both anteriorly and posteriorly. Flexed PD patients add extinction of posterior stimulus on 56.25% (SD 10.26%) of the trials during DSS. The former was significantly different than both non flexed PD subjects who were unaware of posterior stimuli on only 6.25% (SD 6.59%) of DSS trials and the normal controls who had extinction on 5,0% (SD 6,46%) of DSS. We also found that the degree of posterior tactile extinction correlated with the degree of flexion and UPDRS. Conclusions: Anteriorly flexed PD patients have an anterior attentional bias or posterior inattention. The influence of this bias on these patients' posture and gait remains to be determined.

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MAGNETIC RESONANCE IMAGING (MRI) IN SPORADIC CREUTZFELDT-JAKOB DISEASE SUBTYPE MV2. A. Schröter, I. Zerr, M. Finkenstaedt, S. Arlt, C. Jacobi, B. J. Steinhoff, W. J. Schulz-Schaeffer, O. Windl, H. A. Kretzschmar, S. Poser, Neurology, University of Göttingen, MR/CT Institute Hamburg, Neurophysiology, Univ. of Göttingen, Neuropathology, Univ. of Göttingen (Göttingen, Hamburg, D)

Creutzfeldt-Jakob disease (CJD) is a rare transmissible brain disease with a lethal outcome within usually a few months, which typically affects elderly people. Clinically it is characterized by a rapidly progressive dementia and bodily deterioration with neurological symptoms. Usually typical changes were observed in cerebrospinal fluid (CSF, detection of protein 14–3–3) and EEG (periodic sharp wave complexes). MRI shows bilateral symmetric hyperintense alterations in basal ganglia on T2-weighted image. The diagnostic criteria do not content MRI findings so far.

Recently Parchi et al. (Ann Neurol 1999) proposed a new classification of sporadic CJD based on the genotype at codon 129 (polymorphism of methionine and valine, MM, MV, VV) of the prion protein gene (PRNP) and physicochemical properties of protease resistent prion protein (PrPSc, type 1 and 2). He differentiated six distinct clinicopathological subtypes of CJD. Typical MRI changes were found in almost 68% of the two most common subtypes MM1 and VV2. In those cases the CSF analysis has the greatest diagnostic value (our unpublished data). In the rare MV2 subtype with a frequency of 9% of CJD EEG and CSF findings are less reliable.

Therefore we studied clinical features and MRI findings in 10 patients of the MV2 subtype. 8 out of 9 patients (89%) showed hyperintense abnormalities in basal ganglia on T2-weighted MRI, whereas detection of protein 14–3–3 was possible in only 3 out of 10 patients (30%), and none out of 10 patients showed a typical EEG.

We conclude that MRI is a very important investigation in this MV2 subtype and can be helpful, especially in the differential diagnosis of CJD with a long disease duration, ataxia and lack of typical changes in CSF and EEG.

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PATTERNS OF MEMORY IMPAIRMENT AND APOLIPOPROTEIN GENOTYPE IN PERSON WITH ALZHEIMER'S DISEASE. E Luczywek, A Pfeffer, A Nowicka, M Styczynska, B Wasiak, K Czyzewski, M Barcikowska, Neurosurgical Dept. CMDiK PAN, Neurological Dept CMDiK PAN, Nencki Inst. of Exp. Biol. PAN, Neurological Dept. CMDiK PAN/MSWiA (Warsaw, PL)

The ApoE e4 allele, a well-etablished risk factor for Alzheimer's Disease (AD), is one of factors contributing to the heterogenity among AD patients. Some studies suggest that ApoE e4 allele in AD might be associated with severe impairment of memory and learning ability, as it significantly enhances the hippocampal atrophy. The aim of this study was to test the possible relationship between patterns of cognitive deficits – especially impairment of memory processes – and ApoE genotype in patients with AD.

Fifty seven right-handed subjects (31 males and 26 females) were tested in this study. The age of subjects ranged from 50 to 79, the education lasted from 11 to 16 years. All subjects were diagnosed as probable AD patients on the basis of DSM IV and NINCDS-ADRDA criteria. Each subject was examined for: 1/ ApoE genotype, 2/ general level of mental activity (GDS and MMSE), 3/4 neuropsychological evaluation of cognitive processes, using full test battery. 37 patients had at least one of ApoE e4 allele (e 2/4, 3/4 and 4/4) and 20 patients had none of ApoE 4 allele (e 2/3 and 3/3). The group of tested subjects were subdivided into 2 groups. The first group was constituted by 31 patients with 3 stage (according to GDS) of mental activity. Twenty six patients with 4 stage were included into the second group. Those subgroups did not significantly differ if age, education, gender or ApoE allele were considered. Experimental data were normalized and then analyzed using a statistical package SPSS/PC+. The analysis of variance showed that the type of test, stage of disease and two-way interaction ApoE x type of test were highly significant ($P < 0.0001$). Some results were obvious and not surprising (e. g. that results of patients with 4 stage were much worse than results of patients with stage 3). It turned out that the best results were obtained by our patients in naming tests, the worst – in learning test with distraction. Patients with ApoE e4 performed better than patients with none ApoE e4 in the Rey's test, in the similarity test and in the test which required repeating numbers starting from the last one. The differences between the subgroups of patients with different ApoE alleles were confirmed by different distributions of correlation.

All statistical analyses were repeated for more homogenous group of patients (only with stage 3). The pattern of results resembled the previous one (i. e. better performance in the same tests) with one exception: additionally, in delayed recall test patients with none ApoE e4 performed much better that ApoE e4. Our results showed that some cognitive processes depended on ApoE genotype. Patients with ApoE e3 genotype had less severe deficits in delayed recall of new information. On the other hand, working memory appeared to be less affected in patients with ApoE e4 genotype. Independent on genotype, both groups showed similar impairment of learning ability without deficits in remote memory.

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EMOTIONAL HYPERGRAPHIA AND LOSS OF EMOTIONAL SPEECH WITH PURE CINGULATE GYRUS LESION. A. Carota, N. Afsar, J-M. Annoni, A. Nicola, F. Staub, S. Gramigna, P. Combremont, J. Bogousslavsky, CHUV (Lausanne, CH)

Introduction: Hypergraphia has been infrequently reported with stroke, usually with right hemispheral lesion.

Case report: A 75-year-old male right-handed (notion of left-handedness only for writing in the childhood, Oldfield lateralization index 100% right) university professor was admitted with acute behavioral and speech disturbances. Severe abulia and akinesia, marked verbal aspontaneity and hypophonia, intermittent utilization behavior, left grasping, left visual and motor neglect were present. Language examination showed transient word naming difficulty. Diffusion-weighted MRI images showed an ischemic lesion confined to the right cingulate cortex. In the following weeks he spent most of time writing, provid-

ing written answers to oral questions. Words and sentences were sometimes, but not always, associated with perseverations and intrusions. He used to write in four different languages about daily events, his health, artistic and scientific subjects, fragments of visitors' conversations. He wrote that he felt "mental emptiness" and "lack of impulsion". In one day he filled out five sheets with the words" depression " and" suicide ". He was not able to express those feelings verbally or with facial expression. Questioned about the reason why, he wrote "the black hole". At 2 weeks MMSE score was 22/30. Abulia and anxiety but not depression were significantly increased at standardized questionnaires. Hypophonia and verbal output significantly improved together with decreasing hypergraphia over the following 4 weeks.

Conclusions: Cingulate cortex may be involved in vocalizations associated with expressing internal states. Its lesion is known to cause decrease self-awareness with depression, and impaired motor initiation. In our patient, with an ischemic lesion of the right cingulate gyrus, hyperactive meaningful writing contrasted with hypoactive verbal and emotional expression. While in patients with right side lesion, hypergraphia has been considered void of content, this was not the case here, with preserved verbal and emotional communication through writing. We speculate that this observed dissociation may reflect the existence of two partially independent systems for oral and written expression of emotions and ideas.

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POLYMORPHISM AT CODON 129 OF THE PRION PROTEIN GENE IS NOT ASSOCIATED WITH SPORADIC ALZHEIMER'S DISEASE. O. Combarros, M. Sànches-Guerra, J. Llorca, A. Alvàrez-Arcaya, J. Berciano, J. M. Polo, Univ. Hospital Marques de Valdecilla, Univ. of Cantabria School of Medicine (Santander, E)

Background: An association between cognitive performance in the elderly and variability (Methionine or Valine alleles) in the codon 129 of the prion protein gene (PRNP) has been recently described. Objective: We evaluated this polymorphism in a case-control analysis comparing Alzheimer's disease (AD) with cognitively intact individuals. Methods: The 129 PRNP polymorphism and the apoE genotype were studied in 278 AD patients (67 % females; mean age 75.3 ± 9.2 years; range 50–98 years) who met the NINCDS/ADRDA criteria for probable AD, and 268 control subjects (70 % females; mean age 79.9 ± 7.8 years; range 63–98 years) with Mini Mental State Examination scores greater than 28, which were verified by at least one subsequent annual following-up assessment. Results: The odds ratios (OR) for developing AD were calculated as 0.94 (95 % CI = 0.64–1.39) in homozygotes for the Met allele, and 0.68 (95 % CI = 0.39–1.18) in homozygotes for the Val allele. Moreover, when AD was categoryzed in early-onset (< 70 years) and late-onset (370 years) subsets, also no increased risk of AD was observed in homozygotes for either the Met or Val alleles. After stratifying by apoE carrier status, even in the presence of apoE e4 allele there was no association between homozygosity in the 129 PRNP and AD: the OR for the Met/Met genotype was 1.03 (95 % CI = 0.50–2.14) and for the Val/Val genotype was 1.15 (95 % CI = 0.35–4.01). Conclusion: Homozygosity in the 129 PRNP polymorphism does not contribute to AD susceptibility, either through independent association or through interaction with the existing apoE e4 allele risk.

Epilepsy

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THE LATERALIZING VALUE OF THE "FIGURE OF FOUR" AND "ASYMMETRIC ENDING OF CLONIC JERKING" IN SECONDARILY GENERALIZED TONIC-CLONIC SEIZURES. H. Yilmaz, G. Groppel, C. Baumgartner, Celal Bayar Faculty of Medicine (Izmir, TR; Vienna, A)

A striking asymmetry of limb posture may occur during secondary generalization of partial seizures, so that one elbow is extended while the other is flexed during the tonic phase. It is called the "figure of four" and proposed that the extended arm is contralateral to seizure onset. "Asymmetric ending of clonic jerking" is lateralizing sign which was not defined before. So we decid to determine the lateralizing value of these two signs in the Secondarily Generalized Tonic-Clonic seizures (SGTCSs). Methods: Blinded to clinical details, we made a retrospective videotape analysis of 149 SGTCSs in 80 patients with 62 temporal lobe epilepsy (TLE), 18 extratemporal lobe epilepsy (ETLE). We reviewed videotapes with attention paid to "figure of four" and "asymmetric ending of the clonic jerking". Results: "figure of four" occurred in 60.4 % of all seizures with a positive predictive value (PPV) for the sign being contralateral to seizure onset 58.4 %, in 53.7 % of TLE (PPV 50.9 %), in 78 % of extratemporal lobe seizures (PPV 78 %); "asymmetric ending of clonic jerking" occurred in 74.5 % of all seizures with a PPV for the sign being ipsilateral to seizure onset 71.1 %, in 67.6 % of TLE (PPV 63.9 %), in 92.7 % of ETLE (PPV 90.2 %); these two signs were seen together adding to a successful clinical lateralization in 52.3 % of all seizures, in 45.3 % of TLE, in 70.7 % of ETLE. Conclusions: Video-EEG monitoring has made possible characterization of ictal behaviour and correlation with cerebral regions generating the epileptic discharge. Since surgical treatment is a therapeutical alternative in patients with intractable seizures, localization and lateralization of seizure origin are the principal aims in the preoperative assessment. Lateralizing signs can assist in the evaluation of patients for seizure surgery, in particular "figure of four" and "asymmetric ending of clonic jerking" may provide additional lateralizing information in the SGTCSs with medically refractory localization related epilepsy.

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LOCALIZING FINDINGS IN THE SECONDARILY GENERALIZED TONIC-CLONIC SEIZURES: A VIDEOTAPE ANALYSIS. H. Yilmaz, G. Groppel, C. Baumgartner, Celal Bayar Faculty of Medicine (Izmir, TR; Vienna, A)

The clinical characteristics of epileptic seizures have an increasing importance in determining the lateralization and localization of epileptogenic foci. Combined prolonged video-EEG monitoring has improved the understanding of ictal characteristics and their relation to the site of electrical discharge in the brain. With this study, we intend to determine the localizing values of "the duration of the antecedent seizure phase" and "starting time of the version" in the secondarily generalized tonic-clonic seizures (SGTCSs). Methods: Blinded to clinical details, we made a retrospective videotape analysis of 149 SGTCSs in 80 patients with 62 temporal lobe epilepsy (TLE), 18 extratemporal lobe epilepsy (ETLE). All SGTS were classified into two periods, namely the antecendent seizure and the generalized tonic-clonic phase. We reviewed videotapes with attention paid to "the duration of the antecedent seizure phase" and "starting time of the version". Results: "The duration of the antecedent seizure phase" of ETLE was significantly shorter than that of TLE ($p=0.025$), "the onset time of the version" in extra-temporal localization shorter than temporal localization, and this difference was statistically significant (average 15.3 seconds in extra-temporal localization versus 23.7 seconds in temporal localization; independent t test, $p< 0.05$). Conclusions: Seizure semiology is very useful in the diagnosis and classification of seizures. Prolonged video-EEG monitoring has made possible characterization of ictal behaviour and correlation with cerebral regions generating the epileptic discharge. With this study, we reached two important conclusions in localization related SGTCS: First: version which occurred earlier in extra-temporal localized epilepsies than temporal localized epilepsies supported the hypothesis which the frontal lobe was involved in generating version. Second: the duration of the antecedent seizure phase in ETLE is shorter than that of TLE, which meant that generalization occurred more rapidly in ETLE.

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POLYMORPHISM OF NONCONVULSIVE STATUS EPILEPTICUS AND PROLONGED SEIZURES IN EPILEPSY ASSOCIATED WITH RING CHROMOSOME 20. P. Masnou, C. Hort-Legrand, L. Nahum-Moscovici, C. Leonard, CHU de Bicêtre, University Paris-Sud, F)

Nonconvulsive status epilepticus (NCSE) with recurrent prolonged confessional states lasting from several minutes to 1 hour is the main clinical feature of epilepsy associated with ring chromosome 20. Electroclinical characteristics have been described but several features of prolonged seizures and NCSE occurring in the same patient have been rarely presented. This 26-year-old girl began to have seizures at the age of 6. She experienced motor seizures with crying, fearful expression, and upper limb extension (1–3 a day during wakefulness or sleep). Antiepileptic drugs had no efficacy and these short seizures were associated with multiple prolonged seizures or NCSE lasting from few minutes to 1 hour with different aspects: the first pattern is stereotyped and consists in loss of consciousness associated with asymmetrical and asynchronous myoclonic jerks affecting the face and the limbs lasting 1 hour. The second type which is not stereotyped, looks like pseudo-seizures, with subtle mental impairment during several minutes, and sometimes associated with short motor seizures. Ictal EEG showed myoclonic absence status (3-Hz spikes-and-waves) during the type 1 NCSE. During the type 2 NCSE, recurrent or prolonged seizures with a fronto-temporal origin were recorded. Interictal EEG showed a 10-Hz alpha wave rhythm with frequent irregular slow waves or spikes without focalisation. Cytogenetic study revealed the presence of ring chromosome in 37 % of the lymphocytes studied. Cerebral MRI was normal. The IQ (WISC-R) was 69; verbal IQ 68; performance IQ 71. This case illustrates the variability of the NCSE that may be mistaken for abnormal behaviour. Because of the frequent paroxysmal activities it may be difficult to differentiate ictal from interictal activity without a careful clinical examination during the EEG recording.

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ATTRIBUTION STYLE, DEPRESSION AND BEHAVIORAL PROBLEMS IN CHILDREN WITH EPILEPSY. K. Gebauer, D. Mitrovic, K. Bozic, A. Kelemen, B. Bukurov, Institute of Neurology (Novi Sad, YU)

Despite the wealth of evidence showing the comorbidity of epilepsy with various forms of psychopathology, there has been little investigation of children with epilepsy whose emotional and behavioral problems significantly affect their lives. Attribution style (AS) is one of the key variables in the development of self-respect in children, being either positive or negative. AS was measured by the Children's Attributional Style Questionnaire (CASQ) (Seligman), depression was measured by the Center for Epidemiological Studies – Depression Child (CES-DC) and behavior was measured by the Child Behavior Check List (CBCL) (Achenbach). The aim of the study was to investigate the interrelations between type of epilepsy, seizure frequency, duration of remission, depressive mood, children behavior and to determine if and how epilepsy can effect the change in attribution style. A sample of 61 children with definite epileptic syndrome, according to the criteria of ILAE (21 with temporal lobe epilepsy (TLE), 15 with childhood absence epilepsy (CAE), 14 with juvenile myoclonic epilepsy (JME) and 14 children with benign childhood epilepsy with centrotemporal spikes (BECT)), of both sexes, aged 4–18, with normal intellectual functions was divided into two groups: group A: one or more seizures within the last six months; group B: no seizures within 6 months. Peers free of epilepsy were used as controls. RESULTS: Compared to the controls, children with epilepsy showed significantly increased depression scores, emotional and behavioral dysfunction and lower score on the scale of AS. Among the children with JME, BECT and CAE there was no group difference in their psychopathologic symptomatology although patients with JME reported more often emotional and behavioral dysfunction. However CASQ showed group difference. Emotional impairment was a major problem in TLE because 35 % of them scored in the depressive range and they were most pessimistic (40th percentile). The occurrence of seizures, even at low frequencies and duration of remission is associated with depressive mood, behavioral dysfunction and pessimism. All of the scores: CBCL, CES-DC and CASQ showed significant difference between group A and B. CONCLUSION: The results suggest that psychiatric disorders among epileptic children are more common than we would expect, but appear to be overlooked. The results imply the need for appropriate approach in preventing negative influence on children's life.

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MEMORY AND ATTENTION DEFICIT IN CHILDREN WITH EPILEPSY. S. Rudic, K. Gebauer, K. Vlajkovic, K. Bozic, S. Djordjevic, S. Sekulic, Institute of Neurology (Novi Sad, YU)

Cognitive function in children with epilepsy may be affected by brain damage, age of onset, frequency and severity of seizures, seizure type and antiepileptic medication. These factors are not independent variables and their relative importance is difficult to determine, particularly in the individual child. Knowledge is acquired through memory and attention. These processes are the most important variables of cognitive activity. Methods: We evaluated 122 epileptic children, age 4 to 18, with definite epileptic syndrome, according to the criteria of ILAE: 44 with temporal lobe epilepsy (TLE), 8 with occipital lobe epilepsy (OLE), 12 with frontal lobe epilepsy (FLE), 22 with benign childhood epilepsy with centrotemporal spike (BECT), 18 with childhood absence epilepsy (CAE), 14 with juvenile myoclonic epilepsy (JME) and 6 with other idiopathic generalized epilepsy (OIGE). We studied intelligence level (Wechsler Intelligence Scale for Children (WISC III), memory disturbance (Wechsler's Scale (WS), Auditory-Verbal Learning Test Rey (AVLTR), Rey-Ostericht Complex Figure (ROCF) and attention skills. Attention skills: focus on task, concentration (to stay on 'task'), distractibility (reaction to distracting stimuli) and vigilance were descriptively tested during clinical observation. RESULTS: 3.2 % of patients had mental deficiency (mostly from TLE group), 9.8 % had borderline intelligence (70–80), 19.8 % was in lower range of normal intelligence (80–90), only 4.9 % had IQ > 110. Short-term memory disturbance (WS) occurred in 14.7 % of patients and no difference was detected between the groups with different type of epilepsy. 52.4 % of patients showed long-term memory disturbance (AVLTR) in which the group with FLE was significantly impaired. In ROCF performance, 68.8 % of children showed lower score and among them 13.1 % was in the range < 10th percentile (the best results were in groups with CAE, JME and OIGE). Children's ability to focus on the task was disturbed in 11.4 % of cases, concentration in 49.2 %, distractibility in 47.5 % and vigilance was disturbed in 42.6 %. Although the relation remains to be tested directly, it is likely that limited attention and poor long-term memory are causally related. Likewise in AVLTR and ROCF tests, the same groups (TLE, FLE, BECT) were more affected. Exception was in ROCF, where only the group with OLE was significantly impaired. CONCLUSION: The results suggest that cognitive impairments in children with epilepsy are very common. There is a need for long-term neuropsychological monitoring in order to identify the subgroup of children that remain at significant risk of cognitive morbidity.

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A STUDY OF A LARGE BRITISH FAMILY WITH EPILEPSY. A. Siddiqui, M. R. Johnson, P. H. Dixon, L. Kinton, J. Duncan, M. Koepp, S. D. Shorvon, J. W. A. Sander, M. Gardiner, N. W. Wood, Institute of Neurology, The National Society for Epilepsy, University College London (London, UK)

Background: Family studies are providing fundamental insights into the molecular pathogenesis of epilepsy. All of the four idiopathic epilepsy genes identified to date were found by linkage analysis in families with epilepsy. Two types of epilepsy families are observed: those where each affected member of the family has the same syndrome and inheritance is simple Mendelian e. g. Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE) and those where each affected family member manifests one of several possible syndromes and the pattern of inheritance is complex e. g. Generalised epilepsy with febrile seizures plus (GEFS plus). Identification of the loci in epilepsies manifesting complex inheritance is possible if a single culprit variant allele segregates through the pedigree. The first step in such an analysis is the identification of large pedigrees and clinical characterisation of epilepsy phenotypes within the family. Methods: A large family from North London with epilepsy has been identified. There are 12 affected members spanning over 5 generations. All family members underwent careful clinical evaluation using a validated seizure questionnaire. Linkage analysis is being undertaken using a standard methods (predicted lod score > 4), using a panel of 420 fluorescently labelled microsatellite markers (ABI). Results: 22 family members were interviewed. The 12 affected family members manifest a range of epilepsy phenotypes including 4 with febrile seizures alone, 2 with febrile seizures and generalised epilepsy, 1 with febrile seizures and partial epilepsy, 1 with partial epilepsy and 4 with generalised epilepsy. Conclusions: This family resemble the GEFS plus phenotype in that affected individuals manifest a variety of childhood onset epilepsy phenotypes. However, febrile seizures in this family are less common than in previously reported GEFS plus pedigrees. In addition, febrile seizures cease before the age of 6. Such families are important resources for the identification of genes relevant to the epilepsies.

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COMPLEX PARTIAL SEIZURES IN LANGUAGE-INDUCED EPILEPSY. T. Etgen, R. Dux, B. Tegtmeyer, V. Vogt, R. Kornblum, Technische Universität, Knappschaftskrankenhaus, Martin-Luther-Krankenhaus (München, Bottrop, Bochum, D)

Among the rare form of reflex epilepsies in which seizures are reliably provoked by certain stimuli the so called "language-induced epilepsy" has been described only four times. Case report: A 61-year-old right-handed male was admitted after clumsiness of his right hand followed by an unconsciousness had appeared. Apart from smoking his previous medical history and his family history was non-contributory. On examination a tongue bite and loss of urine were noticed and he initially presented slight slowness of movement and responses, otherwise no physical or neurological abnormalities could be detected. In the following days he had several episodes of impaired consciousness which could be triggered by starting a conversation with him: The very start of a dialogue with him was unremarkable since he was fully alert and completely orientated, but after a few sentences he suddenly stopped talking, muttered some sounds and showed an impaired consciousness. With a delay of some seconds he also started to turn his head slightly to the right side and showed clonic convulsions of the right half of his face and his right thumb. Without any medication this stopped after one to two minutes where on examination a mild right-sided hemiparesis with a positive Babinski reflex and slight psychomotor slowing was found. However, other activities involving movements of facial, jaw or throat muscles failed to induce seizures. Furthermore, other aspects of language like reading silently or aloud, calculating or writing did not result in ictal elements. Even the motor aspects of articulation by asking to repeat single words or nonsense syllables were not able to produce EEG or behavioral ictal phenomena. Additional tests like laboratory tests, lumbar puncture, ECG, chest x-ray, abdominal ultrasound, CT brainscan and cranial MRI revealed no relevant pathologic findings. During his 24-hours-EEG he experienced several episodes of those described above and it demonstrated an intermittent left-sided theta-delta rhythm and, synchronized with those epsiodes, also showed left-sided rhythmic 1–2 cps sharp activity. Everytime the patient attempted to speak rhythmic 1–2 cps sharp activity appeared within the left temporal-parietal theta-delta rhythm. On administration of phenytoin no further episodes could be triggered and no epileptic discharges could be recorded in subsequent EEG's although the left-sided slow rhythm persisted. This is the first case in which speaking induced complex partial seizures with epileptic discharges in the dominant hemisphere. Referring to the controversy in literature about the terminology of language-in-

duced epilepsy we suggest using language-induced epilepsy as a collective term as in our case only one part of language (speaking) was able to provoke seizures.

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LATE REVELATION OF A HEMIMEGALENCEPHALY. P. Latour, J. D. Albert, D. Taussig, M. Coustans, A. Biraben, J. Y. Goas, M. Verin, University Hospital Pontchaillou (Rennes, F)

BACKGROUND: Hemimegalencephaly (HME) is a congenital brain malformation characterised by an entire cerebral hemisphere hypertrophy with ipsilateral ventriculomegaly.

CASE REPORT: We report a 26-year-old patient with a normal psychomotor development (he graduated) and without medical history or familial history of neurological diseases until his first symptom. His neurological history began in March 1999 with two sudden episodes of paresis and hypoesthesia of his right arm that lasted a few days. On June 16th he noticed a right hemiparesis when he woke up. Hospitalized one day after due to his persistent weakness, the computed tomography (CT) scan demonstrated a pathological left hemisphere's white matter. Analyses of CSF and biochemical findings were within the normal range. Later he was admitted to our department and his neurological status improved with only a weakness of the right arm and a right pyramidal syndrome. A left macrocrania was noted. Magnetic resonance imaging (MRI) demonstrated overgrowth of the left hemisphere with abnormal underlying white matter, ventriculomegaly, normal underlying gray matter and normal architecture of the cortex. This morphological spectrum evoked a HME. Electroencephalography recordings showed an "alpha-like" activity, non-reactive, in the left central and parietal regions with some spikes. The diagnosis was a partial status epilepticus followed by post-ictal weakness. The evolution has been marked by a recurrence of his paresthesias and weakness of the right side of the body despite a one month treatment with valproate. After several drug trials, the patient has been treated with gabapentine for 6 months with no recurrence of seizures. A mild weakness of the left hand persisted.

DISCUSSION: The HME clinical expression can vary widely. The usual presentation is mental retardation and controlateral hemiparesis generally associated with early refractory epilepsy. Few patients in the literature have minimal neurological symptoms with non-refractory epilepsy or without any epilepsy, but these signs always appeared before the end of the adolescence.

CONCLUSION: Our patient has the mildest clinical features of HME reported in the literature with normal development and drug sensitive epilepsy. No other case of HME revealed that late in life has ever been reported.

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SAFE USE OF A CARDIAC PACEMAKER IN A PATIENT TREATED BY THE VAGUS NERVE STIMULATION (VNS) FOR INTRACTABLE EPILEPSY. R. Ristanovic, R. Billhardt, D. Bergen, Rush Presbyterian St. Luke's Medical Center (Chicago, USA)

VNS is a novel and safe non-pharmacological treatment of epilepsy. It involves implantation of a battery driven generator into a subcutaneous pouch below the left clavicle and its connection via lead wires to electrodes wrapped around the left vagus nerve in the neck. Prior to this case, it was not known how safe would be the simultaneous use of a cardiac pacemaker in a patient already receiving VNS. Rationale: We present a 30 year old patient who was treated with VNS for intractable epilepsy and required concurrent implantation of a cardiac pacemaker. Case History: By the end of 1996 the patient's seizures increased in intensity and duration and were observed to be accompanied by cyanosis. Differential diagnosis of an ictal/postictal apnea versus ictal sinus arrest was entertained. This concern prompted admission to the Epilepsy Monitoring Unit. During hospitalization he had daily 24-hour Holter electrocardiograms (EKGs) performed with the stimulator on and off. EKG during one of the prolonged seizures showed sinus tachycardia with occasional single premature ventricular contractions (PVC's). Interictal EKGs demonstrated primarily sinus bradyarrhythmia with sinus pauses of 3 seconds when the stimulator was off, and a 3.5 seconds pause when the stimulator was on. The patient was asymptomatic during these pauses. EKG monitoring also captured periods of intermittent left bundle brunch block (LBBB) of conduction. It was decided to deactivate VNS and maximize medical treatment of seizures, while monitoring seizure frequency and performing monthly Holter EKGs on outpatient basis. Five months later while bowling, the patient became diaphoretic, lightheaded, dizzy, and ashen in appearance. The symptoms abated after about 30 minutes of resting. The cardiologist recommended placement of a permanent dual chamber (atrial and ventricular) pacemaker in order to prevent pre-syncopal episodes. In June of 1997 a Medtronic Thera DRi pacemaker was implanted and set in the dual chamber pacing mode. Unfortunately, seizures had been gradually increasing in severity and frequency, and reactivation of the VNS became necessary. The re-initiation of the VNS required cardiac monitoring to ensure that the cardiac pacemaker was not affected by the VNS generator's output. In August of 1997, prior to VNS re-initiation, cardiac monitor showed primarily sinus rhythm with occasional atrial pacing and appropriate sensing of the pacemaker. Manual activation of the VNS by a magnet did not influence the cardiac pacemaker, which was being checked at the same time via telemetry. Likewise, telemetry checking of the cardiac pacemaker did not influence VNS. The patient was kept for 24 hours in the cardiac monitoring unit, during which time no bradyarrhythmias occurred and normal sensing and pacing functions continued. Since then he has had no pre-syncopal or syncopal events and seizure frequency has slowly continued to improve. Conclusions: To our knowledge this is the first reported case documenting the safety of simultaneous VNS and cardiac pacing.

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A FAMILY WITH HEREDITARY SPASTIC PARAPARESIS AND EPILEPSY. V. Golzi, L. Guidolin, P. Canovaro, L. Ferini-Strambi, S. Smirne, S.Raffaele (Milano, I)

Familial Spastic Paraparesis (FSP) is a degenerative disorder of the central motor system characterised by progressive spasticity of the lower limbs. Pure and complicated forms have been described. The latter are rare and usually transmitted in an autosomal recessive pattern. Few cases of complicated HSP associated with epilepsy have been reported in the literature. Here we report a family coming from Southern Italy in which 2 members, a brother and a sister are affected by complicated HSP. All 5 living members of the pedigree underwent neurological exam, EEG recordings, genetic analysis and the 2 of them affected, also neuropsychological test such as Wechsler Adult Intelligence Scale (WAIS-R) to determine verbal and non-verbal IQs. (IQTotal score of patient 1= 74, IQ total score of patient 2= 71). Both of them were diagnosed HSP when they were 15 years old and the girl, the older one, developed complex partial seizures when she was 24 with EEG evidence of isolated right temporal sharp waves and diffuse sharp waves during hyperventilation. The boy, who is 23, had no clinical evidence of seizures; his EEG showed bilateral fronto-central paroxystic activity. In our patients the association of HSP and epilepsy seems to be age related. Moreover the emergence of epilepsy should be considered as a possible risk in complicated HSP, by means of EEG recordings, even in the absence of clinical manifestation at the beginning of the disease.

General neurology

P659
SPECIFICITY OF THE NEUROLOGIST APPROACH OF CLINICAL GAIT ANALYSIS. E. Watelain, J. Froger, A. Thévenon, M. Rousseaux, LAMIH, CHRU, CHRU Hôpital Swynghedauw (Valenciennes, Lille, F)

Clinical and functional gait analysis is widely used by different therapists dealing with hemiplegic patients. The aim of this study was to examine the specificity of neurologists (Ns) gait analysis strategies, as compared with those of other therapists from rehabilitation medicine (Rs) and physiotherapy (Ps). Knowledge of these strategies is not only important for patients' treatment, but also for training of young practitioners. Knowledge sampling was carried out from 5 Ns, 5 Rs and 5 Ps, who were asked to study a videotape of the patients' gait, followed by a semi-directed interview. Specialists were aged from 39 to 58 years, and had a 11 to 38 years experience in the treatment of stroke patients. The population consisted of 6 male hemiplegic patients, aged 37 to 58, who had suffered a cerebrovascular accident at least six months before. Results. Fifty-nine common indicators, or gait disorders, were identified from the interviews and grouped in five categories: 'localised' indicators (e. g. a joint); 'regional' indicators (e. g. one limb); 'step parameter' indicators (temporal and stride characteristics); 'overall' indicators (general descriptions of patient behaviour); 'interpretative' indicators (mechanisms that underlie disorders). A cluster analysis made with all indicators highlighted that each professional speciality had a specific strategy of evaluation. The ANOVA made with each category of indicators also indicated typical strategies. The most divergent approaches existed between Ns and Ps, and the most similar between Ps and Rs. The Ns concentrated on finding the pathophysiological origin of the disorders and associating them with lesions in the central nervous system. To do so, they used more 'interpretative' indicators and fewer 'localised' and 'general' indicators. The Rs used more 'step' indicators, which could be related to their interest in describing patient incapacity. Their analyses were first descriptive, then biomechanical. The Ps were essentially descriptive, with less interest in 'interpretative', 'step' and 'regional' indicators. Discussion. Gait assessment is performed very differently by each profession but relatively similarly within the same profession. The different strategies adopted by each speciality contribute to an enrichment of gait analysis and emphasise the importance of collaborations for education.

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ASYMPTOMATIC MYOSITIS AND POLYARTERITIS NODOSA. N. Ramopoulos, P. Petrikis, F. Drakopoulou, K. Michailidis, Panagia Hospital (Thessaloniki, GR)

Asymptomatic myositis refers to inflammation of the muscles, the histopathological characteristics of which resemble those of idiopathic polymyositis but without the clinical features and the biochemical findings of the latter. Asymptomatic myositis has only been described in Zeek's hypersensitivity angiitis and in hypocomplementemic vasculitis. We describe the case of a patient, aged 70, with clinical and laboratory findings of polyarteritis nodosa with general manifestations as fever, loss of weight and multiple mononeuropathy at onset. The diagnosis was based on the American College of Rheumatology 1990's criteria for the classification of polyarteritis nodosa and was proved by small vessel biopsy. The bioptic tissue was taken from the sural area and also included tissue from the sural nerve and muscle. The findings were typical of myositis, although the clinical and laboratory findings (CPK, EMG) were missing. We discuss the rarety of asymptomatic myositis as a clinical symptom of polyarteritis nodosa and the other primary – or necrotic – vasculitis.

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MIRROR MOVEMENTS IN ACQUIRED BRAIN LESIONS. I. Uttner, O. Esslinger, A. Danek, N. Mai, Rehabilitationskrankenhaus Ulm, Ludwig-Maximilians-Universität Ulm (Ulm, D)

Mirror movements (MM), unintended symmetric activity opposite to a voluntary limb movement, normally are a transient phenomenon of the first two decades of life. However, they may reappear in adults after brain damage. To better understand the incidence, extent and neuroanatomical correlates of acquired MM, we performed simultaneous grip-force measurements of both hands. 36 patients (16–82 years) with differently localized cortical and/or subcortical regions brain lesions after a single injury were studied (unilateral lesions, except for one, of e. g. supplementary motor area, SMA, corpus callosum, CC, and basal ganglia as delineated by neuroimaging with CT/MRI). The findings were compared with those of age- and sex-matched healthy controls. We applied two tasks using small force transducers hand-held in pinch grip between thumb and index finger. In the first task, subjects had to repetitively change the grip force of one hand while the other ("mirror") hand was only to prevent the object from dropping. The two hands were examined in turn. In the second task, repetitive force change had to be produced by both hands simultaneously, however in an antiparallel manner. With this instruction we wanted to detect a tendency towards coupling. This type of MM, in the sense of Brinkman (Neurosci. Lett. 1981;27:267), had been observed in macaques after unilateral lesions of the SMA. After scaling to the maximum grip force of each hand, the ratio of unintended activity in "mirror" and voluntary hand was used to quantify MM and compared with the range of ratios found in the controls. In addition, we calculated cross-correlations between the grip forces of the two hands. In the "unimanual" task, only six patients had a MM ratio in the pathological range (> 1.9 %). It reached a maximum of 12,6 % that occurred in a contralesional hand. No associations with patients' age, gender, lesion site, or time since lesion were found. In the "bimanual" condition, most patients showed strong interference between the hands. Here, too, only five showed abnormal results (coupling > r=0.36), again not correlated with any of the variables mentioned. According to our results, MM are an uncommon finding after acquired brain lesions. They seem unrelated to specific sites of damage, such as SMA, CC or the corticospinal tract. Since even the side of the lesion appears of no importance, the concept that a paretic hand receives "support" from the unaffected ipsilesional motor cortex ought to be revised. Alternatively, MM could reflect a deficit of sustaining attention such as often occurs after brain damage.

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CEREBRAL AMYLOID DEPOSITION (AMYLOIDOMA) PRESENTING AS A BRAIN MASS. H. El Fertit, L. Bauchet, C. Campello, P. Smadja, F. Segnarbieux, P. Labauge, DPT of Neurosurgery, DPT of Neurology, DPT of Neuroradiology (Montpellier, Nimes, F)

Amyloidosis is defined by extracellular deposition of abnormal protein material. Immunohistochemical analysis leads to characterize the types of the proteins. We present radiological and immunohistochemical data of localized amyloid deposition in the brain. Case report. A 46-year-old patient, without any past medical condition, suffered from focal seizures for the last 8 years. CT scan and Magnetic Resonance Imaging (MRI) showed two lesions in the right frontal and temporal lobe appending to the lateral ventricles (seen as hypointense signal on T1WI and hyperintense signal T2WI). Histological analysis of the lesion from the temporal lobe showed deposition reacting positive with PAS and Congo red stains. The immunohistochemical analysis detected AL lambda amyloid. The search for systemic amyloidosis was negative. Discussion: Brain localized amyloid deposition (amyloidoma) are rare findings. Only 16 observations were previously reported in the literature. Most present in adulthood and mainly produce seizures and focal signs. On MRI studies, T1-weighted images showed iso-, hypo- or hyperintense lesion and T2-weighted images demonstrated mixed signal intensity. No perilesional edema is observed. All amyloidomas are close to the periventricular area and/or choroid plexus. Immunohistochemical studies invariably reveal AL lambda subunit. Search of systemic amyloidosis is constantly negative. Conclusion. Although rare, brain amyloidoma has to be suspected in case of brain tumor. Association of the lesion with the periventricular area and / or choroid plexus suggests this diagnosis. Firm diagnosis of amyloidoma relies on histologic analysis.

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CLINICAL FEATURES AND TREATMENT RESPONSE OF TRAUMATIC BENIGN PAROXYSMAL POSITIONAL VERTIGO. C. Gordon, R. Levite, N. Gadoth (Kfar Saba, IL)

Although head trauma is the cause of benign paroxysmal positional vertigo (BPPV) in about 15 % of cases, the clinical features and response to treatment in this particular group of patients was not previously evaluated. Goals: To evaluate clinical features and response to physical treatment of traumatic BPPV. Design/Methods. We present 12 cases of traumatic BPPV seen in our neuro-otology clinic in the past three years. All patients had the onset of positional vertigo within 3 days of well-documented head trauma. They were diagnosed by the Hallpike manoeuvre and treated by the Epley procedure. Treatment results were compared to those of 36 consecutive idiopathic BPPV patients. Results. There was a wide spectrum of causes and severity of head trauma: road accident with multiple trauma (4), whiplash injury (2), fall off stairs (1), removal of occipital osteoma (1), V-P shunting (1), dental surgery (1), speedboat shaky trip (1), "ball bump" (1). Two of the patients who were involved in road accident experienced loss of consciousness. None of the patients were involved in litigation. Only two patients were diagnosed as BPPV prior to the referral to our clinic. Eight patients (66 %) required repeated physical treatment until complete resolution of BPPV was achieved. Thirty of the 36 idiopathic BPPV patients (83 %) had complete resolution of signs and symptoms after a single treatment. During follow-up, 4 "trauma" patients (33 %) had recurrent attacks of BPPV. These 12 patients with traumatic BPPV constitute only 8 % of the 151 cases of BPPV seen in our neuro-otology clinic during the same period of time. Conclusions. Traumatic BPPV is probably unrecognised or misdiagnosed in clinical practice. Response to a single physical treatment seems to be less favorable than in idiopathic BPPV.

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BRAIN DEATH: DIAGNOSTIC VALUE OF MRI AND MR ANGIOGRAPHY. G. M. Hadjigeorgiou, A. H. Karantanas, K. Paterakis, D. Sfiras, A. Poultsakis, A. Komnos, University of Thessalia (Larissa, GR)

Purpose. To investigate the findings in brain death patients with MR imaging (MRI) and MR angiography (MRA).

Materials-methods. Six patients in whom brain death was established by applying standard neurological and EEG criteria, were examined with MRI and MRA. A 1T scanner with maximum gradient strength of 15mT/m was used along with a quadrature coil. The MRI examination consisted of a Turbo-Flair (CSF=0) and a T2-TSE pulse sequences. The MRA was performed with a 3D-inflow with magnetization transfer contrast pulse sequence. In two patients a 3D-phase contrast venography was applied. The MIP reconstructions in MRA and MR venography were performed in a separate workstation.

Results. MR images showed in all patients marked edema with diffuse swelling of the cerebral gyri, small ventricular system and basilar subarachnoid spaces and central and tonsillar herniation. The MRA in all patients revealed no arterial flow in the intracranial circulation. In two patients the additional MR venography showed no opacification of the sagittal and straight sinuses. In all MRA examinations there was opacification of the extracranial arteries. Conclusion. MRI and MRA are noninvasive and reliable methods for use in determining brain death. An accurate and early diagnosis is very important when attempting organ transplantation.

P665
A DOUBLE-BLIND TRIAL OF INTRADERMAL VS. SUBCUTANEOUS BOTULINUM TOXIN A FOR THE TREATMENT OF PALMAR HYPERHIDROSIS. J. C. Martinez-Castrillo, A. Mariscal, Servicio de Neurología Hospital Ramón y Cajal, Servicio de Neuroanestesia (Madrid, E)

Objectives. Intradermal and subcutaneous Botulinum toxin A (BTA) infiltrations are an effective treatment in palmar and axillar hyperhidrosis. These two routes of infiltration have not been compared. We have compared if intradermal

botulinum toxin administration in patients with primary palmar hyperhidrosis is as effective as subcutaneous one. We have also compared adverse events, particularly pain and hand muscles paresis, and time required in each intervention. Methods. Patients: Seven patients (four women) with severe primary palmar hyperhidrosis were included in the trial. They had not been treated with BTA previously. Mean age was 26 years. The patients received BTA intradermally in one hand and subcutaneously in the other. The hands were not visible to the patients during the infiltrations, and they were not informed about the route used. The side was randomly assigned. BTA infiltration: 100 U of BTA (Botox O, Allergan) were diluted in 1 ml of 0.9 % saline. Both, left and right, cubital and median nerves were anaesthetised with lidocaine 1 %. Each hand was divided in a graticule of 1.5 cm, and 2.5 U of Botox (0.025 ml) were administrated in each point, intradermally in one hand and subcutaneously in the other. Thenar eminence was preserved. The mean number of injected points per hand has been 42 (range 32–56). Measures: Minor sweat test was performed before and 1, 3 and 6 months after treatment. A visual analogic scale (VAS) was used for subjective sweat rating at the same periods. Adverse events were checked at each visit, including one week after treatment. All measures were done by a blind physician.

Results. Four patients received BTA intradermally in their right hands. The mean time spent for intradermal injection point was 26 seconds, while for subcutaneous one was 11 seconds. There were significant differences between basal and all after treatment visits in Minor sweat test and VAS (p= 0.002). There were no differences in Minor test nor in VAS for sweat between the hands injected intradermally or subcutaneously. Pain, assessed by VAS one week after treatment, was significantly more severe in the hands treated intradermally (p=0.005). A mild weakness of lumbricales and palmar interossei were observed in three patients. In one of these patients the weakness was in both hands. In the other two, it was related to the hand infiltrated subcutaneously. It lasted between 2 and 4 weeks, and did not interfere with daily living activities of these patients. Conclusions. Subcutaneous and intradermal injections of BTA are equally useful in the treatment of palmar hyperhidrosis. Intradermal injections are more painful and probably more time consuming (we have a far larger experience in subcutaneous route). Mild weakness is more probable in subcutaneous infiltrations.

P666
UNUSUAL MRI FINDINGS IN AN ELDERLY PATIENT WITH HASHIMOTO'S ENCEPHALOPATHY. A. Behin, J.-B. Hamon, E. Meary, J.-F. Meder, J.-L. Mas, Hôpital Sainte-Anne (Paris, F)

Hashimoto's encephalopathy is a rare neurological condition characterised by myoclonus, seizures, stroke-like episodes and elevated anti-thyroglobulin antibody titers. CT scan and MRI are usually normal and pathogenesis remains unclear. We report a case of Hashimoto's encephalopathy with unusual contrast enhancing MRI lesions. A 76-year-old woman was admitted for acute confusion. Subsequently, she developed a left hemiparesis with progressive alteration of consciousness leading to coma with decorticate rigidity. Biological examination revealed high CSF protein level with pleocytosis, biological hypothyroidism and very high titers of antithyroid antibodies in the blood (antithyroglobulin antibodies: 1/5120; antimicrosomial antibodies: 1/6400). Bacteriology and virology findings in CSF and blood were negative. CT scan showed periventricular hypodensity with contrast enhancement, which on MRI appeared as T2-weighted hypersignals and T1-weighted hyposignals enhanced with gadolinium. The patient was treated with corticosteroids (intravenous methylprednisolone therapy: 1 gram daily for 3 days followed by oral prednisolone 1 mg/kg per day). She improved gradually and one month later, she was able to walk and the MMS was at 18/30. Neuroimaging showed a leukoencephalopathy without contrast enhancement. Prednisolone was decreased gradually during 1 year. Six months after withdrawal of treatment, the clinical status and neuroimaging was unchanged, but high antithyroid antibodies titers had reappeared. Several hypotheses have been suggested to explain Hashimoto's encephalopathy, including autoimmune vasculitis, direct toxicity of TRH or antithyroid antibodies. In the present case, neuroimaging findings, lymphocytic meningitis as well as clinical, radiological and biological improvement under steroids are in favour of an inflammatory process. The reappearance of high antibodies titers without clinical deterioration argues against a direct role of antithyroid antibodies.

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SCIATICA AND THE SACRO-ILIAC JOINT: A FORGOTTEN CONCEPT? I. Casetta, L. Visser, J. van der Plas, E. Buijs, G. Groen, M. van Gestel (Tilburg, Utrecht, Katwijk, NL)

Objective: to describe the role of the sacro-iliac joint (SI) in patients presenting with sciatica. Background: In the twenties the SI joint was considered to play an important role as a cause for sciatica (Yeoman,1928). A sacroiliac strain was a common diagnosis. Barre and Duprey considered even the diagnosis of sacroiliac sciatica. By the 1930s it became apparent that the lumbar disc could create sciatica and interest in the SI joint waned. In 30% of the patients with a strong presumptive diagnosis of a lumbar disc herniation no herniated disc is revealed on imaging studies or even during operation. Our clinical experience is that patients with sciatica without underlying lumbar disc abnormality often complain of pain in the sacroiliac area. Method: we examined patients with sciatica. A neurological examination was performed, the leg raising test and SI provocation tests. In all MRI of the lumbar spine was performed. Results: Five patients with a presumptive clinical diagnosis of a lumbar disc herniation with normal lumbar MRI will be presented. SI provocation tests were positive in these patients. Intra-articular injection with local anaesthetics gave a complete or almost complete reliefe of their pain. Conclusions: Recognizing that sciatica can be referred pain from the SI joint is important, since it may prevent unnecessary investigations and operations.

P668
CLINICAL, MRI AND PROTON MR SPECTROSCOPY FEATURES OF A REVERSIBLE TOXIC LEUKOENCEPHALOPATHY ASSOCIATED WITH HEROIN. N. C. Silver, D. G. MacManus, R. Walker, D. H. Miller, Institute of Neurology, Royal London Hospital (London, UK)

A severe and permanent leukoencephalopathy characterised by spongiform degeneration of central nervous system white matter with vacuolating myelinopathy and axonal disruption has been associated with smoking heroin pyrolysate ("chasing the dragon"). Cerebellar involvement is usual and may be associated with other neurological impairment. The occurrence of epidemics has implicated an unknown toxic contaminant. We report two cases of atypical toxic leukoencephalopathy following injection and inhalation of heroin, associated with psychiatric and extrapyramidal features, an absence of cerebellar involvement and considerable recovery. Case 1. A 36 year male heroin abuser developed rhabdomyolysis after injecting methadone. Five weeks later, he developed acute onset psychosis, poor memory, stereotyped movements, hypophonia, and an akinetic-rigid syndrome. Cerebellar function was intact. He had smoked heroin regularly since the age of 15 years and more rarely used intravenous heroin, cocaine, amphetamines, marijuana or alcohol. Electroencephalogram findings were consistent with encephalopathy. He made a very good recovery from the neurological impairments, but a mild psychosis persisted. Case 2. A 32 year male first smoked and injected heroin during a trip to India, where he presented with septicaemia secondary to heel necrosis. This was followed a few weeks later by severe psychosis, poor memory, hypophonia and an akinetic-rigid syndrome. Cerebellar function was intact. He had in the past used occasional LSD, cocaine, cannabis, ketamine and "Ecstasy". Psychiatric recovery was complete and followed by marked resolution of the neurological features. In both cases, T2-weighted MRI revealed diffuse symmetrical increased signal throughout the cerebral hemispheres. Cerebral hemisphere magnetization transfer ratios (a putative marker for myelin disruption) were significantly reduced (by as much as 29%); cerebellar values were normal. Proton MR spectroscopy revealed evidence of axonal disruption / dysfunction (reduced N-acetylaspartate), myelin disruption (raised choline and the presence of "free" lipid resonances) and possible macrophage involvement (raised lactate). These cases have some similarities to previously described cases of pyrolysate leukoencephalopathy, but appear atypical in their mode of clinical presentation, lesion distribution and subsequent recovery. We propose that pyrolysate leukoencephalopathy might not result from exposure to a single toxic agent, but that the aetiology may be multifactorial.

P669
ACUTE TRANSVERSE MYELITIS AFTER VACCINATION: REPORT OF THREE CASES. A. Ferreira, J.-L Renard, H. Taillia, F. Flocard, D. Béquet, D. Felten, Hôpital Val-de-Grace, Hôpital Legouest (Paris, F)

Acute disseminated encephalomyelitis (ADEM) is a monophasic inflammatory syndrome occurring in the context of an infection or vaccination. Lesions are usually prevalent in the brain. We report three cases of acute myelitis, developed from some hours to some weeks after vaccinations. The first case was a 16-year-old girl who complained of lower limbs paresthesia eight hours after the booster injection of the anti-HBV recombinant vaccine. She developed acute cervical transverse myelitis with intrathecal oligoclonal IgG secretion and a C2 hypersignal on the MRI T2 sequences of the cord. She was treated with an intravenous steroid therapy and all the symptoms except a Lhermitte sign resolved in 19 days after onset. One year later, the cord hypersignal persisted but less intense. The level of anti-HBs antibodies was very high not only at the onset but also one year after. The second case was a 24-year-old man who developed paresthesia in the lower limbs 26 days after vaccination against diphtheria, tetanus, poliomyelitis and meningococcus A and C. In three days appeared urinary retention, weakness in the lower limbs and sensitive impairment with a T8 level. MRI of the cord showed a T2 sequences hypersignal between T5 and

T9 and MRI of the brain showed bilateral hypersignals of the occipital white matter. The lumbar puncture showed a mild lymphocytic meningitis. Two months later, the brain MRI was normal and the cord hypersignal reduced in size. On physical examination one year after onset, muscle strength returned to normal but genital and bladder disturbances and hypoesthesia below dermatome T9 persisted. The third case, a 21-year-old man, was vaccinated against meningococcus A and C six weeks before developing a meningo-myelitis with flaccid paraplegia and urinary retention. He presented a pharyngitis and myalgia one week before the first neurological symptoms. The MRI showed a T2 hypersignal with swelling of the cord between C5 and T2. Extensive laboratory screening for a causative infectious agent was negative in all three cases. The time between the vaccination and the first symptom is less than two months, which is the maximal time limit usually accepted to correlate both phenomena. The vaccinations, which have been already involved in ADEM, are principally vaccinations against variola and rabies but also against rubella, cholera, poliomyelitis, typhoid, diphtheria, tetanus, hepatitis B and influenza. Our third case seems to involve the vaccination against meningococcus A and C and there is no similar report in literature. The relationship between vaccinations and ADEM cannot be formally proven and the pathophysiology is discussed. The level of post-vaccinal immunization could be one interesting tool to support this relationship. Further studies are needed.

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TITIN AND RYANODIN RECEPTOR ANTIBODIES IN MYASTHENIA GRAVIS: CLINICAL CORRELATIONS. L. Apollonio, E. Granieri, E. Paolino, V. Govoni, E. Fallica, G. O. Skeie, University of Ferrara, University of Bergen (Ferrara, I; Bergen, N)

A proportion of Myasthenia Gravis (MG) patients have autoantibodies against non-acetylcholine receptor proteins of striated muscle, such as myosin, actin, alpha-actinin, ryanodine-receptor and also against titin. The aim of this study was to investigate sera from MG patients for the presence of antibodies to titin (AT) and antibodies to ryanodine-receptor (ARR) and to look for a possible association between these antibodies and some clinical characteristics of the disease. Methods: The study included 40 MG patients (19 men and 21 women). The mean age at onset was 52.6 years ± 14 Standard Deviation (SD), and the mean duration of the disease was 6.75 years ± 5.5 SD. Sera from all patients were tested for the presence of AT in ELISA and for the presence of ARR in Western Blot. Results: AT were detected in 13 subjects (32.5%). Of these 7 had a thymoma. ARR were detected in 10 patients (25%), 8 of whom had a diagnosis of thymoma. We found a significant correlation between AT and thymoma in late onset MG (> 40 years) and between AT and late onset severe MG without thymoma. The detection of ARR correlated positively with the presence of thymoma in late onset MG. Conclusions: The preliminary data from this study suggested that AT and ARR can be detected above all in late onset MG, with and without thymoma and that their presence could be a marker of disease severity.

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LIPOPROTEIN OXIDATION AND ANTIOXIDATIVE VITAMINS IN SERUM AND CSF OF PATIENTS WITH CREUTZFELDT-JAKOB DISEASE. S. Arlt, A. Kontush, C. Jacobi, A. Schröter, I. Zerr, S. Poser, U. Beisiegel, Department of Neurology, Medical Clinic (University of Göttingen, University of Hamburg, D)

In the last years it became more and more evident that oxidation is part of the pathomechanisms of several slowly progressive neurodegenerative disorders like Alzheimer's or Parkinson's disease and amyotrophic lateral sclerosis. To assess the possible role of oxidative stress in the pathogenesis of Creutzfeldt-Jakob disease (CJD), a rapidly progressive and fatal transmissible neurodegenerative disorder, we evaluated the oxidation status of 10 patients suffering from CJD versus 12 control subjects without neurodegenerative disorders. Therefore we measured the oxidizability of lipoproteins as well as the antioxidants ascorbate and alpha-tocopherol in both serum and cerebrospinal fluid (CSF). The concentration of the major hydrophilic antioxidant ascorbate in CSF was found to be significantly decreased in the CJD group (127.8 ± 51.6µM vs. 222.7 ± 45.3µM; $p < 0.0005$). Similar results were obtained for the concentration of the major lipophilic antioxidant alpha-tocopherol (24.3 ± 11.4nM vs. 49.3 ± 15.1nM; $p < 0.005$). The oxidation of CSF lipoproteins, measured as an increase of the formation of conjugated dienes over time, started significantly earlier as demonstrated by a shortened lag-phase (3.7 ± 0.68hrs vs. 7.8 ± 3.7hrs; $p < 0.005$). This is consistent with the decreased level of CSF antioxidants. The results shown for CSF could also be demonstrated in serum of CJD patients. The antioxidants ascorbate and alpha-tocopherol were decreased and oxidizability of serum lipoproteins was increased. The results of this pilot study lead to the conclusion, that lipoprotein oxidation in the central nervous system might play an important role during pathogenesis of CJD. This finding might open the door for new concepts on the pathophysiology of this severe neurological disorder.

P672
DELAYED RADIATION MYELOPATHY: CLINICAL, RADIOLOGICAL AND OUTCOME PROFILE. J. De Seze, T. Stojkovic, J. Y. Gauvrit, J. P. Pruvo, P. Vermersch, R Salengro Chu de Lille (Lille, F)

BACKGROUND: Clinical, radiological and outcome profile of delayed radiation myelopathies (DRM) has been rarely studied.

AIM OF THE STUDY: To define the clinical and radiological profile of DRM and to evaluate the potential efficacy of corticosteroids.

METHODS: We retrospectively studied clinical, magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) data in 4 cases of DRM. We also evaluated the outcome and the therapeutic efficacy in 3 patients treated by corticosteroids.

RESULTS: The mean interval between radiation and myelopathy was 4.3 years (1–7 years). Severe motor deficit with sphincter dysfunctions were found in 3 cases. CSF was normal in all cases. During the acute phase, spinal cord MRI showed a hypersignal in T2-weighted images with a widening of the cord. After at least 6 months the cord was atrophic in the 3 severe cases. Functional outcome was poor in these 3 cases. We did not find any improvement after corticosteroid treatment.

CONCLUSION: DRM induce severe acute myelitis with usually an irreversible neurological deficit. The diagnosis should be evoked in patients with a past history of radiotherapy, hypersignal and widening of the cord on MRI and normal CSF. Response to corticosteroids is poor.

P673
MRI FINDINGS AND CLINICAL DISCREPANCY IN PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY: A CASE REPORT. M. Coletti Moja*, P. Meineri, L. Gozzoli, P. Gerbino Promis, F. Perla, E. Grasso, Azienda Ospedaliera S. Croce e Carle (Cuneo, I)

Progressive Multifocal Leukoencephalopathy (PML) is a JC virus induced fatal demyelinating disease in which MRI sensitivity and contrast enhancement activity are controversal as a prognostic index. We report the case of a 68 year old male who referred to our department in April 1999. Hotel dealer with no anamnestic relevant pathologies; in January 1997 a benign monoclonal gammopathy was diagnosed with leukopenia, arthralgia and malaise and in april 1997 a systemic lupus erhithematosus with mild renal failure appeared that was treated by oral prednisone therapy (12.5 mg die). In november 1998 leukocytes count was abnormal with severe joint impairment so that steroid therapy was increased to 25 mg and Methotrexate 10 mg die with better clinical conditions. In mid-April 1999 a sudden left limbs hyposthenia appeared and a MRI scan was performed in suspicion of vasculitic HIV negative encephalopathy and showed an irregular hypointensity on T1-weighted and hyperintensity in T2-weighted scans in the superior frontal and precentral right gyrus, mostly in subcortical regions, not contrast enhancing. In the following days a mild left facial deficit was detected with complete lower limbs plegia and left Babinski sign. A SPECT study and a brain angiography were negative. On these grounds both a brain biopsy made on the right fronto-parietal lesion and a JC virus nested PCR positivity detected in cerebrospinal fluid were diagnostic for PML. Four days later, the patient became unconscious with low cognitive performances, increasing motor deficits and a visual impairment with blurry vision so that a second MRI was performed which showed just a mild width increase in the right frontal subcortical lesion. Ten days later dyplopia appeared with complete both limbs plegia and Babinski sign and patient was deteriorated and confused with right sided gaze evolving in a complete gaze palsy and comatous state; a last MRI scan was performed one day before patient's death. This third MRI showed an increase of the white matter lesion in the 1st and 2nd right cortical frontal gyrus with appearance also of hyperintensity signals in the right diencephalon, mesencephalon and medulla, consistent with patient clinical deficits, without contrast enhancing. We conclude that our patient clinical deficits long preceded MRI imaging positivity, as oculomotion palsy was observed two weeks before any neuroimaging evident lesion and we mark that MRI permanent absent contrast enhancement could indicate a very short term survival.

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DEVIC'S NEUROMYELITIS OPTICA AND VASCULITIS. J. De Seze, T. Stojkovic, G. Breteau, U. Michon-Pasturel, E. Hachulla, F. Mounier-Vehier, P. Y. Hatron, P. Vermersch, R Salengro CHU de Lille (Lille, F)

BACKGROUND: Devic's neuromyelitis optica is usually considered as a particular form of multiple sclerosis or as an idiopathic disease. However, a few cases have been described associated with vasculitis.

AIM OF THE STUDY: To determine the frequency of Devic's neuromyelitis optica in cases of myelitis secondary to vasculitis.

METHODS: We retrospectively studied 13 cases of acute myelitis associated with vasculitis (7 cases of Sjögren syndrom, 5 cases of systemic lupus erythematosus, and 1 case of antiphospholipid antibodies syndrome). We evaluated the frequency and the clinical presentation of Devic's neuromyelitis optica in this particular group of myelitis.

RESULTS: Seven patients (54 %) met the usually established criteria of Devic's neuromyelitis optica. The vasculitis was known in only 2 cases at the time of the neurological episode. The 6 remaining patients were isolated myelitis without optic neuritis. There was no difference concerning neurological and radiological features between Devic's neuromyelitis optica and isolated myelitis. However, outcome was worst in Devic's neuromyelitis optica.

CONCLUSION: Devic's neuromyelitis optica is frequently found in vasculitis myelitis. Vasculitis needs to be investigated in all cases of Devic's neuromyelitis optica as prognosis is poor in this subgroup of myelitis. Immunosuppressive drugs should be rapidly proposed in these cases. However, further prospective studies are necessary to evaluate the frequency of vasculitis in Devic's neuromyelitis optica.

P675
NEUROSARCOIDOSIS: LONG-TERM OF CLINICAL COURSE IN 23 CASES. D. Ferriby, J. De Seze, T. Stojkovic, E. Hachulla, P. Y. Hatron, A. Destée, P. Vermersch, R Salengro Chu de Lille (Lille, F)

BACKGROUND: Neurological manifestations of sarcoidosis are rare and clinical course after many years is not well documented in the literature.

OBJECTIVE: The aim of this study was to evaluate the long-term clinical course of patients with neurosarcoidosis.

PATIENTS AND METHODS: We reviewed 48 cases of neurosarcoidosis. Long-term following data (at least 5 years) were available in 23 of these patients. We studied clinical course and treatments during this period.

RESULTS: Mean age at onset of neurosarcoidosis was 44 years (range: 27–62). Patients were followed for a mean time of 7 years (range: 5–18). All patients received oral and/or intravenous corticotherapy (mean time 4.2 years, range 0.7–12), 6 of them (26 %) required immunosuppressive treatment (3 with cyclophosphamide, 5 with methotrexate, 2 with azathioprine, 1 with ciclosporine) because of worsening signs or lack of improvement. Complete recovery and improvement were respectively observed in 10 (43 %) and 4 (17 %) cases. Six (26 %) patients were clinically stable and 3 (14 %) worsened. No patients died.

DISCUSSION: Neurosarcoidosis needs intensive and prolonged treatment (corticosteroids or/and immunosuppressive drugs) in most of the cases. However, in contrast with previous studies suggesting that neurosarcoidosis is of poor prognosis, we demonstrate that long-term clinical course is frequently associated with remission, even if residual disability remains possible.

Motor neuron disease and motor neuropathy

P676
RELIABILITY OF HAND-HELD MYOMETRY STRENGTH TESTING IN PATIENTS WITH SPINAL MUSCULAR ATROPHY. A. Solari, L. Morandi, G. Lolli, E. Mazzone, C. Angelini, E. Bertini, C. Minetti, T. Mongini, G. Vita, L. Merlini, Istituto Nazionale Neurologico Besta (Milan, Bologna, Padua, Rome, Genoa, Turin, Palermo, I)

Objective. In an Italian multicenter, single blind trial on the efficacy of gabapentin in spinal muscular atrophy (SMA) type II-III, the main outcome measure was maximal voluntary isometric contraction (MVIC) measured in upper and lower limb muscle groups by hand-held myometry. Preliminary assessment of reliability of MVIC measurement between and within raters was part of the trial.

Design/Methods. MVIC was evaluated by hand-held myometry in 33 SMA patients (17 males), with a median age of 22.9 years (SD 11.4, range 5–64 years). The following movements were examined: elbow flexion, hand grip, three-point pinch, knee flexion, knee extension, and foot extension. Each movement was assessed for three times on the patient's preferred side only. The patient performed each movement three times for 3–5 seconds, with 6–12 seconds of rest; the highest score obtained was considered. Each patient was independently tested by two evaluators (GL, EM), and re-tested by one evaluator (EM), with at least one hour rest between tests. Inter-rater testing order was randomly determined. Reliability was assessed by means of the intraclass correlation coefficient (ICC). The raters' scores were also plotted and the line of equality was drawn. Finally, a graphical method based on plotting the difference between the two sets of measurement against their mean was applied.

Results. Inter-rater reliability was good to excellent for upper limb strength, with ICC ranging from 0.91 for three-point pinch (95 % confidence interval [CI] 0.85–0.96) to 0.99 for hand grip (95 % CI 0.98–0.99). At lower limbs reliability was moderate, with ICC=0.62 for knee flexion (95 % CI 0.34–0.96), and 0.66 for foot extension (95 % CI 0.46–0.93). Graphical results showed mean inter-rater differences ranging from 0.2 for hand grip to 0.9 for three-point pinch, and from 1.8 for knee extension to 5.6 for foot extension. Test-retest results were excellent with ICC > 0.80 in all instances; graphical results showed mean differences ranging from 0.2 for knee extension to 2.4 for foot extension.

Conclusions. MVIC measured by hand-held myometry is easily performed in SMA patients at different ages and strength. It is a reliable measure of limb muscle strength and can be implemented in longitudinal studies and clinical trials on the disease.

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P677
MONOMELIC AMYOTROPHY: STUDY OF 21 BRAZILIAN CASES. M de Freitas, O. Nascimento (Niterói- RJ, BR)

Monomelic Amyotrophy (MA) is a rare motoneuron disease usually found mostly in upper limb of young adults of Japanese or Indian origin. It consists of weakness of one limb predominantly in young males. Electromyographic (EMG) findings are consistent with chronic denervation. Symptoms and signs progress for several years before spontaneous arresting. We report twenty-one patients with MA. All cases are sporadic. There were 13 males and 8 females. In 16 cases the amyotrophy was in the lower limb and in 5 it was in the upper limb.The EMG findings disclosed a severe incomplete denervation of the affected muscles with signs of mild denervation of the seemingly normal muscles of the same limb. In a few patients there was denervation of other limbs. MRI of the cervical and lumbar cord was normal. In a few cases we performed MRI of the affected limb. In these cases there was unequivocal amyotrophy of different muscles in these segments. In all patients the condition stabilized in 2–4 years. Our findings suggest that MA is a chronic disease of the anterior horn cells with a benign course and with a good prognosis. In our consecutive series the lower limb was more affected than the upper limb. This finding differs from most cases described in the medical literature.

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VITAL CAPACITY IMPROVEMENT AFTER PERCUTANEOUS ENDOSCOPIC GASTROSTOMY IN PATIENTS WITH MOTOR NEURON DISEASE. V. Bonito, G. Marchesi, G. Morlini, F. Negrini, M. Migliori, P. Arnone, M. Poloni, Ospedali Riuniti Bergamo (Bergamo, I)

Percutaneous Endoscopic Gastrostomy (PEG) is supposed to extend survival of MND patients (1) (2). There are few and inconclusive data about the change of respiratory function after PEG (3). Our aim is to compare the trend of FVC before and after PEG. Patients and methods: we retrospectively examined clinical data about 25 MND patients that had PEG in 1997-'99. 9/25 had at least two FVC measures in the six months pre- and post PEG so it was possible to estimate a slope (SL= FVC1-FVC2/months). We calculated the percentage of FCV variation (%SL= SL/FVC1*100). Results: in 7/9 % SL changed from negative value, i. e. decline before PEG, to positive value i. e. improvement after PEG. In one patient %SL remained unchanged (–7 % before, –8 % after). One patient had pneumonia after PEG and the FVC worsened (–6 % before, –41 % after). Conclusion: PEG has been proposed as symptomatic treatment of dysphagia in MND, our data suggest that FVC can improve after PEG and this supports the hypothesis that PEG extends survival of patients with MND. Ref.: (1) Mazzini L., et al. (1995): Percutaneous endoscopic gastrostomy and enteral nutrition in ALS. J. of Neurol, 242: 695–698. (2) Chiò A, et al. (1999): Safety and factors related to survival after PEG in ALS. Neurology, 53: 1123–5. (3) Kasarskis EJ, et al. (1999): A retrospective study of PEG in ALS patients during the BDNF and CNTF trials. J Neurol Sc, 169: 118–125.

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REVERSIBLE INVASIVE VENTILATION IN PATIENTS WITH MOTOR NEURON DISEASE. V. Bonito, G. Marchesi, M. Poloni, Ospedali Riuniti Bergamo (Bergamo, I)

We know that decline in respiratory function is irreversible in MND patients but respiratory failure may be either irreversible i. e. respiratory muscles paralysis or reversible i. e. bronchial obstruction, choke, pneumonia, gastric distension. Various modes of mechanical ventilation can be used to palliate symptoms of respiratory insufficiency and also to prolong survival beyond respiratory failure. Our aim is to evaluate how many patients recovered spontaneous breathing after invasive mechanical ventilation. Patients and methods: we collected data

of 73 MND patients cared for in the period 1995-'99. All patients were informed about diagnosis and prognosis and were able to choose and access ventilatory support. Results: From 1995 to 1999, 14 patients had procedures of invasive ventilation: 9 were the tracheal intubation without tracheotomy; after tracheal intubation 1 patient totally recovered spontaneous breathing, and 1 partially recovered to non invasive ventilatory support (BiPAP). 13 were the tracheotomy, in 4 out of 13 there was recovery of spontaneous breathing. The duration of respiratory autonomy in these 6 patients ranged from 2 to 46 months, the median was 19 months (to death or to permanent mechanical ventilation). 1/6 refused permanent ventilation and deceased after 2 months; 1/6 passed in permanent ventilation, 3/6 are in intermittent support ventilation, 1/6 remains in spontaneous breathing through tracheotomy. Conclusions: Six out of 14 i. e. 43 % patients recovered respiratory autonomy after invasive ventilation procedures which were useful to overcome acute, reversible respiratory failures.

P680
NEUROAXONAL DYSTROPHY SPHEROIDS CONTAIN HEAVY METALS. V. Di Carlo, G. Moretto, R. Garner, G. Di Carlo, University of South Florida, Università di Verona (Tampa, USA)

In previous research, heavy metal-containing spheroid-like organelles were isolated from the CSF of ALS patients (V. Di Carlo, Canad. J. Neurol. Sci. 1993). Among studies aiming to better evaluate this finding, an investigation was carried out on infantile neuroaxonal dystrophy autopsy material. Consecutive sections of formalin-fixed and paraffin-embedded spinal cord and medulla specimens (N=6) were alternatively stained or left unstained. The stained sections allowed us to identify tissue areas containing neuroaxonal spheroids, while the corresponding areas of the unstained ones were used to harvest neuroaxonal spheroids and globules. Individual spheroids or clusters of spheroids and globules were photographed in a scanning electron microscope and analyzed by energy dispersive X-ray spectroscopy. These organelles appeared morphologically similar to those observed in the CSF of ALS patients. They all were found to contain heavy metals, in variable relative concentrations: as much as 2.86 % Al and 8.6 % Hg; from 1.62 % to 11.5 % Cu; as much as 12.6 % Zn; from 0.22 % to 2.86 % Cd, etc. These results argue in favor of a close similarity between typical neuroaxonal spheroids and the heavy metal-containing microbodies retrieved from the CSF in adult neurodegenerative diseases. They also suggest that heavy metal accumulation in sub-cellular organelles can start at a very early age, in association with neurodegeneration. That heavy metals may play a role in the pathogenesis of adult neurodegenerative diseases is considered a likely possibility by many investigators. Apparently, the infantile neuroaxonal dystrophies should probably be added to this list.

P681
INFLUENCE OF SMOKING ON THE INCIDENCE AND PROGRESSION OF AMYOTROPHIC LATERAL SCLEROSIS. V. E. Drory, M. Birnbaum, A. D. Korczyn, Tel-Aviv Sourasky Medical Center (Tel-Aviv, IL)

Department of Neurology, Tel-Aviv Sourasky Medical Center, 6 Weizman St., Tel-Aviv, Israel

OBJECTIVE: To evaluate the possible association between cigarette smoking and amyotrophic lateral sclerosis (ALS).

BACKGROUND: Several studies have suggested an inverse association between smoking and two related neurodegenerative diseases, Parkinson's disease as well as Alzheimer's disease.

DESIGN/METHODS: 98 ALS patients and 130 controls of similar age, gender, ethnic origin and sociocultural status were asked for their smoking habits and their answers were expressed as pack-years (packs of cigarettes per day multiplied by years smoked) until onset of ALS.

RESULTS: Patients and controls reported similar mean pack-years of smoking. In the patient group, those who reported never to have smoked were compared to those who reported heavy smoking (< 30 pack-years). No differences were observed in these two subgroups regarding age at disease onset, frequency of bulbar onset, time of progression to moderate disability (defined as 20 points on the ALS functional rating scale) and survival.

CONCLUSIONS: Differently from other neurodegenerative diseases, smoking seems to have no significant influence on the occurrence and rate of progression of ALS.

P682
HEXOSAMINIDASE A MUTATION IN ISRAELI ALS PATIENTS. L. Peleg, M. Birnbaum, V. E. Drory, A. D. Korczyn, Tel-Aviv Sourasky Medical Center (Tel-Aviv, IL)

OBJECTIVE: To evaluate the frequency of the Hexosaminidase A (Hex A) mutations in Israeli ALS patients.

BACKGROUND: Hex A deficiency causes accumulation of GM2 ganglioside in lysosomes, leading to degeneration of nerve cells, including spinal anterior horn motoneurons. Clinically, patients with adult type GM2 gangliosidosis may show a picture similar to amyotrophic lateral sclerosis (ALS). Mutations in this gene are very common in the Jewish population in Israel.

DESIGN/METHODS: DNA samples of ALS patients (n=25) were examined for the two most common mutations in the Hex A gene among the Ashkenazi Jewish population (+1278 TATC and IVS12+1G→C). Patients of Iraqi or Moroccan origin (n=7) were checked also for 2 other mutations (F304/305 and Arg170Gln), common in this ethnic group.

RESULTS: One Ashkenazi ALS patient was found to be a heterozygous carrier of the +1278 TATC mutation.

CONCLUSIONS: The frequency of mutations in the Hex A gene among Israeli ALS patients is not different from the healthy Israeli population (1:27). Coupled with data suggesting that the frequency of ALS is not higher in Israel than it is in other countries (in spite of the higher frequency of Hex A gene mutations) we conclude that being a heterozygous carrier of a Hex A mutation does not seem to be an important risk factor for ALS.

P683
INTERLEUKIN–1 BETA CONVERTING ENZYME/CASPASE–1 (ICE/CASPASE–1) AND SOLUBLE APO–1/FAS (SAPO–1/FAS) RECEPTOR IN AMYOTROPHIC LATERAL SCLEROSIS (ALS) PATIENTS. J. Ilzecka, Z. Stelmasiak, B. Dobosz, University School of Medicine (Lublin, PL)

Apoptosis is likely to be an important mechanism of cell loss in ALS. The activation of caspases appears to play a key role in programmed cell death. ICE/Caspase–1 is a cysteine protease that shares sequence homology with the protein product of ced–3, the gene for cell death of the Caenorhabditis elegans, and can induce apoptosis in different cellular systems. APO–1/Fas is transmembranous glycoprotein involved in cell death signaling. Binding of Fas ligand or agonistic anti-Fas antibody to Fas kills the cells by apoptosis, but soluble APO–1/Fas (sAPO–1/Fas) is able to protect cells from Fas-mediated apoptosis. The aim of this study was to investigate ICE/Caspase–1 and sAPO–1/Fas in the sera and in the cerebrospinal fluid (CSF) from patients with ALS. ICE/Caspase–1 and sAPO–1/Fas levels were measured by ELISA in the sera and in the CSF from 25 ALS patients (mean age 57 years, range 34–77) and 15 control patients (mean age 55 years, range 32–69). Mean ALS duration was 1,4 year (range 3 months–4 years). Mean levels of ICE/Caspase–1 and sAPO–1/Fas in controls were: 56,06±14,50 pg/ml, 1530,24±431,38 pg/ml in the sera, and 16,46±9,99 pg/ml, 184,60±28,65 pg/ml in the CSF, but in ALS patients mean levels were: 91,08±31,43 pg/ml, 1781,62±702,69 pg/ml in the sera and 6,36±4,55 pg/ml, 188,28±36,00 pg/ml in the CSF. ICE/Caspase–1 level was statistically significantly higher in the sera from ALS patients than in controls; the difference was 33, 93±21,99 pg/ml (t=5,97, p< 0,05), and statistically significantly lower in the CSF from ALS patients than in controls; the difference was 10,53±11,64 pg/ml (t=3,50, p< 0,05). sAPO–1/Fas level was statistically insignificantly (p> 0,05) higher in the sera and in the CSF from ALS patients compared with control subjects; the differences were 138,14±577,34 pg/ml (t=0,92) and 9,43±53,88 pg/ml (t=0,67). Our results indicate that ICE/Caspase–1 plays an important role in apoptosis in ALS and suggest that pharmacologic inhibition of ICE may be a useful treatment for ALS. This study has shown low activity of inhibition of Fas-mediated apoptosis in this disease.

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KYNURENIC ACID (KYNA) AS AN ENDOGENOUS NEUROPROTECTANT IN AMYOTROPHIC LATERAL SCLEROSIS (ALS) PATIENTS. J. Ilzecka, Z. Stelmasiak, K. Gustaw, T. Kocki, W. A. Turski, University School of Medicine (Lublin, PL)

Endogenous excitotoxins have been implicated in neurodegeneration in amyotrophic lateral sclerosis (ALS). Glutamate is the principal excitatory neurotransmitter in the central nervous system. Neural toxicity is caused by excessive stimulation of glutamate receptors which leads to neuronal injury and cell death. The synthesis of NAD or NADP from tryptophan involves a series of enzymes and the formation of intermediates which are called "kynurenines". Kynurenine aminotransferase converts kynurenine into kynurenic acid (KYNA). KYNA can reduce excitotoxin – induced neuronal death by antagonising ionotropic glutamate receptors. The aim of this study was to investigate KYNA in the sera and in the cerebrospinal fluid (CSF) from patients with ALS. KYNA concentrations were measured by HPLC chromatography in the sera and in the CSF from 20 ALS (mean age 54 years) and from 23 control patients (mean age 58 years). ALS was recognized basing on El Escorial criteria WFN. Mean ALS duration was 18 months. Mean concentrations of KYNA in controls were: 0,045± 0,01 pmol/ml (range 0,028–0,063) in the sera, and 0,050± 0,019 pmol/ml (range 0,03–0,095) in the CSF, but in ALS patients mean concentra-

tions of KYNA were: 0,346±0,07 pmol/ml (range 0,21–0,48) in the sera, and 0,072± 0,017 pmol/ml (range 0,04–0,098) in the CSF. KYNA concentration was statistically significantly higher in the sera from ALS patients than in controls; the difference was 0,3± 0,071 pmol/ml (t=18,79, p< 0,05), and statistically significantly higher in the CSF from ALS patients compared with control subjects; the difference was 0,022± 0,026 pmol/ml (t=3,72, p< 0,05). Because KYNA diminishes the risk of excitotoxic neuronal damage our results indicate that this acid has a marked neuroprotective action in ALS patients.

P685
SPINAL MUSCULAR ATROPHY: MUTATIONAL SCREENING OF SMN AND NAIP GENES IN ITALIAN FAMILIES. C. Gellera, B. Castellotti, D. Vacca, P. Boffi, F. Lalatta, L. Morandi, C. Mariotti, M. Zeviani, Istituto Nazionale Neurologico, Osp. Inf. "Regina Margherita", Clinica Ginecologica "Mangiagalli" (Milano, I)

Spinal Muscular Atrophy (SMA) is a common autosomal recessive neuromuscular disorder with an incidence of 1 in 10000 live births and a carrier frequency of about 1: 50. The disease is characterized by degeneration of spinal cord motor neurons and muscular atrophy. Clinical classification, based on age of onset and disease progression, distinguishes three forms of SMA (type I, II and III). Survival motor neuron gene (SMN), located on chromosome 5q13, is the SMA determining gene. SMN is present in multiple copies, in a telomeric (SMN1) and in a centromeric (SMN2) variant. Most of SMA patients carry a homozygous deletion in the SMN1 gene; a few patients are heterozygous for the deletion of exons 7–8 in one allele and a micromutation in the other allele. In SMA deleted patients a deletion is also frequently found in an adjacent gene, named neuronal apoptosis inhibitory protein gene (NAIP). We report here the molecular analysis of 100 SMA patients: 40 patients were clinically diagnosed as having type I SMA; 24 patients had type II SMA, and 36 patients had type III SMA. Molecular screening for the deletion in SMN gene has been performed by PCR amplification followed by specific restriction enzyme analysis of exons 7 and 8. The presence of deletion in exons 5 and 6 in the NAIP gene has been determined by multiplex PCR. We found a SMN1 gene deletion in 69/100 patients: 37 with SMA type I (37/40; 92%); 20 patients with SMA II (20/24; 83%); 12 patients wih SMA III (12/36; 33%). A NAIP gene deletion was present in 22/37 SMN1 deleted patients with SMA I, in 9/20 patients with SMA II and in 0/12 patients with SMA type III. A 14-month old girl with type II SMA, was found to be heterozygous for a SMN1 deletion in one allele and a previously reported deletion of 5 nucleotides in exon 3 in the other allele. She had no deletions in NAIP gene. Her younger brother died at age 3 with a clinical diagnosis of type I SMA. Two patients, with SMA type I and type III, respectively, were found to be heterozygous for SMN1 deletion, but no mutations could be detected on the other allele. Interestingly, these two patients were also heterozygous for deletion in the NAIP gene. Mutational screening of SMN gene led to molecular diagnosis in 70% of SMA patients, and to the identification of carriers within the families. Due to the high frequency of carriers, SMN1 gene analysis is a fundamental tool for genetic counseling and prenatal diagnosis. A systematic search for SMN mutations in SMA type II and III patients is underway.

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NEW INSIGHTS ON THE VIRAL THEORY OF AMYOTROPHIC LATERAL SCLEROSIS: POSSIBLE ROLE OF HUMAN HERPESVIRUS 8. P. Sola, R. Bedin, F. Casoni, P. Barozzi, E. Merelli, Neurological Department, Department of Internal Medicine (Modena, I)

In the last years, three new herpesviruses, HHV–6, –7, and –8, have been discovered. Like retroviruses, these herpesviruses share interesting biological characteristics for a possible role in the development of both neurological and lymphoproliferative diseases. On the basis of the controversial viral hypothesis for the pathogenesis of amyotrophic lateral sclerosis, in a previous study we searched by the polymerase chain reaction (PCR) for the presence of HHV–6 specific sequences in patients with definite ALS and healthy controls, but we could not demonstrate a relation between this virus and the disease. More recently, specific viral sequences belonging to HHV–8 have been found in autoptic brain specimens from multiple sclerosis patients, normal adults died for traumatic cause, and new-born children, suggesting that, like HHV–6, also this novel herpesvirus is provided of neurotropism. Besides being strongly associated to Kaposi's sarcoma, HHV–8 has been found related with several lymphoproliferative diseases. This is an unusual herpesvirus in that its genome contains the expected open reading frames (ORFs) encoding for enzymes and viral structural proteins found in other herpesviruses, but it also contains an unprecedented number of ORFs pirated during viral evolution from cellular genes. The translation products of ORFs reveal HHV–8 to be a molecular pirate, able to produce homologues of several human gene products, resulting in alterations in cell cycle, in apoptosis and cell-mediated immune responses. These peculiarities may account for a possible role of HHV–8 in the development of both lymphoproliferative diseases and some neurological diseases, including ALS. On these observations, together with the evidences of autoimmune alterations in ALS, and association between motor neuron diseases and lymphoma/gammopathies, we investigated by the PCR and nested-PCR, the presence of specific sequences of HHV–8 in the peripheral blood mononuclear cell DNAs from 20 definite ALS patients and 20 controls, and in the cerebrospinal fluid from 37 ALS patients. The results obtained by the PCR showed sequences specific for HHV–8 in only one out of 20 ALS and in none of the 20 controls. The HHV–8 positive ALS patient was affected by a rapidly progressive bulbar form of disease, and laboratory examination did not show gammopathy and lymphoproliferative disorders. The results of CSF PCR are still in progress. In spite of the failure of scientific efforts in defining a causal agent of ALS, new insights on the mechanisms by which viruses may interact with the host cell genome, and with the human immune system make the viral hypothesis of ALS still worthy of further studies. In particular, viruses or retroviruses able to cause persistent and latent infections, and able to interfere with cellular gene expression and regulation, appear to be suitable candidates for a possible role in ALS development.

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MOTOR NEURON DISEASE ASSOCIATED WITH A CEREBRAL ASTROCYTOMA. F.I Monton, N. Ruiz-Lavilla, M.A Benitez, P. Perez-Lorenzu, J. Dominguez, Hospital N.S Candelaria (SC Tenerife, E)

Objective: To describe a motor neuron disease (MND) preceding the discovery of an asymptomatic occipital astrocytoma. Background: MND may rarely be associated with systemic cancer. However, whether MND can be considered a paraneoplastic syndrome is controversial. A cerebral tumor is not considered a neoplasm associated with paraneoplastic MND. Case report: A 64 year old man came to our observation for weakness of the upper limbs which had slowly progressed during the previous 6 months. Muscle atrophy and weakness were more pronounced on the right side. Deep tendon reflexes were abolished in upper limbs and right leg; left ankle and knee jerks were brisk and the Babinski's sign was present on the left side. Electromyography (EMG) showed denervation-reinnervation exclusively on upper limbs; nerve conduction studies were normal without conduction block. Laboratory studies including anti-Hu and antibodies to GM1, GM2, GM3, asialo-GM1, GD1a, GD1b, GD3, GT1b, GQ1b and sulfatide were negative. A CT scan showed a right occipital expansive hypodense lesion compatible with an astrocytoma. Cervical MRI was normal. After tumor resection no clinical improvement was observed on upper limbs weakness. An EMG performed 6 months after surgery showed no evidence of acute denervation on the legs. Conclusions: Exceptionally, a MND can be associated with cerebral tumors and precede the appearance of brain symptoms.

P688
EFFECTS OF SPIKY ADMINISTRATION OF LARGE POOL OF AMINOACIDS ON DENERVATED RAT MUSCLES. L. Bet, P. Bazzi, S. Rapuzzi, M. Moggio, F. Dioguardi, L. Marabini, A. Prelle, G. Cavaletti, M. Serafini, C. Mariani, G. Tredici, M. Braga, University of Milan, IRCCS "S. Maria Nascente", University of Milan II, "Bicocca" (Milan, I)

Rationale: – This study aims at verifying whether the administration of a large pool of aminoacids can limit muscle wasting in denervated rats. Recent studies show that the spiky administration of an aminoacidic pool can generate a synthetic drive. Dietary allowance maintains the ratio between plasma and intracellular aminoacid concentration ("delta") quite constant and low, therefore proportionally lowering the anabolic drive. The "delta synthetic drive" hypothesis suggests that repeated and intermittent assumptions of aminoacids are more efficient than one single dose of a comparable amount of aminoacids, because multiple assumptions are followed by repeated synthetic drives if intracellular concentrations are allowed to return to low values by matching quantity and timing of administration. Starting from this observation, we performed morphological studies on rat skeletal muscle in order to verify whether spiky treatment with large pool of aminoacids is able to interfere with muscle wasting due to denervation, as seen in motor neuron disease. Materials and methods: – We treated 10 male Sprague-Dawley rats aged 42 days with a mixture of aminoacids composed of L-leucine, 3750 mg; L-lysine, 1950 mg; L-isoleucine, 1875 mg; L-valine 1875 mg; L-threonine 1050, mg; L-cystine 450, mg; L-histidine 450, mg; L-phenylalanine 300 mg; L-methionine 150, mg; L-tyrosine 90 mg; L tryptophan, 60 mg. The total daily dose was of 2 gr./Kg. of the mixture divided into 3 oral administrations by gavage. Mean rat weight was 186.4 gr. at the beginning of treatment and 323.5 gr. at the end. 10 aged-matched control identical rats received placebo per os in the same way. All rats were denervated by complete section of the right Sciatic Nerve. Treatment was started the day after surgery. 14 days later all the animals were sacrificed and different muscles (Soleus; Gastrocnemius; Extensor Digitorum Longus, EDL) immediately removed and frozen in liquid nitrogen cooled isopentane for histochemistry. Left leg muscles were used as controls for both treated and untreated rats. Results:

– Untreated undenervated muscle fiber examination showed type II prevalence in both Gastrocnemius and EDL whereas type I predominance was evident in Soleus. Treated undenervated muscles revealed the same pattern. Untreated denervated muscles showed diffuse type I and type II hypotrophy, in all muscles. Moreover an overt shift from type I to type II muscle fibers was seen, particularly in Soleus muscle. All treated denervated muscles showed 1) less severe fiber hypotrophy compared with untreated denervated muscle; 2) reduced evidence of muscle fiber type shift. Discussion: – Reduced evidence of skeletal muscle hypotrophy and muscle fiber type shift in denervated muscles from aminoacid-treated rats demonstrates that spiky administration of aminoacids may interfere with muscle metabolism. Muscle fiber protein synthesis studies are in progress.

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SOD–1 MUTATIONS IN THE IRISH AMYOTROPHIC LATERAL SCLEROSIS (ALS) POPULATION. M.D Alexander, BJ. Traynor, B. Corr, E. Frost, A. Greene, O. Hardiman, Beaumont Hospital, Irish MND Association, National Centre for Medical Genetics (Dublin, IRL)

Mutations of the gene Copper/Zinc Superoxide Dismutase (SOD–1) accounts for between 13–24 % of familial ALS (FALS) and 1 % of all ALS cases. In a prospective study of the well-defined homogeneous Irish population, we sought to determine the frequency of SOD–1 mutations in sporadic ALS (SALS), and to further characterise the 4 novel mutations identified thus far in our population. 2 mutations have been identified in the 3' region of the gene, close to a polyadenylation site. Polyadenylation plays an important role in post-transcriptional processing, and mutations in this region could affect post-transcriptional splicing. The significance of mutations in this region is at present unclear with respect to the pathogenesis of ALS, as they would predict a loss of enzyme function. METHODS. To date DNA has been collected from 70 SALS and 6 FALS patients, which approximates 45 % of the Irish ALS population. DNA was extracted and subjected to PCR, SSCP and heteroduplex analysis. Mobility shifts were further analysed by restriction enzyme digest and DNA sequencing. The mutations in the 3' untranslated region (UTR) of exon 5 were further characterised by reverse transcription PCR (rt-PCR). Blood was obtained from the parents of 2 of the apparent SALS cases. DNA from 80 unrelated control subjects was similarly analysed. RESULTS. A point mutation resulting in an Alanine to Valine substitution has been identified at codon 95 in a member of a known FALS kindred. Codon 95 forms part of the SOD–1 beta-barrel structure and is highly conserved in most species. 2 mutations in 2 unrelated SALS patients have been identified in the 3' UTR of exon 5. These comprise a point mutation (cytosine to guanine at position 333) and a 4 base pair deletion. No such changes have been observed in the 80 controls. Both mutations occur adjacent to a polyadenylation site. The functional significance of these is currently being investigated by rt-PCR, and by analysis of enzyme activity. The fourth mutation occurred in a SALS patient with rapidly progressive disease, and results in a His 80 Arg substitution. This site is known to be involved in Zinc ligand binding. Autopsy of this patient has been performed, and findings will be presented. The family of this patient does not exhibit the His 80 Arg mutation. CONCLUSIONS. Rates of SOD–1 mutations in the Irish ALS population are similar to those found elsewhere, although the Irish population appears to contain novel mutations. Cases of truly sporadic SOD–1 mutations have been identified in the Irish population. Mutations in the 3' UTR of exon 5 may be of pathological significance.

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ENTERAL FEEDING IN AMYOTROPHIC LATERAL SCLEROSIS (ALS): RADIOLOGICALLY INSERTED GASTROSTOMY OR PERCUTANEOUS ENDOSCOPIC GASTROSTOMY? MD. Alexander, B. Corr, M. Gorman, E. Frost, M. Lee, F. Murray, O. Hardiman, Beaumont Hospital, Irish MND Association (Dublin, IRL)

Patients with ALS are at risk of sub-optimal fluid and caloric intake. The role of nutritional support with percutaneous gastrostomy (PEG) has been well established in this patient population. Patients with a forced vital capacity (FVC) below 50 % of predicted are at increased risk of morbidity and mortality following PEG, and the procedure is not recommended in this group. An alternative approach to PEG is the use of radiologically inserted gastrostomy (RIG) which can be performed with minimal sedation. There have been suggestions that RIG is safer in patients with a reduced FVC. We report our experience with both PEG and RIG in ALS over a 2 year period. RESULTS. Between January 1998 and December 1999, 24 of our ALS patients developed symptoms of nutritional insufficiency, and were referred electively for gastrostomy. The average interval between diagnosis and gastrostomy was 27.5 ± 16 months, with purely bulbar-onset patients accounting for most of the earliest referrals. Eighteen patients (75 %) were initially referred for PEG. The average interval between diagnosis and PEG insertion was 20 months. PEG insertion was unsuccessful in 5 cases (28 %), predominantly due to the failure to transilluminate at the time of percutaneous puncture. Failure to transilluminate was associated with a reduced FVC (45–55 %) in all cases. One patient died 24 hours after PEG insertion due to perioperative aspiration of a mucus plug with subsequent bronchospasm and respiratory arrest. The remaining 4 patients who had failed PEG insertion subsequently had successful RIG placement with no serious immediate or long-term complications. Six of the 24 patients (25 %) were electively referred for RIG, including one patient who was ventilated via a tracheostomy tube. All attempted RIG insertions were successful. The average interval between diagnosis and insertion of elective RIG was 11.7 months. There was no significant difference between the PEG and RIG populations with respect to mean vital capacity or nutritional status. No serious peri- or post-operative complications were associated with RIG placement. Currently, there is no significant difference in survival between the 2 groups. CONCLUSIONS. RIG is well tolerated by ALS patients. The procedure appears to be a safe, reliable and effective form of gastrostomy in ALS patients. A randomised trial between PEG and RIG is advocated.

P691
FRONTAL LOBE DEMENTIA AND MOTOR NEURON DISEASE: A CLINICAL CASE. A. Rodríguez-Campello, J. Pascual, J. Peña-Casanova, J. Roquer, M. Gomis, E. Munteis, J. Izquierdo, A. Pou, Hospital Del Mar (Barcelona, E)

The association of dementia and motor neuron disease has been estimated in 5 % of cases. The neuropsychological syndrome is a frontal lobe type dementia with linguistic and behavioral disturbances. Previous reports have shown a characteristic semiological pattern and single photon emission computed tomography (SPECT) fronto-temporal hypoactivity. AIMS: We describe clinical, neuropsychological features and SPECT pattern in a new case of frontal-lobe dementia (FLD) with progressive development of diffuse upper and lower motor neurone signs of sporadic amyotrophic lateral sclerosis (ALS). CASE REPORT: The patient was a 57 year old male who presented a 12 month history of slow personality change, with depressive state, sadness, apathy and excessive alcohol consumption. There was no family history of neurological disease. He had a progressive reduction of speech with echolalia and perseveranve. General examination was normal. Neurological examination revealed signs of corticospinal pathway disfunction, with enhanced jaw jerk, hyperreflexia, Hoffmann's sign, bilateral grasping and palmomentonian reflexes together with diffuse limb muscle fasciculations and moderate degree of amyotrophy. No bulbar disfunction was seen. Sensation, coordination and gait were normal. Neuropsychological testing revealed frontal lobe dysfunction in absence of amnesia, perceptual, spatial or praxic disorders. CT scan and MRI revealed an important cortical fronto-temporal atrophy more marked in the left hemisphere. EEG was normal. SPECT demonstrated reduced uptake in both frontal lobes and left temporal lobe. Electromyography confirmed signs of diffuse denervation in the four limbs. DISCUSSION: The reported case confirms the association between FLD and ALS and establishes new insights that both disorders could represent the same entity. We don't exclude the possibility of being a peculiar form of Creutzfeldt-Jakob disease. Finally, we emphasize the convenience of a long follow-up in patients with FLD.

P692
REDUCTION OF DROOLING IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS AFTER INJECTIONS OF BOTULINUM TOXIN A INTO THE SALIVARY GLANDS. R. Giess, M. Naumann, E. Werner, R. Riemann, M. Beck, I. Puls, K. V. Toyka, University of Würzburg (Würzburg, D)

Background: Drooling is a disabling symptom in up to 20 % of patients with amyotrophic lateral sclerosis (ALS). The use of anticholinergic drugs is often unsuccessful and limited by undesirable side-effects. Inhibition of secretion of the salivary glands by local injection of Botulinum toxin A (BoNT/A) could be considered as a new approach in palliative care of bulbar ALS patients.

Methods: In five patients with bulbar ALS and disabling sialorrhea, six to 20 mouse units (MU) BoNT/A were injected into each parotid gland. If the clinical response was insufficient, the same dose was reinjected two weeks later. The submandibular glands were injected only if parotid gland injection alone was insufficient. As a simple method to quantify drooling, all patients assessed the response to BoNT/A by counting the number of paper handkerchiefs used per day. Additionally, before the first and two weeks after the last treatment salivary gland secretion was quantified by salivary gland scintigraphy.

Results: Three patients received BoNT/A injections into the parotid glands only, two patients required subsequent injections into the parotid glands and an additional injection of 5 MU BoNT/A into each submandibular gland. The mean total dose injected into each parotid gland was 46±16.9 MU BoNT/A (range 30 to 72 MU). A reduction of sialorrhea was first noticed three to five

days after injection. A marked reduction of drooling measured by the number of paper handkerchiefs used per day was found four weeks after the last injection. Two weeks after the last injection, a reduction of radiotracer uptake in both parotid glands was demonstrated in salivary gland scintigraphy. One patient with a very rapidly progressive course of the disease did not show a clinical benefit even after repeated parotid and submandibular gland injections. We did not observe potential adverse effects such as drying of the mouth, deterioration of dysphagia, infections of the salivary glands or salivary ducts, hematomas, salivary duct calculi, local injuries of the carotid artery or of branches of the facial nerve.

Conclusion: Our small study shows that the injection of BoNT/A into the parotid and/or submandibular glands is beneficial in patients with drooling secondary to bulbar ALS. Although no major adverse events have been observed in our patients, BoNT/A has to be injected carefully and the total dose must be limited in order to avoid interference with the paralysis caused by the motoneuron disease. A full clinical trial is needed to sufficiently evaluate the risks and benefits of BoNT/A injections for palliative treatment in bulbar ALS.

Multiple sclerosis

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CLINICAL ASPECTS AND SEVERITY OF PAIN SYNDROMES IN A MULTIPLE SCLEROSIS POPULATION: A DESCRIPTIVE STUDY. L. P. Marchello, C. Scandellari, O. Cameli, C. Trocino, L. Sabattini, S. Stecchi, U. Ecari, Multiple Sclerosis Center, Farmades (Bologna, Roma, I)

BACKGROUND: To determine the prevalence and nature of pain in Multiple Sclerosis (MS) patients.

PATIENTS and METHODS: We evaluated by questionnaire, interview, clinical and laboratoristical chart review a sample of 352 MS patients (236 females and 116 males) followed in the Multiple Sclerosis Center of Bologna. Disability was assessed using the Expanded Disability Status Scale (EDSS). All patients had a clinically definite MS diagnosis according to the criteria of Poser et al. (1983).

RESULTS: We distinguished two groups. The first consisted of 148 patients who did not feel pain associated to MS: 79 females (mean age: 46.2 yy; mean disease duration: 15.1 yy; mean EDSS: 3.5) and 69 males (mean age: 43.9 yy; mean disease duration: 15.6 yy; mean EDSS: 4.0). The second 204 patients were troubled by one or more pain syndromes lasting more than one month, 157 females (mean age: 48.6 yy; mean disease duration: 15.6 yy; mean EDSS:4.4).

CONCLUSION: We report the preliminary data relative to frequency of pain syndromes in MS: 57.9%. Detailed clinical characteristics and disability of various pain syndromes. Correlation of pain with degenerative disease, polineuropathy and headache. Correlation with EDSS and clinical form of MS. Correlation with chronic therapy as interferon or immunosuppressant. At last efficacy of pharmacological treatment in different types of pain.

P695
WEBER'S SYNDROME AS A FIRST MANIFESTATION OF MULTIPLE SCLEROSIS. A. Solida, A. Carruzzo, M. Schluep, F. X. Borruat, F. Vingerhoets, J. Bogousslavsky, CHUV, Department of Neurology, CHUV, Department of Ophthalmology (Lausanne, CH)

Introduction: The association of a third nerve palsy and a contralateral hemiparesis, known as Weber's syndrome, is usually caused by vascular (infarct, haemorrhage) or neoplastic lesions involving ventral midbrain. It has been reported that, in multiple sclerosis, isolated third nerve palsy may exceptionally occur as first manifestation (Newman, 1990; Uitti 1986), but no case of Weber's syndrome has yet been reported in the setting of a demyelinating disease of CNS. We describe a patient with a fascicular intra-axial oculomotor palsy associated with contralateral motor and sensitive hemiparesis (Weber's syndrome) as first manifestation of multiple sclerosis.

Case report: A 28 year-old man with no previous remarkable medical history developed oro-cheiro-podal paraesthesia on the right side over several days. A week later he complained of blurred vision with diplopia, partial drooping of the left eyelid and weakness of the right upper and lower limb. Neurologic examination showed a left complete third nerve palsy with ipsilateral ptosis and mild mydriasis. Abduction and inward cyclorotation of the left eye were preserved. Visual acuity, colour vision, visual fields and fundoscopic examination were unremarkable. There was also a right proportional mild hemiparesis and cheiro-oral dysesthesia. Brain MRI revealed a large hyperintense T2 lesion on the left ventrolateral part of the midbrain and several small white matter lesions in both hemispheres that had no relevance to the clinical symptomatology. Cerebrospinal fluid examination revealed a lymphocytic pleocytosis (50 cells/mm^3) and intrathecal synthesis of oligoclonal immunoglobulins G. Blood and CSF work-up (including a work-up) were negative for vasculitis, Lyme disease, syphilis and HIV. A diagnosis of laboratory-supported definite multiple sclerosis was made and intravenous corticosteroids (methylprednisolone 500 mg/d) were initiated. Symptoms improved in few days. One month later, the neurological examination was normal, except for persistent mild right corticospinal signs.

Conclusion: We report the first case of a III fascicular intra-axial palsy associated with a contralateral hemiparesis (Weber's syndrome) secondary to multiple sclerosis. We demonstrated using MRI that an acute demyelinating lesion, extending from left ventral medial midbrain to cerebral peduncle, was responsible for the symptomatology. Weber's syndrome is usually secondary to vascular or neoplastic midbrain lesions, but our observation suggests that demyelinating disease should also be considered in the differential diagnosis.

P696
NATURAL HISTORY OF APHASIA IN MULTIPLE SCLEROSIS AND MRI FINDINGS CORRELATION. N. Grigoriadis, A. Triantafilou, I. Mavromatis, S. Tsounis, M. Paschalidou, I. Milonas, AHEPA Univ Hosp (Thessaloniki, GR)

Aphasia is thought to be uncommon in Multiple Sclerosis (MS) and has never been reported among the initial symptoms of the disease. However, there are a few reports on the occurence of aphasia as part of MS exacerbations, although in a limited number of these reports, a correlation between the clinical presentation of aphasia and the correspondent neuroimaging findings, was attempted. Here we report two cases of MS where aphasia was among the presenting symptoms of MS and serial MRIs were performed during a two year follow up of the patients.

Both patients, one with relapsing-remitting MS (case A) and the other with primary progressive MS (case B), presented non fluent aphasia and agraphia. In case A, language impairment was severe enough and a large demyelinating plaque was detected in the subcortical frontotemporal region of the dominant hemisphere. Both language and motor deficits responded well to methylprednizolone IV treatment. During a 3, 6 and 16 months follow up, while the patient was under interferon treatment, the language improvement was complete and a slight diminution of plaque size was evident in the last two MRI recordings.

Aphasia is thought to be uncommon in Multiple Sclerosis (MS) and has never been reported among the initial symptoms of the disease. There are only a few reports on the occurrence of aphasia as part of MS exacerbations. Nevertheless, in a limited number of these reports, a correlation between the clinical manifestation of aphasia and the correspondent neuroimaging findings, has been attempted. We report two cases of MS with aphasia among the presenting symptoms in which serial MRIs were performed during a two year follow up.

Both patients, one with relapsing-remitting MS (case A) and the other with primary progressive MS (case B), presented non fluent aphasia and agraphia. In case A, language impairment was severe enough and a large demyelinating plaque was detected in the subcortical frontotemporal region of the dominant hemisphere. Both language and motor deficits responded well to methylprednizolone IV treatment. During a 3, 6 and 16 months follow up, while the patient was still under interferon treatment, the language improvement was complete and a slight diminution of plaque size was evident in the last two MRI recordings.

In case B, the aphasia was not as severe as in the previous patient. In accordance, MRI demonstrated a middle sized plaque in the posterior subcortical frontal area of the dominant hemisphere. During 3, 6 and 18 months follow up, no change in plaque size could be detected in MRI. Language deficits of this patient were either less or slightly altered during follow up, but never absent.

Our findings suggest that the presentation of aphasia in MS is correlated with the anatomic location of the demyelinating plaque. In addition, it seems that the natural history of this symptom may be correlated with the size of the underlying lesion.

P697
VISUAL RECOVERY UNDER MITOXANTRONE THERAPY IN A YOUNG MAN WITH THE RARE COMBINATION OF PRIMARY LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON) AND A MULTIPLE SCLEROSIS-LIKE DISEASE. C. Buhmann, J. Gbadamosi, C. Heesen, Universitätskrankenhaus Eppendorf (Hamburg, D)

We describe a young man with Leber's hereditary optic neuropathy (LHON) carrying a homoplasmatic mitochondrial DNA point mutation at locus 11778 and additionally having laboratory supported definitive multiple sclerosis (MS) according to the Poser criteria.

LHON with the 11778 mutation predominantly affects young men and causes severe central visual loss with ultimately optic atrophy. The combination of LHON and a MS-like disease is known in females but in men only described in a few case reports. Our patient recovered clinically remarkably from

subtotal loss of vision to a sufficient vision under immunosuppressive therapy with mitoxantrone. Under consideration of the reports in the literature and the presented case we suggest to search for LHON mutation in MS patients with predominant visual impairment independently of patients' sex. The observed therapeutic effect of immunosuppressive based therapy in our case raises the hypothesis of an underlying immunological process in the etiology of LHON with associated MS-like disease and therefore of a therapeutic possibility in these cases.

P698
VALUE OF URODYNAMICS IN MULTIPLE SCLEROSIS (MS). W. Feneberg, N. König, Marianne-Strauss-Klinik (Berg/Kempfenhausen, D)

Background: Lower urinary tract symptoms (LUTS) are common in MS. Also they are said to be harmless compared with those in spinal cord injury in the long term follow up, many MS patients suffer from recurrent urinary tract infections and some develop severe bladder and upper urinary tract deterioration.

Aims of the study: Assessment of LUTS in inpatients with MS. Are clinical and anamnestic data sufficient to manage the individual bladder symptoms successfully?

Methods: 148 consecutive inpatients with MS (138 definite, 10 probable according to criteria of Poser) and the complaint of voiding disorders were investigated (mean age 47 years (range 26–77), mean disease duration 16 years (range 2–50), mean EDSS 5,9 (range 2–9)). Each patient underwent detailed neurological and neurourological evaluation, urine studies, several measurements of residual urine (RU) and got a voiding diary for several days. The urodynamic testing (UT) performed in each patient consisted of a transurethral cystometry and pressure-flow study, together with EMG of the pelvic floor muscles and a voiding cystourethrogramm (VC),

Results: Most patients complained of irritative (84%) and obstructive (86%) symptoms. 47% had al least one urinary tract infection/year. Incontinence was common (71%). 45% had average RU greater than 100 ml. During UT 84% showed detrusor hyperreflexia (DH), 12% detrusor areflexia, 84% detrusor-sphincter dyssynergia (DSD), 87% reduced or no control of the external urethral sphincter. Abnormalities on the VC included vesicoureteric reflux (n=15, 3115 bilateral), bladder diverticula (31%) and bladder trabeculation (85%). Most patients with RU greater 100 mi showed DH and DSD. The voiding symptoms of the patients, together with RU and clinical examination were not suitable for predicting type and severity of the underlying bladder dysfunction.

Conclusion: In MS patients with obstructive and irritative bladder symptoms UT is indispensable and should be recommended early to improve the management of the bladder dysfunction and try to avoid lower urinary tract destruction.

P699
AN UNUSUAL CASE OF REGRESSIVE MULTIPLE SCLEROSIS. I. Achiti, J. Grimaud, Th. Moreau, Ch. Confavreux, Hôpital Neurologique (Lyon cedex 03, F)

A 71-year old patient affected by multiple sclerosis for 45 years has presented a steady regression of his disability over the last eight years. Born in 1927, his multiple sclerosis appeared in 1954 with paraparesis and sphincter disturbances. The disease entered the progressive phase in 1972. CSF biological analysis, evoked potentials, brain CT and MRI confirmed the diagnosis. From 1983 to 1991, the patient suffered from paraplegia, internuclear ophthalmoplegia, cognitive and sphincter disturbances. EDSS score was 8.0 (wheelchair bound). All along that period, the treatment with azathioprine (1972–1983) and natural intrathecal interferon (11 monthly injections in 1983) did not prevent from worsening. Since 1991 without any disease modifying agent, the neurological examination and disability have improved continuously. In January 1999, EDSS score was 6.5. Cognitive impairment and brainstem signs have almost disappeared.

This unusual improvement shows that a persistent level of disability, though sustained and confirmed after 6 months, is not irreversible. Some recovery mechanisms may occur (remyelination?) and lead to a significant clinical improvement. Axonal loss would not be the only cause for the clinical progression of multiple sclerosis.

P700
DISSOCIATION BETWEEN RELAPSES AND DISABILITY PROGRESSION IN MULTIPLE SCLEROSIS. S. Vukusic, T. Moreau, P. Adeleine, C. Confavreux, Service de Neurologie, Hôpital Neurologique, Hôpital de la Croix Rouge (Lyon, F)

Background. Licensed disease-modifying treatments in multiple sclerosis have shown reduction in frequency of relapses. Efficacy on progression of disability is less convincing. We studied the influence of relapses on accumulation of residual disability in multiple sclerosis.

Methods. 1844 consecutive patients with multiple sclerosis were examined within the same reference centre since 1957 for following determinations: date of onset of multiple sclerosis; inaugural course of multiple sclerosis, whether exacerbating-remitting or progressive; dates of relapses; dates of entry into residual Kurtzke Disability Status Scale scores; occurrence of a progressive course, either secondary to a relapsing-remitting course or primary. Survival analyses were performed for time to entry into DSS4 (limited walking but without aid), DSS6 (walking with unilateral aid) and DSS7 (wheelchair-bound) scores.

Results. Median time intervals from onset of multiple sclerosis to entry into DSS4, DSS6 and DSS7 were longer in cases with an exacerbating-remitting onset (11.4, 23.1, and 33.1 years) than in cases with a progressive onset (0.0, 7.1, and 13.4 years; $p< 0.0001$ for all comparisons). Transitions from one level of disability to another were similar whatever the inaugural course of the disease ($p=0.74$, 0.70, and 0.48 for DSS4 to DSS6, DSS4 to DSS7, and DSS6 to DSS7 transitions). In patients with a secondary or a primary progressive form of multiple sclerosis, these transitions were either not influenced or delayed by presence of superimposed relapses by comparison to cases without superimposed relapses.

Conclusions. There is a relative dissociation between relapses and progressive accumulation of disability in multiple sclerosis.

P701
NEUROPSYCHOLOGICAL EFFECTS OF INTERFERON BETA 1-B IN RELAPSING-REMITTING MULTIPLE SCLEROSIS. M. A. Hernandez, T. Wollmann, M. P. Sanchez, M. D. Gonzalez, A. Nieto, T. Y. Olivares, J. Barroso, Hospital ntra. sra. Candelaria, University of La Laguna (Santa Cruz Tenerife, E)

Background: Some degree of cognitive impairment can be detected in 40 to 60% of Multiple Sclerosis (MS) patients, depending on both the clinical and demographic characteristics of the sample studied and the neuropsychological tests administered. Recently a new question has arisen, concomitantly with the therapeutic advances in MS: Does the interferon treatment produce beneficial effects on neuropsychological deficits of MS patients?.

Objective: The aim of the present study is to examine the changes that occur in some cognitive functions after one year on treatment with interferon beta 1-b.

Methods: We have studied 14 patients with relapsing-remitting MS treated with interferon beta 1-b and 38 normal controls recruited from the community. The neuropsychological tests administered were: Mini-Mental State Examination (MMSE),Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT),Visual Reproduction (WMS-R),Wisconsin Card Sorting Test (WCST), Stroop Test. The patients were tested twice. The first testing (baseline) was done before the start of treatment and the second testing was done one year after. The controls were tested only once, at baseline.

Results: MS group did significantly worse than did the controls on speed of information processing, reaction time (both decision and motor time), attention and memory measures. No significant differences were found on general cognitive status (MMSE), problem solving, flexibility nor susceptibility to perceptual interference. Significant differences were found between first and second testing in the MS group on WCST (categories achieved and perseverance index), Stroop Test (color-word interference trial and interference index) and memory measures (Logical Memory and Visual Reproduction). No improvement was observed on SIP (PASAT and SDMT) nor RT measures.

Conclusions: The patients showed significant improvement on problem solving, flexibility, selective attention and recent memory measures after one year on treatment with interferon beta 1-b

P702
THE EFFECT OF IMMUNOMODULATORY THERAPY ON COGNITIVE PROCESSING IN MULTIPLE SCLEROSIS – A PILOT STUDY. S. Evers, T. Ellger, A. Frese, R. Lüttmann, F. Bethke, University of Muenster (Münster, D)

Patients with Multiple Sclerosis (MS) show cognitive impairment which increases with the course of the diseases both in the relapsing-remitting and in the

chronic type. This impairment can be evaluated by measurement of event-related potentials (ERP). We designed an open pilot study in order to evaluate the effect of different immunomodulatory therapies on cognitive processing of MS patients as measured by ERP, in particular by the P3 component.

We enrolled 27 patients with a definite diagnosis of MS who had an indication for immunomodulatory therapy. Patients gave informed consent to receive either intravenous immunoglobulin treatment, interferon beta, or copolymer 1 in the routine dose and application. Nine patients refused to take such a medication. On the day of enrolment, ERP were measured on the same time of day and in the same setting for all patients but not during an acute phase. A visual oddball-paradigm was used to elicit the P3 component which was measured at centroparietal. The latencies of the P2, N2, and P3 components, the amplitude of the P3 component, and the mean choice reaction time were evaluated. Patients were asked to return after one year and to take no other psychotropic drugs during this time regularly. Only patients fulfilling these criteria were enrolled in the analysis. Nonparametric tests were used for statistical analysis.

There were no significant differences in age and sex between the 4 different treatment groups at enrolment. However, the EDSS score was significantly higher in the immunoglobulin group (5.2 ± 0.9; n=7) as compared to the copolymer 1 group (3.0 ± 1.7; n=4), to the interferon beta group (2.9 ± 2.8; n=7) and to the group without treatment (4.2 ± 1.9; n=9). After 1 year, the EDSS score increased significantly in the interferon beta group (3.8 ± 3.2; $p< 0.05$) and in the group without treatment (4.3 ± 2.2; $p< 0.05$) but remained stable in the other groups. During this time, the P3 latency (in ms) increased significantly in the group without treatment (470 ± 61 versus 487 ± 53; $p< 0.05$) and in the interferon beta group (452 ± 56 versus 462 ± 67; $p< 0.05$), decreased in the copolymer 1 group (534 ± 113 versus 483 ± 70), and did not change in the immunoglobulin group (449 ± 36 versus 456 ± 39; not significant).

Our data, although preliminary because of the open and not randomized design and because of small numbers, suggest that there is a decline of cognitive processing in MS during one year in patients without treatment. This decline was also seen in patients with interferon beta treatment but not in patients with copolymer 1 or immunoglobulin treatment. Further randomized studies are warranted to support the hypothesis that treatment with copolymer 1 or immunoglobulin can stop or delay the cognitive decline of patients with MS.

P703
EVALUATION OF MXA ASSAY IN THE VIRAL HYPOTHESIS OF MULTIPLE SCLEROSIS. A. Mackowiak, V. Chieux, G. Forzy, D. Hober, P. Gallois, P. Hautecoeur, Saint Philibert Hospital Neurology, Lab. of virology, C. H. R. U. (Lomme Cedex, Lille, F)

The etiology of multiple sclerosis (MS) remains unknown. Although epidemiological data support the idea of an environmental agent, which could be viral, up to now, no direct proof of such hypothesis has been found.

Interferon alpha is a natural secreted cytokine synthesised during viral aggression. It plays a major function in non-specific antiviral defence by production of intracellular proteins with antiviral activity in target cells. Myxovirus protein A (MxA) is one of the best biochemically and functionally characterized interferon-induced proteins. The aim of our current study is to evaluate MxA assay in MS patients.

Using a chemoluminescent labelling, MxA assay was performed on 144 MS patients during a 2 years period. Statistical data are not yet completely analysed but this assay seems to be of a great interest to validate the viral hypothesis in the pathogenesis of MS.

Variations of the MxA ratios, according to clinical patterns and age of the disease, relapses, and immunomodulatory treatment by interferon beta are also analysed.

P704
HIGH-DOSE INTRAVENOUS CYCLOPHOSPHAMIDE PULSE THERAPY IN SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS. P. Perini, S. Marangoni, B. Tavolato, P. Gallo, University of Padova (Padova I)

Background/Aim of the study: cyclophosphamide (CTX) is widely used in the treatment of severe progressive autoimmune diseases, such as systemic lupus erythematosus and multiple sclerosis; we evaluated the safety and clinical efficacy of high-dose i. v. CTX pulse therapy in patients with secondary-progressive multiple sclerosis (SPMS).

Materials and Methods: 10 patients with SPMS (4 males, 6 females; mean age±SD = 31.9±9.1) were included in the study. The mean EDSS value was 4.3±0.9 one year before therapy, and 5.8±0.9 at CTX therapy initiation; mean disease duration at entry was 7.3±3.5. Treatment consisted in monthly i. v. pulse CTX at a dosage of 800 to 1200 mg/m^2 for 1 year. Clinical evaluation was based on the EDSS, and was performed every month; MRI scans were obtained before therapy (T0) and after one year (T12). Disease progression was defined as confirmed deterioration of at least 1 point on EDSS in the previous year.

Results: the administration of CTX was safe and well tolerated by all the patients; no severe side effects were observed; a transient but moderate scalp alopecia was experienced by all the patients; nausea was a common symptom the day after CTX infusion; menstrual irregularities were also frequently observed. At T12, the mean EDSS score was 4.4±1.5 (T12 vs T0, p=0.02), an EDSS improvement 3 1 was observed in 5 patients, = 0.5 in 4 patients, while only one patient did not improve, but maintained his EDSS score. The mean relapse rate in the previous two years was 2.6±1.5; in the year of therapy, only two patients had a relapse. The MRI showed a significant decrease in the T2 lesion load, while no new gadolinium enhancing lesion was observed. Conclusions: this study confirms that monthly high-dose CTX therapy may be safely administered in SPMS patients; our findings further suggest that intensive immunosuppressive therapy may result in improvement or stabilisation of the disease in patients with SPMS.

Neuro-immunology

P705
RIFN BETA–1A AND SICAM–1 EFFECTS ON CD4+CD45RO+ PBTLS EXPRESSING LFA–1 IN RR MS: IN VIVO AND IN VITRO STUDY. C. Avolio, M. Ruggieri, P. Cafforio, F. Giuliani, F. Silvestris, P. Livrea, M. Trojano (Bari, I)

Recombinant Interferon beta (rIFN beta) induces an increase of soluble Intercellular Adhesion Molecule–1 (sICAM–1) serum levels in relapsing-remitting (RR) Multiple Sclerosis (MS) treated patients and this paralleled a reduction of clinical disability and percentage of patients with Gd-enhancing MRI scans. rIFN beta downregulates the expression of ICAM–1 on rat and human endothelial cells. Leukocyte Function Antigen–1 (LFA–1; CD11a/CD18) represents the counter-receptor of ICAM–1. Goals: To investigate, in vivo and in vitro, the effects of rIFN beta–1a and, in vitro, of recombinant sICAM–1 (rsICAM–1) on CD4+CD45RO+ memory-effector peripheral blood T-lymphocytes (PBTLs) expressing LFA–1 in rIFN beta–1a treated MS patients. Methods: Blood samples were obtained from 10 RR MS patients before and after 2, 4 and 6 months of rIFN beta–1a (Avonex) treatment. For each sample the percentage of CD4+CD45RO+CD11a+ T-cells was evaluated in ex vivo PBTLs and in untreated and treated (either 1000 U/ml of rIFN beta–1a or 400 ng/ml of rsICAM–1) cultured PBTLs by triple fluorescence flow-cytometry (FACS analysis). Results are presented as percent of positively stained cells. Results: The percentage of CD4+CD45RO+CD11a+ PBTLs increased in vivo after 4 and 6 months of rIFN beta–1a treatment compared to pretreatment ($p< 0.01$) and 2 months of treatment ($p< 0.05$). In these T-cells, CD11a+ dim expression prevailed (p=0.005) compared to bright expression. This in vivo rIFN beta–1a-induced CD4+CD45RO+CD11a+ T-cell increase was in vitro not affected by the addition of a further amount of rIFN beta–1a but it was reduced by high doses of rsICAM–1 ($p< 0.05$). Conclusions: rIFN beta–1a increases the CD4+CD45RO+ memory-effector PBTLs expressing LFA–1 in RR MS treated patients but, as observed in vitro, this effect may be modulated by the contemporary increase in serum sICAM–1. Moreover rIFN beta–1a seems to favour dim expression of LFA–1 on these T-cells.

P706
AMYLOID PRECURSOR PROTEIN (APP) EXPRESSION IN THE SUBSTANTIA NIGRA AND STRIATUM IN THE MPTP MICE MODEL OF PARKINSON'S DISEASE. T. Litwin, I. Kurkowska, A. Czlonkowski, A. Czlonkowska, Institute Psychiatry i Neurology, Department of Pharmacology (Warsaw, PL)

The beta-amyloid precursor protein (APP) bears characteristics of an acute-phase protein and thus may be involved in the glial response to the brain injury. 1-methylo–4-phenylo–1,2,3,6-tetrahydropiridine quite selectively damages dopaminergic neurons of the substantia nigra and deplete dopamine level in striatum. The neuronal necrosis is accompanied by micro- and astroglial activation and lymphocytes infiltration. We studied in this model APP expression in the SN and striatum. Methods: We used immunohistochemical methods to show microglial and astroglial reaction and APP expression on the 1st, 2nd, 3rd and 7th day following MPTP intoxication. Additionally three groups of animals were pre-treated with anti-inflammatory drugs: dexamethasone (1 mg/kg) propentofilline (10 mg/kg) indomethacine (3 mg/kg) and sacrified on the 3rd day after MPTP administration. Results: APP expression was observed from the 1st day both in the SN and striatum was the biggest on the 3rd day and completely disappeared on the 7th day. The majority of APP reactive cells there were CR3 positive microglia which showed in double labelling for CR3 and APP. APP expression diminished in striatum of mice treated with propentofilline and indomethacine and in the SN of mice treated with indomethacine. Dexametha-

sone did not influence APP expression however diminished slightly microglial reaction. Conclusions: Following MPTP intoxication, APP is induced in the SN and striatum mainly in microglial cells. Indomethacin and propentofillin inhibit totally APP expression in striatum and partially in the SN. Such inhibition may suggest different level of brain injury in these regions.

P707
MODULATION OF MICROGLIAL FUNCTIONS WITH POLYCLONAL IMMUNOGLOBULINS: AN IN VITRO STUDY. M. Stangel, A. Compston, Klinikum Benjamin Franklin, University of Cambridge (Berlin, D; Cambridge, UK)

Controlled trials in multiple sclerosis (MS) and case reports in acute demyelinating encephalomyelitis (ADEM) have shown that intravenous immunoglobulins (IVIg) are of therapeutic benefit in central nervous system (CNS) inflammatory diseases. Studies in experimental autoimmune encephalomyelitis (EAE) have suggested that modulation of the cytokine network and T cell responses contribute to the positive effect. However, there are no data on the influence of IVIg on the local immune reaction in the CNS, the site of inflammation in EAE. We have therefore studied the effect of IVIg on cultured rat microglia, the main immune cell in the CNS. IVIg increased nitric oxide (NO) production in a dose dependent manner in cells stimulated with IFN-gamma and LPS, but not in untreated microglia or after stimulation with TNF-alpha or PMA. This enhancement of NO production depended on the Fc portion of IVIg and could be abrogated by the pharmacological inhibition of Syk and phosphatidylinositol 3-kinase, two enzymes involved in the signalling cascade of Fc receptors. TNF-alpha secretion was dose dependently stimulated by IVIg in both untreated microglia and after stimulation with LPS or IFN-gamma. Again, this effect was mediated through the Fc portion. Finally, we examined Fc receptor-mediated phagocytosis that was inhibited by IVIg, presumably by blockade of the Fc receptor. These different effects may protect oligodendrocytes from antibody mediated phagocytosis and on the other hand could terminate the immune reaction by induction of apoptosis in infiltrating T cells via NO and TNF-alpha. We propose that IVIg, in addition to the known effects on the peripheral immune system, may also modulate the local immune reaction in CNS inflammatory disease.

P708
LITHIUM INDUCED MYASTHENIC SYNDROME. T. Ronzière, P. Auzou, C. Özsancak, D. Hannequin, M. Vérin, CHU Rennes, CHU Rouen, CHU Rennes Hôpital Pontchaillou (Rennes, Rouen, F)

Lithium is classically contra-indicated in myasthenia gravis (MG). However, only very few observations of neuromuscular junction disorders due to lithium have been reported. It has been suggested that lithium may either induce reversible myasthenic syndromes or unmask MG but the exact pathogenic mechanism is often difficult to determine. A 51-year-old man treated by lithium for a bipolar manic-depressive psychosis complained of asthenia. Clinical examination and electromyography (EMG) with repetitive nerve stimulation at 3 Hz showed a significant decrement leading to the diagnosis of MG. When lithium was stopped, the clinical symptoms disappeared and the EMG became normal. After a 3 years follow-up, the patient remains asymptomatic. Lithium is considered to act on the nerve terminal mainly at presynaptic level. A postsynaptic level effect has also been demonstrated. Lithium might also induce an immunologic reaction against nicotinic receptors. The distinction during lithium treatment between revealed MG and an induced myasthenic syndrome is important for its prognostic and therapeutic implications. In the literature, three cases were considered to be drug induced, the last one was considered as an unmasked MG. A long period of time is necessary to be certain of the underlying mechanism. The possibility of neuromuscular dysfunction should be kept in mind during lithium treatment. A lengthy follow-up after the withdrawal seems to be necessary to distinguish lithium-induced syndrome from MG.

P709
PURE NEUROPSYCHIATRIC COLLAGENOSIS: A CASE REPORT. S. Zieroth, F. Blaes, M. Kaiser, M. Klotz, M. Bienroth, M. Strittmatter, W. Werner, Neurology, SHG-Kliniken, Neurology, Justus-Liebig-University, Psychiatry, SHG-Kliniken, University Saarland (Merzig/Saar, Giessen, Homburg/Saar, D)

Central nervous system involvement is common in the course of systemic lupus erythematosus. Diagnostic difficulties occur if a patient exhibits only psychosis and no signs of systemic involvement. Eight months after delivery, a 28 years old former healthy nurse developed a dissociative-like syndrome. She complained of intermittent hemidysaesthesia, derealisation and problems with thinking. During examination she demonstrated "abasia" and "hemiataxia". However, the neurological status was unremarkable and she was fully orientated. During the following days the psychic symptoms changed progressively to a psychotic disorganization with delusion, optic hallucinations and severe behaviour disorder. Much later also generalized seizures occurred but subsided after prescription of valproate. The clinical picture seemed to progress to dementia. CT and MRI examinations were normal. EEG showed bilateral diffuse slowing at 3–4 Hz with occipital maximum without reactivity to eye opening. Other systems showed no pathological findings or laboratory tests. Routine CSF examination including isoelectric focussing was unremarkable. Antinuclear antibodies (ANA) titer was 1:320 in serum and 1:128 in CSF, indicating intrathecal synthesis of the ANA. Antibodies against double-stranded DNA and ribosomal P protein, however, were negative. After high dose intravenous prednisolone (500 mg/d) for 5 days, followed by 80 mg/d oral for 28 days the patient showed a dramatic improvement of the psychiatric state. The EEG improved progressively to a normal alpha EEG. Within 25 days after starting prednisolone ANA titers decreased significantly, in CSF more than in serum. Azathioprine was started and prednisolone could be slowly tapered over weeks under control of EEG and CSF. This case of a woman with reversible psychosis and seizures and unremarkable routine CSF and MRI represents an isolated collagenosis of the central nervous system. The decrease of the intrathecally synthesized ANA in association with the clinical and electroencephalographic improvement may be a hint for a pathogenic role of intrathecally synthesized autoantibodies in autoimmune CNS disorders. Additionally, the EEG seem to be a suitable method for the follow up in this disease.

P710
NEUROPSYCHIATRIC CHANGES IN A GROUP OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE). A. Francia, A. Puzella, S. Pascucci, G. Ercolani, M. Gasparini, L. Finamore, S. Giuliani, A. Mitterhofer, G. Kotzalidis, University of Rome, La Sapienza III Clinica Neurologica (Rome, I)

BACKGROUND. Neuropsychiatric and personality changes, such as seizures, neuropathy, cerebrovascular accidents, coma, movement disorders, organic brain syndrome, psychosis, mood changes, and anxiety co-occur often with SLE, but the role of autoimmunity or personality in these changes is not yet established. We aimed at assessing neurological and psychiatric symptoms, and personality in a sample of SLE patients and correlate them with immunological and socioepidemiological measures, to clarify etiopathogenesis of SLE.

MATERIALS AND METHODS: We included outpatients with SLE referring to the 3rd Neurological Clinic of the University of Rome "La Sapienza" during the second semester of 1999; patients were assessed through neurological examination, magnetic resonance imaging (MRI), visual event-related potentials (VEPs), a neuropsychological battery, autoantibody titres and other routine immunological tests, the Montgomery-Åsberg (MADRS) and Hamilton Depression (HAM-D) Rating Scales, the Hamilton Anxiety (HAM-A) and Brief Psychiatric (BPRS) Rating Scales, the Clinical Global Improvement (severity) scale (CGIs), and the Minnesota Multiphasic Personality Inventory (MMPI). Cut-off for statistical significance was set at p less than.05.

RESULTS: We included 27 patients with SLE (three men and 24 women). Mean age was 41.5 years (range 21–63), standard deviation (SD) was 11.17; age at onset was 30.96, SD=12.25; duration of illness was 10.54 years, SD=10.61. Based on MADRS scores, we subdivided the sample into a nondepressed (ND; N=18 [comprising all men], with MADRS less than 14 at baseline) and a depressed (D; N=9; MADRS scores at least 14) subgroup. ND subjects scored not higher than 10 on the HAM-D, whereas D subjects scored at least 9. Mean age, age at onset, illness duration, HAM-A scores, and all MMPI scales did not differ significantly between the two groups. However, the D group scored higher on neurotic scales and displayed a depressive pattern, as opposed to the hysteric pattern of the ND group. The frequency of autoantibody, MRI, PEV and neurological abnormalities did not differ between the two groups. However, headache occurred more frequently in the depressed subsample (Yates corrected chi-square= 4.69; p=.0304). Only one third of patients in the D group vs. one half in the ND group manifested neurocognitive abnormalities, but this did not reach statistical significance. Other sociodemographic variables, such as educational level, job, and marital status did not differ significantly between the two sub-groups, neither did scores on the BPRS, in the normal range for all patients. CGIs scores in the D subgroup were significantly higher than those of the ND group (1.88 in the latter, SD=1.23 vs 4 in the former, SD=1; Levene's Test of Homogeneity of Variances: F=25.93627; p=.000009). Immunological parameters did not correlate with any other measure. CONCLUSIONS: Patients with SLE and clinically significant depression have significantly higher rates of occurrence of headache and severity of psychiatric impairment.

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A CASE OF OLIGOSYMPTOMATIC SYSTEMIC LUPUS ERYTHEMATOSUS WITH PRIMARY CENTRAL NERVOUS SYSTEM INVOLVEMENT CLINICALLY MIMICKING MULTIPLE SCLEROSIS. K. Stingele, R. Kretz, B. Storch-Hagenlocher, B. Wildemann (Heidelberg, D)

Background: Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease which involves the central nervous system (CNS) in approximately half of all patients. In those cases symptoms usually are psychiatric, seizures or focal neurological deficits. If symptoms represent the only or predominant manifestation SLE can mimic other neurological disorders.

Purpose: We present a case, where relapsing remitting course of disease, type of symptoms, magnetic resonance imaging (MRI) features and good response to intravenous steroids suggested multiple sclerosis (MS). The initial absence of systemic manifestation delayed the diagnosis for several years.

Case report: We report the case of a 37-year-old woman who initially developed optical neuritis and tetraparesis in 1992. MRI revealed signal abnormalities in the medulla oblongata. Cerebrospinal fluid (CSF) showed elevated protein content. She was diagnosed with autoimmune transverse myelitis and remission occurred under corticosteroids. In 1993, the patient suffered from bilateral optical neuritis. MS was suspected. From 1994 to 1999 several relapses developed with spinal symptoms at different levels and of varying severity (sensory symptoms, para- or tetraparesis, urinary retention). Occasionally, a relapse was preceded by severe back pain, fever, or flu-like symptoms and was associated with leuco- or thrombopenia. During the course of disease, MRI showed enhancing lesions of increasing number throughout the spinal cord reaching from the medulla oblongata to lumbar segments. Cranial MRI remained normal. CSF revealed lymphocytic pleocytosis, elevated protein content but oligoclonal bands remained negative. Corticosteroids invariably improved the neurological deficits. In 1999, photosensibility was described. Laboratory diagnostic revealed positive antinuclear antibodies (ANA) in serum and CSF and positive extractable nuclear antigens (ENA) in serum. Oligosymptomatic SLE without initial systemic manifestations was diagnosed. Treatment with immunoglobulins, methylprednisolone and pulsed cyclophosphamide resulted in slow but steady improvement of clinical symptoms.

Conclusion: The constellation of recurrent optical neuritis and myelitis in SLE may mimic MS. In the present case, findings suggesting an etiology other than MS were elevated protein content and negative oligoclonal bands in CSF and normal cranial MRI throughout the course of disease. Findings indicative of SLE were the development of back pain and fever in association with the relapses, laboratory parameters such as positive ANA and ENA, recurrent thrombo- or leucopenia and photosensibility in the course of disease. We therefore conclude that laboratory parameters indicative of collagen vascular disease should be included in routine MS diagnostics if CSF or MRI findings are atypical in a case of suspected MS.

P712
SIDE EFFECTS IN TREATMENT OF NEUROLOGICAL DISEASES WITH INTRAVENOUS IMMUNOGLOBULINS. M. Wittstock, R. Benecke, U. K. Zettl, University of Rostock (Rostock, D)

Therapy with intravenous immunoglobulins (IVIG) is thought to be a safe treatment for immune-mediated neurological diseases. The published data about adverse effects range widely, reporting a frequency from 11 to 81 %. We present our experience in a large group of patients with neurological disorders in a university hospital setting.

In a prospective study we analyzed the medical records of 54 patients (age 19–77 years) who were given IVIG for a neurological disease (number of patients): chronic inflammatory demyelinating polyneuropathy (13), diabetic amyotrophy (2), inclusion body myositis (2), multiple sclerosis (26), Guillain-Barre syndrome (4), Miller-Fisher syndrome (2), multifocal motor neuropathy (2), myasthenia gravis (2), polymyositis (1). IVIG therapy was given in a dose of 0,4 g/kg body weight/d in a total of 364 therapy courses.

31,5 % had adverse side effects. Most patients presented with only minor side effects, mostly asymptomatic laboratory changes. Rash or mild headache (without neck stiffness) occurred in patients when IVIG was given with infusion flow higher than 10 g/h. Only one patient (1.9 %) showed a severe complication with deep vein thrombosis. In this patient, the IVIG therapy was temporarily interrupted and resumed later without further side effects. There was no termination of IVIG therapy due to side effects. According to the literature, severe adverse effects seem to be more frequent in patients with pre-existent heart disease, renal insufficiency or bed-bound state.

In conclusion, IVIG is an effective and safe therapy. Most patients have no or minor adverse side effects. We suggest prophylaxis of deep vein thrombosis by low-dose heparin during IVIG therapy, especially in immobilized patients. Infusion flow should not be higher than 10 g/h.

P713
BLOCKADE OF VLA–4/VCAM–1 PATHWAYS IN EXPERIMENTAL AUTOIMMUNE NEURITIS (EAN) LEADS TO INCREASED T-CELL APOPTOSIS IN SCIATIC NERVE. V. I. Leussink, U. K. Zettl, R. B. Pepinsky, R. R. Lobb, U. Enders, K. V. Toyka, R. Gold, University of Wuerzburg, University of Rostock, Biogen Inc. (Wuerzburg, Rostock, D; Cambridge, USA)

Background: Integrins play a crucial role in the induction and effector phases of inflammatory demyelinating diseases. Therapeutic blockade of either the adhesion molecule VCAM–1 or its counterligand VLA–4 attenuates the disease course of EAN. Objective: We characterized the early effects of anti-VLA–4 and VCAM–1 antibody therapy on T-cell infiltration and apoptosis in EAN.

Methods: Adoptive transfer (AT)-EAN was induced in female Lewis rats by i. v. injection of P2-specific, activated CD4-positive T-cells. At maximum of disease on day 6, groups of 5 animals were treated with 500 microgram of the anti-VCAM–1 mAb (IgG2a) via tail vein injection 18 hrs, 12 hrs, 6 hrs before perfusion, or 500 microgram of the anti-VLA–4 mAb (IgG1) or the respective isotype m Ab controls. For immunohistochemistry, tissue sections of the sciatic nerve were stained with mAb B115–1 to identify T-cells and in-situ-tailing (IST) to detect apoptotic cell nuclei. All sections were evaluated by a masked investigator. Results: In pilot experiments, we observed a twofold increase of apoptotic T-cells without concomitant decrease of T-cell infiltration 18 hrs after blockade of VCAM–1/VLA–4. In time kinetic studies, blockade of VCAM–1 led to a rapid and significant increase of apoptotic T-cells with a maximum after 6 hrs (mean % T-cell apoptosis % SD: 20±5 % vs. 10±2 % in controls, p=0.005), whereas a significant decrease of T-cell infiltration was observed only 18 hrs after anti-VCAM–1 treatment (mean T-cell infiltration/mm2 ± SD: 193±137/mm^2 vs. 515±122/mm^2 in controls, p< 0.005). Similarly, after anti-VLA–4 treatment, the maximal increase of T-cell apoptosis was seen after 12 hrs, but slightly missed statistical significance (p=0.07).

Conclusions: In addition to its cell adhesion, VLA–4/VCAM–1 interaction may have a novel signaling component in EAN. In vivo blockade of VLA–4/VCAM–1 pathways by anti-VCAM–1 or VLA–4 therapy led to a rapid increase of T-cell apoptosis within 12 hrs, before a decrease of T-cell infiltration occurred. The early increase of T-cell apoptosis cannot be explained by decreased access of T-cells to the sciatic nerve, and its underlying mechanisms deserve further investigation.

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P714
THROMBOTIC-THROMBOCYTOPENIC PURPURA AFTER POLYSTYRENE INCINERATION. J. Koester, J. Berrouschot, A. Grothe, A. Wagner, D. Schneider, University of Leipzig (Leipzig, D)

Background: Thrombotic-thrombozytopenic Purpura (TTP, Mb Moschcowitz) is a rare disease with extensive petechial hemorrhages, jaundice due to hemolytic anemia and fluctuating neurological deficits. The etiology is still not clear.

Case report: This is the case of a 30 year old male patient, who was suffering from flu-like symptoms (fever, myalgia, headache) over a few days after incineration of a huge amount of polystyrene. 2 days later petechial hemorrhages, jaundice and tarry stool were noted. After hospital admission hemolytic anemia and thrombocytopenia were detected. In the following days the clinical condition deteriorated dramatically. The patient had to be intubated due to loss of consciousness, meningism and repetitive seizures. Under suspicion of meningoencephalitis the patient was transferred to our neuro critical care unit. After exclusion of other diseases (malaria after holidays in Kenya, systemic lupus erythematodes, borreliosis after tick bite) the diagnosis of TTP was confirmed due to fragmentocytes (28 %) in differential blood count. The patient was treated with plasmapheresis (22 cycles), high dosed glucocorticoids and symptom based intensive care. 14 days after transferral the patient could be extubated. 2 weeks later only slight tetraparesis was present.

Discussion: In all probability TTP in this patient has a toxic origin. During incineration of polystyrene a great amount of lipophile aromatic substances (benzen, toluene) is released. 14 days after the event low levels of benzen were detected. Abnormalities in differential blood count also fulfilled criteria of massive benzen poisoning. After exposure of volatile aromatic substances and combination of hematological changes and neurologic symptoms physicians must be aware of the differential diagnosis of TTP.

P715
TREATMENT OF AUTOIMMUNE ENCEPHALOMYELITIS AND UP-REGULATION OF TGF-BETA1 IN SITU BY INHIBITION OF DIPEPTIDYLPEPTIDASE IV (CD26). A. Steinbrecher, D. Reinhold, N. Tresser, K. Neubert, R. Martin, S. Ansorge, S. Brocke, Neuroimmunology Branch, NINDS, NIH, Institute of Exp. Internal Medicine, Inst. of Biochemistry (Bethesda, MD, USA; Univ. of Halle/Saale, Univ. of Magdeburg, D)

CD26 or dipeptidyl peptidase IV (DP IV) is expressed on various cell types, including T cells. While T cells can receive activating signals via CD26, the physiological role of CD26/DP IV is largely unknown. We used the reversible DP IV-inhibitor Lys[Z(NO2)]-pyrrolidide (I40) to dissect the role of DP IV in experimental autoimmune encephalomyelitis (EAE) and to explore the therapeutic potential of DP IV-inhibition for autoimmunity. I40-administration in vivo prevented clinical and neuropathological signs of adoptive transfer EAE and even suppressed ongoing disease. I40 blocked DP IV-activity in vivo and increased the secretion of the immunosuppressive cytokine transforming growth factor beta1 (TGF-b1) in spinal cord tissue and plasma during acute EAE. In vitro, while suppressing autoreactive T cell proliferation and tumor necrosis factor alpha-production, I40 consistently upregulated TGF-b1 secretion. A neutralizing anti-TGF-b1-antibody blocked the inhibitory effect of I40 on T cell proliferation to myelin antigen. These data suggest that DP IV-inhibition represents a novel and specific therapeutic approach protecting from autoimmune disease by a mechanism that includes an active TGF-b1-mediated anti-inflammatory effect at the site of pathology.

P716
MODULATION OF CYTOKINE EXPRESSION IN IMMUNE CELLS BY BDNF AND NGF. A. Bayas, N. Kruse, F. Weber, V. Hummel, N. F. Moriabadi, K. V. Toyka, P. Rieckmann, University of Würzburg, University of Göttingen (Würzburg, Göttingen, D)

Background: There is increasing evidence, that neurotrophic factors, like brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF), have variable effects in the nervous system and in the immune system. It is also known, that immune cells themselves are capable of producing BDNF and NGF. Here we analyzed the specific role of the neurotrophins BDNF and NGF in the regulation of cytokine expression in immune cells. Materials and methods: Peripheral blood mononuclear cells (PBMCs) from human healthy donors stimulated with anti-CD3 as well as antigen specific T-cell lines were cultured for 16 h and treated with BDNF and NGF in a concentration of 100 ng/ml in order to stimulate both trk and low affinity nerve growth factor receptors. Antigen specific T-cells were additionally treated with a blocking antibody against the low affinity nerve growth factor receptor (p75NGFR). Levels of Th1- and Th2-related cytokines were measured by quantitative polymerase chain reaction (PCR). Cytokine protein levels were measured by enzyme linked immunosorbent assay (ELISA). The presence of the p75NGFR was demonstrated by flow cytometry. Results: In PBMCs we found a significant correlation of BDNF and NGF effects on IL4, but not TGF-beta and TNF-alpha mRNA expression in comparison to untreated cells. The p75NGFR was expressed already under baseline conditions. Treatment of antigen specific T-cells with p75NGFR blocking antibodies resulted in a significant decrease of interferon-gamma mRNA and protein expression. The co-treatment with BDNF and p75NGFR blocking antibodies resulted in a significant overcome in interferon-gamma mRNA expression compared to antibody treated cells alone. Conclusions: Our results indicate that in immune cells cytokine expression can be modulated by neurotrophins. The results achieved by blocking the p75NGFR demonstrated that this receptor is differentially involved in signal transduction by neurotrophic factors and paracrine effects might also play a functional role.

P717
HLA CLASS II MOLECULES AND IMMUNODOMINANT MBP 85–99 PEPTIDE PRESENTATION IN MS: GENETIC AND FUNCTIONAL STUDY. E. Quelvennec, O. Bera, D. Smadja, F. Jugdé, G. Edan, G. Semana, University of Rennes, University Hospital de Fort France (Rennes, F)

Among candidate genes involved in MS genetic susceptibility, MHC genes and particularly HLA-DRB1 *1501 – DQB1 * 0602 haplotype play a major role. The existence of self peptides that are selectively presented by these MS-associated HLA molecules and are the target of autoreactive T cells would explain this genetic association. Based on the strong linkage disequilibrium observed in Caucasians between DRB1 *1501 and DQB1 *0602 allele, it is impossible to draw a firm conclusion about the DRB1 or DQB1 locus involvement. In order to address this issue a strategy associating a genetic and a functional approach was conducted in a population of non Caucasian MS patients. We observed that in Martinicans (50 MS and 100 controls), the DRB1 *15 allele is the only one allele associated with the disease (OR = 2.3). However, the most common DRB1 *15 subtype was *1503 and not *1501 as well in MS as in controls (57% and 73%). Morever, in Martinicans, DQB1 *0602 found in linkage disequilibrium with other DRB1 alleles than DRB1 *15, was not increased in non DRB1 *15 MS patients (9.7% versus 10% in controls) suggesting a neutral role of DQB1 *0602 in MS genetic. In a second step, we have tested the capability of DRB1 *1503 allele overrepresented in MS Martinicans to present the peptide MBP 85–99 (considered as immunodominant autoantigen in MS) to a DRB1 *1501 restricted MBP specific T cell line generated in a Caucasian subject. The proliferation intensity was similar in both contexts of presentation (ie DRB1 *1501 or DRB1 *1503 homozygous EBV transformed B cell line used as APC), with a D cpm of 11 000 and 10 000 cpm respectively. No proliferation was observed when non relevant peptide (control peptide) was used in the same conditions. In the whole, our results show a prominent role of DRB1 locus (DRB1 *1501 and/or DRB1 *1503) in peptide presentation of immunodominant MBP 85–99 peptide in genetically different MS patients and suggest a neutral role of DQB1 encoded molecule in MS susceptibility.

P718
PHAGOCYTOSIS OF APOPTOTIC INFLAMMATORY CELLS BY MICROGLIA: MODULATION BY CYTOKINES. A. Chan, T. Magnus, K. V. Toyka, R. Gold, University of Würzburg (Würzburg, D)

Objective: To investigate the effects of different proinflammatory and down-regulating cytokines on microglial phagocytosis of apoptotic leukocytes in vitro.

Background: Apoptotic cell death of autoaggressive T-cells in the CNS is an effective, non-inflammatory mechanism for the termination of autoimmune T-cell inflammation in multiple sclerosis (MS) and the animal model experimental autoimmune encephalomyelitis (EAE). The role of microglia in the removal of apoptotic inflammatory cells and the modulation by cytokines has not been investigated so far.

Materials/Methods: Lewis rat microglia was used in an in-vitro phagocytosis assay of apoptotic autologous thymocytes or myelin-basic protein (MBP) specific, encephalitogenic T-cells. Effects of recombinant rat interferon-gamma (IFN-gamma), interferon-beta (IFN-beta) and interleukin–4 (IL–4) on microglial phagocytosis of apoptotic cells were investigated by a standardized light-microscopical assay.

Results: Microglia has a high capacity for the uptake of apoptotic thymocytes as well as MBP-specific, encephalitogenic T-cells in contrast to non-apoptotic target cells. The proinflammatory cytokine IFN-gamma enhances microglial phagocytosis of apoptotic cells by up to 75%. The increased phagocytosis appears to be selective for apoptotic cells. Microglial uptake of apoptotic cells is also increased by IFN-beta in a dose-dependent manner. Conversely, IL–4 inhibits phagocytosis of apoptotic cells by microglia.

Conclusions: 1. Phagocytosis of apoptotic T-cells by microglia may be an important mechanism for the termination of autoimmune inflammation in the CNS. 2. Augmentation of microglial phagocytosis by the proinflammatory cytokine IFN-gamma might constitute a feedback mechanism for the accelerated elimination of apoptotic inflammatory cells. 3. Increased clearance of apoptotic cells by microglia may represent a hitherto unknown mechanism of action of IFN-beta, which is a mainstay in the therapy of EAE and MS.

P719
ENZYME LINKED IMMUNOSORBENT ASSAY USING RECOMBINANT HUD-ANTIGEN FOR SERODIAGNOSIS OF PARANEOPLASTIC NEUROLOGICAL SYNDROMES. S. Rauer, R. Kaiser, University Hospital (Freiburg, D)

Paraneoplastic neurological syndromes (PNS) are frequently associated with autoantibodies that crossreact with both neuronal tissue and the underlying tumor. Demonstration of high titers of anti HuD-antibodies in the presence of paraneoplastic symptoms provides strong diagnostic evidence of PNS, even without direct proof of a neoplasm. Methods: Paraneoplastic HuD-antigen was expressed in Escherichia coli as a recombinant protein, purified by metal chelate affinity chromatography and used in an enzyme linked immunosorbent assay (HuD-ELISA). The cutoff for optical density readings at OD410 was set 3 standard deviations above the mean of 145 sera from healthy persons (cut off = 0.15). Results: 20 sera from patients with PNS and evidence of anti-Hu antibodies in an immunoblot employing human cerebellar crude extraction as antigen were tested. 18/20 sera revealed a clear positive result (ODs: 0.4–2.4) in the HuD-ELISA, demonstrating a sensitivity of 90%. Two sera out of 150 sera from patients with various infectious, autoimmune and neoplastic diseases (excluding PNS) showed a weak positive result (ODs: 0.22 and 0.28) in the HuD-ELISA. This reveals a specificity of more than 98%. Ten serum/cerebrospinal fluid (CSF) pairs from patients with Hu-syndrome were adjusted to equal IgG concentrations and were tested in parallel in the HuD-ELISA. A specific antibody index (AI = ODCSF/ODserum) over 1.5 indicates intrathecal antibody

synthesis. 6/10 patients revealed an AI > 1.5, one was borderline (AI = 1.5), and three had no hint of intrathecal production of specific HuD-antibodies (AI = 0.9–1.2). There seems to be a correlation between elevated AIs (> 1.5) and proof of oligoclonal bands in the CSF. Conclusion: Based on the high sensitivity (90%) and specificity (> 98%) the recombinant HuD-ELISA appears to be a suitable test for detection of anti-HuD antibodies in patients with putative PNS. Compared with the immunoblot, an ELISA is a quantitative method which seems to be appropriate for the estimation of specific intrathecal HuD-antibody synthesis. Furthermore, it will be possible to monitor the concentration of anti-HuD antibodies by means of the HuD-ELISA during the clinical course of PNS.

Clinical neurophysiology

P720
ANALYSIS OF HEAD MOVEMENTS IN NORMAL SUBJECTS WITH THE USE OF QUANTITATIVE ELECTROMYOGRAPHY (TURNS-AMPLITUDE ANALYSIS). S. W. Cichy, C. W. Glazowski, M. Wieclawska, Institute of Psychiatry and Neurology (Warsaw, PL)

An assessment of head movements (voluntary or involuntary) by visual inspection or clinical rating scales is rather subjective and imprecise. Activity of some representative neck muscles involved in head movements can be more adequately quantified by automatic electromyographic (EMG) analysis such as turns-amplitude analysis. This technique measures the number of turns per second (NT) (turn – positive or negative deflection of EMG signal of amplitude > 0.1 mV), mean amplitude between turns (MA), and NT/MA ratio. We studied 20 healthy volunteers aged 20–37 years. In all subjects we measured maximum force used during head rotation, tilt, neck flexion, neck extension, and shoulder elevation. Simultaneous automatic EMG (turns-amplitude analysis) was performed during a gradual increase in force (at 0, 10%, 20%, ..., 90% of maximum force) in 4 pairs of neck muscles: sternocleidomastoid (SCM), splenius capitis (SPL), cervical paraspinals (PAR), and trapezius (TRA). The parameters analysed were: NT, MA and NT/MA ratio. Normal values of these parameters were established for the above muscles at rest and at maximum force. At rest the lowest mean NT was found in SCM muscle (2 turns/s), the highest in SPL and PAR muscles (15 and 10 turns/s, respectively). At maximum force of contraction the lowest NT were recorded in TRA (358 turns/s), the highest in SCM muscle (768 turns/s). We studied also changes in NT, MA and NT/MA ratio in relation to force (percentage of maximum force for a given muscle). The NT increased approximately linearly up to 40–50% of maximum force and then reached a plateau (SCM and PAR muscles) or continued to rise linearly throughout the whole force range (SPL and TRA muscles). The MA presented a positive (linear) correlation with force in all tested muscles. The NT/MA ratio did not show a regular relation to force, usually the ratio increased to some degree of effort and then remained stable or decreased. Establishing normal values of NT, MA and NT/MA ratio in the tested neck muscles can improve a quantitative assessment of head movements. Such an electrophysiological model can serve as a basis for studying involuntary muscle activity (e. g. dystonias) and can be a valuable adjunct in clinical evaluation.

P721
ARM STIFFNESS IN HEALTHY YOUNG ADULTS AND ELDERLY: A QUANTITATIVE METHOD. N. Feigel, R. Inzelberg, T Flash, E Schechtman, Weizmann Institute of Science, Hillel Yaffe Medical Center, Weizmann Institute of Science, Ben Gurion University (Rehovot, Hadera, Beer Sheva, IL)

Objective: Quantitatively measure and compare arm stiffness in neurologically healthy young adults and elderly. Background: When the hand is displaced from equilibrium, muscles generate elastic forces to restore the original posture. Hand stiffness (HF) which describes the relation between force and displacement vectors in the vicinity of the equilibrium position, can be represented as an ellipse characterized by its size, shape and orientation. HS and joint stiffness (JS) can be calculated and represented as matrices. Methods: The subject (young=4, elderly=5) was holding a two-joint manipulandum; hand position was monitored. Displacements were imposed in different directions on the hand at 7 target locations. Force-displacement relationships were measured and used to calculate HS and JS. Effects of GROUP, TARGET and their interaction were analyzed by ANOVA with repeated measures. Results: In most measurements, the HS ellipses' major axis was nearly coaligned with the radial axis of shoulder-hand connection. The orientation of the ellipse differed between groups ($p < 0.06$) and was strongly influenced by target location ($p < 0.001$). Its shape was significantly different in elderly vs. young subjects ($p < 0.002$). The gradual change with target location in HS ellipse's shape was significantly less evident in elderly subjects. Conclusions: Our results show that arm stiffness displays different patterns of variation in the workspace in elderly subjects as compared to young adults. These differences are possibly a consequence of changes in patterns of muscle activation, rather than globally augmented muscle tone in this population.

P722
SERIAL RECORDING OF SOMATOSENSORY EVOKED POTENTIALS IN PATIENTS WITH CEREBRAL INFARCTION. K. Bozic, J. Mihaljev-Martinov, G. Misic-Pavkov, S. Gvozdenovic, K. Gebauer, I. Kovac, S. Knezevic, I. Divjak, Institute of Neuropsychiatry, MC "Hilel Jaffe" (Novi Sad, YU; Hadera, IL)

The purpose of the study was to investigate the relationship between somatosensory potentials evoked by stimulation of median nerve (SEPs) and recovery from stroke. Methodology: SEPs were recorded in 40 patients suffering their first supratentorial cerebral infarct. SEP were performed within the first week, the third week and after six weeks from the onset of ischaemic symptoms. SEP results were correlated with clinical findings. Infarct location was confirmed by computerized tomography (CT) and/or by magnetic resonance imaging (MRI) of the brain. Clinical evaluation included assessment of motor (stroke severity score-Canadian Neurology Scale) and sensory deficit (sensibility assessment). Results: A high frequency of SEP abnormality (70%) was found in the acute stage (2,72 ± 0,75 days after stroke onset), which declined to 68,5% at 2–3 weeks (17,7 ± 2,01 days) and to 35% after six weeks follow-up (61,9 ± 5,04 days). Changes in SEP and clinical findings were significant in the follow-up period. Neurophysiological and clinical course showed an improvement with the maximum after six weeks from stroke onset. The normalization of initially abnormal SEP findings corresponded with the statistically significant improvement of deep and cortical sensory impairment. Conclusion: Our results suggest that early and serial SEP studies could be used in monitoring the recovery process in stroke patients especially in quantifying the recovery of lemniscal and parietal dysfunction.

P723
ELECTROPHYSIOLOGICAL STUDY OF FOREARM SENSORY FIBER CROSSOVER IN MARTIN-GRUBER ANASTOMOSIS AND DEMONSTRATION OF TWO NEW CASES. S. Simonetti, E. O. Ospedali Galliera (Genova, I)

Although anatomical studies have shown that a crossover of sensory fibers is not rare in forearm median-ulnar anastomosis (Martin-Gruber anastomosis, MGA), this condition has been electrophysiologically described in only two subjects (Santoro et al. 1983, Claussen et al. 1996). We thus investigated, through a near-nerve needle technique, the electrophysiological possibility of detecting a forearm median-ulnar crossover of sensory fibers in 24 arms of 21 subjects with monolateral or bilateral MGA, by stimulating digit V and recording along the median nerve. In the median nerve, we found small amplitude elbow responses in 10 of the 24 arms, but, in 8 of them, they disappeared following a lidocaine block of the ulnar nerve immediately distal to the elbow sulcus, thus indicating their volume-conducted origin. In one subject affected by a carpal tunnel syndrome and a subclinical elbow ulnar neuropathy, the median elbow (ME) response was not modified by the ulnar nerve block, thus confirming a forearm sensory anastomosis. A forearm sensory anastomosis was additionally found in a subject with MGA, in whom a clear-cut sensory response was recorded at ME but no anaesthetic block was performed since no ulnar responses were present above the elbow sulcus following a severe elbow lesion. We conclude that a forearm crossover of sensory fibers to digit V is not frequent in MGA, and that the new above-described technique seems crucial for its detection and verification.

P724
NORMATIVE VALUES OF THE MASSETER REFLEX (MYOTATIC MASSETER REFLEX). S. Fitzek, C. Fitzek, H. C. Hopf, University of Jena, University of Mainz (Jena, Mainz, D)

Clinical use of the masseter reflex (MassR) includes disorders of the peripheral trigeminal nerve, pontine, and mesencephalic lesions. Although there are some presentations of normative MassR analysis in healthy volunteers, there has been little formal evaluation of the number of events needed for data of a defined reproducibility, the best mode of analysis, the intraindividual stability of the reflex, and the normative values depending on age and gender. Patients and Methods: The MassR is elicited by a brisk tap on the jaw using a reflex hammer. The mechanical trigger is recorded by piezoelectrode mounted in the hammer. The reflex response is recorded by surface electrodes simultaneously from both muscles with the recording electrode over the belly above the mandibular margin and the reference over the jugular bone at the edge of the orbit. Studies were

performed on 105 healthy subjects (45 male, 60 female), ages 5 to 78 years (mean 42). In 30 volunteers performance was done three times on different days to study the individual stability of the reflex. Results: The MassR reflex is highly reproducible. There is a linear correlation between age and reflex latency and a negative correlation between age and amplitude. Men had slightly longer latencies of MassR. Discussion: We present data concerning the normative values of reflex latencies, amplitudes, and side differences depending on age and gender, and discuss methods of measurement and calculation. Clinical examples of patients with brainstem infarctions and pathological MassR are demonstrated.

P725
CORTICAL EVOKED RESPONSES: THE PROGNOSTIC VALUE IN POST TRAUMATIC CHILDREN. E. Castelli, V. Scaioli, C. Triscari, G. Poggi, P. Profice, Irccs Eugenio Medea (Bosisio Parini Lc, Polo Di Ostuni, I)

Traumatic brain injury (TBI) is the most common cause of acquired disability in developmental age. The clinical assessment, the rehabilitative program and the evaluations of sequelae after TBI require the use and an interdisciplinary coordination. The recording of cortical evoked responses seems to be of prognostic value in adult post traumatic patients in the acute phase. Goals of the study: We studied the prognostic value of cortical evoked responses from visual (VER), auditory (BAER) and somatosensory (SSEP) stimulation in post traumatic injured children in sub acute phase. Methods: 18 patients with closed head injury (12 male and 6 female) were followed in our Rehabilitative Unit for acquired brain injury in developmental age. Patients with pre traumatic pathologies or spinal chord injuries were excluded. All patients underwent complete multidisciplinary examination with collection of clinical history and assessment of clinical features, EEG recording, neuroradiological imaging, sensorial evaluation, cognitive and psychological examination. Cortical evoked responses from BAER, VER and SSEP stimulation were recorded in all patients 2 and 4 months after trauma. Evoked potentials latency and amplitude over 2.5 standard deviation from coeval controls were considered abnormal. Outcome was assessed using FIM and WeeFIM rating score (WFrs). Results: Mean age at traumá was 7.2 ± 4.4 years, the mean Glasgow Coma Scale score in acute phase was 5.7 ± 2.5 and the mean duration of coma was 4.4 ± 4.2 weeks. 65% of patients presented focal cortical contusions, 44% had intracranial hematomas, 11% had raised intracranial pressure, 76% sustaining injury to other body regions, 93% had frontal lobe lesions. Abnormal BAER recording were present in 50% of cases, with bilateral impairment in 28%. Abnormal VER recording were present in 61% of cases, with bilateral disorders in 33%. SSEP recording abnormalities were present in 88.9% of children and with bilateral anomalies in 50%. The mean WFrs score was 62.3 (range 14.3–96.8). Pearson's correlation coefficients between WFrs vs SSEP, WFrs vs VER e WFrs vs BAER were –0.83, –0.75 and –0.55 respectively. SSEP appears the main cortical evoked response related to outcome. Conclusions: Cortical evoked responses recording are important prognostic factors after trauma in developmental age.

Migraine and Neuropathic Pain

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FAMILIAL HEMIPLEGIC MIGRAINE: CESSATION OF AURA SYMPTOMS FOLLOWING INTRANASAL APPLICATION OF THE NMDA-RECEPTOR ANTAGONIST KETAMINE. J. Herzog, H. Kaube, T. Kaeufer, H. C. Diener, M. Dichgans, Klinikum Grosshadern, National Hospital for Neurology, Department of Neurology (Muenchen, D; London, UK; Essen, D)

Background: Migraine aura is probably caused by cortical spreading depression (CSD). In the experimental animal CSD can be blocked by glutamate N-methyl-D-aspartate (NMDA) receptor antagonists. Familial Hemiplegic Migraine (FHM) is a rare, autosomal-dominantly inherited subtype of migraine with aura caused by mutations in CACNA1A, a gene coding for a neuronal P/Q-type calcium channel. In FHM the aura is characterised by transient hemiparesis in addition to visual, sensory and speech disturbances. Purpose: The aim of this study was to investigate the effect of the NMDA antagonist ketamine on the severity and duration of neurological deficits in FHM. Methods: 13 patients from 8 families applied each 25 mg ketamine intranasally to treat 27 attacks. Treatment effects were documented by means of self assessment questionnaires to be completed every 15 minutes during the attack and extensive follow-up interviews. Evaluation and scoring included severity of motor deficits (0–5), presence or absence of visual hemifield disturbances and dysphasia, progression from one system to another, headache severity (0–3) and vegetative symptoms. Duration of aura and headache phase was evaluated seperately. Results: 7 patients from 4 families reported marked reduction of the severity and duration of aura symptoms in all 14 attacks treated: compared to untreated attacks. In 5 patients the typical march of symptoms' progression was stopped after 15–30 minutes, 4 patients also experienced improvement of their regular headache. No benefit at all was observed in 6 patients. We did not find correlations between therapeutic response and the genetic linkage status of the patients (linkage/ non-linkage to CACNA1A). Conclusion: We conclude, that in some patients with FHM the spread of migraine aura can be blocked or attenuated by ketamine. This study also provides evidence, that CSD or a pathophysiologically related process is involved into the generation or propagation of aura in FHM. NMDA-receptor antagonists might have a potential role in the treatment of other forms of severe or prolonged migraine aura.

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PAROXYSMAL CENTRAL PAIN SYNDROME AS EPILEPTIC SEIZURES ELICITED BY CORTICAL CENTRAL AND POSTCENTRAL LESIONS. C. Helmchen, C. Gaebel, A. Thuemen, J. Scholz, Medical University (Luebeck, D)

Paroxysmal central pain of cortical origin is rare. The critical lesion site and the mechanisms of epileptic seizures eliciting spontaneous pain is not known yet. We present two patients with paroxysmal pain syndromes as the pure manifestation of focal epileptic seizures. Both patients suffered from attacks of spontaneous stabbing pain with sudden onset and offset lasting seconds to 2 min. Neurological examination in the interval was normal, particularly there was also no sensory deficit. In one patient the pain syndrome showed some evolution, starting from the left foot and marching to the knee. Interestingly, she noticed some pain relief after foot elevation. In addition, she had rare attacks with clonic jerks in her left foot without any pain sensation. On EEG recordings, she showed a slowing focus in the right centro-precentral region. In accordance, cerebral MRI detected a tumor in the right central region most likely indicating a meningioma. The other patient noticed the attacks of pain in her right arm. Like the first patient, she also had clonic jerks in the same extremity independently of the painful attacks indicating that pain is not produced by contraction or spasms. On EEG recordings, she showed paroxysmal epileptic discharges predominantly in the postcentral region bilaterally. However, MRI was normal. Somatosensory evoked potentials were normal in both patients. The paroxysmal pain attacks disappeared in patient #1 and decreased in patient #2 after anticonvulsive therapy with phenytoin. Evidence for the epileptic pathomechanism comes from the epileptic patterns in EEG recordings and the disappearance after anticonvulsive therapy. Both lesion sites affected the central/postcentral area. These findings support not only the physiological but also pathological role of the primary (SI) and secondary somatosensory cortex (SII) in pain processing as recently shown by fMRI studies.

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CLINICAL STUDIES OF VALPROATE FOR MIGRAINE PROPHYLAXIS. Ü. Türk, M. Gümüs, M. Akdogan, Kartal Research Hospital (Istanbul, TR)

There are numbers of effective drugs in the prophylaxis of migraine. But a significant number of patients can't be treated satisfactorily with existing drugs. Sodium valproate seems to have a prophylactic effect in migraine. We performed an open prospective study of the prophylactic efficacy of sodium valproate in 98 patients with migraine. Patients and Methods: The patients were randomly selected from outpatients headache clinic. Six patients (% 6.1) men and 92 patients (% 93.9) women fulfilling patients criteria for migraine of the International Headache Society Classification were included. The inclusion criteria were a diagnosis of migraine, a history of migraine for at least one year, three to ten days with migraine per month and age between 19 and 57 years (mean: 32.03±8.81). 64 (%65.3) patients received a long acting preparation of sodium valproate (Depakin LA®, Sanofi-Dogu) 500 mg/day. Second group 34 (%34.7) patients received 1000 mg/day long-acting preparation of sodium valproate for six months. Therapeutic efficacy was expressed on a S-point scale headache frequency during the 6th month of the treatment. In statistical analysis between two groups the effect on migraine frequency and comparing the side effects was used Mann-Whitney test. Results: The study was completed by 98 patients with mean age 32.03±8.81 years (range 19–57). The patients had an initial migraine frequency of 6.4 days per month (range 3–10 day). Fourteen (% 14.3) patients showed no improvement or less < 25% improvement. 14 (% 14.3) patients who showed improvement between % 25 to 50% response after medication. 34 (34.6%) patients showed improvement between 50% to 75%, 36 (36.7%) patients showed 7> = improvement. There were 22 (22.4%) patients who had adverse events. Group A showed 7,8% side effect, group B showed 50% side effect. There were tremor 3 (% 3.1), weight gain 2 (%2.1), nausea and vomiting 9 (% 9.2), hair loss 5 (% 5.1), and irregular ovarian cycle 1 (% 1.0), somnolence 17 (% 17.3) gastrointestinal intolerance 15 (% 15.3). Discussion: Sorrenson first suggested the usefulness of sodium valproate in migraine prophylaxis. In placebo control trials of migraine, sodium valproate was

reported to be effective in 86.2% of patients (Herry and Kuritzky 1992) or to reduce migraine frequency at least by half in 60% (Saper Mathew 1993 and Jensen at al. 1994.) 71.3% of our patients showed > = 50% improvement. No correlation was found between clinical efficiency and blood levels of sodium valproate (Herry and Koritzky 1989). In our study was found that the correlation between clinical efficiency and daily dose were not statistically significant ($p > 0.05$). Our results are comparable to those reported in a placebo-controlled two month study by Herry and Kuritzky (1989). Our study has longer treatment period. The reported number of side effects varies considerably between different quantities of the same drug in migraine prophylaxis. The tolerance of sodium valproate was good in 500 mg daily dose. The side effect were statistically significant between two groups ($p < 0.05$). Patients who received 1000 mg/day sodium valproate had more side effects ($p < 0.05$). Sodium valproate could therefore become a first choice prophylactic agent in patients with severe migraine.

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TRIGEMINAL NEURALGIA: COMPARISON OF TWO MR IMAGING TECHNIQUES. G. M. Hadjigeorgiou, A. H. Karantanas, K. Paterakis, M. Psomiadou, A. Poultsakis, University of Thessalia (Larissa, GR)

Purpose. To compare two Magnetic Resonance Imaging (MRI) techniques for demonstration of vascular contact or other causes of trigeminal neuralgia (TN). Methods & materials. Fifteen patients with unilateral and one patient with bilateral TN (total symptomatic nerves = 17) and 25 control subjects underwent the examination protocol which consisted of: a) a Turbo-Flair (CSF=0) sequence for a baseline imaging of the brain, b) an unenhanced 3D-inflow with magnetization transfer contrast Magnetic Resonance Angiogram (MRA) and c) an enhanced 3D-T1 w Turbo Field Echo (TFE) sequence in the coronal plane. Only patients with neoplasm accepted surgery. Results. In two patients, neoplasms (meningioma and epidermoid) were the cause of the TN. In one patient, herpes neuritis was diagnosed 6 months before MRI examination which showed enhancement of the nerve and ganglion, not obvious on MRA. Unilateral vascular contact with trigeminal nerve at the root entry zone was seen on TFE in 13 out of 14 (13/14, 93%) remaining symptomatic nerves and in one asymptomatic nerve. The MRA revealed only 2 (2/14, 14%) vascular contacts with symptomatic nerves ($p < 0.001$). The vessels responsible for the contact were superior cerebellar artery (n=11) and ectatic basilar artery (n=2). Conclusion. 3D-T1 w TFE enhanced imaging with multiplanar reconstruction manipulation is superior to the 3D-inflow MRA for demonstrating viral neuritis and the vascular contact with the trigeminal nerve at the root entry zone in patients with TN. In our population, the frequency of vascular contact causing TN seems to be high (93%).

P730
BETA-ENDORPHINS PLASMATIC LEVELS IN MIGRAINE PATIENTS. M. Blanco, E. Toribio, A. Hernanz, E. Diez-Tejedor, P. Barreiro, University Hospital La Paz (Madrid, E)

There are many studies that establish a relationship between beta-endorphins and migraine pathophysiology. In previous studies we were able to see a reduction of the beta-endorphins plasmatic levels in migraine patients. We now intend to analyse the value of beta-endorphins plasmatic levels in this type of patients and what is the role of them in the pathogenesis of migraine. Material and methods: We distributed all patients into three groups: migraine with aura (MA), migraine without aura (MO) and a control group©. Blood was collected by basilical venopuncture in the intercrisis period and the beta-endorphins plasmatic level (EPL) was measured using the IRMA (Nichols) method. We then used the ANOVA test for statistical analysis. Results: We included 15 patients, all of them women, between 18 and 62 years of age. The mean frequency of headaches was 4 crises per month. The patients were divided: MO, 6 patients; MA, 3 patients; C, 6 patients. The EPL in MO patients was 19 ± 3 pgr / mL, in MA patients 20 ± 4 pgr / mL and C patients 12 ± 3 pgr / mL. We observed statistical difference between MA and C patients, and M and C patients ($p < 0.05$). We were not able to find any difference between migraine patients. Conclusions: These results show a significant increase in the beta-endorphin plasmatic levels in migraine patients. This points to the involvement of the beta-endorphins in the migraine pathophysiology, might be related with the opiate neuropeptides role in stress and pain regulation. People with many headaches would need higher beta-endorphin levels in order to control the pain and stress. Further studies are necessary to confirm these results.

P731
ANALGESIC-INDUCED HEADACHE IN CHILDREN AND ADOLESCENTS. R. Hering-Hanit, A. Cohen, Z. Horev, N. Gadoth, Meir General Hospital, Sapir Medical Centre, Pediatric Ambulatory center (Kfar Saba, IL)

Abuse of ergotamine and analgesics is common in adults. It coexists with headache and may lead to medication-induced headaches. Ten to fifteen percent of the patients attending headache clinics and one percent of the general population suffer from chronic daily headache due to medication misuse. Indeed, this phenomenon was recently regarded as an epidemic. Nonetheless, analgesic induced headache in children and adolescents was not reported until 1998. We report our experience with adolescents with daily or almost daily headache and daily or almost daily analgesic intake. Methods: Over a period of 3 years, we have evaluated 26 adolescents (19 girls and 7 boys) referred to our headache clinic because of chronic daily or nearly daily headache related to daily analgesic intake. Results: The mean age of the group was 14.2 (range 12–18) years and the mean headache history duration was 1.6 (range 0.3–4.5) years. The mean headache days per month was 28.1 (range 19–31). All 20 adolescents had no history of migraine and were using at least one dose of analgesic drug for each headache while 16 were using analgesic drugs daily. The weekly analgesic intake averaged 28.1 (range 19–41) tablets. The majority of the adolescents abused simple analgesic; 21 were taking paracetamol alone. Five took a combination: 4 combined paracetamol, caffeine and codeine and one combined aspirin, caffeine and codeine. All patients were informed as to the phenomenon of medication-induced headache and were encouraged to achieve drug withdrawal. Withdrawal led to complete cessation of all headaches in 20 patients. In 6, the daily headache resolved, however they suffered from intermittent episodic migraine attacks, which were frequent enough in 3 to initiate prophylactic medication. One adolescent continued to have daily headache. Conclusions: Analgesic headache does occur in adolescents. Abrupt withdrawal from the offending medication was successfully achieved without hospital admission or interference in daily life with complete disappearance of the induced chronic daily headache in all but one.

P732
ACTIVATION OF THE COAGULATION SYSTEM IN MIGRAINE WITH AURA. R. Hering-Hanit, Z. Friedman, I. Schlesinger, M. Ellis, Meir General Hospital, Sapir Medical Centre (Kfar Saba, IL)

Prothrombin factor 1.2 (F1.2) is a cleavage product of prothrombin. Its plasma level is raised in patients with hypercoagulable states. Measurements of plasma F1.2 have been shown to be sensitive and a specific marker of ongoing thrombin generation, and thus may serve as an indicator of activation of the clotting cascade. A hypercoagulable state has been purported to be present in migraineurs. Patients with migraine with aura may have an increased risk for strokes. Aim: Determine the plasma F1.2 level in patients with migraine with and without aura. Methods: Plasma levels of F1.2 were measured by ELISA (Enzygnost, Behring Germany) in 35 migraine patients and in 24 healthy volunteers age and sex matched. All subjects were screened for: a deficiency of protein C, protein S or antithrombin, the presence of activated protein C resistance, the presence of anticardiolipin antibodies. Results: Migraine type: 35 patients – 22 with migraine with aura and 13 with migraine without aura. Age: 23–52 years. 11/22 (50%) patients with migraine with aura had an elevated F1.2 level (between 1.25–3.5 ng/mL). All patients with migraine without aura had normal F1.2 blood levels (< 1.1 ng/mL). All healthy volunteers had normal F1.2 blood levels (< 1.1 ng/mL). Conclusions: Prothrombin F1.2 levels are elevated in some patients with migraine with aura. This finding suggests that there is activation of the clotting system in some patients with migraine with aura. The increased risk of stroke in patients with migraine with aura may support our finding. More studies are required to confirm our findings.

P733
THE EFFECT OF MEDICATION WITHDRAWAL ON SLEEP PATTERNS IN MIGRAINEURS WITH CHRONIC DAILY HEADACHE. R. Hering-Hanit, A. Yavetz, Y. Dagan, Meir General Hospital, Sapir Medical Centre, Sheba Medical Centre (Kfar Saba, Ramat-Gan, IL)

Background and objectives: Medication misuse by migraineurs causes chronic daily headache. It has been shown that abrupt medication withdrawal could be achieved with the help of Baclofen. Migraine patients and chronic headache patients were found to have a high incidence of sleep disturbances. The aim of this study was to define sleep patterns of migraineurs with drug induced headache before and following withdrawal of the abused medications. Methods: Sixteen females with migraine and drug induced headache were treated for 3 months. Baclofen 30 mg was given to 11 patients, and in 5 withdrawal wasn't supported by any medication. Polysomnography was performed and a self-assessment questionnaire determining sleep quality was filled out before and following

medication withdrawal. Headache frequency and severity as well as medication intake were recorded. Results: By 3 months of medication withdrawal a significant increase in total sleep time and sleep efficiency and a significant decrease in the number of arousals were recorded in both groups. Total sleep time increased from 308.8 min. before to 329.2 min. after withdrawal, $p< 0.005$, sleep efficiency – from 80.54 to 84.6, $p< 0.005$, and the number of arousals declined from 92 to 31.53, $p< 0.001$. Headache frequency and medication intake significantly decreased in both groups ($p< 0.001$), and headache severity significantly declined in patients treated with baclofen ($p< 0.001$). Conclusions: Polysomnography as well as a self-assessment questionnaire have shown that migraineurs with chronic daily headache due to medication misuse suffer from a high incidence of sleep disturbances. Withdrawal from the offending medication significantly improved objective and subjective sleep quality in baclofen-treated and in untreated patients, along with an amelioration of headache frequency and severity.

P734
UNUSUAL PRESENTATION OF UPPER CERVICAL CAVERNOMA. E. Verdun, P. Cerrato, D. Imperiale, M. Giraudo, C. Baima, M. Grasso, B. Bergamasco, Division of Neurology (Torino, I)

We describe a patient with greater occipital neuralgia (Arnold's neuralgia) as isolated symptom of upper-cervical cavernous angioma. A 59-year-old woman was referred to our neurological ward in January 1999 because of intractable cervico-occipital pain lasting for two years. Pain involved right occipital region. It was sharp and burning with paroxysms triggered by skin rubbing and pressure at level of emergency of the greater occipital nerve (namely in the paramedian suboccipital area besides "inion" point). Neurological examination was normal: there were neither sensory-motor deficits nor signs of mielopathy, the only abnormality was an asymmetry of deep tendon reflexes which were predominant in the right limbs. Cervical radiogram was normal; spinal MRI showed a lesion in the upper (first and second myelomer) cervical tract characterized by weak irregular hyperintensity on T1-weighted scans. T2-weighted images showed unhomogeneous signal characterized by an hyperintense core surrounded by annular hypointensity. A weak contrast enhancement was appreciated. Cervical CT scans outlined a diffuse specked hyperdensity at level of the lesion, finding consistent with thin calcifications. Spinal angiography scan was normal. The patient was last seen in May 1999 and her clinical situation was stable. She is now taking gabapentin 2000 mg pro die with a partial remission of pain. Clinical course and instrumental findings in the case above reported are suggestive of a diagnosis of spinal cavernous malformation. Its peculiarity consists in neuralgic pain as isolated symptom without signs of myelopathy.

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CYTOKINE EXPRESSION IN PAINFUL AND NON-PAINFUL NEUROPATHIES. M. Empl, S. Huber, B. Erne, P. Fuhr, A. Straube, N. Schaeren-Wiemers, A. J. Steck, Klinikum Grosshadern/ University Munich (Munich, D)

Neuropathies, regardless of their etiology, can be divided in painful and non-painful forms, although clinical experience shows that inflammatory neuropathies are more often painful. As some cytokines have recently been recognised as pain mediators, the expression of TNF-alpha and Interleukin–6 was analysed immunohistochemically in 20 human nerve biopsies of patients with painful (n=10) or non-painful (n=10) neuropathies. Additionally, serum soluble TNF-alpha Receptor I (TNF-RI) and Interleukin–6 levels were measured in 28 patients with neuropathies, 19 painful, 9 painless. TNF-alpha was found in the perineurium, in epi- and endoneurial blood vessels, in epineurial cells as well as in structures corresponding to Schwann cells. Double fluorescence staining with S–100 and TNF-alpha demonstrated a clear colocalization of human Schwann cells and TNF-alpha. The mean density of TNFalpha staining was measured with an image analysis system and put in relation to the background staining in the epineurium. We found a stronger TNF-staining in myelinating Schwann cells of patients with a painful neuropathy compared to those with a non-painful neuropathy (1.010 ± 0.053 vs 0.949 ± 0.047, $p< 0.05$). Interleukin–6 staining was weaker, located to immune cells, perineurium and blood vessels and showed no difference between the two groups. For serum cytokine levels, no difference could be found between painful (n=16) and non-painful (n=8) neuropathies (for TNF-RI: 1412 ± 545 pg/ml vs. 1318 ± 175 pg/ml; for Interleukin–6: 2.91 ± 2.3 pg/ml vs. 1.93 ± 0.74 pg/ml). Patients showing a mechanical allodynia (n=10) had elevated serum TNF-RI (1627 ± 645 pg/ml vs. 1229 ± 206 pg/ml, $p< 0.05$) and Interleukin–6 (3.42 ± 2.53 pg/ml vs. 1.75 ± 0.75 pg/ml; $p< 0.05$) compared with patients without allodynia (n=13). In summary, our study demonstrates, that human Schwann cells express TNF-alpha. Our results further indicate that TNF-alpha might be upregulated in painful neuropathies. The elevation of TNF-RI and Interleukin–6 in patients with mechanical allodynia is in keeping with observations from animal studies.

P736
HEADACHE IN MULTIPLE SCLEROSIS – A PROSPECTIVE STUDY USING THE IHS CLASSIFICATION CRITERIA. W. Feneberg, W. Pöllmann, Marianne-Strauss-Klinik (Berg/Kempfenhausen, D)

Background: Several previous studies have disagreed about frequency and types of headache syndroms (HS) in patients with MS. They all followed the diagnostic criteria of the Ad Hoc Committee of 1962, to the best of our knowledge no data are available following the classification criteria of the international headache society (IHS) of 1988.

Methods: we prospectively and consecutively examined 130 patients (PAT), 87 women and 43 men, with clinically definite or probable MS according to the Poser criteria (mean age 44 years (range 19–77); range of EDSS 1,0–8,5). All PAT were asked to use a headache diary during their 3–5 weeks stay in our hospital.

Two interviewers obtained a detailed headache history. Onset, frequency, location, duration, quality and intensity of pain, family history, triggering factors and associated symptoms were included. Also associations between headache and beginning or exacerbation of multiple sclerosis were noted. Headaches were classified according to the IHS criteria.

Results: We found 96 HS in 76 PAT (58%): 52 headaches of the migraine type, 20 tension type headaches, 6 stabbing headaches, 3 cold stimulus headaches, 1 benign exertional headache, 2 headaches associated with vascular disorder or non-cephalic infection. 12 HS were not classifiable.

29 PAT had a positive family history for headache. 24 HS started at the onset (18) or an exacerbation (6) of the MS, the 12 not classifiable HS were all in this group.

Conclusion: To the best of our knowledge this is the first prospective study in MS PAT using the diagnostic criteria of the IHS. Especially migraine type headache is a very common symptom in MS PAT. In one third of our PAT the start of their headache was associated with the onset or an exacerbation of their MS. The possible pathogenesis and implications for differential diagnosis will be discussed.

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TREATMENT OF CLUSTER HEADACHE AND SLEEP APNEA SYNDROME WITH CPAP AND CONTINUOUS OXYGEN SUPPLY. P. Lüdemann, A. Frese, S. Happe, S. Evers, Westfälische Wilhelms University (Münster, D)

Introduction: Obstructive sleep apnea syndrome (OSAS) seems to be common in patients with episodic cluster headache (1). There are four case reports of reduced headache attacks in patients with cluster headache and obstructive sleep apnea syndrome (2–4). We report on a patient with OSAS, central sleep apnea syndrome (CSAS), and cluster headache who is asymptomatic under treatment of the apnea syndromes.

Case report: A 48 year old man with a more than 20 year history of episodic cluster headache according to the criteria of the International Headache Society was admitted to our hospital with at least two headache attacks per night. He did not respond to prophylactic treatment with verapamil, prednisone and valproate. Onset of the headache was exclusively out of sleep. These observations could be verified polysomnographically. Additionally, we found mixed apneas (apnea index, AI > 40/h) and nasal CPAP therapy was initiated. All snoring and obstructive apneas were eliminated, but a CSAS with an AI > 30/h persisted. During this night with CPAP, there was only one headache episode. The next night we added continuous oxygen (initially 2 l/min, later 4l/min) to the CPAP mask. Under oxygen at 4 l/min AI was normalised, and there was no headache. Two nights later, the patient forgot to turn on the oxygenator, and headaches returned. After 4 months, the patient still uses the CPAP machine with oxygen supply without recurrence of headache clusters.

Conclusion: This observation supports the use of polysomnography in nocturnal cluster headache. If cluster headache and CSAS share a common etiology, the brainstem chemoreceptor dysfunction theory (5) is supported.

(1) Kudrow L, et al. Cephalagia 1984;4:33–38; (2) Buckle et al. Sleep 1993;16:487–489; (3) Nath & Chervin Sleep research 1997;26:576; (4) Nath et al. APSS 1998 (abstract); (5) Kudrow. Curr Opin Neurol 1994;7:278–282

P738
ESTIMATION OF ANALGESIC EFFECT OF ANTICONVULSIVE DRUGS IN PATIENTS WITH CHRONIC NEUROPATHIC PAIN. W. Zabielski, P. Lyczak, A. Radek, Navy Hospital Gdansk (Gdansk, PL)

Chronic neuropathic pain is a big medical problem, because it is not dependent on typical methods of pain treatment. In the last decade in many publications we observed progress in researches on mechanism of neuropathic pain and using with this treatment new anticolnulsants for example neurontin (Gabapentin) and lamotrygine (Lamictal). Aim of the study: Estimation of analgetic effect of new anticonvulsant: selective GABA agonist – tiagabina (Gabitril) and comparison the effect with an analgetic influence of antiepileptic drugs: carbamacepine, lemotrygine and placebo.

Material and method: We observed a group of 0 patients with insulinodependent diabetes mellitus. In this group we researched peripheral neuropathy and chronic neuropathic pain on the base neurological and specifical signs for example: allodynia, hyperalgesia, paresthesia. They were divided into 4 groups: 20 subjects treated with carbamacepine (100–400 mg per day), 20 subjects treated with lamotrygine (50–200 mg per day), 20 with thiagabine (10–30 mg per day) and 20 persons with placebo. Estimation of analgetic effect was measured on 1st, 7th and 14th day of treatment on the base of an 11-point Likert scale (0- no pain to 10-worst possible pain), elements of McGill Pain Questionaire (MPQ) and Brief Pain inventory (Short form).

Results: Beneficial analgetic effect (regression or decrease of pain) was obtained on 14th day of treatment in 68% patients treated with karbamasepine, 63% patients treated with gabapentine, 54% treated lamotrygine, 58% ones treated with tiagabine versus 20% persons with placebo. Adverse events like somnolence, dizziness, tremor, fatigue in the lamotrygine and thiagabine treated group were statistically less than in group treated with carbamacepine and the same in the group with placebo.

Conclusions: The results prove that tiagabine like carbamasepine and lamotrygine is an effective medication in chronic neuropathic pain. In cases when other anticonvulsants are contraindicated tiagabine seems to be an alternative drug use.

Peripheral neuropathy

P739
AXONAL NEUROPATHY ASSOCIATED WITH POEMS SYNDROME AND IGA-MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE. A CASE REPORT. L García, A Jaramillo, J Idiáquez, R Espinoza, Hospital Naval A. Nef (Viña del Mar, RCH)

A 64 year-old woman with a ten-year-old history of seborrheic dermatitis, without history of Diabetes mellitus, began the last four years with distal numbness, tingling, prickly pain and progresses in a "stocking and gloves distribution". Besides, she presented a weakness of arms and legs with a distal predominance. The reflexes were lost early. The skin was dark, thickened, with oedema, hypertrichosis, seborrheic dermatitis and thin white nails. The liver was enlarged. The blood samples detected elevated levels of TSH and prolactin. T3, T4, FT4, testosterone, androstenedione and Cortisol were normal. The FSH, LH, estradiol and progesterone were reduced. The protein electrophoresis detected IgA-lambda monoclonal gammopathy. The cerebrospinal fluid was normal. Finally, the skin biopsy showed solar elastosis. These findings suggest a POEMS (Polyneuropathy, organomegaly, endocrinopathy, monoclonal band and skin changes) syndrome. Electrophysiology showed axonal neuropathy features in motor and sensory fibres with severe reduction of conduction velocity and amplitudes, fibrillation potentials and positive sharp waves in involved muscles. Sural nerve biopsy showed a diffused axonal losts with infiltration of collagen type 1 in the endoneurium using electronic microscopy. The myelin was normal without amyloid deposition. The patient was initially treated with plasmaphoresis which did not help. After she was treated with Cyclophosphamide 1 g intravenous monthly during the following seven months with electrophysiological improvement but without clinical response. Discussion: POEMS syndrome is a multisystemic disease that usually presents in early middle age, that can be associated to a IgA- monoclonal gammopathy of unknown significance (MGUS). Patients with IgA lambda immunoglobulin often present a demyelinating and axonal polyneuropathy, with amyloid deposition. We report a case with selective axonal polyneuropathy and IgA lambda, without Amyloid deposition in a patient with POEMS syndrome.

P740
FUNCTIONAL STATUS IN PATIENTS WITH SIGNS AND SYMPTOMS SUGGESTING A POLYNEUROPATHY, BUT WITH NORMAL ELECTROPHYSIOLOGICAL STUDIES, TWO YEARS AFTER ONSET. C. W. Slotema, N. R. Rosenberg, P. Portegies, M. de Visser, J. E. Hoogendijk, R. de Haan, M. Vermeulen, Academic Medical Centre, Academic Hospital (Amsterdam, Utrecht, NL)

Objectives: 1) To investigate the final diagnosis and functional status in patients with signs and symptoms suggesting a polyneuropathy, but with normal electrophysiological studies. 2) To investigate whether there is a different outcome between patients with or without neurological signs at the first neurological examination. Design: A chart review and interview, including the sickness impact profile scale (SIP), of a consecutive group of patients with signs and symptoms suggesting a polyneuropathy, but in whom electrophysiological studies appeared normal two years after the first visit at the outpatient clinic. Setting: Outpatient clinic of a university department of neurology. Participants: All patients who presented at the outpatient clinic between 1993 and 1997 with signs and symptoms suggesting a polyneuropathy, but in whom electrophysiological studies appeared normal. Main outcome measures: Final diagnosis and functional status at least two years after the first visit at the outpatient clinic. Results: We included 38 patients. A total of 27/38 (71%) patients did have neurological signs at neurological examination at the first visit. In 19 patients a final diagnosis was established, in the other 19 patients a final diagnosis could not be made. Half of the patients (19) had a poor outcome (SIP> 10). In patients with neurological signs at neurological examination at the first visit a final diagnosis was made in 18/27 (67%) versus 1/11 (9%) in the group of patients without neurological signs. A total of 10/11 (91%) patients without neurological signs at neurological examination at the first visit had a good outcome (SIP< 10) versus 10/27 (37%) in the group of patients with neurological signs. A total of 15/19 (79%) patients with a final diagnosis had a poor outcome (SIP> 10) versus 4/19 (16%) in the group of patients without a final diagnosis. A total of 16/19 (84%) patients without a final diagnosis had a good outcome (SIP< 10) versus 3/18 (21%) in the group of patients with a final diagnosis. Conclusion: 1) A final diagnosis is established more frequently in patients with neurological signs than without neurological signs at neurological examination. 2) Patients with an established diagnosis have a worse outcome than patients without a diagnosis. 3) Patients with clinical features suggesting a polyneuropathy, but without neurological signs at neurological examination have a better outcome than patients with neurological signs.

P741
CHRONIC PROGRESSIVE MIXED AXONAL NEUROPATHY (CPMAN): A CLINICO-NEUROPHYSIOLOGICAL FOLLOW-UP AND NECROPSIC FINDINGS. J. Pascual Calvet, F. Alameda, J. Roquer, A. Rodriguez Campello, A. Pou Serradell, Hospital Del Mar (Barcelona, Barcelona, E)

Chronic immune mediated neuropathies can simulate Amyotrophic Lateral Sclerosis (ALS): Multifocal motor neuropathy with conduction block (MMN), motor neuropathies associated with paraproteinemia or elevated anti-GM1 antibodies and a pure motor variant of chronic inflammatory demyelinating neuropathy (CDIP). AIMS.- The goal of our presentation is to show the clinical, electrophysiological and morphological (nerve biopsy and the complete necropsy) findings in a patient, whose clinical and electrophysiological data evoked a CPMAN, that died four years after the onset of the disease. CASE REPORT.- A 66 year old man, without familiar history of neurological disease nor previous pathological events began to complain of a progressive right hand weakness and drowsiness which spread proximally in a few weeks. At this time, cervical MRI disclosed disc protrusions C5-C6-C7 and a T2 slight hyperintensity signal at the same level in the spinal cord. He was submitted to surgical treatment (discectomy), but weakness and wasting progressed for the following 3 years, involving successively the right and left lower limbs, and left arm. Neurological examination at this time disclosed a flaccid tetraparesis involving asymmetrically distal and proximal muscular groups at the four limbs, with amyotrophy and fasciculations in the right upper limb and quadriceps. There was distal hypoesthesia of the upper and lower right limbs. The CSF showed mild increase of CSF protein content (70 mg/dl), without cells. Neurophysiological examination showed features of a severe mixed axonal multifocal neuropathy, sensitive nerve action potentials (SNAP) and somesthesic evoked potentials (SEP) were not elicited. No motor conduction blocks were present. All the studies made to find systemic illness were negative, as well as anti-GM1 and anti-Hu antibodies. Sural nerve biopsy showed a great loss of myelinated fibers, no inflammatory infiltrate or vasculitic changes were found. The patient progressively worsened, and did not respond to corticosteroid or endovenous immunoglobulins treatment. Six months before he died from respiratory failure, a complete tetraparesis, lingual fasciculations, dysarthria, right soft palatal paresis, right trigeminal hypoesthesia appeared. Post mortem examination was performed. There was no evidence of systemic tumour or other lesions. Neu-

ropathological findings included: 1) Severe mixed axonal neuropathy, 2) Loss of neurons with chromatolysis in anterior and posterior horns, 3) Loss of dorsal root ganglion cells, 4) Sparse lymphocytic infiltrates in the white matter of the cerebral hemispheres and 5) Inflammatory lymphocytic infiltrates in anterior and posterior roots. CONCLUSIONS.- The findings of the necropsy in this patient confirmed that lesions were not restricted to peripheral nerves but also motor and sensitive neurons of the spinal cord were impaired. The presence of inflammatory infiltrates in the nerve roots and the absence of malignancy or vasculitic changes, allows us to believe that the etiology of the neuropathy was of immunologic origin.

P742
HEREDITARY MOTOR AND SENSORY NEUROPATHY WITH HYPERTROPHY OF THE CAUDA EQUINA AND CONCOMITANT DEMYELINATING WHITE MATTER LESIONS; REPORT OF A CASE. B. Ertl-Wagner, A. Staebler, C. Helmchen, F. Fassmann, M. Reiser, Dept.of Radiology, Univ. of Munich, Dept. of Neurology, Univ. of Luebeck, Radiological Imaging Center (Munich, Luebeck, Nuernberg/Erlangen, D)

Hereditary motor and sensory neuropathy (HMSN) is a hereditary disease of the peripheral nerves. There are usually no signs of central nervous involvement. In contrast, we report the case of a 48-year old patient with a longstanding history of a hereditary demyelinating motor and sensory neuropathy and a strongly positive family history (autosomal dominant inheritance mode). Over the course of the disease, the patient gradually developed signs of a cauda syndrome. Moreover, she also showed signs of a central nervous system relapsing-remitting demyelinating white matter disease (subsequent episodes of optic neuritis on both eyes and trigeminal neuralgia). Clinically and electrophysiologically, HMSN I was likely but could not be confirmed by genetic data (17p11, PMP–22 negative). In accordance with the cauda syndrome, spinal MR imaging revealed gross enlargement of the cauda equina fibers in the spinal canal and multiple lumbar radicular compressions in the neuroforamina due to severe nerve hypertrophy. Unlike expected from this neuropathic disease, cranial MRI showed periventricular and callosal demyelination in the patient. Thus, a possible association between HMSN and central nervous system demyelination as a distinct nosological entity is discussed.

P743
HETEROGENEITY OF NEUROPATHY IN DIABETIC PATIENTS. P. Lozeron, L. Nahum, C. Lacroix, A. Ropert, JM Guglielmi, G. Said, Service de Neurologie (Le Kremlin Bicêtre, F)

Besides the common patterns of neuropathy represented by distal symmetrical sensory polyneuropathy (DSSP), which is often associated with autonomic disturbances, and focal and multifocal neuropathies, diabetic patients are exposed to other causes of neuropathies. It is important to distinguish those that are directly or indirectly related to diabetes from those that have a coincidental relationship. In order to evaluate the frequency of non diabetic neuropathies observed in diabetic patients, we reviewed the clinical and pathological data of 100 consecutive diabetic patients (66 males, 34 women, mean age: 57 years), referred from March 1996 to July 1999 for a disabling neuropathy. Twenty-six patients were on treatment with insulin. Patients had been on treatment for diabetes for 8 years on average. Clinical examination, electrophysiological and biological tests were performed in all of them; a biopsy of an affected nerve was performed in 50 patients for diagnostic and/or prognostic purpose. Results: Chronic inflammatory demyelinating polyneuropathy (CIDP), which was diagnosed in 9 patients (6 men, 3 women), was the single most common cause of non diabetic polyneuropathy in this population. Features of CIDP were similar to those found in non diabetic patients. Alcoholic polyneuropathy was diagnosed in 5 patients. Diabetic DSSP was diagnosed in 60 patients including 17 with symptomatic autonomic disturbances, proximal diabetic neuropathy in 14, focal diabetic neuropathy in 6 patients. In 10 patients another cause of neuropathy was associated with DSSP, including carpal tunnel syndrome in 3, alcoholism in 3, motor neuron disease in 1, spinal root lesions in 2 and CIDP in 1. Our recruitment of diabetic patients is biased by our specialisation in peripheral nerve disorders. Thus diabetic patients were referred mainly when they manifested uncommon neuropathic features including motor deficit, upper limb involvement, focal or multifocal sensory or sensory-motor deficit, severe autonomic disturbances or intractable neuropathic pains. Nevertheless our results show that the diagnosis of diabetic neuropathy must be established only after careful exclusion of other causes of neuropathy, especially when a motor deficit is present and/or in cases with focal or multifocal sensory-motor deficit.

P744
CHRONIC DEMYELINATING PREDOMINANTLY SENSORY POLYNEUROPATHY ASSOCIATED WITH IGG MONOCLONAL GAMMOPATHY AND ANTI-SULFATIDE ANTIBODIES. S. Apostolski, I. Tripkovic, R. Trikic, J. Drulovic, Z. Stevic, V. Rakocevic-Stojanovic, S. Pavlovic, D. Lavrnic, Clinical Center of Serbia School of Medicine, University of Belgrade (Belgrade, YU)

Monoclonal or polyclonal antibodies to sulfatide have been reported in association with predominantly sensory demyelinating and axonal neuropathy. We have observed specific clinical, electrophysiological and immunological features in 4 patients with polyneuropathy associated with IgG monoclonal gammopathy of undetermined significance. Two men and two women (mean, 62; range, 49–72) experienced hand numbness and tingling as the initial sensory symptom and later developed severe sensory loss in both hands, feet and lower legs that involved pinprick, touch, vibration, and joint position sensations. They had a disabling sensory ataxia, with mild distal muscle weakness and areflexia. The course of the disease was chronic relapsing in all of them. Electrophysiologically, three patients fulfilled strict criteria supportive of primary demyelination (slow conduction velocities, prolonged distal latencies, prolonged F-wave latencies) whereas the remainder demonstrated a mixed axonal and demyelinating neuropathy. All patients showed elevated CSF protein concentration (> 0.45 g/L) (mean, 0.77 g/L; range, 0.56 to 0.88 g/L) and normal cell count. The serum protein immuno-electrophoresis revealed monoclonal IgG, and skeletal survey and chest and abdominal CTs were normal as well as the bone marrow biopsy in all patients tested. The monoclonal gammopathy was confirmed in all patients by agarose gel electrophoresis and isoelectric focusing of the serum and CSF, disclosing 3 to 5 parallel monoclonal IgG bands. Circulating immune complexes were increased in only two patients (> 0.5 nm). Serum of each patient was assayed for antibodies to ganglioside GM1 and sulfatide using ELISA methodology. The anti-sulfatide IgG antibodies were positive in all serum samples (1:3,200–1:6,400). GM1 antibodies were negative. The patients poorly responded to steroid immunosuppression. The addition of intravenous immunoglobulin (0.4 g/kg, five days) resulted in significant improvement in all of them. We postulate that the clinical, electrophysiological and immunological findings in our patients support the potential demyelinating role of anti-sulfatide antibodies.

P745
AUTONOMIC NEUROPATHY IN PATIENTS WITH CHRONIC HYPOXEMIA. H. Lahrmann, M. Wild, I. Werner, H. Zwick, U. Zifko, W. Grisold, Neurological Dept., Kaiser Franz Josef Hospital, LBI of Environmental Pneumology, Rehabilitation Clinic (Vienna, Bad Pirawarth, A)

Long term hyperglycemia may cause autonomic neuropathy (ANP) in diabetic patients, but little is known of the effect of chronic hypoxemia on the autonomic nervous system. We investigated the influence of hypoxemia in patients with chronic obstructive pulmonary disease (COPD) on autonomic nervous system function. Methods: In 7 normoxemic (arterial oxygen (PaO_2) > 75mmHg) and 13 hypoxemic (PaO_2 < 75mmHg) COPD patients with various degrees of hypoxemia we measured lung function and blood gas values. To assess autonomic function we analysed heart rate variation during quiet and deep breathing, valsalva maneuver and orthostasis. Additionally we recorded the sympathetic skin response after stimulating the median nerve at the wrist. Results: According to the criteria of Ewing and Clark 2 normoxemic patients had early and 1 definitive ANP, whereas 6 hypoxemic patients had an early ANP, 3 patients a definite, and 2 patients a combined ANP. We found a significant correlation between the degree of ANP and the decrease in PaO_2. The 7 hypercapnic patients had the most pronounced ANP. Conclusion: In our study 11 of 13 hypoxemic COPD patients had signs of dysfunction of the autonomic nervous system. ANP was most pronounced in patients with severe hypoxia and hypercapnia. These results indicate that chronic hypoxemia may cause autonomic dysfunction.

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P746
LPS STRUCTURE DETERMINES ANTI-GANGLIOSIDE ANTIBODY SPECIFICITY AND CLINICAL FEATURES IN PATIENTS WITH GUILLAIN-BARRÉ AND MILLER FISHER SYNDROME. C. W. Ang, B. C. Jacobs, M. A. De Klerk, A. P. Tio-Gillen, N. Van Den Braak, H.Ph. Endtz, P. A. Van Doorn, Erasmus University Rotterdam (Rotterdam, NL)

In patients with the Guillain-Barré syndrome (GBS) and Miller Fisher syndrome (MFS), anti-ganglioside antibodies are thought to be induced by a preceding Campylobacter infection through molecular mimicry between C. jejuni lipopolysaccharides (LPS) and neural gangliosides. We characterized the purified LPS fraction of 18 Campylobacter strains isolated from GBS or MFS

cases with a panel of GM1-positive and GQ1b-positive serum samples. LPS from 17/18 strains showed reactivity with GM1 and/or GQ1b positive serum samples, confirming the frequent presence of ganglioside-like epitopes in GBS and MFS associated strains. GBS patients frequently had a GM1-like epitope and all MFS patients had a GQ1b-like epitope. All patients but one had antibody reactivity against the LPS fraction from the strain isolated from himself/herself. The presence of a GQ1b-like epitope in the LPS fraction correlated with serum reactivity against GQ1b and the presence of oculomotor symptoms. Our results demonstrate that serological typing of the LPS fraction can predict the anti-ganglioside specificity and clinical features in post-Campylobacter neuropathies.

P747
EXPRESSION OF E-CADHERIN AND ß-CATENIN IN MOUSE SCIATIC NERVE DURING DEVELOPMENT, WALLERIAN DEGENERATION AND EXPERIMENTAL MODELS OF HEREDITARY DEMYELINATING NEUROPATHIES. D. M. Menichella, P. L. Baron, E. Scarpini, S. Livraghi, G. Conti, G. Ardolino, F. Cogiamanian, M. Shy, J. Kamholz, IRCCS Ospedale Maggiore, Wayne State University (Milano, I; Detroit, USA)

E-cadherin is a major adhesive glycoprotein in Schwann cells, localized at the paranode, at Schmidt-Lanterman incisures and associated with adherens-type junctions. E-cadherin is connected to the actin cytoskeleton through the interaction with p-catenin, which is part of the cadherin complex mediating intercellular adhesion and signal transduction. To investigate the functional role of E-cadherin / B-catenin in Schwann cell biology, we studied their expression and localization in mouse sciatic nerve during development, Wallerian degeneration or crush and in experimental models of hereditary demyelinating neuropathies, using Northern and Western blot analysis as well as teased fiber immunohistochemistry. In normal sciatic nerve, E cadherin gene expression is similar to that of other myelin proteins because it increases during development and is downregulated following permanent axotomy or nerve crush. On the contrary, levels of P-catenin mRNA and protein do not change during development or after nerve lesion. In genetically engineered mutants with severe peripheral demyelination, such as PO knock out and Trembler mice, the localization of E-cadherin/ P-catenin is altered because cadherin is diffusely distributed throughout the fibers whereas p-catenin is detectable in the perinudear region of myelinating Schwann cells. However, E-cadherin / p-catenin are normally localized in Trembler-J mice, where demyelination is less severe and compaction is preserved. The results of this study indicate that the expression of E-cadherin but not that of P-catenin is regulated in concert with other myelin proteins and depends on axonal interaction(s). The process leading to restricted localization of E-cadherin/p-catenin at the paranodal region is disrupted in the peripheral nerve lacking compact myelin. Therefore, myelin compaction contributes to the process of reorganization of the Schwann cell membrane and is important in paranode formation. On the other hand, the absence of adherens junctions caused by altered localization of E-cadherin/p-catenin could be involved in structural changes of the paranodal region and of the Node of Ranvier with perturbed transmission of impulses along axons.

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P748
SCREENING FOR PERIPHERAL NEUROPATHY IN PATIENTS WITH LEPROSY. J. Grimaud, B. Verchot, F. Chapuis, G. Discamps, J.-M. Vallat, J. Millan, Hôpital Hôtel Dieu, Lab. d'analyse de biologie médicale, Hôpital Universitaire Dupuytren, Institut de Léprologie Appliquée (Dakar, SN; Lyon, Bordeaux, Limoges, F)

Background: In leprosy, early detection of peripheral nerve damage is essential for the prevention of disability.

Design: In this prospective study, we examined the effectiveness of five clinical tests to assess radial cutaneous nerve damage.[1] Light touch was assessed by two nylon threads (based on the Semmes-Weinstein monofilaments testing technique)[2] bent on the skin at a pressure of 0.5 and 0.2 gram. Pinprick and cooling sensations were examined by a pin and a drop of ether. The nerve thickness was assessed by palpation. Clinical tests were then compared to histological findings of the same radial cutaneous nerve. The patient group consisted of 81 leprosy sufferers who attended the Institut de Léprologie Appliquée de Dakar. Diagnosis and classification were based on Ridley and Jopling's criteria.[3]

Results: Sensitivity and specificity were 0.42 and 0.95 for nylon 0.5 gram; 0.64 and 0.85 for nylon 0.2 gram; 0.38 and 1 for pin, 0.48 and 0.89 for ether; 0.60 and 0.86 for palpation. Combination of 2 of the 4 last-mentioned tests gave a sensitivity between 0.89 and 0.94 and a specificity between 0.35 and 0.54.

Conclusion: Assessment of both abnormal perception of nylon 0.2 gram and nerve thickening, is the most sensitive test to detect peripheral nerve damage in patients with leprosy.

References:
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3 Ridley DS, Jopling WH. Int J Lepr Other Mycobact Dis 1966; 34: 255–273.

P749
A FAMILY WITH AUTOSOMAL DOMINANT MUTILATING NEUROPATHY NOT LINKED TO EITHER CHROMOSOME 3Q13-Q22 OR 9Q22 LOCI. C. Rodolico, A. Toscano, E. Bellone, E. Di Maria, D. Cassandrini, A. Mazzeo, P. Girlanda, G. Vita, A. Pizzuti, F. Ajmar, P. Mandich, University of Messina, University of Genova, University of Milano (Messina, Genova, Milano, I)

The clinical separation of CMT2 from HSAN I may be difficult in some kindreds in which the sensory and motor symptoms and deficits are approximately alike. The genetic studies of CMT2 families are as well controversial; one form of CMT2 was shown to map on chromosome 3q13-q22 and named CMT2B; the HSAN I locus was mapped to 9q22.1. We describe a family with an autosomal dominant inheritance in which at least three members, belonging to three different generations, developed a progressive neuropathy that combined limb weakness, wasting and severe distal sensory loss leading to prominent mutilating changes. The onset was in late childhood with progressive weakness in the lower limbs and later in the hands, resulting in severe paralysis in the feet in one patient. Sensory disturbances were pronunced in two of them, leading to poorly healing ulcerations with osteomyelitis and amputation in one foot and mutilating lesions of both hands. Electrophysiological investigations revealed an axonopathy with a consistent motor damage. Sural nerve biopsy showed a reduction in the density of both, myelinated and unmyelinated fibers, with regenerating clusters.

Linkage analysis by using 5 microsatellites markers (D9S176, D9S196, D9S197, D9S287, D9S318) within to the critical 9q22 region was performed. Lod scores of this family calculated by LINKAGE package excluded association to this locus. We also performed linkage studies with chromosome 3q markers (D3S1290, D3S1551, D3S1744, D3S1769, D9S1267) associated to the CMT2B locus. Lod scores excluded this locus as well as responsible of the familial phenotype. The severity of motor involvement would suggest to classify the disorder of this family as a form of HSMN II rather than HSAN thus indicating that a new locus is involved in the pathogenesis of this disorder.

P750
CANOMAD. S. Ponsford, P. K. Thomas, H. Willison, Institute of Neurology (London, UK)

CANOMAD (chronic ataxic neuropathy with ophthalmoplegia and other craniobulbar motor signs, M protein, cold agglutinins and anti-disialylosyl antibodies) is an increasingly recognised form of paraproteinaemic neuropathy. In a recent long term (5–42y, mean 13.7y) follow-up study of 50 patients with peripheral neuropathy associated with benign monoclonal gammopathy (S. Ponsford et al. Muscle and Nerve, in press), 2 out of 38 patients with IgM paraproteins had CANOMAD. One was male. Both had IgM lambda paraproteins and presented with progressive predominantly large fibre sensory polyneuropathy with an age of onset at 28y and 40y respectively. This was associated with recurrent oculofacial weakness and sensory and motor signs in the limbs. Nerve conduction studies showed patchy demyelination in contrast to the uniform showing seen in IgM paraproteinaemic neuropathy with antibodies to myelin associated glycoprotein. Both patients showed some response to intravenous immunoglobulin treatment. CANOMAD appears to represent a clinically and immunologically distinct subgroup of paraproteinaemic neuropathy. Its recognition is important in view of prognosis and the possible response to treatment.

P751
REFSUM DISEASE IN AN ARABIAN FAMILY. E. Fertl, D. Starkel, C. Vass, B. Molzer, K. Vass, E. Auff, H. Bernheimer, Univ. Klinik Neurologie Wien (Vienna, A)

Background: First presentation of an Arabian family from Egypt with Refsum disease. Methods: During an observation period of 9 years, details on history, clinical examination, electrophysiological and laboratory findings were collected to corroborate the diagnosis. Results: In 1991, a 34-year-old Arabian male (M.M.) from Egypt presented with unsteadiness of gait, symmetrical weakness and wasting of foot and calf muscles, severe sensorimotor demyelinating polyneuropathy, bilateral visual field constriction, elevated protein content in the cerebrospinal fluid, and bilateral shortening of the fourth metatarsal bones. Symptoms of polyneuropathy started at an age of 32 years. According to electrophysiological findings (median nerve motor conduction velocity = 32 m/s) and sural nerve biopsy, a diagnosis of hereditary demyelinating neuropa-

thy (CMT I) was made. Seven years later, details on family history were available: The marriage of M. M.'s parents was consanguineous, and one brother suffered from night-blindness and severe sensorimotor polyneuropathy since the age of 28 years (diagnosis of Neurological Department of Cairo University Hospital, 1986). In our index patient, confirmation of retinitis pigmentosa by electroretinography and elevated plasma level of phytanic acid (23 mg/dl) revealed Refsum disease. Specific dietary treatment was introduced with reduction of phytanic acid and phytol intake by eliminating all dairy products and by minimizing ruminant meat and fat. During a 24-months follow-up interval M. M.'s plasma phytanic acid levels raised, indicating lipid mobilisation from body tissue storages. Nerve conduction studies and visual as well as neuromuscular function remained unchanged. Finally, in 1999 blood samples were taken from all family members, confirming the presence of Refsum disease in the above mentioned male sibling. Conclusion: This first report on Refsum disease in an Arabian family from Egypt alerts physicians to a rare, but well-treatable inherited disorder of lipid metabolism. A moleculargenetic examination of M. M. to determine the mutation responsible for the clinical syndrome – whether similar to Caucasian Refsum patients – is forthcoming.

P752
SHORT AND LONG TERM EFFECT OF INTRAVENOUS IMMUNOGLOBULIN TREATMENT IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY: A STUDY OF 38 PATIENTS. L. Nahum-Moscovici, V. Plante-Bordeneuve, D. Adams, G. Said, Hôpital de Bicêtre (Paris, F)

Intravenous immunoglobulin (IVIg) is currently considered an effective immunomodulatory treatment in CIDP. However, data on the long term response rate to repeated infusions remain scarce. IVIg effect was assessed in 38 CIDP patients seen in our center, between 1983 and 1999. The diagnosis relied on clinical examination, electrodiagnostic studies and nerve biopsies, performed in 36 cases. A monoclonal gammopathy was excluded in all cases. The IVIg treatment was given initially or as a second line treatment during the course of the disease. It was introduced on average 5.2 years after the first manifestations of CIDP. The prescribed doses were 1 to 2 g/kg body weight, over a 2 to 5 days period. All patients were evaluated, shortly (1 to 3 months) after the first infusion, on a clinical assessment including a standardized evaluation of the walk, a score of strength in 22 muscle groups and a functional grading score. The same clinical parameters were evaluated, in all patients, at intervals, on an average period of 5 years (1–19 years). There were 26 men and 12 women with a mean age of onset of symptoms of 50 (21 to 78 years). Half of the patients had a relapsing and half a chronic progressive course. The majority of patients (34) presented with sensory-motor manifestations. Eleven patients had an associated disease including diabetes (5), autoimmune disorders (4), renal transplant (2), viral hepatitis B (1). At the initial evaluation performed 1 to 3 months after the first IVIg course, 19 patients (50%) had improved, 19 patients remained severely disabled (12 cases) or had deteriorated (7 cases) requiring another immunosuppressive therapy. Severe side effects were observed in 2 patients, shortly after the onset of the IVIg. One kidney transplanted man had a reversible acute renal tubular necrosis, another had a chronic viral hepatitis. On the long term follow up, among the 19 patients who initially improved, 7 deteriorated despite additional IVIg infusions and 12 had sustained improvement. At the last evaluation, 6 patients improved to a neurological function compatible with a normal daily life activity. Only 4 out of the 38 patients of the cohort continue to benefit from regular IVIg infusions.

Conclusion: IVIg is a well tolerated treatment in CIDP. After a mean follow up of 5 years, 10% of the patients of this survey still benefit from recurrent infusions.

P753
ONE YEAR FOLLOW-UP IN DIABETIC PATIENTS AFTER SURGICAL TREATMENT OF CARPAL TUNNEL SYNDROME. A. Barada, M. Reljanovic, R. Bilic, J. Kovljanic, Z. Metelko, Vuk Vrhovac University Clinic, Orthopedic Clinic (Zagreb, HR)

The clinical disorder known as carpal tunnel syndrome (CTS), the result of chronic entrapment of median nerve beneath the transverse carpal ligament, occurs more frequently in diabetics cohorts than in the general population. Diabetic nerves are more vulnerable to compression, stretch or repeated trivial injury. Moreover, it is the most common entrapment neuropathy in diabetic patients.

The aim of the study was to evaluate clinical and neurophysiological changes in diabetic patients operated for carpal tunnel syndrome (CTS).

The group consisted of 61 diabetic patients with stage severity of CTS 2 b: symptoms and findings and electrophysiologic diagnostic (by P. Dyck), with mean age 50.3 (± 27.3) and diabetes duration 13.5 years (± 8.9).

Response to treatment was evaluated using visual analogue scale (VAS) for pain and for paresthesias before operation, 3 and 12 months after. In the same time we compared median motor distal latency, amplitude of motor nerve action potentials, sensory conduction velocity and amplitude of sensory nerve action potentials in distal segment of median nerve as well as vibration perception threshold. Improvement was found for pain (baseline VAS 4.5 cm vs. follow-up VAS 1.5 cm; Wilcoxon p=0.00365) and paresthesias (baseline VAS 5.4 cm vs. follow-up VAS 0.8 cm; Wilcoxon p=0.00000) after 3 months. Subjective pain and paresthesias assessment remained at the improved level after 12 months of follow-up. Neurophysiological parameters measured were shown to improve after 3 and 12 months of follow-up period: median motor distal latency (baseline 5.9 ms/6 cm, 3 months 4.8 ms/6 cm, 12 months 4.1 ms/6 cm; ANOVA p< 0.00000), amplitude of median motor action potential (baseline 4.8 mV, 3 months 5.6 mV, 12 months 6.6 mV; ANOVA p< 0.01040), median sensory conduction velocity in distal segment (baseline 37.9 m/s, 3 months 43.0 m/s, 12 months 47.3 m/s; ANOVA p< 0.00464), vibration perception threshold (baseline 9.8 V, 3 months 7.6 V, 12 months 6,8 V; ANOVA p< 0,00006).

Concerning our results, clinical and neurophysiological parameters support surgery as the definitive treatment for CTS.

P754
FEMORAL NEUROPATHY FROM A PERIPHERAL PRIMITIVE NEUROECTODERMAL TUMOR (PNET) ARISING IN THE PSOAS MUSCLE. S. Simonetti, R. Datti, R. Bandelloni, E. O. Ospedali Galliera (Genova, I)

We describe a 69-year-old woman who presented with a 5-month history of progressive pain and sensation loss over the right anterior thigh and knee, and weakness of the right hip and knee extension. Neurological examination showed severe weakness of the right iliopsoas, plegia and atrophy of the right quadriceps muscles, remarkable sensation loss over the right anterior thigh, knee and medial calf, and absent right knee reflex.

EMG investigation showed complete denervation of the right quadriceps muscles where no motor responses were evoked after femoral nerve stimulation at the inguinal ligament, and normal findings in the right hip adductors, tibialis anterior and lumbar paraspinal muscles. No sensory response were evoked along the right saphenous nerve. These data indicated a severe right femoral neuropathy. US and CT scans showed a mass within the inferior half of the right psoas which was surgically resected through a retroperitoneal approach. Microscopic and immunohistochemical studies of the tumor tissue demonstrated a peripheral-type primitive neuroectodermal tumor (PNET). Chemotherapy with adriamycin and ifosfamide was then administered.

Neoplastic involvement of the psoas is most frequently encountered in adults with primary retroperitoneal sarcomas or carcinomas arising in the pancreas, adrenal glands or kidneys. Isolated tumors of the psoas muscle are rare. To our knowledge, only one PNET of the psoas has been described on electron microscopic basis, in a 16-year-old boy. The present report is the first description of an immunohistochemically-proven PNET arising in the psoas and manifesting in adult age.

P755
TREATMENT OF CHRONIC INFLAMMATORY DEMYELINATING NEUROPATHY (CIDP) WITH EXTRACORPOREAL ANTIBODY-BASED IMMUNOADSORPTION VERSUS HIGH-DOSE INTRAVENOUS IMMUNGLOBULIN INFUSION: A RANDOMIZED CROSSOVER STUDY. M. Toepfer, M. Schroeder, M. Walter, H. Schiffl, W. Müller-Felber, D. Pongratz, University of Munich (Munich, D)

Background. Chronic inflammatory demyelinating neuropathy (CIDP) is a paralytic syndrome, causing considerable progressive disability. Plasma exchange and administration of intravenous immunglobulins (IVIg) are established treatments for chronic inflammatory demyelinating neuropathy, proved in several clinical trials. Efficacy of selective Ig-immunoadsorption remains unproved. This study is designed to prove whether Ig-immunoadsorption may provide a more effective treatment than IVIg therapy. Objective end points are neurological disability score, score of muscle weakness, sensibility score and electrophysiological tests including nerve conduction velocities.

Study design. Patients with chronic inflammatory demyelinating neuropathy are randomly treated cross-over with either Ig-immunoadsorption or high-dose IVIg. Each treatment period lasts four months. 1) Ig-immunoadsorption was performed with extracorporeal antibody-based immunoadsorption (Ig-Therasorb, Plasmaselect, Germany) three times per week every third week processing 6–7 L plasma volume each session. 2) IVIg therapy is administered every four weeks (initially 0,4 g/kg body weight for five consecutive days, then 0,4 g/kg for 2 days). Patients are prospectively examined using the clinical scores and electrophysiological tests mentioned above with subsequential examination every second week.

Results. Six patients have finished the study protocol. In four of six patients Ig-immunoadsorption was more effective than IVIg therapy with respect to all

endpoints. In two patients efficacy of Ig-immunoadsorption showed no difference compared to IVIg therapy.

Conclusion. We conclude that in patients with chronic inflammatory demyelinating neuropathy, extracorporeal selective Ig-immunoadsorption has an ameliorating effect on neurologic dysfunction and nerve conduction; in some patients selective immunoadsorption may be a more effective treatment than high-dose IVIg therapy. In addition, this result supports the assumption that a humoral factor or factors may play a role in the neurologic deficit of chronic inflammatory demyelinating neuropathy.

Sleep disorders

P756
ITCHING – AN ATYPICAL PARESTHESIA IN RESTLESS LEGS SYNDROME. H. von Lindeiner, I. Eisensehr, S. Noachtar, Klinikum Grosshadern, LMU Muenchen (Munich, D)

We report on a 60 year old female: she reported itching of the whole body, especially the head, which occurred while resting in the evening and at night leading to insomnia with frequent awakenings (3–10 times/night, total sleep time (TST) 2–7 hours), and subsequent excessive daytime sleepiness. The paresthesia could be relieved by moving around and cooling the body with ice. An observer reported of leg jerks during the patient's sleep. Further history was unremarkable. Neurological, internal and dermatological examination and laboratory assessment were normal. Polysomnography (PSG) revealed a highly increased number (49,6 /hour TST) of limb movements (LMs, 60 % periodic limb movements [PLMs]). Half of the PLMs were associated with arousals and consecutive sleep fragmentation (TST 141,5 min, sleep efficiency/time in bed 29,2 %). The patient reported good relief of symptoms with L-DOPA (250 mg/day) treatment (1 awakening/night, TST of 6–7 hours). PSG at follow-up (3 months) with L-DOPA treatment showed a marked reduction of the LMs (4,8 /hour TST, 30 % PLMs). This case demonstrates Restless Legs Syndrome characterized by unusual paresthesias (whole body and head itching). Our diagnosis is supported by PSG and positive response to dopaminergic therapy.

P757
PIRIBEDIL IS EFFECTIVE IN RESTLESS LEGS SYNDROME. V. Evidente, St. Luke's Medical Center (Quezon City, PI)

Restless legs syndrome (RLS), like Parkinson's disease (PD), is thought to be due to dopaminergic dysfunction. Levodopa is particularly effective for RLS, but often leads to augmentation and rebound. Thus, dopamine agonists may be a better alternative. GOAL: To describe the effect of piribedil, a D2/D3 dopamine agonist, on 12 patients with RLS. METHODS: 12 consecutive RLS patients (6 male, 6 female) were treated with piribedil (Trivastal retard 50) ± domperidone (to prevent nausea) in an open label trial that started in February 1999. Patients were rated using an RLS scale (0–10) pre- and post-treatment with piribedil. RESULTS: Mean age was 66.5 years (range 39–87). 8/12 (67 %) had idiopathic RLS, while 4/12 (33 %) had neuropathy. 4/12 (33 %) had PD, while 1/12 had uremia (on regular dialysis). 10/12 (83 %) responded to piribedil, with a mean subjective improvement of 78.3 % (range 0–100 %); 8/12 (67 %) had 100 % response. The RLS score dropped from a mean of 9.92 pretreatment to 3.25 post-treatment (p=0.0003). Effective dose ranged from 25–350 mg/day (mean dose 110 mg/day). 9/10 responded to low dose piribedil (150 mg/day or less), while 1/10 (with severe uremia and neuropathy) needed 350 mg/day. Duration of response for the 10 responders has ranged from 1–12 months (mean 6.2 months); all have ongoing benefit. 1/12 (a nonresponder) experienced sleepiness and mental clouding at a dose of 50 mg/day and stopped the drug. The other nonresponder stopped piribedil due to poor benefit at a dose of 200 mg/day. None experienced nausea or vomiting when piribedil was preceded by domperidone. CONCLUSIONS: Piribedil is an effective treatment for RLS, even at low doses. Side effects are minimal. A double-blind placebo-controlled study is warranted.

P758
CATAPLEXY ASSOCIATED WITH CHANGE IN CARDIOVASCULAR STATUS. N. C. Silver, M. Kibuuka, J. Fearnley, Institute of Neurology, Royal London Hospital (London, UK)

Cataplexy is the pathological loss of muscle tone experienced periodically in narcoleptics. It is typically precipitated by emotion. The physiological changes responsible for the triggering of cataplexy are unknown. Cataplexy is frequently associated with mild autonomic symptoms and it has been hypothesized that cardiovascular variables have a role in precipitating cataplectic attacks. We present a patient who experienced profound bradycardia during typical cataplectic attacks. A 78 year patient presented with an exacerbation of cataplexy whilst being investigated and treated for carcinoma of the prostate. He was diagnosed narcoleptic at 40 years, with daytime somnolence, "sleep" attacks, and cataplexy. He stopped amphetamine treatment at 58 years (current medication, lansoprazole and senna). Cataplectic attacks were reproducibly provoked by surprise and involved him slumping into a chair or onto the bed, and falling to the floor on 2 occasions. His head would fall to one side, jaw sag, and eyes flicker. He would mumble and, on occasions, his knees would buckle. There was no colour change, abnormality of respiration, or loss of consciousness. Recovery was immediate and full, within 1–4 minutes. During initial severe attacks, absent peripheral and central pulses were noted. Systemic and neurological examination were otherwise normal. ECG and 24 hour ECG were unremarkable. EEG telemetry over 48 hours recorded 8 attacks, confirming tachycardia at attack onset (mean=108 beats per minute (bpm)), followed by immediate bradycardia (mean pulse reduction =31 %, range = 25–48 %; lowest recorded heart rate=51bpm) with slow recovery to the resting value. EMG showed marked reduction in muscle artefact during the attack, consistent with atonia. No EEG abnormalities were noted (normal alpha rhythm throughout each attack). Treatment with imipramine abolished all attacks. Profound bradycardia has been associated with attack onset in narcoleptic dogs. It has been suggested that cataplexy may represent a homeostatic reflex, triggered by interactions between blood flow, central chemoreceptors, and muscle atonia control mechanisms in the medulla. We are not aware of such marked cardiovascular change in human studies. The data presented support the hypothesis that emotional triggers for cataplexy might be associated with changes in cardiovascular function and resultant changes in brainstem bloodflow, leading to production of atonia in patients with narcolepsy.

P759
PERSISTENCE OF MOVING TOES DURING SLEEP IN 2 PATIENTS WITH A PAINFUL LEGS/MOVING TOES SYNDROME. R Crols, P De Deyn, A. Z. Middelheim (Antwerpen, B)

Painful legs/moving toes syndrome (PLMT) is a rare disorder characterized by painful legs and moving toes in patients with peripheral neurological disorders. until now, PLMT is not recognised as a cause of nocturnal movement disorder. we like to present 2 patients with PLMT and insomnia caused by persistence of moving toes during sleep.

Patient 1: A 48-year-old woman presented with a paraparesis due to ethylism, folic acid deficiency and diabetes type 2. The paraparesis recuperated well after treatment, but 3 months later the patient developed a PLMT of the right leg, and 6 months later also of the left leg. She also complained of insomnia caused by pain and nocturnal moving toes. A polysomnography with video-monitoring was performed with continuous registration of the electromyography (EMG) of the right extensor digitorum brevis muscle (m. EDB). On falling asleep, the EMG activity immediately stopped, but this resumed promptly during arousals. During rapid eye movement (REM) sleep, periodical EMG activity was noted and intermittent movements of the toes were seen on video-monitoring.

Patient 2: A 6'-year-old man has complained of PLMT for one year. In 1967 he was operated of a hernia discalis at L4/L5. Later he developed an arachnoiditis with severe chronic low back pain, irradiating in both legs, not responding to a neurostimulator. A polysomnography with video-monitoring was performed with continuous EMG registration of the left m. EDB. EMG persisted periodically during stage 1 and 2 sleep and sometimes also during REM sleep with intermittent movements of the toes on video-monitoring.

Conclusions: Our findings confirm insomnia due to persistence of moving toes during sleep in PLMT. This diagnosis should be added to the causes of sleeping disturbances caused by movement during sleep.

Although the exact physiopathological mechanisms causing PLMT remain unknown, they seem to be controlled by descendings pathways under the influence of the sleep/wake cycle.

P760
SLEEP BENEFITS WITH APOMORPHINE IN PARKINSON'S DISEASE: REPORT OF 3 CASES. J.-E. Vanderheyden, M. Kerkhofs, C. H. U. Vesale (Montigny-le-Tilleul, B)

Aim: We are reporting sleep data obtained in 3 patients suffering from idiopathic Parkinson's disease (IPD) in which polysomnography was performed without and with a continuous subcutaneous infusion of Apomorphine.

Material and methods: Two sleep polygraphic recordings were performed for each patient, one night without Apomorphine or other anti-parkinsonian drugs at night, another with continuous subcutaneous infusion of Apomorphine. The second record occurred two or several nights later, without other modifi-

cation of treatment, except an eventual decrease in daily dopatherapy in order to maintain a good motor balance.

Patient #1: Man 71; IPD from 8 years; wearing-off and on-off from 4 years; diurnal drowsiness.

Patient #2: Man 70; IPD from 5 years; wearing-off from 2 years; bad quality of sleep, tired at morning.

Patient #3: Woman 64; IPD from 17 years; wearing-off and on-off from 8 years; hyposomnia and tiredness.

Results (table removed by the editor)

Conclusions: With continuous subcutaneous Apomorphine, a decrease of REM time is observed, very likely due to an anticholinergic effect mediated by Apomorphine. Nevertheless all the patients reported a dramatic improvement of their quality of sleep probably due to a decrease of SOT, PLMS, and A + MA index. A clear clinical effect on akinesia, tremor and rigidity has also to be considered. Interestingly, our patient #1 demonstrated an "indifferentiate" sleep EEG (continuous theta 6–7 Hz) on high L-Dopa doses, but showed closer to normal sleep EEG pattern, with low L-Dopa doses + Apomorphine, suggesting a different central action on sleep mechanisms.

P761
PERIODIC LEG MOVEMENTS IN SLEEP (PLMS) IN ACUTE STROKE. A. Iranzo, J. Santamaria, J. Berenguer, M. Sanchez, A. Chamorro, Hospital Clinic de Barcelona (Barcelona, E)

Objective: To determine the prevalence and significance of PLMS in acute supratentorial ischemic stroke (ASIS). Methods: We prospectively studied 47 patients (28 men, mean age 66.8 years) with ASIS. Polysomnography, including both anterior tibial surface electromyogram recording, was performed the first night after the stroke. Clinical severity at admission and after 6 months was evaluated by the Scandinavian Stroke Scale (SSS) and the Barthel Index (BI). Infarct size was evaluated by Magnetic Resonance Imaging the first week. Results: PLMS index (number of PLMS per hour) greater than 5 was found in 27 patients (57.7 %). Mean PLMS index was 44 ± 29. PLMS were observed in the nonparetic (75 %) and paretic (25 %) legs. PLMS index and PLMS number were significantly associated with greater age (p=0.01), higher SSS scores at admission (p=0.01) and at six months (p=0.01), lower BI scores at admission (p=0.02) and at six months (p=0.02), and greater infarct area (p=0.002) and volume (p=0.004). PLMS were not associated with the apnea index and infarct location. PLM during waking was only related with greater age (p=0.01). Conclusions: In acute supratentorial ischemic stroke, periodic leg movements in sleep are frequent, predominantly in the nonparetic limb and are associated with greater age, greater infarct size, severe clinical disability at admission and poor clinical outcome at six months. Supported by CARBUROS METALICOS and FIS 97–1088.

P762
A CASE OF OBSTRUCTIVE SLEEP APNEA SYNDROM AFTER POSTERO-INFERIOR CEREBELLAR INFARCT. A. Triquenot, P. Athoy, E. Massardier, C. Hemet, Y. Onnient, B. Mihout, Charles Nicolle (Rouen, F)

A 45 year old man, without medical history, suddenly experienced left latero-cervical pain during footing. Two hours later, he developed vertigo, nausea, vomiting and was admitted at hospital. At admission, the examination showed left facial palsy, left Claude Bernard Horner syndrome, left cerebellar dysfunction, dysphonia, dysphagia and nystagmus. MRI with angiography showed left postero-inferior cerebellar artery infarct with left vertebral artery dissection. Six months later, he consulted for recent sleep disorders. He complained of snoring and hypersomnia with Epworth sleepiness score at 11. His clinical examination showed left facial palsy, static and left cinetic cerebellar syndrome. Body Mass Index was scored at 24.6. A polysomnography monitoring was performed and showed severe obstructive sleep apnea (OAS) with a number of apneas plus hypopneas per hour of sleep at 222. The apnea/hypopnea index was 38 and the minimun Sa 02 was 57 %. Continuous positive airway pressure therapy was performed with success. Brainstem strokes or other lesions of medullary respiratory centers have been reported to produce central sleep apnea. OAS may be a consequence of bulbar or pseudobulbar palsy leading to pharyngeal muscle dysfunction. Prospective studies with systematic polysomnography after recent stroke emphasize silent u. asymptomatic OAS as the most common form of sleep-disordered breathing. On the other hand, it is also considered as predisposing condition of stroke. In our case, OAS represents the result of stroke rather than a predisposing condition. It seems important to look for and treat OAS in case of infra-tentorial stroke.

Poster session – 5

Epilepsy

P763
QUALITY OF LIFE SELF-ASSESSMENT AS A FUNCTION OF LATERALIZATION OF LESION IN CANDIDATES FOR EPILEPSY SURGERY. F. Andelman, I. Fried, M. Y. Neufeld, Tel-Aviv Sourasky Medical Center (Tel-Aviv, IL)

OBJECTIVE: To investigate the relationships between unilateral brain insult, personal factors such as state/trait anxiety and quality of life (QoL) in candidates for epilepsy surgery. BACKGROUND. Lateralization effects were reported on personality and emotional processing. If true these trends should differentially influence, on a group level, the level of anxiety and possibly the subjective experience of QoL in fight vs. left hemisphere damaged patients.

DESIGN/METHODS: We examined patients who were candidates for epilepsy surgery. There were 20 adults (ages 19–61y) with right hemisphere epilepsy (RHE), 20 adults (ages 21–50y) with left hemisphere epilepsy – (LHE) and 20 matched normal controls. The Spielberger Trait/State Anxiety questionnaire and the QOLIE–31 questionnaire for self-assessment of QoL were submitted and analyzed. ANOVA, Pearson correlations and linear regression analyses were performed on Group, Anxiety level and QOLIE variables.

RESULTS: Patients with LHE focus tended to show higher levels of anxiety and lower estimates of QoL than patients with RHE. Multiple regression analysis demonstrated a significant interaction between seizure worry and the level of state anxiety in LHE as compared to RHE patients (p=.003).

CONCLUSIONS: LBE patients who show higher level of state anxiety systematically tend to rate their QoL lower than RHE patients. RHE patients show a reverse trend and, on a group level, tend to show emotional reactions that are incongruent with their perceived QoL. Thus RHE patients as a whole tend to express emotions with less intensity than LHE patients.

P764
REVERSIBLE MRI FINDINGS FOLLOWING SEIZURES, SIMILAR TO THOSE OF HYPERTENSIVE ENCEPHALOPATHY AND ECLAMPSIA. R. Divari, A. Terentiou, K. Striggaris, C. Kokkinis, A. Papadimitriou, Red Cross Hospital, General Hospital (Athens, GR)

Reversible MRI lesions have been described in hypertensive encephalopathy and eclampsia. Moreover transient MRI abnormalities have been reported following Status Epilepticus or seizures, migraine, cyclosporine toxicity and porphyria. In this study we compare the reversible MRI findings of a patient with seizures to the also reversible MRI lesions of a case of hypertensive encephalopathy and one of eclampsia. The first case was a 45 year old male with a 15year history of epilepsy, admitted for multiple seizures. The MRI was performed one week after admission, because of the poor control of seizures. Previous MRI of the brain was normal. The second case was a 20 year drug- abuser admitted for hypertensive encephalopathy due to nephritis and the third one was a 16 year pregnant female with seizures due to eclampsia. In all three cases the brain MRI scans, performed on the first days, revealed quite similar bilateral high intensity lesions on T2W images in the cortical and subcortical areas mainly of the parietoccipital lobes. The lesions were totally reversible in all three cases, as follow-up MRI scans performed 1–2 months later had no pathological findings.

Conclusion: Reversible MRI findings may be revealed following seizures. These lesions are similar to those found in hypertensive encephalopathy and eclampsia. Considering that these lesions in cases of hypertensive encephalopathy and eclampsia are consistent with edema due to disruption of blood-brain barrier and breakdown of cerebral autoregulation, it may be suggested that a similar pathogenetic mechanism is implied in cases of status epilepticus or seizures.

P765
THE EFFECTIVENESS AND SAFETY OF LONG-TERM MONOTHERAPY WITH HIGH DOSES OF GABAPENTIN IN PATIENTS WITH DRUG-RESISTANT EPILEPSY. P. Czapinski, Jagiellonian University (Krakow, PL)

Background: The aim of the paper was the determination of the effectiveness and safety of high doses of gabapentin (GBP) in monotherapy of patients with drug-resistant epilepsy.

Methods and results: The study included 24 patients (16 women and 8 men) with drug-resistant epilepsy with partial seizures (at least two episodes per month). The investigation was divided into four stages:

1. Addition of GBP at a dose of 1,600 mg/day to the already employed 1–2 antiepileptic drug protocol; selection of responders (RRatio ≤ –0.33) and partial responders (RRatio ≤ –0.25) on the basis of the RRatio value = 100 (T-B/T+B) – 3 months
2. Administration of increasing GBP doses up to 2,400–3,600 mg/day – 1 month
3. Withdrawal of other drugs, with a possible increase of dosage up to 4,800 mg/day – 3 months
4. GBP monotherapy – up to 24 months.

In Stage 1, 15 patients manifested an at least 33 % reduction of the number of seizures (mean RRatio –0.36). When GBP doses were increased (Stage 2), 13 patients maintained the improved seizure rate, and the RRatio value was more beneficial, reaching –0.62. Withdrawal of other drugs (Stage 3) reduced the number of respondents to 9, while the RRatio was similar to that achieved in Stage 2 (–0.59). A shift to monotherapy (Stage 4) did not result in any change in the number of responders, while increasing the dose of GBP at this stage improved the RRatio so that its value reached –0.82. Increasing the dose did not result in an increasing number of adverse effects and the shift to GBP monotherapy even led to a decrease in adverse effect incidence.

Conclusions: Approximately 1/3 of patients with drug resistant epilepsy with partial seizures can be successfully treated with high doses of GBP. In the course of a long-term monotherapy, no decreased therapeutic effectiveness was noted.

P766
PROGNOSTIC VALUE OF SOME FACTORS INFLUENCING THE OUTCOME AND PROGNOSIS OF STATUS EPILEPTICUS – A RETROSPECTIVE ANALYSIS. P. Czapinski, Jagiellonian University (Krakow, PL)

A retrospective analysis included 139 cases of status epilepticus (SE) in 99 patients aged 17–87 years treated at Department of Neurology, Collegium Medicum, Jagiellonian University in Cracow, Poland. The following factors were analyzed: etiology, type of seizures, seizure duration by the time of admission, effectiveness of treatment and SE outcome.

The most common causes of status epilepticus were alcohol-related, discontinuation of antiepileptic drugs or inproper antiepileptic therapy, vascular brain damage, systemic infection, brain tumor, cerebral infarct, abuse of medications, head trauma and meningitis. In 50 % of patients SE involved primary generalized tonic-clonic seizures, 39 % – SE of simple partial seizures with or without secondary generalization, 2 % – SE of partial complex seizures, and 1 % – of myoclonic seizures. The most numerous group included patients up to 39 and above 60 years of age. More than 40 % of the patients were admitted between the first and third hour after the onset of status epilepticus.

In the analysis, a classification was developed into acute (with concomitant brain damage) and static status epilepticus (without brain damage). The results of the analysis allow for the formulation of the following conclusions:

- SE is most common in patients below 39 and above 60 years of age.
- The mean duration of SE prior to admission was longer in younger patients than in older subjects, but the efficacy of treatment was similar.
- Acute SE (19 %) was characterized by longer duration, more frequent drug resistance and negative outcome than static SE.
- There were no differences in SE duration and drug resistance between patients previously treated for epilepsy and subjects with the first seizure episode.
- Partial SE was associated by longer duration and more frequent drug resistance than generalized SE.
- The risk of SE recurrence was 19 %. The mean duration of recurrent SE was longer and patients from this group more often showed generalized status epilepticus. No mortality was noted in these subjects.
- The most important factors affecting mortality were the duration of SE and age, with longer duration and more advanced age increasing the risk of death.

General Neurology

P767
PLASMA CYTOKINE LEVELS IN NEURODEGENERATIVE DISEASES. P. Bongioanni, M. Metelli, M. Tararà, G. Marcacci, B. Rossi, University of Pisa, Hospital of Livorno (Pisa, Livorno, I)

Cytokines represent a family of peptides having modulatory effects on immunity and trophism, even in the central nervous system (CNS). In the CNS neurodegeneration, the cytokine network may be deranged, leading to both altered immunomodulation and impaired neurotrophism. In the present work, we assayed plasmatic cytokine levels in "de novo" patients with Alzheimer's disease (AD), motor neuron disease (MND), and Parkinson's disease (PD), compared to sex- and age-matched healthy controls. We found that patients with neurodegenerative disease had higher tumor necrosis factor (TNF)-alpha and interleukin (IL)-12 levels, lower IL-10 levels, and inconstantly higher soluble TNF-receptor (I and II) and IL-6 levels than controls. The highest IL-12 amounts were assayed in AD patients (with intermediate values in MND), whereas the TNF-α was most increased in plasma from MND patients. These data might be linked to a preferentially Th1-response (IL-12 and TNF-alpha-mediated) in neurodegeneration, together with an enhanced apoptotic pathway (as shown by the increase in the TNF-alpha system).

P768
ARACHNOIDAL CYST WITH INTERMITTENT HYDROCEPHALUS IN MELAS-SYNDROME. T. Etgen, V. Vogt, T. Lunke, B. Tegtmeyer, R. Dux, R. Kornblum, Technische Universität, Knappschaftskrankenhaus, Martin-Luther-Krankenhaus (München, Bottrop, Bochum, D)

Complex partial status epilepticus in association with the syndrome of mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) has recently been reported. We present the case of a patient with a long history of intermittent hydrocephalus in whom a complex partial status epilepticus resulted in the diagnosis of MELAS. Case report: A 35-year-old right-handed man with a long history of unexplained sensorineural deafness and insulin-dependent diabetes developed recurrent behavioral and linguistic changes combined with mild sensory disturbances on his right side. Brain scan demonstrated a large arachnoid cyst in the left temporal-parietal region. Lumbar puncture revealed raised glucose (184 mg/dl) and increased lactate (41.9 mg/dl). Spinal fluid scintigraphy showed a left-sided dysfunction of spinal fluid circulation and absorption. Diagnosis of intermittent hydrocephalus was made and after another episode operation of the cyst was performed. Two years later he presented for the first time with a prolonged complex partial status epilepticus. At this time a mitochondrial encephalopathy was clinically suspected and could be confirmed by mitochondrial analysis showing the typical point mutation in transfer ribonucleic acid (A-to-G at position 3243 of tRNA). The association of arachnoid cyst and intermittent hydrocephalus with mitochondriopathies could be interpreted as a possible mitochondrial dysfunction in the absorbing cells of spinal fluid compartment.

P769
CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKO-ENCEPHALOPATHY (CADASIL) A NEW DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS (MS). R. Schimana, W. Pöllmann, N. König, B. Mayr, Marianne-Strauss-Klinik (Berg, D)

The diagnosis of MS always implies the exclusion of other neurological diseases. We report about a difficult differential diagnosis of a 55 year old woman who 5 years ago developed sensory deficits on both legs and gait disturbances, later an attack of vertigo, nausea and vomiting for a few days, fatigue, dizziness, deficits in proprioception, fine motoric skills and cognitive impairments. Brain – MR showed multiple white matter lesions, CSF an increase of protein; and the evoked potentials (ep's) being normal. Metabolic disorders like metachromatic leukodystrophy and adrenoleukodystrophy were excluded. Diagnosis at this stage was leukencephalopathy of unknown etiology; multiple sclerosis was still discussed. Clinically she had a slight tetraparesis with a gait ataxia; the actual grade of disability on EDSS of Kurtzke was 4.0. A second cerebrospinal puncture shows a normal liquor inclusive various neurotrope vires. The ep's were also completely normal. The white matter lesions on MR1 were increasing very severe including occurrence of the medullary layer of the temporal lobe. An amyloid angiopathy could be excluded by a T2* weighted gradient – echo MR1. Searching for mutations of the Notch3 gene on chromosome 19 relative to CADASIL were negative, but the skin biopsy was positive. Aspects for screening for CADASIL in our case are the lack of abnormalities in ep's, the IVIRI, the normal CSF respectively elevated protein in liquor and a migraine without aura in the history. MS and CADASIL share various symptoms with babinski sign, dysarthria, cognitive impairments, bladder and mood disorders and white matter lesions on MRI. Mainly different are the frequency of dementia, sensory deficits, visuals symptoms and eye movement disorders. Decisive also the occurrence of lesions of the medullary layer of the temporal lobe on IVIRI, CSF and the skin biopsy (granular, electron dense, osmiophilic material in small vessels). So CADASIL may be an important differential diagnosis in cases of a suspected MS.

P770
BICKERSTAFF BRAINSTEM ENCEPHALITIS AND CLINICALLY ISOLATED SYNDROMES OF THE BRAINSTEM. A COMPARISON OF RADIOLOGICAL PATTERNS. J. Sastre-Garriga, S. Pedraza, C. Nos, M. Tintoré, P. Villoslada, A. Rovira, X. Montalban, Hospitals Vall d'Hebron I. D. I.-Unitat de Ressonància Magnètica (Barcelona, E)

BACKGROUND: Bickerstaff's brainstem encephalitis is an acute/subacute monophasic severe condition of unknown cause; it is preceded occasionally by a prodromal infection. Its main clinical manifestations are ophthalmoparesis and ataxia, joining occasionally drowsiness, sensori-motor impairment, alteration of lower cranial nerves. Usually a good recovery is observed (often ad integrum). A clear-cut differentiation with a first attack of a demyelinating disease (i. e. multiple sclerosis (MS)) is often very difficult to establish.

PURPOSE: To compare the findings of magnetic resonance imaging (MRI) scans from patients diagnosed of Bickerstaff's encephalitis (BE) with those from clinically isolated syndromes of the brainstem (CISB).

METHODS/PATIENTS: We have reviewed the clinical records and MRI scans of 45 patients with CISB suggestive of MS seen at our unit since January 1995 and we have compared these findings with those from five patients diagnosed as having BE in the same time lapse aforementioned.

RESULTS: In the group of CISB we have found 25 out of 45 having brainstem lesions and matching radiological criteria for multiple sclerosis (Paty, Fazekas or Barkhof). Five out of 45 were found to have only brainstem lesions (mainly in medium cerebellar peduncle and pons). One patient out of 45 had a midbrain (tectum and tegmentum) lesion and the rest (14 out of 45) had no brainstem lesions (only supratentorial lesions or normal MRI brain scans). The five patients with BE had a clear-cut radiological pattern showing midbrain (tectum and tegmentum) affectation.

CONCLUSIONS: BE is easily confounded with a first attack of a demyelinating disease; interestingly enough, three out of five patients with BE were under suspicion of having MS in some point of the clinical evolution. Tectum and tegmentum mesencephalicum affectation is fairly characteristic of BE. The presence of lesions in both locations should arise the suspicion of a monophasic condition and be of help in ruling out MS.

P771
MAGNETIC RESONANCE FINDINGS ON SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD COMPLICATING VITAMIN B12 DEFICIENCY. P. Sauleau, Y. Rolland, T. Ronzière, J. F. Pinel, Y. Guegan, G. Edan, Chu Pontchaillou (Rennes, F)

BACKGROUND: Magnetic resonance imaging (MRI) in subacute degeneration usually shows increased T2-weighted signal of the cervical and thoracic cord. This unknown feature can lead to false diagnosis especially in old patients. METHODS: We report the case of a 87-year-old man suffering from tetraparesia and a loss of sensitivity in both legs gradually worsening in the last 16 months. Five years earlier, he underwent a partial gastrectomy for an adenocarcinom and was only treated with acid folinic supplement whithout vitaminotherapy B12. The diagnosis of subacute combined degeneration was confirmed by both biological and MRI findings. Laboratory examination revealed macrocytic anemia and a very low serum vitamin B12 level. MRI showed increased T2-weighted signal in the posterior and lateral columns of the cervical, thoracic and lumbar spinal cord, normal signal on T1 sequences without contrast enhancement. Cervico-arthrosis features were also present on cervical images and this patient was initially hospitalised to undergo a surgical treatment. He was treated with vitamin B12; clinical improvement was observed after 4 months and MRI improvement after 6 months.

DISCUSSION: This case has to be pointed out for 3 reasons. 1) the clinical history is particular with a double risk factor for such a pathology: an absorption defect and an overconsumption of vitamin B12 by acid folinic treatment. 2) only few reports have shown such lesions in the whole spinal cord. 3) the advanced cervicoarthrosis was not reponsible for the clinical feature and cervical surgery would have worsened this patient.

CONCLUSION: Vitamin B12 deficiency has to be systematically evoked facing a clinical cervical myelopathy especially in old people. A complete analysis of the spinal cord may show high T2-weighted signal spreading beyond the cervical cord.

P772
TIMING AND DOSE EFFECT OF SMOKING, ALCOHOL AND COFFEE CONSUMPTION ON THE RISK OF PARKINSON DISEASE: PRELIMINARY RESULTS. P. Ragonese, G. Salemi, F. Scoppa, D. Buffa, P. Aridon, G. Savettieri, University of Palermo (Palermo, I)

Background: The effect of several risk factors including cigarette smoking, alcohol and coffee consumption on Parkinson's Disease (PD) is still controversial. Objective: To determine whether a time- or a dose-response relationship exists between cigarette smoking, alcohol and coffee consumption and the risk of PD. Methods: Cigarette smoking, alcohol, and coffee consumption were investigated in idiopathic PD patients at the Neurological clinic of the University of Palermo. They were matched by age (± 2 years) and sex to randomly selected controls (1:1). The exposure of PD patients and controls was assessed through a structured questionnaire which also evaluated the timing and the dose of each exposure. Subjects with a MMSE < 24 were excluded. Relative Risks (RR) and 95% confidence intervals (CI) were calculated. Multiple logistic regression analysis was also performed. Results: Forty-two PD patients and their matched controls were interviewed. At univariate analysis both heavy coffee consumption (RR= 0.52, CI= 0.32–0.85, p= 0.004) and heavy cigarette smoking (RR= 0.38, CI= 0.14–1.07, p= 0.02) showed an inverse association with the risk of PD. Stratifying by age at onset of PD (< 65 years versus > 65 years), an inverse association was observed only for the younger group of PD patients for coffee consumption (RR= 0.52, CI= 0.29–0.91, p= 0.01) and cigarette smoking (RR= 0.36, CI= 0.1–1.22, p= 0.04). Multivariate analysis confirmed the inverse association between PD and the dose of coffee and cigarette consumption. It showed also a significant association with the time of exposure to cigarette smoking.

Conclusions: Our data on cigarette smoking consumption confirm the "protective" effect of this habit especially among younger patients. The inverse association between coffee consumption and PD risk needs further investigation.

P773
CORTICOBASAL DEGENERATION–A CASE REPORT: CLINICAL AND PATHOLOGICAL FEATURES. C. Januário, O. Rebelo, L. Cunha, University Hospital University of Coimbra (Coimbra, P)

Corticobasal degeneration is a rare neurodegenerative disorder characterized by a motor syndrome (asymmetric parkinsonism) and cognitive disturbance. We report a patient with this syndrome according to the criteria of Lang et al. (1994). The diagnosis was later confirmed by a cerebral stereotaxic biopsy. The patient was 55 years old when a parkinsonian syndrome was noted; at the same time, the presence of a dystonic left limb with focal myoclonus was found. The cerebral biopsy showed ballooned cells. Tau positive neuronal inclusions were present in the parietal cortex. This is the first case with neuropathological confirmation, reported in our country.

P774
PROGRESSIVE OCCURRENCE OF MYOPATHY, NEUROPATHY AND MYASTHENIA IN A PATIENT WITH PRIMARY AUTOIMMUNE HYPOTHYROIDISM. A. Toscano, C. Rodolico, M. Valenti, M. C. Monici, A. Baradello, M. Buccafusca, P. Girlanda, S. Benvenga, C. Vita, University of Messina (Messina, I)

Disorders of the thyroid function may cause a wide variety of neuromuscular disturbances. An overt myopathy has been rarely reported as an isolated clinical finding of hypothyroidism. Peripheral neuropathy is thought to be common. There is, on the other hand, a significantly greater incidence of myasthenia gravis in patients with autoimmune hypothyroidism. We report here a 57-year-old man, who presented a 2 year-history of diffuse myalgia, cramps and proximal muscle weakness. He had increased CK levels (2223 IU/l; n. v. 25–200). Examination revealed a mild proximal weakness at lower limbs. Electromyography (CNEMG) and neurography (NG) were normal. Muscle biopsy revealed some atrophic fibers. Thyroid function was not investigated in this occasion. After 3 years the patient started to complain also of paresthesia at feet. CK levels persisted elevated. Examination showed absent ankle jerks and dysesthesia at feet. NG was consistent with a mild sensory-motor neuropathy. Serum TSH was 149 mU/ml (n. v. 0.23–4), FT3 and FT4 were markedly reduced; antibodies against thyroid were consistently increased (Antithyroglobulin Ab: 13240 IU/ml; n. v. 0–50). Thyroid sonography evidenced an atrophic gland. A diagnosis of primary hypothyroidism due to the atrophic variant of Hashimoto's thyroiditis was made. The patient was treated with L-thyroxin (100 mg/day) with resolution of symptomatology and progressive normalization of CK levels. After 3 years he came back to our department because of the onset of muscular fatigability, fluctuant diplopia, dysphagia and dysphonia. An investigation of neuromuscular junction by single fiber electromyography led to the diagnosis of myasthenia. A treatment with pyridostigmine and prednisone was started with clinical recovery. A large spectrum of different neuromuscular disorders, during primary autoimmune hypothyroidism, has never been reported so far in the same patient.

P775
MYASTHENIA GRAVIS: A RETROSPECTIVE STUDY OF 330 CASES. N. Balakas, C. Potagas, H. Molari, P. Mourtzouhou, A. Tavernarakis, G. Dellatolas, Evangelismos General Hospital (Athens, GR)

We studied the files of 330 myasthenic patients hospitalized in our center in Athens during the last 30 years (1970–1999), focusing on the age of appearance of the disease and also on clinical manifestations and laboratory findings (thymus aspects, Ach receptor antibodies, thyroid, associated immune diseases or cancer) that might give some indications for the establishment of subgroups of patients. The present study confirms previous findings, including from our center (HAKAS et al., 1984), of an apparent increase of the mean age of appearance of the disease in recent years both in men and women, mainly due to the increase of proportion of persons presenting the disease after the age of 60 years. Three subgroups of patients are clearly distinguished: a) patients with thymoma, men and women, in whom myasthenic symptoms appeared at middle ages (40 to 50 years); b) patients in whom the disease started at young ages, mainly women; c) men and women in whom the disease started at older ages. The subgroups tend also to be different concerning clinical symptomatology. The existence of these subgroups is in favor of a heterogeneity in the pathogenesis of the disease, that could be related to differences in the subtypes of the HLA system.

P776
HEADACHE ASSOCIATED WITH UNILATERAL OPHTHALMOPLEGIA: GRANULOMATOUS OF THE CAVERNOUS SINUS. A. Cheldi, M. F. Donato, G. Castellani, Desio Hospital (Desio, I)

We describe the clinical case of a 53 year-old man who suffered from chronic, severe, frontal and periocular headache from three months, with periodic poussees. During the acute attacks, the pain was associated with intrinsic and extrinsic left oculomotorius deficit. Four months before, the patient was treated with antibiotic and steroid therapy for left ethmosphenoidal sinusitic process, documented by neuroraiological studies. Since the symptomatology worsened with persistence of left oculomotorius deficit and no benefit was obtained from symptomatic treatment, the patient was admitted in our department.

Standard CT scan was normal; contrast angio-MRI focused on cavernous sinus (CS) showed stenosis and extrinsic compression of the left internal carotid artery for the presence of abnormal granulomatous inflammatory tissue in CS. Neoplasm and aneurysm were excluded.

Because of the previous left ethmosphenoidal sinusitis, we considered the inflammatory intracavernous tissue as an extension for contiguity from the original focus.

Successful treatment with prednisone was undertaken; pain and ophthalmoplegia relieved completely in a few weeks.

In the presence of painful ophthalmoplegia with excellent response to steroid therapy, the finding by MRI of granulomatous tissue in the cavernous sinus is highly suggestive of Tolosa-Hunt syndrome; etiopthogenesis of this syndrome is almost always unknown; in our case it was identified in an inflammatory tissue extended to the CS from sphenoidal contiguous region.

P777
PALATAL MYOCLONUS APPEARING 8 YEARS AFTER REMOVAL OF A CEREBELLAR LOW-GRADE ASTROCYTOMA. B. Legros, Z. Sheikoleslam, J. Hildebrand, D. Balériaux, M. Manto, Hôpital Erasme (Bruxelles, B)

Palatal myoclonus (PM) is a relatively rare movement disorder characterized by a rhythmic and involuntary contraction of the soft palate occurring at a frequency of 100–160/min. Symptomatic PM (SPM) results from lesions located in the Guillain-Mollaret triangle, which extends from the contralateral dentate nucleus via the brachium conjunctivum and the ipsilateral central tegmental tract to the inferior olive (dentato-rubro-olivary tract). Although this tract is physiologically influenced by the activity of the ponto-cerebellar afferences, a role of these fibers in the pathogenesis of PM has not been considered so far. The most common causes of SPM are stroke, trauma, infections and inflammatory diseases. Only 10 cases of SPM due to a cerebellar tumor have been described. SPM associated with removal of a low-grade cerebellar tumor is exceptional and occurs within 12 months (J Neurosurg 1998;88:1107–1110). Our patient is a 55-year-old man who underwent surgery in 1991 for a low grade astrocytoma located in right cerebellar hemisphere. Neurological examination showed scanning speech, dysmetria of limbs and kinetic tremor on the right side. Postoperative MRI showed sequelae in right cerebellar hemisphere, with involvement of the right inferior and right middle cerebellar peduncle. The neurological deficits and brain MRI were followed regularly from 1991 until 1999. He subsequently complained of a bilateral earclick, predominating in right ear. In addition to ataxia of eye movements, to dysmetria and tremor on the right side, neurological examination revealed PM without lingual or facial myoclonus. MRI showed similar lesions, without recurrence. We conclude that SPM can develop several years after surgery for a benign cerebellar tumor, suggesting a very slow trans-synaptic degeneration of the dentato-rubro-olivary tract. We hypothesize that the long delay between surgery and appearance of PM is due to the concomitant disruption of the crossed ponto-cerebellar projections (mossy fibers running in the middle cerebellar peduncle) towards the cerebellar granule cells, which exert a facilitatory effect on the discharges of Purkinje cells. Our case was also peculiar by the presence of earclick, which is rarely reported in patients with SPM.

P778
NEWLY DIAGNOSED EPILEPSIES IN A TERTIARY NEUROLOGY DEPARTMENT: FINDINGS AT PRESENTATION. K. Garganis, S. Raxioni, V. Kapitzoglou-Logotheti, I. Milonas, Ahepa Hospital Univ. of Thessaloniki (Thessaloniki, GR)

OBJECTIVE: To describe a population of patients with newly diagnosed epilepsies by a tertiary neurology university department, in terms of time-delays in diagnosis, etiology, seizure types and syndromic classification.

MATERIAL-METHODS: Retrospective study of in-patients, admitted to our neurology ward and having a diagnosis of epilepsy, for first time in their life, following evaluation. Each patient had to have experienced at least one unprovoked epileptic seizure before admission. Time of occurrence of first seizure was noted, an etiology was established, when feasible, and a syndromic classification as well.

RESULTS: Sixty (60) patients were evaluated as in-patients during years 1998 and 1999 (39 male and 21 female). Mean age at evaluation time 45.16 years (range: 6–83 years). The first seizure, by history, occurred at a mean time of 21.08 months (range: 1 day–30 years) before establishment of diagnosis. 25% of patients had had their first seizure occurring 1 or more years before diagnosis, and 16.7% 4 or more years before. An etiology could be established in 75% of cases, mass lesions (38.3%) and ischemic cerebrovascular disease (18.3%). Patients with first seizure occurring 1 or more years before diagnosis were significantly less likely to have an underlying etiology compared to patients with first seizure occurring within one year before diagnosis (33% versus 89%). Most patients (71.6%) were classified to the partial/symptomatic syndromic category.

CONCLUSIONS: Most cases of newly diagnosed epilepsies, and evaluated as in-patients, had partial symptomatic forms of disease, secondary mainly to mass lesions and cerebrovascular events. This is indicative of a referral bias towards directing more complicated cases, with structural and evolving lesions, to our inpatient service. A subgroup of patients, almost 25% of the original population, may present with a long delay between time of first seizure occurrence, and diagnosis. They are less likely to harbour structural lesions, suffer more benign forms of the disease, and are directed to specialized tertiary centers because of diagnostic uncertainty.

Genetics

P779
A GENE FOR AUTOSOMAL DOMINANT DUANE'S SYNDROME MAPS TO CHROMOSOME 2Q31; CONFIRMATION AND NARROWING THE CRITICAL REGION. N. J. Gutowski, J. Evans, S. Ellard, Department of Neurology, Department of Genetics (Exeter, UK)

Duane's syndrome is an unusual congenital form of strabismus. It is due to paradoxical anomalous lateral rectus innervation of the affected eye by axons destined for the medial rectus. Up to 10% of cases are familial, usually autosomal dominant and without associated abnormalities. Recently a locus on chromosome 2q31 has been identified in one family, within a 17.8cM region between genetic markers D2S2330 and D2S364. A large kindred of autosomal dominant Duane's syndrome without associated abnormalities is reported. This kindred spans four generations from which 9 affected and 13 unaffected individuals agreed to participate and underwent clinical examination. Genetic analysis using 5 microsatellite markers within the 2q31 region demonstrated significant evidence for linkage (lod score was 3.8; a lod score > 3 is significant). Two recombinants were observed, thus narrowing the genetic interval from 17.8cM to 8.8cM. This study confirms the localisation of a gene for Duane's syndrome to chromosome 2q31 and has narrowed the critical region. The definition clinically and genetically of Duane's syndrome sub-groups will provide a valuable insight into brain-stem axonal guidance to the extraocular muscles during human development.

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ENU MOUSE MUTAGENESIS PRODUCES AN AUTOSOMAL RECESSIVE MYOPATHY RESEMBLING CENTRONUCLEAR MYOPATHY. F. Gekeler, B. Rathkolb, E. Wolf, M. Hrabé de Angelis, R. Balling, T. Klopstock, Klinikum Großhadern LMU Munich, LMU Gene Center, GSF Research Center (Munich, Oberschleißheim, D)

In a large-scale ethylnitrosurea (ENU) mouse mutagenesis screen we have identified two mouse strains suffering from an autosomal recessive form of myopathy. G3 offspring of mutagenized C3HeB/FeJ founders were clinically screened and blood samples were investigated for a broad spectrum of clinical-chemical parameters. Two autosomal recessive strains showed elevated creatin kinase (CK) ranging from 512–1734 U/l in 10 out of 25 mice in strain 1 and from 728–1392 U/l in 4 out of 10 mice in the second strain. Post mortem muscle biopsies in two affected mice of each strain showed central nuclei in nearly all muscle fibers and increased endomysial and perimysial adipose and fibrous connective tissue. The electron microscopic examination substantiated the alterations seen by light microscopy. Muscle morphology in these mice resembles the characteristic histopathological findings in human centronuclear myopathy. This congenital myopathy is characterized by early childhood onset and slow progression. The major histologic feature is the high frequency of centrally placed nuclei. Centronuclear myopathy is genetically heterogeneous and occurs in autosomal dominant, autosomal recessive and X-linked recessive forms. Serum CK ranges from normal to elevated concentrations in patients with the congenital autosomal recessive form of the disorder. Backcrosses of the affected mice will allow mapping of the gene locus and identification of the human syntenic region.

P781
UNUSUAL CLINICAL LATE ONSET OF PARAPARESIS IN A CASE OF SACRAL AGENESIS (SCRA1) WITHOUT CURRARINO TRIAD. D. Tessarolo, P. Scarano, M. Liguori, A. Pingi, San Camillo Hospital (Rome, I)

We report an unusual case of a long history of sphincteric disorders and subacute adult onset of paraparesis associated to partial sacral agenesis with presacral mass, anterior meningocele and tethering of the cord. In addition, clinical, neuroradiologic and gastrointestinal investigations were performed to other members of patient's kindred in order to evaluate the familiar trait and the autosomal dominant inheritance according to sacral agenesis syndrome (SCRA 1 –176450 OMIM). Methods and results: A 53-year old male with a long clinical history (about 20 years) of chronic constipation and episodic urinary retention was admitted to the hospital because of a subacute paraparesis syndrome and recurrent bilateral sciatic pain experienced in the last year. A magnetic resonance imaging (MRI) of the lumbar sacral spine was performed on a 1.5 T Unit (Philips Gyroscan ACS-NT) with spinecho (SE) and turbospinecho (TSE) weighted sequences in the sagittal, axial, and coronal planes and revealed a right hemisacral dysgenesis with intact first sacral vertebra, anterior meningocele, S1 and S2 vertebral rachischisis, presacral mass (lipoma) and tethered cord. The MRI of the brain, cervical and thoracic spinal cord, and the atlasoccipital region resulted morphologically normal. The patient was urgently submitted to surgical relief of tethered filum terminale, with good clinical resolution of paraparesis. The investigations of the gastrointestinal system excluded anorectal malformation, as part of Currarino triad (sacral agenesis, presacral mass and anorectal malformation). Conclusions: Subacute spinal paraparesis and a long history of sphincteric disorders should be considered as possible manifestations of sacral dysgenesis with adult onset. This case suggests the presence of variable clinical expressivity of disorders caused by mutation in Homeobox genes, such as proposed in dominantly inherited sacral agenesis (HLXB9 major locus). References: Yates V.D. et al. – J.Pediatr. 1983; 102(2):239–42; O'Riordain D. S. et al. – Br. J.Surg. 1991; 78(5):536–8; Ross A. J. et al. – Nature Genetics 1998; 20:358–361; Sakho Y. et al. – Dakar Med. 1998;43(1):13–20; Riebel T. et al. – Eur. Radiol. 1999;9(7):1348–53; Guardiola A. et al. – Arq. Neuropsiquiatr. 1999; 57(1):101–5.

P782
AN AUTOSOMAL DOMINANT DISORDER WITH EPISODIC ATAXIA, VERTIGO, TINNITUS AND MYOKYMIA. J L Steckley, G. C. Ebers, R. S. McLachlan, University of Oxford Wellcome Trust Center for Human Genetics, London Health Sciences Centre (Oxford, UK; London, ON, CDN)

The autosomal dominant episodic ataxias are a clinically and genetically heterogeneous group of disorders that are characterized by recurrent episodes of cerebellar ataxia, along with other neurological symptoms. Episodic ataxia type 1 (EA1) is associated with myokymia and attacks that may last for only a few minutes, occurring up to several times per day. Episodic ataxia type 2 (EA2) is associated with interictal nystagmus and attacks that last for several hours to a day. Methods: A large Canadian kindred of Mennonite heritage segregating episodic ataxia was identified. All members of the family underwent personal interview. Affected individuals were given a complete neurological examination and filled out a detailed questionnaire. A genetic linkage study was begun on consenting family members by conducting two-point linkage analysis of microsatellite markers tightly flanking the EA1 (12p13) and EA2 (19p13) loci. Results: Clinical examination revealed 26 family members (8 male, 18 female) affected with brief episodes of truncal and gait ataxia, vertigo and imbalance. The mode of inheritance is autosomal dominant with high penetrance. Episodes of ataxia were responsive to acetazolamide and were associated with tinnitus (17/26), headache (14/26), myokymia (13/26), blurred vision (10/26) and diplopia (9/26); however, nystagmus was not described or seen in any patients, other than a congenital form of nystagmus in one individual. Two-point linkage analysis of microsatellite markers flanking the EA1 and EA2 loci excluded linkage to the other episodic ataxias with lod scores less than –2.00. Conclusions: We report an acetazolamide responsive autosomal dominant episodic ataxia in which the associated symptoms (vertigo, tinnitus and myokymia) are clinically different from EA1 and EA2. Linkage studies of the EA1 and EA2 loci show that this disorder is also genetically distinct from the other autosomal dominant episodic ataxias.

P783
EXCLUSION OF FHM-MUTATIONS IN THE CACNL1A4 GENE IN 95 PATIENTS WITH COMMON FORMS OF MIGRAINE. T. Wieser, S. Evers, T. Deufel, S. Zierz, Martin-Luther-Universität Halle, Westfälische Wilhelms Univ. Münster, Friedrich-Schiller-Universität Jena (Halle/S., Münster, Jena, D)

Migraine is a frequent disabling condition of unknown origin; familial clustering of migraine has been known for long, a positive family history can be found in 45 % to 90 % of cases. In common forms of migraine, however, the impact of genetic factors in the aetiology is still unclear. In 1996 mutations in the gene CACNL1A4 were identified causing the phenotype of familial hemiplegic migraine, a rare subtype of migraine with aura, which is transmitted in an autosomal dominant fashion. Evidence from studies using indirect methods like association analysis and sib-pair analysis indicates that this gene is also involved in common forms of migraine. In the present study we tested 95 patients with migraine both with and without aura, independently of their family history, for the presence of the four mutations R192Q, T666M, V714A and I1811L in the CACNL1A4 gene known to result in the FHM phenotype. We used SSCP analysis for screening of the exons 4, 16, 17 and 36, maximising sensitivity by using three different temperatures (4°, 15° and 22°C). PCR products resulting in aberrant running patterns were subjected to dideoxy sequencing using a35 S dATP label and Sequenase PCR-Product Sequencing Kit (Amersham). The presence of the known mutations R192Q in exon 4, T666M in exon 16, V714A in exon 17 and I1811L in exon 36 was excluded. Additionally, no other nucleotide changes were detected in the sequenced sections, which comprised roughly 75 % of the coding sequence of each exon. In conclusion, we have ruled out the presence of four mutations known to lead to the migraine phenotype in the CACNL1A4 gene in 95 migraine patients. Bearing in mind that the T666M mutation is quite frequent in chromosome 19 linked families, the results support our hypothesis that this locus is not likely involved in common forms of migraine.

P784
ISOLATED SPASTIC PARAPARESIS LEADING TO FRIEDREICH'S ATAXIA DIAGNOSIS. G. Castelnovo, B. Biolsi, M. Schmitt, B. Barbaud, P. Labauge, DPT of Neurology, Laboratoire de Genetique, DPT of Neurology CHU Montpellier-Nîmes (Nîmes, Strasbourg, F)

Friedreich's ataxia is one the most common hereditary ataxia. This neurological disorder was initially defined by the association of ataxia, cerebellar syndrome and pyramidal signs. Atypical forms are increasingly recognized. The gene was mapped to 9q13-q21.1 in 1988 and identified in 1996. We report herein an observation characterized by a spastic paraparesis, of which molecular analysis confirmed the diagnosis of Friedreich's ataxia. Case report. A 39 year old woman without any past condition presented with difficulty in walking since the age of 20. Neurological examination showed a spastic paraparesis, with tetrapyramidal signs, including bilateral Babinski signs and brisk reflexes. No other neurological abnormalities were found; notably proprioception and vibration sense, and cerebellar function were normal. No skeletal deformities were found. All hematological investigations (including lactate and pyruvate levels, cholesterol, apolipoproteinemia, Vitamin E, arylsulfatase, very long chain fat acid and hexosaminidase concentrations) were normal. Electromyography and cardiologic test (electrocardiography, transthoracic echocardiography) were normal. Cerebral and spinal resonance magnetic imaging (MRI) were normal. No familial condition was found, except the sister who presented the same symptoms. The molecular analysis of the gene coding for Friedreich'

s ataxia was performed by Southern blot from peripheral blood extracted DNA and showed two abnormal expansions of 2.5 kb and 3.1 kb on the chromosome 9q13-q21.1. Diagnosis of Friedreich's ataxia identified by an isolated paraparesis was definitively retained. Discussion and conclusion. Friedreich's ataxia (FDRA), is a genetically homogeneous condition. The frataxin gene (9q13-q21.1) was identified in 1996. The mutations are the most often GAA expansions located in the first intron. Previous reports have noted that patients with FDRA could present important spasticity, usually associated with other neurological signs. Our report of isolated paraparesis confirmed that the phenotypic spectrum of FDRA is much broader than previously considered.

P785
MRI STUDY OF PATIENTS WITH NEUROFIBROMATOSIS TYPE 1. R. Poniatowska, R. Krawczyk, R. Boguslawska, J. Ryterski, H. Mierzewska, Institute of Psychiatry and Neurology (Warszawa, PL)

Neurofibromatosis type 1 (NF1) is the autosomal dominant disease from the group of phakomatoses with the genetic defect of the long arm of chromosome 17. It appears in 1 in 3000 in the population and is often called "childhood" or "peripheral" form of neurofibromatosis. Clinical diagnosis of NF1 has to meet two of the following criteria: six or more "cafe-au-lait" skin macules, Lisch nodules, bilateral optic nerve gliomas, osseous dysplasia, two or more neurofibromas, plexiform neurofibroma and family history of the disease. Patients with NF1 often have other symptoms: kyphoscoliosis, pseudoarthrosis, seizures, endocrine, gastrointestinal or pulmonary abnormalities. Material and Method: 32 patients with NF1 were studied. All patients underwent MR study of the brain and of the spinal cord. The examinations were performed using standard SE sequence with T1- and T2-weighted images in orthogonal planes. In all cases T1-weighted scans in all planes were repeated after paramagnetic contrast injection. Results: The MR study of the brain showed: in 15 cases hyperintensity signals in globus pallidus, in 8 in cerebellum, in 5 in pons. In 9 cases glioma of II cranial nerve occurred. The other pathologies were: ponto-cerebellar tumor (3), optic chiasm tumor (6), frontal lobe tumor (2), cholesteatoma of pyramid (1), tumor of upper palpebra (6). The MR study of the spinal cord findings were in 12 cases extramedullary tumors. The additional abnormalities: tumors of mediastinum (2), pelvis subcutaneous tumors (4). Conclusion: MR study shows a wide spectrum of pathologies in brain and spinal cord in patients with neurofibromatosis type 1 and can be used as confirmation of the disease.

P786
NO ASSOCIATION BETWEEN A2-MACROGLOBULIN DNA POLYMORPHISM AND ITALIAN SPORADIC ALZHEIMER'S DISEASE. B. Nacmias, A. Tedde, E. Cellini, P. Forleo, A. Orlacchio, C. Petruzzi, B. Guarnieri, A. Serio, S. Sorbi, University of Florence, Casa di Cura Villa Serena (Florence, Pescara, I)

In 1998 Blacker et al. reported a significant association between the a2-macroglobulin gene (A2M) polymorphism corresponding to a deletion near the 5' splice site of exon 18 and Alzheimer's disease patients. a2-macroglobulin is a serum proteinase inhibitor codified by the A2M gene on chromosome 12 that has recently been reported to be associated with late onset Alzheimer's disease (LOAD). A2M is present in senile plaques and may play a role in metabolism of amyloid beta peptide. A 5 bp deletion/insertion polymorphism and an Ile1000Val polymorphism at the A2M gene have been identified as potential susceptibility markers for LOAD. In order to analyse a possible correlation between two polymorphisms and Italian sporadic Alzheimer's disease (AD) we have studied the segregation of the deletion polymorphism in 74 AD (mean age at onset 66.64 ± 8.2), sporadic subjects and 68 controls and the Ile1000Val polymorphism in 88 AD patients (mean age at onset 66.53 ± 8.2) and 82 controls. We did not find statistically significant differences in the distribution either of the deletion/insertion polymorphism or the A2M Ile1000Val polymorphism in the AD group with respect to controls. Moreover a stratification of our data on individual ApoE e4 dose revealed that AD patients, within the ApoE e4 carrier group did not show statistically significant differences with respect to e4 not carriers in relation to allele frequencies. We failed to detect an allelic association between polymorphisms in the A2M gene, such as the 5 bp deletion/insertion polymorphism and the Ile1000Val polymorphism of the A2M gene, and sporadic Alzheimer's disease. Our data do not support a role for the A2M gene as genetic risk factor for Alzheimer's disease.

P787
ABSENCE OF UNIDENTIFIED CAG REPEAT EXPANSION IN PATIENTS WITH HUNTINGTON'S DISEASE-LIKE PHENOTYPE. I. Vuillaume, P. Meynieu, S. Schraen-Maschke, A. Destee, B. Sablonniere, University Of Lille, University Of Lille Hopital Roger Salengro (Lille, F)

Huntington disease (HD) is an autosomal dominant neurodegenerative disease caused by an expanded (CAG)n repeat on huntington gene. The HD diagnosis includes involuntary choreiform movements, cognitive and psychiatric disturbances and family history. HD can now be confirmed by direct genetic testing, which is both highly sensitive and specific. This study focused on patients whose clinical phenotypes show strong similarity to HD, but who do not have an expanded CAG in huntington gene. Patients and laboratory methods: In the Lille cohort of 200 patients who were assessed for diagnosis confirmation, 32 patients were gene-negative. 11 of them clearly appear to be sporadic cases and 21 could be considered as suffering from a possible hereditary neurodegenerative disease similar to HD. Neurological and psychiatric evaluation as well as MRI results were analyzed. The CAG repeat length was determined by PCR amplification using primers HD1 and HD2. Samples were also screened for other triplet-repeat diseases with similar presentation: DRPLA, SCA–1, SCA–2, SCA–3 and SCA–6. We used the RED technique to detect uncloned CAG repeat expansions and samples were also analyzed for expansions of the polymorphic CAG ERDA–1 and CTG 18.1 trinucleotide repeats by use PCR. Results: All patients studied were negative for the IT15 expansion and for other triplet-repeat diseases screened. RED detected expansions greater than 40 repeats in two patients. One of them had typical HD features making no other alternative diagnosis evident, whereas diagnosis seemed more complex in the other, regarding the presence of atypical symptoms, such as dystonia, seizures, pyramidal and cerebellar syndromes with diffuse cerebral atrophy. In this patient, the expansion detected by RED may be accounted for by an expansion of 63 repeats at the ERDA–1 locus. In the opposite, in the first patient, the RED results could not be explained by an increase in trinucleotide number, neither at the ERDA–1 nor at the CTG 18.1 locus. Conclusion: Our results suggest that unstable CAG or CTG repeat expansions corresponding to either known or unknown sequences are not involved in the etiology of HD-like disorders even in patients with a family history of neurological disorder. Further work is needed to confirm these findings in a larger series of HD-like patients. We hypothesize that some of these phenocopies correspond to mutations in other unknown genes.

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STIMULATION OF MYELINATION BY AN INTERLEUKIN–6 RECEPTOR-INTERLEUKIN–6 CHIMERA. S. Haggiag, P.L Zhang, V. Shinder, A. Kumar, G. Slutzky, J. Chebath, M. Revel, Weizmann Institute of Science (Rehovot, IL)

Synthesis of myelin proteins and axon myelination is induced during the late differentiation stages of Schwann cells (SC) and oligodendrocytes. This is a reversible process as shown by the reversal to non-myelinating SC in post-traumatic and neurodegenerative demyelination. We studied induction of myelin gene expression by signal transduction through gp130, the common receptor of the Interleukin–6 (IL–6) family cytokines, which is also a receptor subunit for the neurotrophic factors CNTF and LIF. For efficient activation of gp130 we used an IL6RIL6 chimera, containing the entire soluble IL–6 receptor fused to IL–6, which exhibits high affinity for isolated gp130 and does not require the LIF-receptor subunit. In cultures of mouse and rat dorsal root ganglia (DRG) from E15 embryos, addition of IL6RIL6 induced Myelin Basic Protein (MBP) and Po mRNA and proteins (after 1 week). The same was observed with DRG from various pre- and perinatal stages. In two-weeks cultures with ascorbic acid, IL6RIL6 increased the formation of myelinated nerve fibers sprouting from the DRG. In isolated SC cultures, IL6RIL6 was also efficient to induce MBP and Po gene expression after 24 and 72 hours. The interaction of Schwann cells with neurons was increased by IL6RIL6. For these experiments, sciatic nerve derived SC were labelled with Fluorogold and added to DRG neuronal cultures obtained by NGF treatment under conditions which inhibit glial cell growth. Addition of IL6RIL6 markedly increased the number of fluorescent SC that attached to axons within 5 hours. The SC rapidly elongated and aligned along the axons, whereas without gp130 activation the SC remained round and only few were seen to attach. IL6RIL6 had only weak mitogenic effects on isolated SC lines but foci of stellar cells formed in DRG cultures, which when isolated showed a dependence on IL6RIL6 for their growth, suggesting that IL6RIL6 is a survival and growth factor for some stage of glial cell differentiation. These IL6RIL6-dependent cells readily attached to axons in co-culture with neurons. IL6RIL6 was also found to induce the transdifferentiation of melanoma B16-F10.9 cells into glial cells, with growth arrest, loss of melanogenesis morphological elongation and induction of MBP, CNPase, MAP–2 and GFAP. Pax–3, a paired homeodomain transcription factor expressed in Neural crest cells and in non-myelinating SC but repressed in myelinating SC, was

strongly down-regulated by IL6RIL6 at the mRNA and protein level. Pax–3 transactivates the microphthalmia transcription factor MITF gene (which in turns activates tyrosinase and melanogenesis). IL6RIL6 repressed MITF at the promoter level, part of the effect being mediated by loss of Pax–3 and part by a reduced function of the cAMP response element after IL6RIL6 treatment. Since Pax–3 represses myelin genes (such as MBP) the down regulation of Pax–3 by IL6RIL6 may be relevant to its myelination stimulating activity, although gp130 activation may have a wide range of other effects favoring nerve fibers remyelination (Work supported by Ares-Serono and InterPharm Ltd).

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INTERLEUKIN –1 GENE POLYMORPHISMS: RELEVANCE OF A SPECIFIC COMBINATION (ASSOCIATED WITH DISEASE SEVERITY) TO IL–1B /IL–1RA PRODUCTION IN MS PATIENTS AND CONTROLS. H. M. Schrijver, J. van As, J. B. A. Crusius, C. D. Dijkstra, B. M. J. Uitdehaag, Academic Hospital Vrije Universiteit Amsterdam (Amsterdam, NL)

Interleukin (IL)1B is a major pro-inflammatory cytokine that has been related to several chronic inflammatory diseases. In MS it is produced by macrophages and microglial cells in and around the edge of MS lesions and might be involved in the destruction of CNS myelin. Some protection against the disease provoking effects of IL–1B is provided through the IL–1 receptor antagonist. This cytokine competes for the same receptors but prevents activation of the target cell. The genes of these cytokines are polymorphic. Recently, we described an association between a specific combination of the IL–1B and IL–1RA genes and disease severity in MS. Patients that were carriers of this combination had a significantly higher rate of progression on the EDSS than non-carriers. However, the mechanisms by which these gene polymorphisms apparently influence the clinical course are unknown. It is conceivable that the levels of cytokine production are – at least partially – under genetic control. Hence, this study addresses the question whether polymorphisms in the IL–1B and IL–1RA genes influence the production of these cytokines. Materials & methods: We selected from the population in which we had established the association with disease severity (148 patients) 10 MS patients that were carriers of the specific combination (i. e. IL-RA allele 2+ /IL–1B allele 2 –) and 10 MS patients that were non-carriers of the specific combination (i. e. IL-RA allele 2- /IL–1B allele 2 –). Carriers and non-carriers were matched for sex, age, and type of disease. Each group comprised 4 relapsing-remitting, 4 secondary progressive, and 2 primary progressive patients. Likewise, 20 healthy controls that were carriers or non-carriers of the specific combination were selected. Production of IL–1B and IL–1RA in whole blood was measured with ELISA after stimulation with 10 ng/ml LPS for 6 and 24 hours. RESULTS: Patients that were carriers of the IL-RA allele 2+ / IL–1B allele 2 – combination showed approximately 40 % higher production of IL–1RA (24 hours) than patients that were non-carriers. Similarly, patients that were carriers of the IL-RA allele 2+ / IL–1B allele 2 – combination had a higher level of IL–1RA production than controls carrying the same combination.

No significant differences in IL–1B levels were observed. Discussion: Patients that carry a specific combination of the IL–1B/IL–1RA genes (consisting of absence of IL–1 allele 2 and presence of IL–1RA allele 2) progress faster on the EDSS scale. In the present study we have shown that those patients produce in vitro more IL–1RA than patients with another combination. This is in line with a recent study in which the same combination was associated with higher IL–1RA levels in plasma of healthy blood donors. In view of the current knowledge our results might indicate the following: The described combination determines the innate, potential production capacity for IL–1RA. Whether this capacity to produce IL–1RA at high levels actually takes place probably depends on triggers in the cytokine network. This can explain our observation that patients and controls with an in this respect identical genetic make-up differ in their IL–1RA production. However, the significance of a high level of IL–1RA in the cascade of events eventually causing inflammatory damage remains to be elucidated.

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MOLECULAR ANALYSIS OF THE MECP2 GENE IN ITALIAN RETT PATIENTS. P. Nicolao, B. Giometto, M. Granatiero, V. Lazzerini, S. Pelagatti, C. Biondi, M. Giovannucci-Uzielli, P. Gasparini, Dept. of Neurological Sciences, IRCCS CSS, Genetics and Molecular Medicine (Padova, S. G. Rotondo (FG), Firenze, I)

Rett syndrome is a neurodevelopmental disorder of genetic origin that exclusively affects girls. Rett patients show a marked delay of psychomotor development and loss of acquired skills, after 6–18 months of apparently normal infancy. Stereotyped hand movements together with poor social contact, breathing irregularities, growth failure and seizures are the main clinical features. Clinical diagnostic criteria for Rett syndrome have been developed. Mutations in the MeCP2 gene, located on Xq28 region, have recently been reported in classical Rett patients. MeCP2 (methyl CpG-binding protein), a transcriptional repressor which binds to methylated DNA, is essential for embryonic development in the mouse. We report here the results of the screening of the MeCP2 gene in a group of 40 sporadic Italian classical Rett patients. MeCP2 coding exons have been amplified using 9 primer pairs and the purified products have been analysed by RNA-SSCP (single strand conformation polymorphism). The fragments showing an abnormal band have subsequently been analysed by direct sequencing. Both nonsense and missense mutations have been identified, among which some were previously unreported. T158M and R168X mutations showed multiple recurrences, whereas R22X, P152R, S194T and A201L were identified in isolated cases. All missense mutations are located within the MBD (methyl binding domain) of MeCP2 and involve amino acids conserved in evolution. Among nonsense mutations, R22X suggests functional emizygosity. As previously reported, most nucleotide substitutions are C-> T transitions at CpG hotspots. R22X is caused by an A-> T transversion, 100 (A-> T), P152R and S194T are caused by a C-> G and a G-> C transversion, 455 (C-> G) and 581(C-> G). A comparison between the phenotype of Rett patients and MeCP2 mutations has been made.

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ADULT POLYGLUCOSAN BODY DISEASE (APBD) DUE TO TYR329SER MUTATION IN GLYCOGEN BRANCHING ENZYME (GBE). H. Rosenmann, A. Lossos, M. Halimi, G. Amir, Z. Ne'eman, O. Abramski, V. Barash, Hadassah University Hospital (Jerusalem, IL)

Adult Polyglucosan body disease (APBD) is a late-onset, slowly progressive disorder manifested by cognitive impairment, pyramidal tetraparesis, peripheral neuropathy, and neurogenic bladder. The pathological hallmark of APBD is the widespread accumulation of polyglucosan bodies (PBs), amylopectin-like polysaccharide inclusions, throughout the nervous system. Recently, we have shown that Ashkenazi Jewish APBD patients have reduced GBE activity and carry the Tyr329Ser mutation in the GBE gene. Similar biochemical and pathological findings are shared by glycogen storage disease type IV (GSDIV), an early childhood disorder with primarily systemic manifestations.

So far, we have studied 16 APBD patients: 10 of them were homozygous for the Tyr329Ser mutation, while 6 were heterozygous and did not carry other previously reported mutations in the GBE gene, suggesting compound heterozygosity for a yet unknown genetic variation.

To elucidate the pathogenesis of APBD, we further investigated whether the GBE deficiency and the accumulation of PBs are generalized or restricted to the nervous system. For this purpose, we tested the GBE activity and the presence of PBs in several available tissues derived from APBD patients: cultured skin fibroblasts, granulocytes, lymphocytes, muscle biopsies and sural nerve biopsies. We found that while reduced GBE activity (0–25 %) was demonstrated in all tissues tested, PBs were detected only in the sural nerve.

The finding that the reduced GBE activity was generalized, whereas the presence of PBs was limited to the nervous system, may be related to differences in turnover of glycogen among tissues; and in addition to the reduced GBE activity, other yet unidentified factors are involved in PBs accumulation.

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GENERALIZED EPILEPSY WITH FEBRILE SEIZURES PLUS (GEFS+): EVIDENCE FOR FURTHER CLINICAL AND GENETIC HETEROGENEITY IN A LARGE FAMILY. Y. G. Weber, H. Baier, K. Jurkat-Rott, K. Kunkel, H. Bode, A. C. Ludolph, F. Lehmann-Horn, H. Lerche, University of Ulm (Ulm, D)

Generalized epilepsy with febrile seizures plus (GEFS+) is a recently described benign childhood epileptic syndrome with autosomal dominant inheritance. The most common phenotypes are febrile seizures (FS) with or without afebrile generalized tonic clonic seizures (GTCS; phenotypes: FS, FS+). In about one third of the cases, other additional seizure types do occur such as absences, myoclonic, atonic or tonic seizures. The most severe phenotype is myoclonic astatic epilepsy (MAE). In one family, a mutation within the gene SCN1B on chromosome (chr) 19q13 encoding the beta1-subunit of the voltage-gated sodium channel has been described, for other families linkage to chr 2q21–33 was found. Here, we describe the phenotypic variability of GEFS+ in a five-generation family. Inheritance was autosomal dominant with a penetrance of about 80 %. 18 patients out of 72 family members had a variety of predominantly childhood onset generalized epilepsy phenotypes. 3 individuals had FS, 1 had FS+, 2 had GTCS without reported fever, 2 had generalized tonic seizures (GTS) sometimes associated with fever, 4 had atonic seizures and GTS or GTCS often associated with fever, 2 had absences (1 with GTCS) and 4 had unclassified seizures in childhood. The age of onset was between 1.5 and 4 years of age. 3 individuals had GTCS in adulthood. Interictal EEG recordings showed generalized spike and wave discharges in 4 cases. Thus, in this family a lot of patients showed more complex epileptic phenotypes, in particular atonic

seizures, and many did not experience FS. Linkage analysis excluded the previously described loci on chr 2 and 19 indicating further genetic heterogeneity.

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CLUSTERING OF COMMON GENETIC MUTATIONS MAY POSSIBLY CAUSE THROMBOTIC PROCESSES IN A CLINICALLY HEALTHY CIRCULATORY SYSTEM. Z. Szolnoki, F. Somogyvari, M. Szabo, L. Fodor, County Hospital Pandy Kalman (Gyula, H)

It has been reported that the Leiden V and prothrombin G 20210 A mutations can cause thrombotic processes if they are associated with other well-known clinical risk factors such as diabetes mellitus, hypertension, or stenosis of the carotid artery. The Leiden V, prothrombin G20210A, Hong Hong, Cambridge and methylenetetrahydrofolate reductase C677T (MTHFR C677T) mutations and the D allele of angiotensin converting enzyme polymorphism (ACE polymorphism) have not been proved to be major risk factors for thrombosis. There is no published evidence that these genetic factors alone can cause thrombotic processes in a healthy circulatory system. In our clinical study, the aetiological roles of these common genetic mutations were analysed in a subgroup of stroke patients.

400 patients presented and were examined because of ischaemic stroke. Five of them did not exhibit any classical clinical risk factors. The criteria of exclusion included any of the following conditions: hypertension, diabetes mellitus, hyperlipidaemia, hypercholesterinaemia, any kind of heart disease, internal carotid artery or vertebral artery alterations, the presence of anticardiolipin antibody or lupus anticoagulant, heavy smoking or drinking, and age above 60 years. In this clinically homogeneous subgroup of stroke patients, the prothrombin A 20210 G, Hong Kong, Cambridge and MTHFR C677T mutations, ACE polymorphism and apolipoprotein E (APO E) genotype were examined.

All 5 patients displayed a heterozygous Leiden mutation. Heterozygous MTHFR mutations and I/D genotypes for ACE polymorphism were detected in 4 patients, while a homozygous D/D genotype and a homozygous MTHFR mutation were found in 1 patient.

These genetic results suggest that the Leiden mutation might possibly be an aetiological factor for stroke in a small subgroup of patients without any classical clinical risk factors. The roles of ACE polymorphism and the MTHFR C677T mutation in stroke (not as major risk factors but as unfavourable ones) should also be taken into consideration in this subgroup of stroke patients. These genetic factors might perhaps be aetiological factors of clustered together in a clinically risk-free stroke patient.

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INTEREST OF THE GENETIC TEST FOR THE OCULOPHARYNGEAL MUSCULAR DYSTROPHY (OPMD): STUDY OF THE 12 PATIENTS WITH CLINICAL SUSPICION OF OPMD. A. Pou, J. Pascual, J. Roquer, J. A. Urtizberea, B. Brais, Hospital del Mar, Institute de Myologie, CHU (Barcelona, E; Paris, F; Montreal, CDN)

The PABP2 gene presents GCG repeats in short number (until 6) in normal conditions. Short GCG expansions (between 7 and 13) cause OPMD (Brais et al., Nat Gen. 1998, 18: 164–167). Molecular data findings in patients with clinical suspicion of OPMD may contribute to establish the correct diagnosis and to understand the correlation phenotype-genotype if existing. A genetic study for OPMD has been performed in 12 patients under clinical suspicion of OPMD, 6 of them belonging to the same family (C-A) and the other 6 patients to different families (C-M), (T-P), (G-S), (L-G), (S-S) and (Z-S). All these 6 families were not related between them. At least one member of each family had been submitted to a muscular biopsy for searching (electron-microscopy) intranuclear inclusions (IIN). The aim of this study is double: to assess the genetic findings for the OPMD diagnosis and to correlate OPMD phenotype-genotype. All 6 patients belonging to the family C-A and the patient of the family C-M present a (GCG) 9 mutation, their phenotype is rather severe, the onset of the disease is over 50, five of these members present associated limb-girdle (lumbopelvic preferentially) muscle weakness, one of them died recently at 61 because of a severe dysphagia. Patients (T-P) and (G-S) present a (GCG)10 mutation and patient (L-G) a (GCG)11 mutation: all these three patients present exclusively bilateral ptosis (none ophthalmoplegia) and dysphagia, the onset of the disease is under 50. In two patients, without presence of IIN, the OPMD mutation is absent: diagnosis has been reviewed in both cases, in one (S-S) mitochondrial progressive external ophthalmoplegia has been confirmed and in the second (Z-S) the clinical symptoms have been related to an ocular ab-AChR negative myasthenia.

Conclusions: according with our results, the genetic test for OPMD – performed in patients with clinical suspicion of OPMD – guarante the correct diagnosis of OPMD in all cases, it allows us to exclude other diseases and it suggests that OPMD phenotype without the OPMD mutation would be rather rare. It seems (further studies with a greater number of patients will be necessary) that the (GCG)9 mutations implicate a more severe phenotype than patients with (GCG)10 or (GCG)11 mutations.

P795
PREFERENTIAL MUSCULAR GROUPS INVOLVEMENT IN PATIENTS WITH AUTOSOMAL RECESSIVE LIMB-GIRDLE MUSCULAR DYSTROPHIES (LGMD2): A CLINICAL AND MUSCULAR IMAGING STUDY. A. Pou, M. Busto, Hospital del Mar (Barcelona, E)

The clinical heterogeneity which has long been recognized in the LGMD2 has been shown to relate to the involvement of a large number of different genes. By clarifying the clinical characteristics of different muscle involvement subtypes, it may prove useful for establishing the genetic diagnostic and for the prognostic information. The aim of the study pretends to show some specificity of muscular involvement in patients (with a clinical course followed during a course of several years) presenting different forms of LGMD2 with a genetically proven diagnostic. Three patients, one male and two females, with a progressive LGMD2, and different genetic diagnostic, have been chosen for this study: Patient (A) with calpainopathy (LGMD2), patient (B) with a dysferlinopathy (LGMD2B) and patient (C) with an a-sarcoglycanopathy (LGMD2D or Adhalinopathy). Patient (A), a 20 year-old-man, initiated the disease at 12, was operated (Achilles tendon contractures) at 16 and maintains at present a spontaneously walk, shows a selective and symmetrical involvement of serratus major (scapular winging), thigh's adductors (long adductor preferentially), biceps of thigh, semimembranous, semitendinous and gastrocnemius. Patient (B) – a 63 year-old-man, with disease onset at 30, walking at present with helping of a walking stick,– shows a severe and symmetrical involvement of the gluteus and gastrocnemius, less involvement of tibial anterior and complete involvement of the thigh's muscles except sartorius, gracilis and biceps femoris. Patient (C) – a 30 year-old-man, with disease onset at 9, became wheelchair bound at 23 – shows a major, very severe, atrophy of all limb-girdle muscles (shoulder and pelvic limbs) and also a complete atrophy of proximal muscles of the four limbs.

Conclusions: the CT muscle imaging represents a very useful tool to complement the clinical examination in order to establish which are the preferential muscle groups damaged and preferential muscle groups preserved in the well characterized forms of LGMD2. According with our results, the a-sarcoglycanopathy offers a severe and global pattern of muscular involvement, the calpainopathy offers a selective pattern of involvement, and the dysferlinopathy a selective pattern of muscle sparing. New studies with a greater number of patients will be necessary to establish better correlations between phenotypes and genotypes in LGMD2.

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ABSENCE OF LINKAGE BETWEEN FAMILIAL AMYOTROPHIC LATERAL SCLEROSIS. A. Orlacchio, T. Kawarai, A. M. Massaro, P. H. St George-Hyslop, S. Sorbi, University of Toronto, Isola d'Elba, University of Firenze (Toronto, CDN; Elba, I; Firenze, CDN)

Amyotrophic lateral sclerosis (ALS) is a progressive lethal age-dependent paralytic disorder with onset in adulthood caused by degeneration of large motor neurons of the spinal cord and brain. It is characterized by a progessive weakness of the muscles of one or more limbs, swallowing or speech in adulthood. ALS occurs as an apparently sporadic disease (SALS) in 90–95% of cases. However, in 5 to 10% of ALS patients, a family history of the disease can be documented. Familial ALS (FALS) is usually inherited as autosomal dominant trait, although a few families show autosomal recessive inheritance. Approximately 33% of autosomal dominant familial cases and 2.5% of sporadic cases arise from missense mutations in the cytosolic Cu/Zn superoxide dismutase gene (SOD1), localized to human chromosome 21q22.1. Recently, the Copper Chaperone for Superoxide Dismutase (CCS) gene has been proposed as a potential candidate gene for FALS. We investigated the segregation of this gene in two Italian families with Amyotrophic Lateral Sclerosis lacking the mutations in SOD1 gene. We analyzed a total of 56 individuals; 6 people were affected. Diagnoses were made using the El Escorial criteria. The results of our study provide no evidence of a linkage between markers flanking the CCS gene and Familial Amyotrophic Lateral Sclerosis in these FALS kindreds.

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NO LINKAGE BETWEEN FAMILIAL TYPICAL MIGRAINE AND CACLNL1A4 GENE. A. Orlacchio, I. Rainero, L. Pinessi, V. Gallai, University of Toronto, University of Torino, University of Perugia (Toronto, CDN; Torino, Perugia, I)

Migraine is a frequent neurological disorder that shows strong familial aggregation. It is characterized by recurrent attacks of disabling headache, vomiting, photo- and phonophobia. Interest in the localization of a migraine gene came from the recent mapping and subsequent identification of a gene (the calcium ion channel gene, CACLNL1A4, located on chromosome 19p13) involved in the familial hemiplegic migraine (FHG) subtype. Recently, this gene has been proposed as a potential candidate gene for typical migraine too. We investigated the segregation of this gene in two Italian pedigrees with typical migraine without aura. We analyzed a total of 100 individuals; 23 people were affected. Diagnoses were performed by a clinical neurologist following the criteria specified by the International Headache Society (IHS). The results of our study provide no evidence of a linkage between markers flanking the CACLNL1A4 gene and familial typical migraine in these kindreds.

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MAGNETIC RESONANCE IMAGING AND DUPLEXSONOGRAPHY IN THE DETECTION OF NONCHROMAFFIN PARAGANGLIOMAS OF THE CAROTID ARTERY IN A FAMILY WITH HEREDITARY PARAGANGLIOMAS. N. Sieweke, E. Stolz, S. Niemann, H. Traupe, U. Mueller, M. Kaps, Justus-Liebig-University (Giessen, D)

Recently, familial cases of vascular tumors known as 'nonchromaffin paragangliomas' have been described, with a risk of manifestation increasing with age. The majority of these benign and rare tumors appear as carotid body tumors (glomus carotid tumor), but can also derive from structures such as the middle ear (glomus jugulare tumor). As the tumor slowly but extensively grows while eroding surrounding structures and often leading to cranial nerve palsies, diagnosis is hardly ever made prior to occurrence of symptoms. An early diagnosis and thus early surgical intervention seems to be of greater value for a better clinical outcome in these patients.

N = 9 members (4 female, 5 male) of a family with multiple cases of either glomus carotid or jugulare tumor -diagnosed bioptically- were screened for further paragangliomas, primarily focussing on the neck. Only siblings or direct descendants of other affected members were included, mean age 41.8 years. All participants underwent a routine neurological exam. The cranial nerve status was normal throughout. A detailed extracranial color-coded duplexsonography and a Magnetic Resonance Imaging (MRI) including the neck were performed afterwards. In n = 2 cases a suspicious, clearly vasculated tumorous structure of about 2 cm diameter was recognizable close to the bifurcation. Both, ultrasound and MRI revealed similar results as to location, approximate size and vascularization of the tumor. In one participant this structure was identified as a toxic adenoma, whereas the second participant suspicious of a glomus carotid tumor preferred conservative treatment and was scheduled for regular follow-up, therefore a histologic diagnosis is not available so far.

We conclude that screening for glomus carotid tumors in familial cases of paragangliomas is recommendable to family members especially over 40 years of age. Whether duplexsonography and MRI are comparable screening methods regarding sensitivity and specificity should be subject of further studies.

P799
A NOVEL MUTATION IN HPRT GENE RESPONSIBLE FOR LESCH-NYHAN SYNDROME. Y. Ishikawa, F. Kinoshita, S. Morimune, Y. Yamada, Koyoto City Rehabilitation Center, Aichi Prefectural Colony (Kyoto, J)

Lesch-Nyhan syndrome is an X-linked recessive disorder characterized by hyperuricemia, physical and mental retardation, choreoathetosis, and compulsive self-mutilation. This disease is associated with complete absence of activity of enzyme involved in purine metabolism, hypoxantine guanine phospholibosyltransferase (HPRT). The marked genetic heterogeneity of HPRT deficiency is well known. Many different mutations at the HPRT gene locus (deletions, insertions, duplications, abnormal splicing and point mutations at different sites of the coding region from exon 1 to 9 have been reported. We identified novel mutant in Japanese family.

Case 1 is 41-year-old male with marked spastic paraparesis, mild ataxia and hyperuricemia. Case 2 is the younger brother with same symptoms. The activity of HPRT and APRT were measured by radiochemical methods. HPRT activity in erythrocytes was not detected in these two patients. Adenine phosphoribosyltransferase (APRT) was increased about 3.5 fold compared with the control value. The genomic DNA primers for amplification of DNA fragments including each exons were designed from the nucleotide sequence of the human HPRT gene locus. The multiplex amplification of all nine HPRT exons was achieved using the system described by Gibbs et al. The protocols for direct sequencing were slightly modified from those of Seqenase Version 2.0 (United State Biochemical), consulting the direct sequencing method described by Bachmann et al. Multiple amplification from genomic DNA revealed no differences in product sizes between the patients and normal control. By direct sequencing of all nine amplified exons a single nucleotide substitution of A to G was detected in exon 6. Direct sequencing analysis of the RT-PCR product showed a point mutation identical to that found in the genomic DNA. The substitution resulted in a missense mutation, AAG (Lys) to GAG (Glu) at codon 159. This base substitution has not reported previously. The Taq1 restriction site (TCGA) in exon 6 is created in the mutant allele. A family study was thus performed by PCR-RFLP analysis by using this Taq1 site. DNA fragments of 233bp including exon 6 and its franking intron sequences were amplified from the genomic DNAs of the probands and mother. The fragment from the mutant allele should be digested by Taq1 to two bands of 157 and 76 bp. Analysis of the mother's samples revealed three DNA bands, 233 bp band from the normal allele and two bands of 157 and 76 bp from the mutant allele. Sequence analysis of the DNA fragments of the mother showed both A and G bands at the mutation site.

Infection of the nervous system

P800
ACUTE DISSEMINATED ENCEPHALOMYELITIS FOLLOWING LEGIONELLA PNEUMOPHILA INFECTION. J. B. Sommer, F. J. Erbguth, B. Neundörfer, University of Erlangen-Nürnberg (Erlangen, D)

Acute disseminated encephalomyelitis (ADEM) is an acute or subacute inflammatory demyelinating disease of the central nervous system, that occurs 1–3 weeks after viral infection, bacterial infection or immunization. We report on a case of ADEM 3 weeks following a respiratory disease associated with the clinical and serological diagnosis of Legionella pneumophila infection. A 58-year-old male outpatient developed a non-productive cough, fever (103,3 °F), diarrhoea, abdominal pain, and headache. Grepafloxacin (400 mg/day) was given for 5 days, and the patient recovered completely. 3 weeks later, he was admitted to a regional hospital because of headache, nausea and dizziness presenting nystagmus to the left and bilateral horizontal diplopia. 3 days after admission, he developed a right-sided hemiparesis and gradually lost consciousness. Repeated head CT showed no cerebral lesions and the patient was transferred to our neurological ICU. Lumbar puncture revealed: cell count 19/mm^3, protein 70,2 mg/dl, glucose 102 mg/dl, negative oligoclonal bands. T2-weighted MRI showed confluent high signal lesions of bilateral periventricular and subcortical white matter, and left cerebellar peduncle without contrast enhancement. The diagnosis of ADEM was made, and high-dose prednisolone was given for 6 days, followed by an oral taper. Extensive microbiologic and viral studies were negative. However, a highly positive antibody titer to Legionella pneumophila serogroup 1–6 of 1:256 was found indicating a recent Legionella pneumophila infection. Within 3 days after initiation of the steroid treatment, the patient gradually improved and recovered completely in the course of the next 8 weeks. In this patient, widespread neurologic deficits and typical MRI findings led to the diagnosis of ADEM. The preceding respiratory disease could be identified as Legionella pneumophila infection because of its typical clinical syndrome, the highly positive antibody titer, the good response to the fluoroquinolone Grepafloxacin, and the negative serologic studies for many other potential infectious etiologies. In conclusion, Legionella pneumophila should be considered as one of the possible infectious agents to be associated with ADEM.

P801
ACUTE NEUROLOGIC PRESENTATION OF BACTERIAL ENDOCARDITIS. R. Orni-Wasserlauf, A. Mazarib, D. Schwartz, Y. Siegman-Igra, A. D. Korczyn, Telaviv Medical Center (Tel Aviv, IL)

OBJECTIVE: To describe and measure the characteristics and proportion of patients with bacterial endocarditis (BE) presenting as stroke compared to those without neurologic complications (NC).

BACKGROUND: NC are common and well described. Moreover, typical presentation of acute stroke may be the first clinical manifestation of BE, and in the absence of appropriate awareness, the true diagnosis may be missed or delayed.

DESIGN/METHODS: Clinical, epidemiologic, demographic and bacteriologic data were collected on all adults with clinically significant bacteremia during the study period 1995–1998. All cases with definite or possible endocarditis according to Duke's criteria were included, and additional pertinent data (cardiac ECHO, brain CT scans, etc.) were reviewed.

RESULTS: 15 patients presenting with stroke (13), meningitis (1) or transient paraplegia (1) were ultimately diagnosed as having culture positive BE. 7 additional patients developed stroke during the course of BE. Most patients had vascular risk factors for stroke. In 6 of the 15 patients with neurologic presentation blood cultures were not drawn until day 4 or later, when fever was first noted. Staphylococcus aureus was more common (9/22, 41 %) among patients with NC than among those without NC (12/63, 19 %, p=0.05). Definite valvular vegetations were demonstrated in 68 % with NC as compared to 35 % in those without NC (p=0.01). Mortality was 32 % (7/22) for those with NC and 22 % (14/63) for those without (p=0.5).

CONCLUSIONS: Acute neurologic symptoms, mostly due to ischemic stroke, are a common presentation of BE, frequently associated with S. aureus infection. The diagnosis of BE should always be considered in patients admitted with stroke, even in people with evident risk factors for stroke and in the absence of a history of fever.

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A CLINICAL ALGORITHM FOR 14–3–3 TESTING IN DIAGNOSING CREUTZFELDT-JAKOB DISEASE. AW Lemstra, WA van Gool, Academic Medical Centre (Amsterdam, NL)

The 14–3–3 protein immunoassay on cerebrospinal fluid (CSF) has favorable test characteristics as a premortem diagnostic tool in Creutzfeldt-Jakob disease (CJD). However, the 14–3–3 protein is a normal cellular protein expressed in various tissues, and its presence in CSF reflects extensive destruction of the brain tissue as in CJD, but also in ischaemic stroke and meningoencephalitis. Objective: To study whether an algorithm that includes additional diagnostic information could increase the specificity of the 14–3–3 testing in patients suspected to suffer from CJD. Methods: 14–3–3 was tested in the CSF of a prospective series of 111 consecutive CJD-suspected patients. Results: The sensitivity was 97 % and the specificity was 87 %. A simple, diagnostic algorithm is proposed that includes findings of neuroimaging and routine CSF examination before 14–3–3 testing. In this series, use of the clinical algorithm increases the specificity to 97 %, thus raising the prior probability of having CJD of 35 % to 94 % in case of a positive result. Conclusion: The 14–3–3 protein is a highly sensitive and specific marker for CJD when used in the appropiate clinical context.

P803

IS JC VIRAL INFECTION A LEUKOENCEPHALOPATHY OR PANENCEPHALOPATHY? Y Schwammenthal, P Sirota, D Nass, L Shulman, A Eyal, I Blatt, Y Goldhammer, AS Buchman, Sheba Medical Center, Abarbanel Mental Health Center (Tel-Hashomer, IL)

Progressive multifocal leukoencephalopathy (PML) is a progressive diffuse brain disease process that typically affects myelin. We discuss two patients who presented with clinical and radiological evidence of focal gray matter lesions that were shown to derive from JC virus infection. The first patient, a 70 year-old female with a history of low grade lymphoma, was evaluated for the acute onset of dysarthria and left hemiparesis. Her initial CT and MRI showed a non-enhancing lesion in the right thalamus. Stereotactic brain biopsy was suggestive but not diagnostic of PML. The patient rapidly declined and CT done shortly before her demise showed diffuse multi-focal white and gray matter lesions. Post-mortem testing showed intensely positive PCR and in situ hybridization for JC virus DNA. The second patient, a 68 year-old woman, presented with a subacute progressive right hemiparesis and motor aphasia. Her history was significant for metastatic carcinoma of the breast treated with autologous bone marrow transplantation and chemotherapy. She was receiving steroid therapy for a chronic relapsing autoimmune disorder. Initial MRI showed a T1- hypointense, non-enhancing left basal ganglionic lesion without mass effect. Stereotactic brain biopsy showed typical histopatho-logical findings indicative of JC virus infection with positive PCR and in situ hybridization for JC virus DNA. PML is conventionally regarded as a white matter disease. Predominant gray matter involvement in PML is uncommon but has been previously described. These two cases underscore that chronic CNS infection by JC virus is a panencephalopathy, which can present with focal gray matter lesions in immunocompromised patients.

P804

TEMPORAL EXPRESSION OF NOS ISOFORMS IN THE COURSE OF BACTERIAL MENINGITIS. F. Winkler, U. Koedel, H.-W. Pfister, Ludwig-Maximilians University Munich (München, D)

Despite intensive research efforts, the role of nitric oxide (NO) in the pathogenesis of bacterial meningitis is still controversial. In the brain, NO can be produced by the NO synthase (NOS) isoforms endothelial NOS (eNOS), neuronal NOS (nNOS), and inducible NOS (iNOS). NO production in the CNS is increased during bacterial meningitis. However, experimental studies have reported beneficial, no or even detrimental effects of NOS inhibition in this disease. These discrepancies may be explained by differences in (1) the specificity of the inhibitors used and (2) the time point of drug administration. A promising pharmacological intervention requires detailed knowledge of the temporal profile and functional relevance of NOS isoform expression during bacterial meningitis. This is supported by recent studies of our laboratory that eNOS knock-out mice show increased mortality and aggravated CNS complications during pneumococcal meningitis compared to infected wild type mice (unpublished data). The aim of our study was to determine the differential expression of eNOS, nNOS, and iNOS in the time course of experimental meningitis. METHODS: After live pneumococci were injected into the cisterna magna of mice, intracranial pressure (ICP) and cerebrospinal fluid (CSF) white blood cell (WBC) count were determined at different time points (before=0, 4, 8, and 24 hours (h) after infection). The brains were then removed and RNA preparations were made from frozen sections of total brain. RT-PCR using specific primer for eNOS, nNOS, iNOS, and GAPDH was carried out in duplicate. The specificity of the products was confirmed by DNA sequencing. Results: A significant increase in cerebral eNOS mRNA expression was detected 8 and 24 hours after infection (n=4, ratio eNOS/GAPDH: 0 h: 0.38 ± 0.14; 4 h: 0.36 ± 0.14; 8 h: 0.76 ± 0.12; 24 h: 0.77 ± 0.13). A moderate induction of iNOS mRNA expression already occurred 4 hours after infection and further increased to marked levels after 24 hours (n=4, ratio iNOS/GAPDH. 0 h: 0; 4 h: 0.18 ± 0.16; 8 h: 0.19 ± 0.13; 24 h: 1.42 ± 0.14). There was no significant time-dependent change in nNOS expression. ICP and CSF WBC count increased significantly in the time course of pneumococcal meningitis (n=4, 0, 4, 8 and 24 hours: ICP: 4.7 ± 1.5; 9.7 ± 1.5; 14.0 ± 2.6; 18.3 ± 2.1 mmHg. CSF WBC count: 109 ± 74; 1533 ± 445; 5342 ± 1350; 6808 ± 621 cells/µl). CONCLUSION: Our findings suggest that eNOS and iNOS are the sources of elevated NO production during bacterial meningitis. The early induction and marked upregulation at 24 hours of iNOS in mouse brain point to the importance of further studies to elucidate the specific role of this isoform in the pathophysiology of bacterial meningitis.

P805

ENCEPHALOMYELITIS DUE TO CRYPTOCOCCUS NEOFORMANS VAR. GATTII PRESENTING AS SPINAL TUMOUR – A CASE-REPORT. P. Grosse, K. Tintelnot, O. Söllner, B. Schmitz, Charité, Campus Virchow-Klinikum, Robert-Koch-Institute (Berlin, D)

We describe a 24 year old immunocompetent German resident who developed multifocal encephalomyelitis due to infection with Cryptococcus neoformans var. gattii. To our knowledge this is the first description of serologically identified C. neoformans var. gattii infection of the spinal cord. Case report: The patient presented with a history reminiscent of a spinal tumor with a slowly progressing incomplete transverse affection of the spinal cord at level L4 at clinical examination. MRI of the spine showed an irregularly shaped, exclusively intramedullar lesion with smooth border at L1 vertebral level which caused distension and a partial displacement of the caudal myelon and the cauda equina. Further, cerebral MRI detected six lesions with a diameter up to 10mm with a signal behavior similar to the intramedullar lesion. Thoracic CT showed a dorsomedially located soft tissue lesion of the right lung adjacent to the pleura with multiple gas inclusions. Diagnosis was established serologically with a positive test for cryptococcus antigen in the serum and histopathologically from a cerebral lesion. Interestingly, the test for cryptococcus antigen in the CSF was negative despite mild pleocytosis and massive rise of protein concentration. Further serological evaluation could identify the causative agent as Cryptococcus neoformans var. gattii. Despite a rigorous antimycotic regimen laminectomy was necessary because conservative treatment alone could not reduce the size of the lesion and irreversible spinal cord damage was always imminent. After surgery the spinal syndrome gradually improved clinically, but only after two years of continuous antimycotic treatment with fluconazole the spinal and cerebral lesions diminished gradually in size. Discussion: This case not only raises specific epidemiological questions related to the worldwide distribution and prevalence of Cryptococcus neoformans var. gattii being usually considered a disease of tropical regions. It also illustrates the complications due to intramedullary involvement in this mycosis requiring a specific therapeutical approach. In the light of current knowledge on the epidemiology of C. neoformans var. gattii, and the travel history of our patient, we assume that the infection was acquired outside Europe. As exclusive intramedullary involvement is an outstandingly rare manifestation in spinal cryptococcosis the particular diagnostic procedure and the therapeutic stratgegies are discussed and related to other mycoses of the spinal cord.

P806
EARLY MRI FINDINGS IN HERPES SIMPLEX ENCEPHALITIS. D. Felten, S. Coste, C. Lévêque, T. De Greslan, J.-L. Renard, D. Béquet, Hôpital Val-de-Grace (Paris, F)

The prognosis of herpes simplex encephalitis (HSE) has improved owing to the advent of new diagnostic techniques and early treatment by aciclovir. The results of early MRI in four cases in adults are analysed and diagnosis value is evaluated. Case 1: MRI was realised seven days after development of a right hemiparesis, abnormal behaviour and seizures. The whole left temporal lobe was damaged with hypointense signal on the T1-weighted images and hypersignal on T2-weighted images. Bilateral abnormal signal was noted in frontal lobes. There was no contrast enhancement. HSV–1 encephalitis was confirmed by serology. Case 2: MRI was performed five days after neurological signs had appeared: fever, memory impairment, confusion and bilateral choreoathetoid movements. Lesions were strictly unilateral in temporal lobe and cingulate gyrus at left. No lesion was observed in the striatum. HSV–1 PCR was positive in CSF. Case 3: A HSV–2 encephalitis was diagnosed by PCR in the CSF. The patient presented a typical limbic encephalitis with fever, confusion and aural hallucinations. Lymphocytic meningitis was important. Brain MRI was normal 15 days after the first neurological sign. Case 4: First MRI was made five days after the beginning of abnormal behaviour, confusion and memory impairment. T1- and T2-sequencies were normal. Next MRI, five days later showed typical lesions in left temporal lobe (insula) and corpus callosum. There was only meningeal contrast enhancement. HSV–1 PCR was positive in CSF. Herpes simplex encephalitis is a necrotizing limbic encephalitis. MRI is found to be very sensitive in identifying early lesions in temporal lobe, especially hippocampus, amygdala and insula and inferior frontal lobe structures. They appeared as a decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images. The FLAIR sequence is able to delineate better lesions adjacent to CSF. Lesions are most frequently bilateral but asymmetric. Choreoathetosis has been related to HSE in children; in these cases basal ganglia were always spared in MRI, like in our case 2. Corpus callosum lesions were observed in our case 4. We do not find such description in literature. Contrast enhancement of the brain images is unusual in the early stages, when leptomeningeal enhancement is frequent along the temporal lobes, insular cortex and cingulate gyrus. In case 3, MRI remains normal; this atypical HSE is related to HSV–2 that is much less frequent than HSV–1. In case 4, early MRI was normal but typical lesions appeared few days later. We must stress the possibility of such an unusual delay. MRI is today very helpful for revealing the HSE lesions. However, lack of images, as well as atypical ones does not rule out this possibility at early stages. Clinical, biological and EEG data must be associated to MRI findings and acyclovir treatment must be decided in any doubt.

P807
A NOVEL PERMISSIVE ROLE FOR GLUCOCORTICOIDS IN INDUCTION OF FEBRILE AND BEHAVIORAL SIGNS OF EXPERIMENTAL HSV–1 ENCEPHALITIS. T. Ben-Hur, R. Cialic, A. Itzik, O. Barak, R. Yirmiya, J. Weidenfeld, Hadassah – Hebrew University Hospital (Jerusalem, IL)

Objectives: To investigate host brain responses associated with the clinical signs of experimental HSV–1 encephalitis and whether these responses depend on the presence of circulating glucocorticoids. Background: Viral encephalitis often presents with fever and behavioral changes, such as a psychotic and agitated state. Herpes simplex virus–1 (HSV–1) is a lytic virus, considered to induce encephalitis by tissue destruction. The host brain responses that mediate encephalitic signs are not well studied. Methods: HSV–1 was inoculated intraventricularly into adult male rats. Virus titers were measured by a plaque assay. Motor activity and body temperature were measured using battery operated biotelemetric transmitters implanted in the peritoneal cavity. Adrenocortical axis activity was blocked by either surgical adrenalectomy, hypophysectomy or treatment with the glucocorticoid receptor antagonist RU38486. ACTH and corticosterone were measured in peripheral blood by radioimmunoassay. PGE2 synthesis was measured ex-vivo in brain slices. IL–1beta expression was measured in various brain regions by RT-PCR. Results: HSV–1 induced lethal encephalitis in the rats, presenting with fever and behavioral changes, including motor hyperactivity and aggressive behavior. In adrenalectomized rats HSV–1 failed to induce these signs, although mortality rate and virus titers in the brain were identical to sham-operated rats. Hypophysectomy or glucocorticoid-receptors blockade also prevented HSV–1 -induced febrile response. Dexamethasone replacement therapy to adrenalectomized rats fully restored the febrile and behavioral responses to HSV–1 infection. HSV–1 inoculation produced a 2-fold increase in brain PGE2 production. This effect was abolished in adrenalectomized rats and was restored by dexamethasone treatment. HSV–1 infection also induced brain IL–1beta expression. In adrenalectomized rats' brains there was spontaneous IL–1beta gene expression, which was further increased by lipopolysaccharide administration. However, HSV–1 could not increase IL–1beta mRNA above the levels seen following adrenalectomy. Conclusions: The clinical signs of fever, motor hyperactivity and aggressive behavior during experimental HSV–1 encephalitis are mediated by brain responses, such as PGE2 and IL–1 synthesis. Circulating glucocorticoids play an essential permissive role in the induction of these host brain responses.

P808
ASPECTS OF PATHOGENICITY OF LISTERIA MONOCYTOGENES. A. Kolb-Mäurer, I. Gentschev, W. Goebel, Theodor-Boveri-Institut (Würzburg, D)

The Gram positive bacteria Listeria monocytogenes (L. m.) causes severe diseases like meningitis and meningoencephalitis in humans. This report describes the interaction between L. m. and human dendritic cells, which play a crucial role in antigen presentation and are efficient stimulators of T-cells. Dendritic cells were obtained by culturing plastic adherent mononuclear cells from human peripheral blood for seven days in the presence of GM-CSF and IL–4. A high uptake of L. m. into human DCs was demonstrated by electron microscopy. This uptake is independent from adhesion factors (internalin A and B) of L. m. To determine whether L. m. do enter the cytoplasm of DC, we took advantage of a L. m. strain carrying the green fluorescence protein (gfp) gene under transcriptional control of the PrfA-dependent actA promotor. This construct restricts expression of the gfp gene to L. m. that have escaped the phagolysosom resulting in detectable expression of gfp. Using an MOI between 10 and 100, fluorescent bacteria were detected in DCs. The infection causes maturation of the previously immature dendritic cells and strong upregulation of typical makers of human mature DCs like CD83, MHC class II, and the costimulatory molecule B7–2. Our results suggest that effective DC-mediated immunity to L. m. infections hinge critically on the ability of the DC to uptake, kill and process bacteria for antigen presentation, whilst avoiding cell death and productive infection. Both, the ability of human DCs to resist death and to undergo maturation by upregulation of costimulatory signals and MHC class II after infection with L. m. may be important factors in minimising dissemination of the disease and might be disturbed in patients with severe neurological complications from Listeria infection.

P809
BRAIN MR IMAGES AND CLINICAL SYMPTOMATOLOGY OF PATIENTS IN VARIOUS STAGES OF SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE). J. Kulczycki, R. Boguslawska, W. Sobczyk, P. Kozlowski, T. Jakubowska, Institute of Psychiatry and Neurology (Warsaw, PL)

Within last twenty years our Institute became a center of diagnostic and therapy trials of SSPE in Poland. During that time we collected data of more than two hundred patients suffering from this illness. A great part of them were examined, sometimes repeatedly, by head MRI during the course of increasing clinical symptomatology. The analysis has been made on the basis of clinical history of over 30 cases hospitalized in the I-st Neurological Department of our Institute.

At the very beginning of the disease (stage I or early II) we observed first signs of mental deterioration and/or disturbances of some cortical functions: apraxia, acalculia, visual agnosia. Brain MRI revealed in this stage as a rule hyperintense foci in T2- and PD-weighted sequences in the white matter of occipital lobes. During the developed stage II we could observe progression of mental deterioration. Besides that in most patients involuntary movements, usually myoclonia, and anisoreflexia or even slight paretic signs of extremities appeared. In brain MRI progression of the T2-weighted hyperintense foci in white matter of both brain hemispheres was observed.

In stage III clinically motor disability increased in all extremities. Nearly all patients were unable to walk. Pyramidal and extrapyramidal signs appeared as well. Some patients became blind. Brain MRI disclosed very intense changes in T2-weighted sequences involving extensively the whole white matter of both cerebral hemispheres. The symmetric widening of brain ventricles was always progressive and was evaluated as very extensive in final phases of the illness.

The progression of brain changes in the course of SSPE summarized above was not influenced by therapy and independent from sometimes observed slowing of development of clinical signs.

P810
GENE EXPRESSION PATTERN IN AN IN VITRO MODEL OF AIDS DEMENTIA. B. Storch-Hagenlocher, J. Haas, K. Krieglstein, A. Biessmann, E Lorenz, K. Stingele, B. Wildemann (Heidelberg, D)

Background: The pathogenesis of the dementia associated with the acquired immunodeficiency syndrome (AIDS) is only partially elucidated. Histologically AIDS dementia correlates with degeneration of neuronal cells, synaptic

loss and dendritic simplification as well as myelin pallor and reactive astrocytosis. Since neurons and glial cells are not directly infected by the human immunodeficiency virus (HIV1) indirect pathomechanisms are postulated. The available evidence suggests that various molecules and neurotoxins are essential determinants of brain damage.

Objectives: Does HIV1 gp41 induce or suppress gene transcripts in vitro which are of potential importance in the pathogenesis of AIDS dementia?

Material and Methods: Neuronal and glial cells prepared from the cortex of fetal rats were incubated with recombinant gp41. As controls we had mixed cell cultures treated with potassium chloride, bacterial lipopolysaccharide, and proinflammatory cytokines as well as cells without any treatment. Total cellular RNA was extracted and the reverse transcription (RT) of messenger RNA (m-RNA) was carried out to complementary DNA (c-DNA) with three Oligo-T11 ancor primers. Each c-DNA was amplified by differential display polymerase chain reaction (DD-PCR) with 28 different random primers. Differentially expressed gene transcripts were isolated from polyacrylamide gels, reamplified, subcloned, and characterized by sequence analysis. Differentially expressed transcripts were further assessed by reverse Northern blotting and quantitative RT-PCR.

Results: Thus far we identified 16 differentially expressed gene transcripts following stimulation with gp41, among them the upregulation of the guanine nucleotide regulator gene (GNRP), of glucosyl ceramide beta 1,4 galactosyltransferase (UDP-Gal), tyrosinekinase B receptor (Trk-B), and Tandem of P domains in a weak inwardly rectifying K+ channel (TwiK), and several unknown genes. The pathogenetic role of the described alteration of the gene expression remains hypothetical. TwiK is thought to be involved in the control of background K+ membrane conductances and of the synaptic inhibition. Disturbance of the physiological equilibrium of potassium may induce neurotoxicity. The upregulation of Trk-B may reflect a neuroprotective response, however, abnormal regulation of Trk-B and its ligands brain derived neurotrophic factor (BDNF) and neurotrophin–4 (NT–4) may also promote neurotoxic effects via induction of both neuronal and immunological NO synthase (nNOS, iNOS).

P811

PROTECTION BY URIC ACID AGAINST OXIDATIVE BRAIN DAMAGE IN EXPERIMENTAL BACTERIAL MENINGITIS. S. Kastenbauer, U. Koedel, B. F. Becker, H. W. Pfister, Department of Neurology, LMU, Institute of Physiology, LMU (Munich, D)

Background: We have recently identified peroxynitrite as a mediator of pathophysiological alterations in experimental meningitis. In this study, we investigated whether uric acid, a natural scavenger of peroxynitrite, was beneficial in a rat model of pneumococcal meningitis at plasma concentrations relevant to humans. Second, the effect of posttreatment with uric acid was studied. Third, we retrospectively analysed data from patients with bacterial meningitis for a possible correlation of serum uric acid and cerebrospinal fluid (CSF)/serum albumin index and CSF white blood cells count (WBC).

Methods: Adult male Wistar rats were anaesthesized, tracheotomized and artificially ventilated. A catheter was inserted into the cisterna magna and 108 colony-forming units of heat-killed pneumococci (HKP) or phosphate-buffered saline (PBS) were injected intracisternally (i.c.). Intracranial pressure (ICP) was monitored continuously. Five hours after i.c. injection, 1 ml of 1% Evans Blue was injected intraarterially. CSF was sampled at the end of the experiment (6 hours after i.c. injection) for determination of CSF-WBC, spectrophotometry of Evans Blue, quantification of lipid peroxidation (4-hydroxynonenal, 4-HNE and malondialdehyd, MDA) and nitrotyrosine by ELISA. In plasma and CSF, uric acid was determined by HPLC. Experimental groups were as follows: control (PBS), meningitis (MEN), meningitis + pretreatment with uric acid (MEN+UA, 300 mg/kg i.p.), meningitis + pretreatment with UA and oxonic acid, a urate oxidase inhibitor (MEN+OA, 250 mg/kg i.p.) and meningitis+ posttreatment with UA and OA 4 hours after intracisternal injection of HKP.

Results: Results are given in the following order: PBS, MEN, MEN+UA, MEN+OA. UA concentrations at 6 hours were 41.1±28.6, 44.9±10, 169.8±122.6, and 355±79.6 μM in plasma and 9.0±2.5, 30.7±6.3, 71.4±25.8, and 585.4±187.7 μM in CSF. ICP was reduced significantly by UA and UA+OA (0.2±0.7, 11.6±3.0, 4.3±1.2, and 1.4±2.4 mmHg. UA significantly reduced CSF-WBC, which was further attenuated significantly in the MEN+OA group (23±13, 12,767±2,520, 8,376±2,450, 4,190±1,749 cells/μl). CSF Evans Blue was not significantly reduced (0.5±0.8, 28.8±9.0, 19.2±7.5, and 18.6±3.9 μg/ml). 4-HNE/MDA were significantly reduced in the MEN+OA group (6.5±2.7, 86.4±30.9, 69.7±30.9, and 35.5±21.9 μM), as was nitrotyrosine (0.28±0.0, 0.86±0.74, 1.01±0.65, and 0.44±0.48 nMol nitrotyrosine/mg protein). Posttreatment 4 hours after intracisternal injection of HKP significantly reduced ICP, CSF-WBC and CSF Evans Blue (5.95±0.93 mmHg, 6,375±1,969 cells/μl and 11.77±9.06 μg/ml) compared to MEN. By review of patient records we identified 54 patients treated for bacterial meningitis who had serum uric acid, CSF-WBC, and CSF/serum albumin index determined within 24 hours after admission. We found a negative linear correlation of serum uric acid and CSF/serum albumin index (n=38, r=–0.39, p=0.02) while there was no significant correlation of serum uric acid and CSF-WBC (n=54, r=–0.24, p=0.08). Conclusion: uric acid dose-dependently reduced pathophysiological alterations in experimental bacterial meningitis (pre- and posttreatment) and was negatively correlated to CSF/serum albumin index in patients with bacterial meningitis. Therefore, uric acid might be a candidate for adjunctive therapy of bacterial meningitis.

P812

IMPROVEMENT OF CLINICAL AND METABOLIC PARAMETERS IN HIV ASSOCIATED COGNITIVE IMPAIRMENT: A LONGITUDINAL STUDY. B. Stankoff, A. Tourbah, S. Suarez, E. Turell, C. Payen, A. Coutellier, F. Bricaire, J. L. Stievenart, E. Cabanis, L. Lacomblez, C. Lubetzki, Fédération De Neurologie, Service De Neuroradiologie, Service De Neuropathologie, Fédération De Neurologie 2, Service De Médecine Interne, Service De Maladies Infectieuses (Paris, F)

Highly active anti-retroviral therapy (HAART) has reduced the incidence of HIV-associated cognitive impairment. However, influence of treatment on existing cognitive deficit is poorly known. Twenty two patients with AIDS were enrolled in a prospective study. Eleven were cognitively impaired (CI) and eleven were cognitively unimpaired (CU). They were evaluated at study entry (M0), and then every 3 months during 9 months (M3, M6, M9). The neuropsychological battery relies on the Mattis scale and frontal tests. Three metabolic ratios were analysed: N-acetyl-aspartate to creatine (NAA/Cr), choline to creatine (Cho/Cr) and myoinositol to creatine (Myo/Cr). At study entry, CI patients presented with a sub-cortico-frontal deficit. NAA/Cr ratios were decreased in the frontal white matter of CI patients, whereas they were within normal limits in the CU group. Cho/Cr ratios were elevated in both groups, without regional distribution. Myo/Cr ratios were elevated in the posterior white matter of CI patients. Metabolic ratios were within normal range in grey matter. Comparison between M0 and M9 allowed to demonstrate an improvement of both clinical and spectroscopic variables. HIV replication in plasma was also significantly reduced at M9. Our results suggest that effective antiretroviral therapy could induce an improvement of neuropsychological and spectroscopic parameters.

P813

BRAIN CELL PROTECTION IN VITRO AND IN EXPERIMENTAL PNEUMOCOCCAL MENINGITIS BY INACTIVATION OF THE PNEUMOCOCCAL TOXINS PNEUMOLYSIN AND HYDROGEN PEROXIDE. J. Braun, T. Mitchell, E. Tuomanen, J. Cleveland, Humboldt Universität Campus Charité Mitte Neurologische Klinik, University of Glasgow, St. Jude Hospital (Berlin, D; Glasgow, UK; Memphis, TN, USA)

Brain cell damage is a therapeutic problem in bacterial meningitis. Pneumococcus is the most common pathogen in bacterial meningitis and causes the highest rate of neurologic sequelae. The host inflammatory response contributes to brain cell damage in bacterial meningitis. However it is not known which bacterial factors induce brain cell death and if blocking these factors confers neuroprotection in experimental pneumococcal meningitis. We assessed which bacterial factors are significant for brain cell apoptosis. Because of their acute susceptibility to pneumococcal-induced apoptosis we used human microglial cells to screen pneumococcal mutants with defects in specific pathogenicity factors, e.g., adherence (cbpA), transformation (comA), surface IgA-protease (igA), autolysis (lytA), etc. Apoptosis was assessed by acridine orange/ethidium bromide nuclear staining, TUNEL, Annexin-V, and EM. The most effective cytoprotective effect was achieved by inactivation of 2 pneumococcal toxins, pneumolysin and hydrogen peroxide. Incubation of brain cells with the pneumolysin-negative mutant plnA in the presence of the antioxidant N-acetyl-L-cysteine (NAC; inactivating pneumococcal hydrogen peroxide) blocked pneumococcal-induced apoptosis in vitro. To confirm that pneumolysin and hydrogen peroxide were alone sufficient to trigger apoptosis we exposed microglia to purified recombinant pneumolysin or hydrogen peroxide. Physiologically relevant concentrations of both toxins induced apoptosis with kinetics and changes in nuclear morphology indistinguishable from apoptosis induced by live pneumococci. Induction of apoptosis by pneumolysin was associated with its pore forming activity, as pneumolysin point mutants defective in cytolytic activity failed to induce apoptosis, whereas those defective in complement activation induced apoptosis to the same extent as wild type pneumolysin. In experimental pneumococcal meningitis of the rabbit, wild type pneumococci induced neurotoxicity in the dentate gyrus as shown by neuronal loss, shrinkage and condensation. Neuronal damage was only slightly reduced (20%) in animals infected with pneumococcus in the presence of NAC or in animals infected with the pneumolysin-negative mutant plnA. However, inactivation of both pneumococcal toxins by administration of NAC to plnA-infected animals markedly reduced neurotoxicity (ca. 75%) to dentate gyrus neurons. Immunostaining with a pneumolysin-specific antibody detected pneumolysin

in dying neurons of the dentate gyrus of the hippocampus, demonstrating that these neurons are directly exposed to pneumolysin in vivo. Our results demonstrate that both pneumococcal toxins pneumolysin and hydrogen peroxide contribute to brain cell damage in vitro and in vivo. Blocking these toxins may provide a new neuroprotective strategy in pneumococcal meningitis.

P814
MENINGORADICULITIS WITH FACIAL PARALYSIS AND MULTIPLE CRANIAL NERVE PALSY WITH VARICELLA ZOSTER VIRUS. J. Albert, M. Coustans, P. Kassiotis, V. Golfier, V. Kerdoncuff, G. Edan, University Hospital Pontchaillou, University Hospital, Neurology (Rennes, Vannes, F)

OBSERVATION: A twenty-year-old female student was hospitalised for a peripheral facial nerve palsy, ear pain, dysphagia and modification of her voice. She was febrile and had meningeal irritation. These manifestations had appeared a week before. The examination revealed right peripheral facial nerve palsy associated with paralysis of the right ninth, tenth, eleventh cranial nerves. We did not find any auricular rash or oral lesions. The cerebrospinal fluid finding revealed pleocytosis with 1200 lymphocytes and a normal protein content. Bacterial analyses were negative. Cranial magnetic resonance imaging was normal. She was given acyclovir and ampicilline. A second lumbar puncture produced 63 lymphocytes, polymerase chain reaction (PCR) was positive for VZV. The analysis of the serum titer of VZV antibody confirmed a recent infection. Oral corticosteroid therapy was associated with acyclovir. The evolution one month after treatment was good with regression of cranial nerve palsy except facial paralysis which was persistent but to a lesser degree.

CONCLUSION: Facial nerve palsy frequently occurs in patients with cephalic zoster. Involvement of the glossopharyngeal (IX), vagus (X), and accessory (XI) nerve has rarely been reported. In our case these manifestations were associated with a meningoradiculitis. We should note that this patient had ear pain with no auricular rash despite repeated examinations. Only serum and cerebral fluid viral analysis (PCR) confirmed the diagnosis.

P815
LATENCY OF HERPES SIMPLEX VIRUS TYPE 1 IN HUMAN PERIPHERAL VESTIBULAR GANGLIA. V. Arbusow, M. Strupp, R. Wasicky, A. Horn, P. Schulz, T. Brandt, Klinikum Grosshadern, University of Munich, Inst. Anatomy (Munich, D)

Reactivation of herpes simplex virus type 1 (HSV–1) in the geniculate (GG) and vestibular ganglia (VG) is suspected to cause Bell's palsy and vestibular neuritis. It is commonly believed that HSV–1 ascends to the associated sensory ganglia via retrograde axonal transport after primary infection (stomatitis herpetica). It is not yet clear, however, to what extent human sensory ganglia may act as a filter, hindering HSV–1 from migrating to the central nervous system. Therefore we addressed the following questions: (1) Can HSV–1 become latent in human vestibular nuclei (VNc), and (2) is viral latency in brainstem nuclei regularly associated with infection of the ipsilateral peripheral ganglion?

To determine HSV–1 distribution in the GG, VG, and the VNc, ten human temporal bones and ten VNc of five individuals were examined for HSV–1-specific DNA by nested polymerase chain reaction. HSV–1 was found in 3/10 of each peripheral ganglia and in one or both of the VNc in two of the individuals. The different patterns of HSV–1 latency in vestibular structures were compatible with virus migration from vestibular ganglia to vestibular nuclei and from the ipsilateral to the contralateral vestibular nucleus via commissural fibers.

Our study showed that the human vestibular system – the peripheral ganglion in the temporal bone and the central VNc in the brainstem – is a target of HSV–1. Since HSV–1 has now been found in the VNc the question arises whether vestibular neuritis could also be caused by viral inflammation of central vestibular structures.

P816
COMBINED INHIBITION OF TUMOR NECROSIS FACTOR ALPHA CONVERTING ENZYME AND MATRIX METALLOPROTEINASES BY BB1101 ATTENUATES DISEASE, MORTALITY AND BRAIN DAMAGE IN EXPERIMENTAL BACTERIAL MENINGITIS. S. L. Leib, J Clements, R. L. P. Lindberg, L.-A. Pfister, M. G. Täuber, D. Leppert, University of Bern, British Biotech Pharmaceutical splc, Neurology (Bern, CH; Oxford, UK; Basel, CH). 1. Inst. for Med. Microbiol., Univ. of Berne, Berne, Switzerland; 2. Dept. Res., Univ. Hosp. Basel, Switzerland; 3. British Biotech Pharmaceuticals plc, Oxford OX4 5LY, United Kingdom.

Background: Matrix metalloproteinases (MMPs) are effectors of leukocyte extravasation and blood-brain barrier damage. MMPs and the proinflammatory cytokine tumor necrosis factor-alpha (TNF-a) are present at high concentrations in CSF of patients with bacterial meningitis (BM). TNF-a and MMPs are potentially interrelated in BM. TNF-a mediates MMP activation. MMPs, in turn, act as TNF-a-converting enzyme (TACE), which cleaves TNF-a to its active soluble form.

Methods: A rat model of BM was used to assess i) the time course of transcriptional regulation of MMP–2, –7, –8 and –9 by quantitative RT-PCR in brain homogenates and CSF cells, ii) to evaluate an effect of BB–1101 (15 mg/kg s.c. bid), a broad spectrum hydroxamic acid-based combined inhibitor of MMP and TACE activity. Eleven day old rats (n = 127) were injected intracisternally with 5.2 ± 0.5 log10 cfu Streptococcus pneumoniae and therapy with ceftriaxone (100 mg/kg s.c. bid) was started at 18 h after infection. RT-PCR was performed on samples from rats after 0, 4, 8, 12, 16, 18, and 20 h of infection.

Results: In CSF cells and brains from rats with BM (n = 21), MMP–8 and –9 were 100–1000 fold upregulated, reaching a plateau at 12 h after infection, while MMP–2 and –7 remained unchanged. Pretreatment with BB1101 significantly downregulated the CSF concentration of TNF-a compared to controls (255 ±269 pg/ml, n = 36 vs. 3346 ±1512, n = 34; $p < 0.0001$), and decreased the incidence of seizures ($p < 0.001$) and mortality ($p < 0.003$). BB1101 attenuated neuronal injury to the cortex ($p < 0.001$) and hippocampus ($p < 0.03$). BB1101 also reduced both forms of injury when started 18 h after infection (n = 36) together with antibiotics ($p < 0.04$; n = 18).

Conclusion: This study demonstrates a beneficial effect of combined MMP/TACE inhibition on disease severity, mortality and neuropathological outcome in BM.

P817
MULTIPLE CEREBRAL TUBERCULOMAS IN A PREGNANT WOMAN WITH MILIARY PULMONARY TUBERCULOSIS. V. Zouvelou, E. Koutra, D. Kravaritis, P. Angelidakis, N. Balakas, Evangelismos Hospital (Athens, GR)

Intracranial tuberculomas account for up to 20 % of cerebral mass lesions in developing countries, but are relatively uncommon in United States and Europe. Approximately 1 % of tuberculosis patients develop intracranial tuberculomas, usually as a solitary lesion, although 15–34 % are multiple. We report the case of a 46 year-old woman who in the seventh month of pregnancy (accomplished by assisted reproduction) presented with a two weeks history of headache, vomiting, mild confusion and blurred vision. Neurological examination revealed papilledema associated with intracranial hypertension, left abducens palsy and left Babinski sign. Seizures appeared a few days after admission. Brain non-enhanced computed tomography (CT) showed focal hypodense lesions and cerebral edema. Lumbar puncture showed opening pressure 30cmH_2O, an increase in cell count (175/mm^3, 80 % lymphocytes), protein 169 mg/dl and glucose 29 mg/dl (plasma glucose 137 mg/dl). Cerebrospinal fluid (CSF) polymerase chain reaction (PCR) and culture in Lowenstein medium was positive for Mycobacterium Tuberculosis. Brain magnetic resonance imaging (MRI) revealed numerous ring-enhancing and edema surrounded supratentorial and infratentorial lesions, ranging from 0.5 to 2 cm. CT-guided stereotactic biopsy provided evidence of the inflammatory nature of the lesions. Chest-X-ray and thorax CT disclosed miliariform dissemination to both lungs. Antituberculous therapy was initiated. Twenty days after admission the patient gave birth to female and male twins, by an uneventful caesarean section. Mycobacterium tuberculosis was detected from samples obtained from the male offspring. After two months of appropriate therapy she showed paradoxical clinical and radiologic deterioration. Dexamethasone was readministered as adjuvant therapy for eight weeks, with gradual tapering, which resulted in clinical and radiologic improvement. The patient was discharged with mild neurological deficits. Brain CT after two months showed stabilization of the lesions. Six months later she remains asymptomatic. Follow-up is continued. Early antituberculous therapy associated with corticosteroids can improve prognosis, but one must be aware that cerebral lesions may continue to progress despite appropriate treatment, a course which is not satisfactorily explained by any current pathogenic hypothesis. Extrapulmonary tuberculosis and especially central nervous system localization is rare in pregnancy, but it is associated with significant morbidity and increased risk for death for both the women and their infants.

Motor neuron disease and neuropathy

P818
ALS PATIENTS AND PERCUTANEOUS ENDOSCOPIC GASTROSTOMY (PEG): A CLINICAL AND PSYCHOLOGICAL STUDY OF PATIENTS REFUSING PEG. P. Cavalla, A. Cucatto, A. A. Terreni, P. Ghiglione, E. Finocchiaro, R. Galletti, G. Corso, P. Meineri, A. Chiò, Univ. of Torino, Az. Osp. San Giovanni, Osp. di Aosta, Osp. di Cuneo (Torino, Aosta, Cuneo, I)

PEG is a diffuse and effective procedure in the symptomatic treatment of dysphagia in amyotrophic lateral sclerosis (ALS). However, the attitudes and reasons of ALS patients which refuse PEG have not yet been fully characterized. A study on these problems was performed in a series of 68 consecutive patients, collected from 1993 to 1998, who were diagnosed a definite ALS in 3 Italian hospitals. PEG was proposed because of a moderate or severe dysphagia and/or significant weight loss. Of these 51 accepted and 17 (25%) refused the procedure. Age was significantly higher in patients who refused: mean age 67.2 ±10.9 years vs. 61.7 ± 11.5, $p< 0.01$. An excess of women was noted. There was no significant difference in clinical conditions as expressed by mean forced vital capacity percent (66.3% vs. 68.9%) and mean Norris score (54.6 vs. 56.1), nor in nutritional parameters (mean weight loss, mean serum albumin and chloride levels). The two groups did not differ in use of non invasive ventilation. Median survival, calculated from the day when PEG was proposed, was 72 days in patients who refused vs. 185 days in the other group ($p< 0.001$). The fact the patients had no caregiver or lived alone, that the patients or respective family did not understand the goal of the procedure, depressive state, a nihilistic approach to the disease, and old age were reasons for PEG refusal. Our data confirm that PEG is effective in prolonging patients' survival; therefore understanding the causes why such a procedure is sometimes refused is important in order to determine the best way to address the issue with patients.

P819
SUDOMOTOR DYSFUNCTION IN MOTOR NEURON DISEASE. M. Beck, R. Giess, T. Magnus, I. Puls, M. Koltzenburg, M. Naumann, K.V Toyka, Neurology (Würzburg, D)

Background: Autonomic dysregulation including abnormal heart rate variation and increased gastrointestinal transit time is present in motor neuron disease (MND) indicating a multisystem disorder. The clinical observations in our MND-Research Unit suggest abnormal sweating in patients suffering from amyotrophic lateral sclerosis (ALS) as a probable further indicator of autonomic involvement. Methods: We examined unprovoked skin water loss in 25 patients with ALS vs. an age and gender matched control group. Analysis was done in a comfortable seating position after 20 minutes of equilibration at ambient room temperature. Patients treated with sympathomimetic, cholinergic or anticholinergic drugs were excluded from the study. Data were collected over 30s at the thenar and hypothenar eminence and at the medial aspect of the sole using a clinically standardized device based on the vapor pressure gradient (Evaporimeter, Servo Med AB, Kinna Sweden). In 10 patients the measurements were repeated twice after 3 and 6 months. Results: In early disease ALS-patients showed a significant higher skin water loss compared to control subjects (51.09 g/m^2 skin surface per hour vs. 42.97 g/m^2 h). There were no principal differences between the three measured areas. By contrast, in advanced disease water loss was significantly lower when compared to controls (27.07 g/m^2 h vs. 44.62 g/m^2 h). The decline in skin water loss was already detected over a 6 month period (54.2 g/m^{2}h vs. 32.11 g/m^2 h). Conclusion: The data show a disorder of unprovoked skin water loss in MND-patients in advanced disease. Besides secondary mechanisms caused by progressive muscle atrophy and immobilization, skin water loss may indicate postganglionic sudomotor dysfunction supporting the hypothesis of an additional autonomic disorder in MND.

P820
THREE UNUSUAL CASES OF MOTOR NEURON DISEASE. J Visser, M de Visser, JMBV de Jong, D Troost, Academic Medical Centre (Amsterdam, NL)

OBJECTIVE: Report neuropathologic findings of 3 cases of motor neuron disease (MND).

BACKGROUND: MND includes: Amyotrophic Lateral Sclerosis (ALS), Progressive Muscular Atrophy (PMA) and Progressive Bulbar Palsy (PBP). Diagnosis is on clinical and electrophysiological grounds. Pathology includes: loss of motoneurons with focal astrogliosis, cytoplasmatic inclusions, axonopathy, axonal spheroids, degeneration of tracts, motor nerve fibres and endplates, and muscle atrophy.

DESIGN/METHODS: Description of clinical and neuropathological features of 3 cases of MND

RESULTS: Case 1, a 31-year-old female, developed weakness of one arm. The disease was progressive with subsequent involvement of trunk, limb and bulbar muscles. She had no pyramidal signs, and therefore PMA was diagnosed. She died 19 months after her debut. Case 2, a 65-year-old female, developed progressive pseudobulbar signs. Visual disturbances were never found. PBP was diagnosed and she died after 34 months. Case 3, a 63-year-old male, developed progressive arm weakness, and subsequently of shoulder and bulbar muscles. Cognition was normal. Since pyramidal signs were absent a diagnosis of PMA was made. He died 30 months after debut. Microscopic pathology: Case 1 had degeneration of anterior horn cells. Neither motor cortical nor corticospinal tract degeneration was present. The fasciculus cuneatus and gracilis were degenerated. Clarke's column was not involved. Ubiquitin +ve bodies were not observed. The substantia nigra and the pallidum showed degeneration. Case 2 showed nerve cell loss and reactive changes in the motor cortex. The primary visual cortex was also involved. Reactive gliosis and degeneration were observed in pallidum and putamen. The thalamus showed mild gliosis, macrophages and vacuoles. The inferior olives showed ubiquitin neuronal inclusions. There was severe loss of spinal anterior horn cells. Clarke's column was not involved. In case's 3 cortex the motor strip was not involved. Perivascular lymphocytic infiltration was observed. The substantia nigra was degenerated. Inclusion bodies were not present. Severe degeneration of spinal anterior horn cells was found.

DISCUSSION: In all 3 cases histopathology was compatible with MND. Conspicuously, the basal ganglia showed degeneration in all. Case 2 had involvement of the primary visual cortex. These findings raise the question whether our seemingly straightforward cases of MND rather have multiple system degeneration.

CONCLUSIONS: This study demonstrates that histopathology is an invaluable tool in the classification of MND.

P821
MEDICAL END OF LIFE DECISIONS IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS IN THE NETHERLANDS. J. H. Veldink, L. H. van den Berg, J. M. B. V. de Jong, M. de Visser, J. H. J. Wokke, UMCU, AMC (Utrecht, Amsterdam, NL)

Background and objectives: The objective of the study was to gain insight in the process leading to different medical end of life decisions in ALS. Medical end of life decisions include:
- invasive ventilation,
- alleviating dyspnea through opioids with the possible double effect of life shortening,
- withholding or withdrawing life prolonging treatments,
- administering medication with the explicit goal to hasten death (euthanasia)
- self administering of medication by the patient with the explicit goal to hasten death (physician assisted suicide).

Patients and Methods: We performed a retrospective study using a questionnaire. We addressed 104 medical doctors who were involved in the end stage of 106 ALS patients who passed away between 1994 and 1999 in the Netherlands. Our sample included patients with possible (16%), probable (53%) and definite (31%) ALS. We put forward questions concerning the above mentioned decisions as well as the following items: the shortening of life as a consequence of end of life decisions, the patient's autonomy, their marital status, the patient's caregivers, the patient's socio-economic status, the doctor's and patient's religion and the patient's degree of disability an the end of life. In addition, the following items were scored using medical records: duration of disease, sex, age at onset of disease, and limb or bulbar onset of disease.

Results and conclusions: The response rate was 89% and 75% of the questionnaires were completed. Reported causes of death included, respiratory insufficiency (57%), acute cardial (10%), pneumonia (8%) and euthanasia (19%). In 52% of deaths a medical end of life decision was made, including administration of opioids with the possible double effect of life shortening (25%), decision to forgo treatment (7,6%) and euthanasia (19%). Physician assisted suicide did not occur. Euthanasia followed after persistent requests of the patient in all cases. Cases of euthanasia were more likely to have a total paralysis of the arms. There was no association between euthanasia and the presence of enteral feeding, speech impairment and quality of palliative care, including management of pain and availability of professional care.

P822
IDENTIFICATION OF GAL(B1–3)GALNAC BEARING GLYCOPROTEINS IN CEREBROSPINAL FLUID OF ALS PATIENTS. I. Niebroj-Dobosez, A. Mickielewicz, H. Kwiecinski, Medical University (Poland, PL)

Glycoproteins in cerebrospinal fluid of 55 patients with amyotrophic lateral sclerosis (ALS) and 20 healthy controls were separated by PAGE electrophoresis and detected immunochemically with Peanut agglutinin (PNA). In 65 % of the ALS patients there was a significant increase of a 262 kDa glycoprotein. Usually it was connected with a decrease of a 114 kDa fraction. In the remainder patients (35 %) both fractions were either equal in concentration, or the 114 kDa glycoprotein predominated, as it was in controls. The total amount of the separated glycoproteins was increased in 27.3 % of the patients and in the majority of them it was followed by an increase of the percentage of the 262 kDa glycoprotein. There was no correlation between the content of the PNA-labelled glycoproteins and the age of the patients, duration and severity of the disease.

We suppose that in ALS the PNA-labelled glycoproteins can be released in excess into the CSF from the nervous tissues, probably as a result of neuronal degeneration. Subsequently, these glycoproteins might be the target antigens for autoantibodies production in ALS patients.

P823
GLUTATHIONE-S-TRANSFERASE ACTIVITY IN CEREBROSPINAL FLUID IN AMYOTROPHIC LATERAL SCLEROSIS PATIENTS. A. Baranczyk-Kuzma, Z. Jamrozik, M. Kuzma, A. Ciszewska-Pilczynska, Medical University of Warsaw (Warsaw, PL)

Numerous studies suggest a contribution of oxidative stress in the pathogenesis of ALS. Brain glutathione-S-transferase (GST, EC 2.5.1.18) is involved in detoxification of electrophilic compounds. Some isoenzymes of GST also exhibit glutathione peroxidase activity towards organic hydroperoxides, thus they can protect cells against highly reactive free radicals.

The aim of this study was to evaluate the activity of glutathione-S-transferase in CSF from ALS patients, patients with peripheral neuropathy (hereditary and acquired) as disease control and normal controls. The value of peroxidase activity in ALS group was 5.1± 2.0 μmol/min/l (n=19) and transferase activity was 4.5 ± 3.0 μmol/min/l (n=18). It did not significantly differ from control patients, which was 3.8 ± 2.7 μmol/min/l (n=18) and 4.2 ± 3.1 μmol/min/l (n=17) for peroxidase and transferase activities, respectively. In neuropathy group the peroxidase activity was 2.7 ± 2.7 μmol/min/l (n=12) and transferase activity was 10.8 ± 13.9 μmol/min/l (n=14). Activities of the enzyme were not correlated with age, clinical characteristics, disease duration and CSF parameters (protein concentration and cytosis) of ALS patients. Conclusion: peroxidase and transferase activity of glutathione-S-transferase in CSF of ALS patients was found to be unchanged.

P824
NEW INSIGHTS ON THE VIRAL THEORY OF AMYOTROPHIC LATERAL SCLEROSIS: POSSIBLE ROLE OF HUMAN HERPESVIRUS 8. P. Sola, R. Bedin, F. Casoni, P. Barozzi, E. Merelli, University of Modena (Modena, I)

In the last years, three new herpesviruses, HI-IV–6, –7, and–8, have been discovered. Like retroviruses, these herpesviruses share interesting biological characteristics for a possible role in the development of both neurological and lymphoproliferative diseases. On the basis of the controversial viral hypothesis for the pathogenesis of amyotrophic lateral sclerosis, in a previous study we searched by the polymerase chain reaction (PCR) for the presence of HIIV–6 specific sequences in patients with definite ALS and healthy controls, but we could not demonstrate a relation between this virus and the disease. More recently, specific viral sequences belonging to HI-IV–8 have been found in autoptic brain specimens from multiple sclerosis patients, normal adults died for traumatic cause, and new-born children, suggesting that, like HIIV–6, also this novel herpesvirus is provided of neurotropism. Besides being strongly associated to Kaposi's sarcoma, HI-IV–8 has been found related with several lymphoproliferative diseases. This is an unusual herpesvirus in that its genome contains the expected open reading frames (ORFs) encoding for enzymes and viral structural proteins found in other herpesviruses, but it also contains an unprecedented number of ORFs pirated during viral evolution from cellular genes. The translation products of ORFs reveal III-IV–8 to be a molecular pirate, able to produce homologues of several human gene products, resulting in alterations in cell cycle, in apoptosis and cell-mediated immune responses. These peculiarities may account for a possible role of HHV–8 in the development of both lymphoproliferative diseases and some neurological diseases, including ALS.

On these observations, together with the evidences of autoimmune alterations in ALS, and association between motor neuron diseases and lymphoma/gammopathies, we investigated by the PCR and nested-PCR, the presence of specific sequences of III-IV–8 in the peripheral blood mononuclear cell DNAs from 20 definite ALS patients and 20 controls, and in the cerebrospinal fluid from 37 ALS patients. The results obtained by the PCR showed sequences specific for HHV8 in only one out of 20 ALS and in none of the 20 controls. The HI-IV–8 positive ALS patient was affected by a rapidly progressive bulbar form of disease, and laboratory exan-fination did not show gammopathy and lymphoproliferative disorders. The results of CSF PCR are still in progress.

In spite of the failure of scientific efforts in defining a causal agent of ALS, new insights on the mechanisms by which viruses may interact with the host cell genome, and with the human immune system make the viral hypothesis of ALS still worthy of further studies. In particular, viruses or retroviruses able to cause persistent and latent infections, and able to interfere with cellular gene expression and regulation, appear to be suitable candidates for a possible role in ALS development.

P825
EXPRESSION OF METABOTROPIC GLUTAMATE RECEPTORS IN HUMAN NEURONAL AND GLIAL CELLS – EVIDENCE FOR A POTENTIAL ROLE IN AMYOTROPHIC LATERAL SCLEROSIS. J. M. H. Anneser, C. J. Eggett, P. G. Ince, G. D. Borasio, P. J. Shaw, Klinikum Grosshadern, University of Newcastle (München, D; Newcastle, UK)

Selective vulnerability is a characteristic, but poorly understood feature in amyotrophic lateral sclerosis (ALS): While somatic motoneurons degenerate, autonomic motoneurons are much more resistant. Recently, we described a differential expression of group I (mGluR1,5) metabotropic glutamate receptor (mGluR) mRNA in rat spinal cord somatic and autonomic motoneurons, suggesting a protective role for these receptors. Now, we confirmed these results in human spinal cords by immunohistochemistry: Somatic motoneurons showed no or only little mGluR5 and moderate mGluR1 signal, while these receptors were much more prominent in thoracic sympathetic and sacral parasympathetic motoneurons of the spinal cord. Furthermore, we examined the mGluR expression in CNS tissue from ALS patients and controls. We found a prominent mGluR5 signal and a weaker expression mGluR1 and mGluR2/3 in glial cells of ALS, but not control cases. This enhanced glial mGluR expression is detectable in the whole CNS motor pathway (ventral horn, pyramidal tract of the spinal cord and brainstem and white matter of the motor cortex). Since mGluR activation in glial cells has a variety of biological effects in vitro (proliferation, alteration of astroglial glutamate transport, increase of neurotrophic factors), it is tempting to speculate on a possible role for altered glial mGluR expression in the disease process. (JMHA was supported by an ENS fellowship)

P826
SCA–2 PHENOTYPE CULMINATING IN MOTOR NEURON DISEASE. J. Berciano, O. Combarros, J. M. Polo, J. Corral, V. Volpini, Univ. Hospital Marques de Valdecilla, IRO (Santander, Barcelona, E)

Background. Mild amyotrophy occurs in a minority of SCA2 patients usually as a late sign.

Objective: To report a SCA2 patient whose predominant symptomatology in the plateau phase was generalised muscle weakness. Clinical report: This 64-year-old woman developed gait imbalance, dysarthria and intermittent dysphagia in June 1994. Examination six months later revealed severe gait and limb ataxia, spasmodic dysphonia, hyperreflexia with extensor plantar responses, impassive face, rigidity of all four extremities without resting tremor, severe impairment of postural reflexes, disproportionate antecollis and slow saccades. No orthostatic hypotension was noted. MRI showed cerebellar and brainstem atrophy and putaminal hypointensity on T2 weighted imaging, Electromyography of tibialis anterior muscle and nerve conduction studies of peroneal and median nerves were normal. A diagnosis of multiple system atrophy was suspected as genealogical data were then negative [Berciano et al., Movement Disord 1996; 11 (SI): 26]. She was given levodopa with moderate response. As of April 1995 the patient's clinical course drastically deteriorated and was accompanied by progressive weakness, persistent dysphagia and urinary urgency. In September 1995 examination revealed anarthria, bulbar palsy, quadriparesis and widespread muscle wasting and fasciculations. Electromyography showed now fibrillation and fasciculation potentials in all five explored muscles of upper and lower limbs. Her clinical picture progressed to quadriplegia and she died two years later; autopsy was not done. In 1997 we were aware that two parental aunts and one first cousin were affected. Examination of this cousin, a woman aged 46, showed cerebellar gait and limb ataxia, dysarthria, facial myokymia, distal hypopallesthesia and occasional fasciculations in lower limbs. Molecular analysis demonstrated both in the proband and her cousin the SCA2 mutation (22/35 and 22/38 CAG repeats).

Conclusion: Motor neuron symptoms and signs may be an outstanding manifestation in SCA2 masking pre-existent cerebellar-plus semeiology.

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P827

IN VIVO GENE THERAPY APPROACH USING HERPES SIMPLEX VECTOR FOR TAY-SACHS DISEASE. S. Martino, P. Marconi, D. Dolcetta, C. Emiliani, B. Tancini, A. Consiglio, A. Trojani, G. M. Severini, An. Orlacchio, A. Orlacchio, C. Bordignon, telethon institute for gene therapy, scienze biochim. e biotecn. molecolari, Osp. pediatrico Burlo Garofolo (Milano, Perugia, Trieste, I)

Tay-Sachs disease (TSD) is a lysosomal storage disorder due to the deficiency of the alfa subunit of beta-Hexosaminidase A (Hex A) which leads to a massive accumulation of GM2 ganglioside, and related lipids, mainly in neuronal lysosomes, resulting in severe cellular dysfunction and rapid progressive neurodegeneration. Hex A is one of the most important beta-Hexosaminidase isoenzymes (Hex, EC 3.2.1.52). Hex is composed of two subunits encoded by two different genes that dimerize to form Hex A (alpha beta), Hex B (beta beta) and Hex S (alpha alpha). In normal tissues Hex A represents 60 % of the total Hex activity, Hex B represents 40 %, whereas Hex S is absent. Mutations in the gene encoding for the alpha subunit give the Tay-Sachs disease in which the Hex isoenzyme containing alpha subunit (Hex A) is missing. A gene therapy approach could provide a solution for this disease. In addition, information acquired in TSD can be useful to define new therapeutic approaches for other mucopolysaccharidosis diseases with neurologic involvement. Our present understanding of the physiopathology of the disease suggests that a direct enzyme delivery into the central nervous system (CNS) is necessary in order to correct the metabolic defect. To achieve in vivo direct delivery of the gene into the CNS we are using a non-replicating Herpes simplex vector. We constructed a replication-defective herpes simplex virus vector which efficiently transfers and expresses the alpha subunit cDNA of Hex A, therefore infection of deficient cells with this viral vector should result in correction of the enzymatic defect.

A significant increase in Hex A activity was observed in vitro in bone marrow stromal cells, obtained from a TSD mouse, infected with the vector containing the alpha subunit cDNA. The vector activity was also tested in vitro in organotypic brain slides from TSD mice that could mimic the natural expression, processing and secretion of HexA. Results demonstrate an increase in Hex A activity in infected TSD tissue slides and a correct Hex A production in deficient cells. Indeed, the ratio of alpha and beta subunits, necessary for a correct Hex A formation, was normal, as analyzed by DEAE-cellulose chromatography.

In vivo experiments with direct injection of the viral vector in the brain parenchyma of TSD mice are in progress.

P828

FLAIL ARM SYNDROME: A CLINICAL AND STATISTICAL DESCRIPTION OF AN ATYPICAL ALS FORM IN A SERIES OF SPANISH PATIENTS. J. Gamez, C. Cervera, Hospital Gral. Vall d'Hebron (Barcelona, E)

INTRODUCTION: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting the upper and lower motor neurones, characterised by increasing weakness and atrophy affecting the limb, respiratory and bulbar muscles. Death usually occurs approximately five years after onset. The extent of respiratory involvement is a crucial factor in determining prognosis. Recently, there has been increasing interest in distinguishing subgroups among ALS patients as a whole. As a result, two important reports have been published in the last two years (Hu et al. 1998, Sasaki et al. 1999), distinguishing a subgroup of patients affected by ALS that predominantly show severe muscle involvement in the upper limbs, which spares the face and the legs until late in the disease's natural course or until its terminal stage. These patients survived longer.

OBJECTIVE: Investigation of clinical characteristics, predominant muscle involvement, and the effects of the following factors: a) gender, b) age of onset, c) average survival time, and d) prevalence of this form. A series of 207 patients diagnosed with ALS seen in our Neuromuscular Unit between 1990 and 1998 was investigated.

DESIGN/METHODS: 19 amyotrophic lateral sclerosis patients, showing predominantly progressive atrophy and weakness in both arms, with little effect on the bulbar muscles or legs were retrospectively studied. These patients were part of the series mentioned above.

RESULTS: The prevalence of flail arm syndrome in our group of ALS patients was 9.1 %. Average onset age was 55.1 years, a similar figure to the global average of ALS patients. Male patients clearly predominated by a ratio of 8.5:1, compared with 1.6:1 in the global ALS group. Average survival time (57.9 months) was longer than the ALS average (38.4 months). The muscles predominantly affected were the supraspinatus, infraspinatus, pars spinata of the deltoids, teres minor and hand muscles.

CONCLUSIONS: This distinctive form and atypical form of ALS is known by different terms such as scapulohumeral form, Vulpian-Bernhardt's form, amytrophic brachial diplegia, dangling arm syndrome, suspended form, orangutan sign, bibrachial palsy, rizomelic amyotrophy, and neurogenic "man-in-the-barrel" syndrome. It represents a distinctive form of ALS with peculiar characteristics. These include an average survival period longer than other forms of the condition. This is probably due to a lesser extent of respiratory muscle involvement, which occurs at a later stage. The key factors behind the clear predominance in males and the typical distribution of muscles involved are so far unknown.

Multiple sclerosis

P829

PRIMARY SJÖGREN'S SYNDROME IN PATIENTS WITH MULTIPLE SCLEROSIS. C. Iñiguez, J. Mauri, P. Larrode, S. Santos, F. Morales, Neurology (Zaragoza, E)

Multiple Sclerosis (MS) is the best known neurologic disease that follows a relapsing-remitting course and attacks varied areas of the central nervous system. Certain rheumatic diseases can present with a similar clinical course, including Sjögren syndrome (SS). Objective: Brings to attention the difficulty in clinically distinguishing MS from CNS disease in SS. Patients: 150 patients with clinically definite MS were clinically evaluated prospectively for evidence of SS. A patient questionnaire for the assessment of sicca syndrome was administered. Xerophthalmia was evaluated by bilateral Schirmer test and Rose Bengal stain. Xerostomia was evaluated by stimulated sialometry. The patients sera with objective xerostomia, keratoconjunctivitis sicca or both together were tested for the presence of autoantibodies. Results: Two patients exhibited xerostomia and xerophthalmia and Ro(SS-A) antibodies positive in absence of other connective tissue diseases. Case 1: A 62-year-old woman developed several episodes of numbness in left extremity. Thereafter several exacerbations occurred in form of spastic paresis of the left extremity with ataxia. MRI demonstrated high-intensity areas in periventricular white matter, in corpus callosum and in brain stem on T2-weighted images compatible with MS. Protein content and numbers of cell in the CSF were normal, but total IgG was elevated. Initial laboratory studies failed to demonstrate antinuclear antibodies. One year later she developed spastic paresis of the right extremity with numbness in legs. Xerostomia and xerophthalmia were apparent. Schirmer test demonstrated 0 mm per 5 minutes and Rose Bengal stain was positive. Abnormal xialometry was also present. Sensory nerve action potentials were not elicited in the sural nerves but motor conduction velocity and the amplitude were normal. Laboratory examinations showed ANA in a titer of 1:80 and Anti-SSA and anti-SSB were elevated. Case 2: A 58-year-old woman had at the age of 53 mild spastic paresis of the right extremity. Thereafter several remissions and relapses have occurred. Several high-signal foci on MRI were demonstrated in the periventricular white matter. Initial CFS and serum findings including autoantibodies were unremarked. Present neurological findings were paraparesis and marked ataxia. Sicca syndrome, positive Rose bengal and Schirmer test were present. Laboratory investigations included anti-SSA, anti-SSARo52 and ANA were elevated, but anti-SSB was not. Discussion: Primary SS is a chronic autoimmune disease of unknown etiology and pathogenesis. The CNS symptoms are present in 20–25 % of the patients with SS. Some patients have a relapsing-remitting course mimicking MS, with similar changes in the CFS proteins. Focal brain lesions in SS can occur in the cerebral white matter. The features of our patients sufficiently mimicked those of MS that this disorder was the diagnosis in each patient, at the time of initial evaluation. MS and SS may coexist in the same patient, but SS is not more common among MS patients than expected in the general population. SS should be considered in the differential diagnosis of MS.

P830

HIGH-DOSE INTERFERON BETA–1B(IFNB) IN RELAPSING-REMITTING (RR) MULTIPLE SCLEROSIS (MS) PATIENTS. CASE REPORT AND DESIGN OF THE OPTIMS (OPTIMIZATION OF INTERFERON IN MS) STUDY. L. Durelli, OPTIMS Study Group, Torino, Italy (Italy, I)

Controlled trials with IFN beta–1a indicated a dose effect on clinical efficacy. In fact not all patients respond to treatment. We prospectively followed-up 52 patients with RR MS, treated with 8 MIU IFNB every other day for 18–26 months, followed, in 10 neutralising anti-interferon antibody negative nonresponder patients, by 12 MIU for over 18 months. Mean exacerbation rate, total

number of exacerbations, number of patients with exacerbations, number of patients with severe exacerbations, number of patients requiring corticosteroid treatment, EDSS score were outcome measures. After the first 18 months of IFNB treatment at the 8 MIU dose, outcome measures were significantly worse in nonresponders ($p < 0.001$), indicating persistent clinical signs of disease activity in those patients. IFNB dose was, then, increased in 10 nonresponders and, at final evaluation, 18 months after IFNB dose increase, all outcome measures, except EDSS score which did not change, significantly improved in nonresponder patients. In high-dose group patients frequency of side effects was trending higher than in standard-dose group. In order to test efficacy and tolerability of high IFNB doses a controlled multicenter trial was started. MRI is repeated monthly and the main outcome measure is the number of MRI active lesions. After 6 months of treatment at the standard IFNB dose (8 MIU), MRI nonresponders are randomized to 8 or 12 MIU and followed up for a further 6 months.

P831
BETAFERON® (INTERFERON ß–1B) TREATMENT AND FATIGUE IN MULTIPLE SCLEROSIS PATIENTS. A. Link, C. Kabus, J. Haas, Jewish Hospital of Berlin (Berlin, D)

Background: In MS patients fatigue is an early and often severe symptom of the disease. Any exacerbation of fatigue may interfere with the benefit of Betaferon® (interferon ß–1b) with regard to the course of the disease and patients compliance. Therefore we started an open label study in our MS unit with multiple sclerosis patients undergoing Betaferon® treatment over 6 month. Methods: 42 patients with relapsing-remitting or secondary progressive multiple sclerosis were included. The baseline and follow up data (4 weeks, 3 and 6 month after beginning of the therapy) were registered by MUSIS (a software for MS data management). Start dose of Betaferon® was 8 mio IU, except in 5 patients. The data of the patients were compared to 16 MS control patients not treated with interferon ß–1b. Fatigue was quantified by a 29 items questionnaire, the Fatigue Severity Scale (Krupp et al., 1989). The functional status of the patients was measured by EDSS. Results: There was no significant worsening of fatigue in the MS patients treated with Betaferon®. The Betaferon® patients were stable in the EDSS during the treatment period. Conclusion: Long term Betaferon® therapy does not deteriorate fatigue in relapsing-remitting and secondary progressive MS patients.

P832
BETAFERON® (INTERFERON ß –1B) TREATMENT AND SPASTICITY IN MULTIPLE SCLEROSIS PATIENTS. A. Link, C. Kabus, J. Haas, Jewish Hospital of Berlin (Berlin, D)

Background: In the Betaferon® study on secondary progressive MS muscle hypertonia was found in 37.8 % of the verum group versus 27.4 % in the placebo group (p=0.0032). A deterioration of spasticity may interfere with the benefit of Betaferon® (interferon ß–1b) with regard to the course of the disease and patients compliance. Therefore we started an open label study in our MS unit with multiple sclerosis patients undergoing Betaferon® treatment over 6 months. Methods: 62 patients with relapsing-remitting or secondary progressive multiple sclerosis were included. The baseline and follow up data (4 weeks, 3 and 6 months after beginning of the therapy) were registered by MUSIS (a software for MS data management). Start dose of Betaferon® was 8 mio IU, except in 5 patients. The data of the patients were compared to 16 MS control patients not treated with interferon ß–1b. Spasticity was measured computer controlled by spasmography and clinically scored by use of the Modified Ashworth Scale. Functional status was given by 25m- and 50m-walk tests and by EDSS. Results: In the spasmography the mean muscle tone and the mean maxima of muscle tone increased significantly ($p< 0.05$) only after the first three months and decreased within 6 months of Betaferon® therapy. The clinical scores and functional tests demonstrated no significant changes within the study period. Conclusion: The temporary increase of spasticity during initiation of therapy with Betaferon is a minor problem in the daily practice and seldom causes discontinuation of Betaferon® therapy.

P833
RELAPSING SCHILDER'S DISEASE: A PRELIMINARY REPORT. M.E Eraksoy, A. K.A Kiyat Atamer, C.B Bayindir, F.S Seleker, S.G Golbasi, G. A.D Akman Demir, O.Y Yagiz, Ist Tip Fac, Neurology, Ist Tip Fac, Neuropathology, Sisli Children's Hospital, Neurology, SSK Istanbul Hospital (Istanbul, TR)

The nosological status of Schilder's disease (SD) is uncertain, but some authors still regard this as a variant of multiple sclerosis (MS). There have been a few reports on recovering or relapsing SD in the literature.

The aim of this study was to determine the nosological status of SD and its clinical and laboratory characteristics.

Nine patients (6F, 4M) who fulfil the Poser's criteria (1986) were managed at three neurology units between 1987 and December 1999. Clinical and laboratory examinations (including MRI and CSF), metabolic and malignancy screening tests were performed in all patients and patients have taken regular follow-up. Stereotaxic brain biopsy was performed in 6 patients. Mean age at onset was 15 years (ranged from 8 to 24 yrs). Initial presentations were as follows: partial spinal cord syndrome (4), Right hemiparesis (1), right hemiparesis with aphasia (1), left hemiparesis and ataxia (1), left hemiparesis (1), and bilateral optic neuritis (1). All patients had at least one hemispheric attack with large, tumor-like demyelinating lesions on MRI, but none of them developed classical multiple sclerosis plaque at follow up. Brain biopsy specimens revealed subacute MS plaques or gliosis. Oligoclonal IgG bands in CSF were detected in only one patient. The symptoms and signs were reversed with steroids in all patients. Mean duration of first inter-attacks interval was 2.5 yrs and follow-up period was 4.5 yrs (ranged from 2 to 12 yrs).Three of nine patients developed more than two attacks and the remaining of the patients had two attacks at follow-up.

Although this study supports the view that SD is a variant of MS, further long-term, prospective studies are required to provide better insight into this subject.

P834
INTERFERON ß1A (AVONEX™) TREATMENT IN MULTIPLE SCLEROSIS: COMPARISON BETWEEN PATIENTS WITH MILD AND MODERATE DISABILITY. P. Vermersch, J. de Seze, T. Stojkovic, P. Hautecoeur, Hospital Roger Salengro (Lille, F)

BACKGROUNDS. Interferon ß1a (IFNß 1a, Avonex™) has been approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) based on the results of a pivotal trial showing that Avonex™ reduces the annual relapse rate and delays the disease progression. In this trial, criteria for inclusion were baseline expanded disability status scale (EDSS) scores between 1 and 3.5. However, Avonex™ is currently used in RRMS patients with EDSS between 0 and 5.5.

OBJECTIVE. To compare short term clinical follow-up in Avonex™ treated patients with EDSS =< 3.5 and with EDSS > 3.5.

METHODS. One hundred and eighty eight RRMS patients were included, 124 with baseline EDSS =< 3.5 and 64 with EDSS > 3.5. The primary outcome measure was to compare the number of patients in each group with sustained worsening in disability, defined as deterioration by at least 0.5 or 1.0 point on the EDSS persisting for at least 6 months during a 18 month follow-up period. We compared also the number of relapses and the number of treatment dropouts.

RESULTS. Mean EDSS scores were 2.2 in the group =< 3.5 and 4.6 in the group > 3.5. Baseline relapses rates were 1.29 and 1.24 respectively. Percentages of patients with sustained increased EDSS by at least 0.5 or by at least 1.0 were respectively 22.5 and 16.9 in the group =< 3.5 and respectively 29 and 23.4 in the group > 3.5 (not significant). At month 18, the relapse rate decreased by 31.7 % in the group =< 3.5 and by 37 % in the group > 3.5 (not significant). The number of dropouts were significantly higher in the group > 3.5 compared with the group =< 3.5 (p=0.005). For the same deterioration, Avonex™ was stopped more rapidly in the more disabled patients.

CONCLUSION. In an 18 month follow-up period, no difference was observed in terms of clinical responses to Avonex™ between patients with mild and moderate disability. In some cases, limitation of walking may explain the higher percentage of treatment dropouts in the more disabled patients.

P835
PSYCHOLOGICAL STRESS AS A RISK FACTOR FOR RELAPSE IN MULTIPLE SCLEROSIS: EFFECTS OF MARMARA EARTHQUAKE. G. A.D Akman Demir, A.P Polat, M.E Eraksoy, D.T Tunali, N.T Turan, B.B Bilgic, S.Y Yuksel, Ist Tip Fac, Neurology, Ist Fac Med, Psychiatry, Ist Fac Med, Neurology, Ist Fac Med, Biostatistics (Istanbul, TR)

The effects of psychological stress on the relapses in multiple sclerosis (MS) is a controversial subject. A lot of patients tend to relate their problems with social events; however, in most of the studies such a relationship could not be shown. In 17th August 1999 northwestern Turkey was struck by a violent earthquake. This was taken as a common stress factor, and its possible effects on the relapse rate in patients with MS was assessed in this study. Consecutive patients with clinically definite MS (CDMS) evaluated in the 3-mo period after the major earthquake on 17th August, were included. Besides routine neurological assessment at the MS unit, patients from the earthquake region were given Post Traumatic Stress Disorder Scale (PTSDS) and Impact of Event Scale (IES).

Eighty-two patients (54 F, 28M), were seen with CDMS, 55 had relapsing-

remitting MS and 27 had secondary progressive MS. Among these patients 49 (34F, 14 M), were from the earthquake region, and 23 had a relapse within the 3-mo period after the earthquake. These patients had a significantly higher relapse rate than those not from the region. Mean 3-mo attack rate was 0.46 which was significantly higher than the pre-earthquake rate of 0.26 (t:–2.072, $p < 0.05$).15 patients showed PTSD, however this had no relationship with the attacks. On the other hand, Functional impairment subset of the PTSD scale showed such a relationship. Both IES total score and PTSD symptom severity scores were higher in the cases who had a relapse, however, these were without statistical significance. Although this study suggests that there may be a relationship between psychological stress and relapses in MS our data are not sufficient to prove it. Larger prospective studies are needed to clarify this issue.

P836
FATIGUE, SLEEP-WAKE PATTERN, AND MELATONIN LEVELS ASSOCIATED WITH MULTIPLE SCLEROSIS: MODULATION BY INTERFERON-B TREATMENT. L. Melamed, R. Luboshitzky, A. Miller, Carmel Medical Center (Haifa, IL)

PURPOSE: To determine the correlation between fatigue, sleep architecture and melatonin level in multiple sclerosis (MS) patients compared to healthy controls and their modulation by Interferon (IFN)-ß treatment. METHODS: 13 females with MS (aged 40.3±4 years), were included in the study. The effect of fatigue on daily activities was evaluated by Fatigue Impact Scale (FIS). Melatonin was determined by measuring 6-sulphatoxy-melatonin (aMT6s, melatonin metabolite) in urine collection over two consecutive 24h periods using Elisa assay. Sleep-wake pattern was monitored by actigraphs (Mini-ACT, AMA–32, AMI Ardslay, NJ). These parameters were determined at baseline, 6 weeks and 4 months after initiation of IFN-ß (BETAFERON) treatment. The baseline values were compared with those of 13 normal control females (41.2±3y). RESULTS: Patients had a significantly higher baseline FIS than control (63.6±33 and 20.6±24.6 in the MS and control group respectively $p< 0.05$) which did not change following interferon treatment initiation (56.3±38.0 and 50.1±31.0 at 6 weeks and 4 months treatment, respectively). Sleep-wake pattern of patients was not significantly different ($p> 0.05$) from that of controls and was unchanged by interferon treatment. Patients had a significantly lower baseline aMT6s levels than control (11.5±2.6, 28.7±8.6 in the MS and control group respectively). aMT6s levels increased significantly following initiation of IFNb treatment (14.7±7.0 and 23.2±9.1 at 6 weeks and 4 months treatment, respectively, $p< 0.05$. A positive correlation between FIS and IaMT6s levels at baseline ($p< 0.05$), but not after IFNb treatment initiation were observed.

CONCLUSION: MS seems to be characterized by altered levels of the neuro-hormone melatonin which are correlated with fatigue degree. Additionally, IFNb treatment is associated with increased melatonin levels without affecting fatigue or sleep-wake pattern.

P837
UNDERLYING CAUSES OF DEATH IN PATIENTS WITH MULTIPLE SCLEROSIS [MS]. M. Kremenchutzky, J. Baskerville, G. Rice, G. Ebers, LHSC – UC – UWO, Clinical Neurology (London, Ontario, CDN; Oxford, UK)

A study of the underlying causes of death in MS can potentially clarify these questions. What clinical factors contribute to the risk of death in MS patients? What if any, is the increased risk of death in these cases? Do the causes of death in MS differ from the general population? Data on MS patients' survival differ broadly regarding study design, patient type, method of ascertainment, and sample size. In general, most studies focused on mortality rates and patterns rather than the actual cause of death. Some of those addressing causes of death tended to be based on selected cases while others are relatively old and sometimes carried out in the pre-antibiotic era. Objective: to study the underlying causes of death in a geographically based cohort of MS patients. Methods: we studied a series of 1099 patients prospectively registered at the MS clinic between 1972 and 1984. Mean follow-up was 27 years, including complete follow-up (from clinical onset to death) for 337 MS patients (30.66%). None of these subjects received immunomodulatory treatment and eleven with insufficient information were excluded of this analysis. Clinical data regarding disability and end-of-life events were documented when a death certificate was not available. Thus, we divided the underlying causes of death in two categories: 1) directly related to MS; 2) unrelated to MS. Results: For this survey 312 death certificates were available; MS was registered on 275 (88%). Deaths were attributed to advanced MS in 52 subjects and to direct MS complications in 146. In all, 119 deaths (37.5%) were due to other causes such as cancer (12.4%) and cardiovascular disorders (10.3% heart disease and 4.5% stroke) and not related to MS or its complications. Among those MS patients who died (regardless of the cause) there was a higher proportion of males ($p = 0.001$) and a later age of onset (mean 34.39 vs 28.83, $p = 0.0001$). The clinical courses differed, those who died having approximately twice the proportion of progressive disease compared to relapsing remitting MS patients ($p = 0.001$). Patients who died were more likely to have pyramidal ($p = 0.001$) or cerebellar involvement ($p = 0.048$) at onset. Those who died from direct complications of MS had an earlier age of onset of MS ($p = 0.0008$) and died at an earlier age ($p = 0.00005$) than those who died from other causes. We used survival analysis techniques to compare the survival experience of our MS patients with a cohort of Canadians matched by year of birth, sex and conditional on having survived until the age of disease onset. Using this analysis, the overall median survival of our MS patients was estimated to be 78.1 ± 0.31 years, compared to 81.5 ± 0.19 years for the matched general population cohort. Conclusions: Survival in MS is not likely to be substantially shortened except for progressive patients. Early deaths from MS seem set by the dearth of early deaths from trauma, motor vehicle accidents, etc, which are less common in MS. Death is an unambiguous outcome although refinements need to be made with respect to categorization of patients to death from MS or death from other causes.

P838
THE EFFECT OF OSMOTIC BLOOD BRAIN BARRIER DISRUPTION (BBBD) ON EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS (EAE) IN RATS. H. Ovadia, A. Itzik, T. Siegal, Hadassah University Hospital (Jerusalem, IL)

Objective: To test whether disruption of the blood brain barrier may change the course of an ongoing neuroautoimmune disease.

Background: The hyperosmotic induced disruption of the blood brain barrier is used to deliver anti tumor drugs into the nervous system. The disruption allows a narrow time window for the penetration of polar drugs that otherwise cannot easily pass the barrier. This disruption may also permit the passage of circulating factors with a potential to cause an autoimmune insult.

Design: EAE was induced in Lewis rats with PLP+CFA. BBB disruption in one hemisphere was achieved by intracarotid injection of manitol (25%), administered at days 8 or 10 (before the appearance of clinical signs) and 11 or 14 (after the appearance of clinical signs) post immunization. Rats were sacrificed 20 days post immunization. Control animals received intracarotid saline or intravenous manitol.

Results: Rats that were treated with intracarotid manitol (n=5) at days 8–10, later on did not develop either clinical or histopathological signs of EAE. Control rats that received intracarotid saline (n=3) or intravenous manitol (n=3) at the same days developed full blown disease (3 from a scale of 4). Rats that were treated with intracarotid manitol, while exhibiting mild or severe signs of EAE continued the regular course of the acute attack but did not get worse. The mean score of disease (2.56) was not significantly different than the control groups. The number of infiltration foci in the disrupted hemisphere was lower that the contralateral hemisphere.

Conclusion: We conclude that BBB disruption does not worsen an ongoing neuro-autoimmune disease in rats. Albeit the existence of activated cells or inflammatory cytokines in the circulation, the disruption did not enhance the clinical signs or the number of infiltrates in the brain parenchyma. This method may be used in MS patients that may need BBBD for the treatment of CNS tumors.

P839
CARDIOVASCULAR AUTONOMIC DYSFUNCTION IN MULTIPLE SCLEROSIS PATIENTS. Pijanmanova-Karovska L., Barbov I., Bekarovska S., Arsovska A – Health Care Centre Skopje; Neurological Unit, Medical Centre Strumica; Clinic of Neurology Skopje

Autonomic dysfunction is frequently observed in patients with multiple sclerosis (MS), but clinical studies disagree on the frequency and type of abnormalities in autonomic function tests. Orthostatic dizziness (OD) has been reported in up to 49% of patients, but the pathophysiological mechanisms are poorly understood.

This work investigated cardiovascular reflex tests and their association with OD in patients with MS in order to examine the hypothesis that the sympathetic nervous system is specifically involved in these patients.

Twenty four (24) patients with clinically active relapsing-remitting (14) and secondary progressive MS (10) were studied by parasympathetic (heart rate responses to the Valsalva maneuver, deep breathing and active change in posture) and sympathetic function tests (blood pressure responses to active change in posture and sustained handgrip), and by spectral analysis of heart rate variability during rest and during standing.

Abnormal responses on at least one cardiovascular reflex test were observed in 40% of MS patients, with a statistically significant involvement of the sympathetic vasomotor system. Orthostatic intolerance was reported in 50% of patients. The orthostatic intolerance results from impaired sympathetic vasoconstriction.

These results provide further evidence that the sympathetic nervous system is involved in patients with MS.

P840
COPOLYMER–1 EFFECTS ON CYTOKINE PRODUCTION BY LEWIS RAT PERITONEAL MACROPHAGES. I. Siglienti, K. V. Toyka, E. Scarpini, S. Jung, Irccs Ospedale Maggiore, Julius-Maximilians-University (Milano, I; Würzburg, D)

Treatment with copolymer–1 (Cop–1, glatiramer acetate, CopaxoneO) inhibits experimental autoimmune encephalomyelitis (EAE) induced by various encephalitogens in different animal species, and has been shown to reduce the relapse rate in patients with relapsing-remitting multiple sclerosis (RR-MS). The suggested mechanism of action is related to Cop–1 acting as a MHC ligand that inhibits myelin antigen-reactive T cells and induces T-helper type 2 regulatory cells. Moreover, macrophages also are part of the effector pathway in the immune mediated demyelination. The aim of this study was to investigate the immunomodulatory effects of Cop–1 on Lewis rat peritoneal macrophages. We pooled resident macrophages from the peritoneal cavity of naive Lewis rats by rinsing with ice-cold PBS; cells were resuspended in RPMI at a concentration of 1,5 x 10*6/ml and cultured in the presence and absence of Cop–1 and other basic polypeptides such as calf-thymus histone (CTH) at various concentrations; cultures were activated by addition of LPS. Culture supernatants were collected 48h later and analyzed for TNF-a and IL–10 by ELISA. We observed that Cytokine production of macrophages was modified by the presence of Cop–1, as well as CTH. Constitutive and LPS-induced production of TNF-a by macrophages was consistently inhibited by Cop–1 (–40 % at a concentration range between 5 and 20 µg/ml) and by CTH (–35 % concentration range 10–20 µg/ml), while the expression of IL–10 was strongly upregulated by both peptides (75 %).

These findings demonstrated that Cop–1 exhibits a relevant immunomodulatory effect also on macrophages. The cathodic nature of this synthetic polymer is a possible mechanism by which Cop–1 works, as suggested by the similar activity shown by CTH.

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P841
DISTRIBUTION OF CALCIUM CHANNEL SUBUNITS IN DYSTROPHIC AXONS OF MULTIPLE SCLEROSIS AND EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS. B. Kornek, A. Djamshidian, M. K. Storch, R. Weissert, E. Wallstroem, A. Stefferl, F. Zimprich, C. Linington, T. Olsson, H. Lassmann, Brain Research Institute, Dep. of Neurology, Univ. of Vienna, Karolinska Hospital, Max Planck Institute f. Neurobiology (Vienna, A; Stockholm, S; Martinsried, D)

Background: Multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE) are immune mediated diseases of the central nervous system with extensive destruction of myelin sheaths and a variable degree of axonal loss.

Axonal damage is a reliable correlate of permanent clinical disability. The mechanisms of axonal degeneration in inflammatory demyelinating diseases, however, remain unclear.

Materials and methods: In the present study we investigated axonal pathologic changes in MS and EAE by light and electron microscopy. Immunohistochemistry was performed on brain and spinal cord tissue of 22 MS patients and 18 Lew.1N rats with actively induced EAE. The following primary antibodies were used: anti-Amyloid Precursor Protein, anti-alpha1A, anti-alpha1B, anti-alpha1C and anti-beta1.

Results: We found pronounced disturbance of axonal transport in actively demyelinating lesions of MS and EAE as well as minor, but significant acute axonal injury in inactive demyelinated plaques of MS.

Since axonal dysfunction may be due to calcium influx we studied the distribution of subunits of voltage-gated calcium channels by using a large panel of specific antibodies. We found that predominantly alpha1B, the pore-forming subunit of N-type calcium channels is accumulated in axons of actively demyelinating lesions. Immune electron microscopy revealed that alpha1B is not only accumulated, but also integrated in the axonal plasma membrane of acutely injured axons. In addition we found co expression of beta1, a regulatory subunit of voltage-dependent calcium channels in the respective lesions.

Conclusion: Our data suggest that calcium influx through ion-specific channels is a possible candidate mechanism for axonal disturbance in human and experimental inflammatory demyelinating disorders.

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P842
COPOLYMER–1 THERAPY IN RELAPSING REMITTING MULTIPLE SCLEROSIS: FURTHER EVIDENCE OF INFLUENCE OF DRB1*1501 ALLELE ON CLINICAL OUTCOME. C. Fusco, V. Andreone, G. Pirozzi, F. Guerini, G. Coppola, E. Pace, C. Florio, V. Brescia Morra, R. Lanzillo, P. Ferrante, P. Vivo, M. Mini, M. L. Lombardi, G. Orefice, A. O. R. N. A.Cardarelli, Instituto Nationale Tumori, Fondazione Don Gnocchi, Federico II University, University of Milano, Instituto Nazionale Tumori (Naples, Milano, I)

Background. In vitro and in vivo studies suggest that the mechanism of Copolymer–1 (Cop–1) – a random synthetic aminoacid copolymer effective in therapy of multiple sclerosis relapsing-remitting form (RR-MS) – involves its binding to MHC class II molecules as an initial step. Our previous data indicated a relationship between HLA allele DRB1*1501 and positive clinical response to Copolymer–1 in 29 RR-MS patients.

The aim of the present study was to confirm this correlation on a larger series and to demonstrate the specificity of this effect studying as control group RR-MS patients treated with Interferon-beta1a (IFN).

Patients and methods. We selected 45 RR-MS patients treated with Copolymer–1 for at least two years (age: 35 ± 9, disease duration: 12.6 ± 8 years, mean baseline EDSS: 3 ± 1) and 39 patients treated with Interferon-beta1a (age: 33 ± 7, disease duration: 9.6 ± 5, mean baseline EDSS: 2.5 ± 0.8). All patients were typed by molecular methods for HLA class II genes. As clinical outcome measures were considered 1) a combination of EDSS variation and new relapses for each patient, and 2) relapse-rate differences in the two groups.

Results. In Cop–1 patients, DRB1*1501 allele was significantly related to a positive clinical outcome, either considering EDSS variation and new relapses ($p < 0.05$), or considering relapse rate difference ($p=0.01$). In IFN patients we did not find a statistically significant relationship between DRB1*1501 and clinical outcome.

Conclusion. These data provide further evidence that HLA allele DRB1*1501 plays a role in clinical response to Cop–1 therapy in RR-MS patients.

P843
MAGNETIZATION TRANSFER RATIO AND MEAN DIFFUSIVITY OF NORMAL-APPEARING WHITE AND GRAY MATTER FROM PATIENTS WITH MULTIPLE SCLEROSIS. Massimo Filippi, Mara Cercignani, Marco Bozzali, Giuseppe Iannucci, Vittorio Martinelli*, Filippo Martinelli*, Giancarlo Comi*. Neuroimaging Research and *Clinical Trials Units, Department of Neuroscience, Scientific Institute Ospedale San Raffaele, University of Milan, Milan, Italy.

We assessed the feasibility of a new technique based on diffusion anisotropy to segment white and gray matter of the brain. Using this technique, we measured the mean diffusivity ($\bar{D}$) and magnetization transfer ratio (MTR) of normal-appearing white (NAWM) and gray (NAGM) matter from patients with different multiple sclerosis (MS) clinical phenotypes.

Dual-echo turbo spin-echo, MT and diffusion-weighted scans of the brain were obtained from 21 patients with relapsing-remitting (RR) MS, 9 patients with primary-progressive (PP) MS and 18 sex- and age- matched healthy controls. After image co-registration and removal of T2-visible lesions, white and gray matter were segmented from 10 supratentorial slices using diffusion anisotropy thresholds. Histograms of the average MTR and $\bar{D}$ were created for normal white and gray matter of controls and NAWM and NAGM of MS patients.

All the MTR histogram-derived metrics of the NAWM from MS patients were significantly lower than those of white matter from controls. The average $\bar{D}$ and the peak height of the $\bar{D}$ histogram of NAWM from MS patients were also significantly different than those of normal white matter. The average MTR, the peak location of the MTR histogram and peak height of the $\bar{D}$ histogram of the NAGM of MS patients were significantly lower than the corresponding quantities of gray matter from controls. MTR and $\bar{D}$ histogram changes of the NAGM were mainly found in PPMS patients.

We developed a technique to segment white and gray matter with the potential for improving our understanding of the pathophysiology of many neurological conditions. Its application to the study of MS confirms the presence of a diffuse tissue damage in the NAWM of these patients and suggests that subtle changes also occur in the NAGM.

P844
MECHANISM OF ACTION OF HIGH-DOSE METHYLPREDNISOLONE: INDUCTION OF T CELL APOPTOSIS IN MS AND DOSE-DEPENDENT TERMINATION OF INFLAMMATION IN EXPERIMENTAL ENCEPHALOMYELITIS. R. Gold, J. Schmidt, S. Jung, V. I. Leussink, U. K. Zettl, H. P. Hartung, K. V. Toyka, University of Wuerzburg, University of Rostock, University of Graz (Wuerzburg, Rostock, D; Graz, A)

Background: Glucocorticosteroid hormones are pleiotropic agents that act at several levels. Induction of apoptosis of mature T cells may contribute to their efficacy. Objective: To investigate whether methylprednisolone (MP; Urbason ®) induces apoptosis of peripheral blood leukocytes (PBL) from MS patients and in experimental autoimmune encephalomyelitis (EAE) in situ. In EAE both severity of disease and dosage of MP were modulated. Methods: PBL were separated from MS patients before and immediately after MP pulse therapy. Cells were subjected to analyses of apoptosis by flow cytometry, proliferation assays and cytokine secretion studies. In EAE, two pulses of MP were given at the peak of disease and T cell apoptosis assessed on spinal cord cross sections 18 hours after the first injection. MP levels were measured in serum, cerebrospinal fluid (CSF), and spinal cord tissue by HPLC. Results: After in-vivo treatment, apoptosis of unstimulated PBL was markedly and significantly augmented in all three subgroups of MS. Apoptosis affected predominantly CD4-T cells and coincided with decreased concentrations of IL2, IFN-gamma, and TNF-alpha in culture supernatants. In EAE, 10 mg/kg MP augmented T cell apoptosis in severe forms, whereas 50 mg/kg were effective also in mild EAE. With 50 mg/kg MP we obtained tissue- and CSF levels up to 10^{-5} M. Conclusion: These results indicate that steroid pulse therapy is a strong inducer of leukocyte apoptosis, both in peripheral blood and in the inflamed central nervous system. Furthermore, it underscores dose-dependent effects of MP which may not be mediated by the intracellular steroid receptor.

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P845
TREATMENT WITH SILDENAFIL FOR ERECTILE DYSFUNCTION IN MULTIPLE SCLEROSIS (MS) PATIENTS. A PILOT STUDY. Martinez-Yelamos A, Casado V, Santiago O, Martin G, Hernandez J, Arbizu Tx. MS'Unit. Neurology Department. Ciutat Sanithria i Universitaria de Bellvitge. Barcelona. Spain

A high proportion of MS patients had sexual dysfunction. However, the data from different studies differ between 25–75 %. The erectile dysfunction (ED) is the more frequent sexual disturbance found in male MS patients. Recent studies had shown the efficacy of sildenafil in the treatment of erectile dysfunction in males, included these with neurological disorders as spinal cord injury.

Objective: Open pilot study to assess the efficacy and security of treatment with sildenafil in male MS patients with erectile dysfunction.

Patients-methods: We included 12 patients with clinically defined MS by Poser criteria and the International Index of erectile funtion–5 (IIEF–5) lower than 21 points as diagnosis of ED that signed an inform consent. Patients with disorders in ECG, biochemistry, haematology or hormonal analysis were not included. Selected patients were asked to complete the International Index of Erectile Function (IIEF), Beckdepression test, Hamilton anxiety test, SF–36 and Life Satisfaction Check-List (LS-ED) at visits basal, one month and three months. At these visits physical and neurological examinations were performed. All patients began with 50 mg/day po. Statistic: Non parametrical test and Spearman's coffelation index were used with a significance level $p< 0.05$.

Results: Mean age was 44.4±10 years. MS mean duration was 8.3 + 3 years. ED mean time was 2.75±2 years. Mean EDSS at the enrolment was 3.45±2. Fifty per cent of patients had more than 9 points in depression-beck test while only 30 % of patients had anxiety studied by Hamilton test. The REF at enrolment was 26+/A3 significantly lower than IIEF at month 1 (54.6 ±13; $p< 0.05$) and month 3 (60.5±9; $p< 0.05$). Significantly better punctuations were seen in all functions of the IIEF (erectile, orgasmic, libido, sexual act satisfaction and global satisfaction). The LS-ED test improved significantly at month 1 and 3 (basal LS-ED=33.9±6, one month LS-ED 36.7±7, $p< 0.05$; three months LS-ED=36.7±4, $P< 0.05$). There were no differences at month or three months in Beck, Hamilton, SF–36 test or EDSS. The basal EDSS or depression-anxiety test didn't influence the expected response to sildenafil. Only the basal EDSS (Spearman's index =–0.63, $p< 0.05$) and time of evolution of erectile dysfunction (Spearman's index =464, $p< 0.05$) were related with the enrolment IIEF. No patient had been withdrawn by adverse events. The dose was diminished in three patients by colour perception disorder, headache and nasal congestion,

Conclusion: This pilot study shows that sildenafil may be useful for the treatment of ED in male MS patients. The improvement in IIEF and LS-ED may be related with an improvement in the quality of life even though we haven't found differences in SF–36. Sildenafil seems to be safe in patients without any cardiac or systemic affection. Double-blind studies should be necessaries to assess the usefulness of sildenafil in erectile dysfunction of MS patients.

P846
DECREASE OF B LYMPHOCYTES IN CHRONIC PROGRESSIVE MULTIPLE SCLEROSIS PATIENTS DURING THE TREATMENT WITH MITOXANTRONE. M. Zaffaroni, G. Crovetti, A. Zibetti, A. Ghezzi, N. Canal, Centro Studi SM, Centro Trasfusionale (Gallarate, I)

Objective: To evaluate the immunosuppressive effects of Mitoxantrone (MX) in multiple sclerosis (MS) patients with chronic progressive (CP) course.

Background: MX is a cytotoxic agent of the anthracycline family which inhibits topoisomerase II and intercalates with phase "S" DNA. MX has been demonstrated to inhibit active induction, passive transfer, clinical signs and histological lesions of experimental allergic encephalomyelitis. Being well tolerated, it has been recently used for the treatment of CP MS in placebo-controlled phase III trials. The most frequent side effect is mild nausea, vomiting and alopecia being rare. The most relevant dose-dependent toxicity is a reversible myelosuppression with leucopenia and neutropenia. MX becomes cardiotoxic at cumulative doses higher than 140 mg/m^2, but mutagenicity and teratogenicity have been excluded.

Subjects & Methods: 10 mg/ m^2 MX was given intravenously three monthly to CP MS. Leukocytes (WBC), lymphocytes (Ly) and lymphocyte subsets (CD3+, CD4+, CD8+, CD19+, CD16+) were monitored before each drug infusion by laser flow cytometry. WBC nadir was also checked 2 weeks after each infusion.

Results: Available data refer to 6 CP MS patients with a mean age of 40 yr., disease duration of 13 yr. and disability of 6.2 (EDSS score). The mean WBC nadir was 4005 cells/mm^3, never lower than 2500 cells/mm^3. After a treatment of three months, immune cell mean counts were reduced by 4.9 % (CD16+) to 55.4 % (CD19+). At this stage, only B-lymphocytes (CD19+) were decreased significantly from baseline values. After 6 months of treatment, all cells but CD16+ lymphocytes were further and significantly reduced by 5.8 % (WBC), 33.3 % (Ly), 23.6 % (CD3+), 25.3 % (CD4+), 39.5 % (CD8+), 70.3 % (CD19+) respectively.

Conclusions: MX can be safely given to CP MS patients at doses of 10 mg/ m^2 i. v. three monthly, in order to protract an immunosuppressive treatment up to 2 years. All cell type steadily decreased as treatment advanced. A statistically significant reduction of CD19+ cells was obtained early at 3 months and was sustained at 6 months ($p< 0.05$ and $p< 0.02$ respectively, paired t-test). The effect of MX on both T and B lymphocytes makes the profile of this drug unique among several immunosuppressants commonly used in the treatment of MS.

P846-a
CLINICALLY STABLE MS PATIENTS DURING THERAPY WITH GLATIRAMER ACETATE SHOW UPREGULATION OF INTERLEUKIN 4 PRODUCING LYMPHOCYTES. Hoffmann V, Rieks M, Spitzer I, Juschka M, Hellwig K, Schimrigk S, Przuntek H, Pôhlau D. Neurologische Universitätsklinik der Ruhr-Universität Bochum am St. Josef Hospital, Sauerlandklinik Hacher, Sundern-Hachen, Germany

Glatiramer acetate (GA, COPAXONE) is effective clinically and with respect to magnetic resonance imaging (MRI) measures in relapsing-remitting multiple sclerosis (RRMS). Although GA has been shown to interfere with antigen presentation and T-cell activation the precise mechanism of action is not fully elucidated. We examined whether treatment with GA resulted in immune deviation favouring a T-helper-type 2 (Th2) response on T-cell activation. Moreover a possible relationship to clinical efficacy was investigated. The study comprised 19 patients with relapsing-remitting multiple sclerosis (RRMS) participating in an open safety and tolerability trial for one year. Patients with one or more relapses or an increase in the Expanded Disability Status Scale (EDSS) score ~~ 1.0 within the study period were regarded as "clinically progressive". Patients without relapse or significant progression on the EDSS (> /= 0.5) were regarded as "clinically stable". Laboratory studies were performed prior to initiation of treatment (baseline) and every six weeks for one year. We examined intracellular cytokines by flow cytometry choosing interferon-gamma (INFg) as marker of a Th1-type cellular response and interleukin–4 (IL–4) as indicator of Th2-type cells. Statistical analysis was performed using Wilcoxon-rank-test. Additionally antibodies against CD4 were used for identification of Th-lymphocytes. Clinically stable patients demonstrated a significant upregulation in the frequency of IL–4+ lymphocytes at nearly any time point (week 6, 12, 18, 24, 36, 42; $p< 0.05$) after initiation of treatment. This effect could also be shown for IL4+CD4+T-cells at weeks 24 and 42. Again this effect was more pronounced in the clinically stable patients. No upregulation of IL–4+ lymphocytes was detected in patients with clinical signs of ongoing disease activity. We did not find an effect of GA treatment on the frequency of INF-g+ lymphocytes as well as CD4+INFg+T-cells in any patient group. Our results

demonstrate a possible relationship between upregulation of IL–4+ lymphocytes during GA therapy and beneficial clinical response indicating that a systemic immune deviation towards a rather Th2-type response may be useful in MS.

P846-b
ACTIVATION-INDUCED CELL DEATH OF PERIPHERAL T CELLS IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS DURING THERAPY WITH GLATIRAMER ACETATE. Rieks M, Hoffmann V, Juschka M, Spitzer I, Schimrigk S, Hellwig K, Przuntek H, Pöhlau D, Department of Neurology, Ruhr-University Bochum, St. Josef-Hospital, Germany; Sauerlandklinik Hachen, Sundern-Hachen, Germany

MS is regarded as primarily T-cell mediated disorder. The mechanism of activation-induced cell death of T cells might be of importance in the regulation of the inflammatory reaction in MS. Glatiramer acetate (GA, Copaxone@, Copolymer–1) has proven to be effective in the treatment of relapsing remitting multiple sclerosis (RRMS). To evaluate the mechanism of action, we analysed the frequency of activated and of apoptotic T cells during treatment with GA. 19 patients (12 female/ 7 male) with RRMS were enrolled in the study for treatment with 20 mg GA subcutaneously per day for one year. We analysed the patients blood right before treatment with GA (baseline), and at intervals of 6 weeks for overall eight times during treatment with GA.

Using three-color flowcytometry (FACScan@, Becton Dickinson) we analysed the percentage of CD69-positive (CD3-positive) T cells by a standard protocol for staining of surface molecules. Apoptosis of T helper cells was analysed via DNA fragmentation using TUNEL (= TdT-mediated dUTP nick end labelling) technique and by simultaneous staining of CD4 molecules. Cells were analysed by FACScan. For statistical analyses we used the nonparametric Wilcoxon rank test comparing baseline values and the values of each other time point. The treatment group revealed a significant increase in the percentage of activated T cells after 6, 12, 18, 24, 36 and 48 weeks of treatment compared to baseline. This increase in activated T cells paralleled a significant increase of apoptotic T helper cells after 30, 36, 42 and 48 weeks of treatment.

The increase in the percentage of apoptotic T helper cells and simultaneously activated T cells might reflect an increase of activation-induced T cells death caused by therapy with Glatiramer acetate.

Neuro-imaging

P847
MRI STUDY OF PATIENTS WITH CEREBRAL LESIONS AND NEUROLOGICAL SYMPTOMS IN COURSE OF SYSTEMIC LUPUS ERYTHEMATOSUS. R. Poniatowska, R. Krawczyk, W. Palasik, R. Boguslawska, Institute of Psychiatry and Neurology (Warszawa, PL)

Systemic lupus erythomatosus is common autoimmune rheumatic disease. Involvement of central nervous system (CNS) occurs in 15–80 % of patients with SLE. Clinical diagnosis of SLE has to meet four or more of American Rheumatism Association diagnostic criteria: arthritis, skin lesions (discoid lupus, subacute cutaneous lupus erythomatosus), photophobia, oral ulcers, pleurisy, muscle, lung, renal diseases, haematological and immunological disorders, antinuclear antibodies, neurological and psychiatric symptoms. Purpose: The purpose of our study was to assess the correlation between neurological symptoms and magnetic resonance findings in patients with SLE. Material and Method: The MR studies of the brain in 47 patients (43 females, 4 males, aged 20–68 years) with neurological symptoms in course of SLE were carried out. The neurological symptoms included: hemiparesis (15 cases), seizures (6), headache and vertigo (27), balance disorders (3), nausea (2), vision disorders (3). Results: The pathological changes in MR study (hyperintense focuses on T2-weighted scans) were found in 24 patients (51 %). Dominant were disseminated white matter lesions in subcortical and periventricular regions. The MR findings were: in 15 cases single and in 5 multiple small focuses, coexistence of small and large focuses in 4 cases, subtentorial focuses in 3 (2 in cerebellum, 1 in pons), lesions in deep structures in 3 cases. In 1 case occlusion of internal carotid artery siphon with large ischemic focus, in 1 bleeding to choroid plexus occurred. In 16 cases MR examinations showed cortical-subcortical atrophy. Conclusion: MR study of the brain showed significant correlation between localisation, number and size of pathological focuses and neurological symptoms of patients with SLE. This technique allows to assess severity of CNS involvement in course of this disease.

P848
MRI STUDY OF CERVICAL SPINE OF PATIENTS WITH NEUROLOGICAL SYMPTOMS IN COURSE OF RHEUMATOID ARTHRITIS. R. Poniatowska, R. Krawczyk, B. Kwiatkowska, R. Boguslawska, Institute of Psychiatry and Neurology (Warszawa, PL)

Involvement of cervical spine by rheumatoid arthritis occurs in 28–86 % of patients and is second to involvement in joints of the hands and feet. The patients often complain of pain characterised as a dull ache or suboccipital headache. The most common clinical indication for magnetic resonance is suspected myelopathy with spinal cord compression. The neurological symptoms (vertebrobasilar insufficiency symptoms, cranial nerve signs, cervicomedullary spinal cord compression) are often mistaken for signs of degenerative disease. Material and Method: The cases of 75 patients with neurological symptoms in course of rheumatoid arthritis were carried out. In all cases duration of disease was over 15 years. All studies were performed on 0.38T resistive unit. The study consisted of SE sequence with T1- and T2-weighted images in sagittal plane and T1-weighted axial scan. Results: The findings in MR study were: in 69 cases pannus, in 38 anterior atlantoaxial subluxation (AAS), in 9 lateral AAS, in 41 vertical AAS, in 12 subaxial subluxation. In 39 cases occurred erosion of the dents, in 17 erosion of atlas, in 13 vertebral blocks, in 16 osteoporosis. The posterior atlanto-odontoid interval was decreased in 15 cases with spinal cord compression on this level with ischemic focus. 73 patients had degenerative changes and herniations of intervertebral discs. The statistically significant correlation between posterior atlanto-odontoid interval + the subaxial sagittal canal diameter and the presence and severity of paralysis occurred. Conclusion: MRI is the best technique to assess the degree of compression of cervicomedullary junction. It allows evaluation of spinal cord and canal impingement and to plan future management – conservative or surgical treatment, before irreversible changes. Postoperative study after titanium implants fixation allows monitoring of disease progress.

P849
THE ROLE OF MR DIFFUSION-WEIGHTED IMAGING (DWI) IN DETECTION AND EVALUATION OF ISCHEMIC LESIONS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS. J. Walecki, I. Walecka, R. Boguslawska, L. Rudnicka, T. Bulski, CMKP, Institute of Psychiatry and Neurology, ZOZ MSWiA (Warszawa, PL)

Purpose: Central nervous system involvement is common in systemic lupus erythematosus (SLE. Vasculitis, vasculopathy, hypercoaguability lead to brain infarcts. The purpose of our study was to assess the value of DWI in precise characterisation of focal ischemic lesions in SLE patients. Material and Method: Twenty-three patients with neuropsychiatric symptoms in course of SLE (20 females, 3 males, aged 35–66 years) were examined. Clinical manifestations included headache, seizures, hemiparesis, hemiplegia, aphasia, ataxia, sensory and visual deficits, depression and psychosis. All patients underwent cranial CT and MR at 1,5T unit. SE and FSE sequences were used as well as DWI with apparent diffusion coefficient (ADC) mapping. Results: Both CT and MR revealed cerebral and/or cerebellar atrophy of a varied degree in all the patients. CT showed big ischemic lesions in the region of MCA supply in 2 cases and hypodense foci in 10. Focal lesions were detected in all patients on MR (SE, FSE, DWI). Precise evaluation of the time and extent of infarct by means of conventional MR techniques (SE, FSE) was possible in 17 cases. DWI allowed it in all cases. Conclusion: Precise evaluation of ischemic foci in patients with CNS involvement in course of SLE influences their therapy. DWI imaging allows more accurate detection and characterisation of lesions than conventional MR and CT techniques.

P850
HOW DO WE MOVE OUR FEET? A FMRI STUDY OF THE CORTICAL REPRESENTATION PATTERN OF ISOMETRIC AND DYNAMIC FOOT MOVEMENT. M. A. Rocca, T. Schenk, M. Filippi, T. A. Yousry, Neuroimaging Research Unit, Klinikum Grosshadern, Neuroimaging Research Unit Scientific Institute Ospedale San Raffaele (Milan, I; Munich, D)

The paracentral lobule is regarded as the site of the representation of the primary motor area of the foot. However, the cortical and subcortical areas involved in different activation patterns have not been evaluated yet. This study was designed 1) to assess the common cortical areas activated in isometric and dynamic foot movements and 2) to define the most suitable conditions to localize the primary motor area of the foot. Twelve right-handed healthy volunteers were studied (3 women and 9 men) using a 1.5 Tesla machine. Functional magnetic resonance imaging (fMRI) was performed using T2*-weighted echo planar imaging (TR/TE=96/66 ms, matrix=128x128, 20 axial slices with a thickness of 5 mm). Using a box-car design, where epochs of activation were alternated with epochs of rest, all subjects were scanned in three different con-

ditions. During the first condition (COND1), they repeatedly flexed and extended their right feet. During the other two conditions, a home-made device, which allowed them to perform only an isometric movement with their feet, was used. In the second condition (COND2), the subjects had to flex their right feet against the resistance of the device, whereas, during the third condition (COND3), they had always to extend their right feet against the resistance of the device. The study was performed in the same way for the left feet. Image analysis was performed using SPM99b. The data were motion corrected, spatially normalized into stereotactic Talairach space and smoothed with a 10 mm three filter prior to statistical analysis. Specific effects were tested by applying appropriate linear contrasts. Significant haemodynamic changes for each contrast were assessed using t statistical parametric maps (SPMs). After this first-level analysis, a second level random-effect analysis was performed, to make inferences about generic activations in the group of our subjects. Since we had similar, although mirrored, results for the right and the left feet, we report here only the data related to the right foot. During COND1, a significant cortical activation was detected in: 1) the left paracentral lobule near the paracentral sulcus; 2) the precentral and the postcentral gyri; 3) the left superior frontal gyrus; 4) the superior temporal gyrus, bilaterally; 5) the pars opercularis of the inferior frontal gyrus, bilaterally, and 6) in the insula, bilaterally. We also detected a significant activation in the left basal ganglia and thalamus and in the right cerebellum. During COND2, the same areas of activation were found, but the activation in the basal ganglia was bilateral, while there was no activation in the thalamus. During COND3, the same regions of COND1 were activated, with the exception of the cerebellum. An additional area in both angular gyri was also detected. We identified the activation area near the paracentral sulcus as the area of the primary motor cortex devoted to the movement of the foot. This area was significantly more active during COND1 than during COND2 and COND3. Our study shows that the pathways involved in the control of isometric and dynamic foot movements are different not only at a cortical, but also at a subcortical level. Moreover, dynamic foot movement seems to represent the most suitable task to identify the cortical area of foot representation in the primary motor cortex.

P851
INTERSUBJECT VARIABILITY IN THE LOCALIZATION OF MT/V5: A FMRI STUDY. T. A. Yousry, M. A. Rocca, T. Stephan, M. Dieterich, Klinikum Grosshadern, Neuroimaging Research Unit, Neurology, Klinikum Grosshadern (Munich, D; Milan, I)

MT/V5 is the area of the human visual cortex specialized for the detection of movement. From its first description, several studies have been performed in the attempt to give a precise location of this area, and several authors are in agreement locating it at the boundary of Brodmann's areas 19 and 37, to the junction of the ascending limb of the inferior temporal and lateral occipital (LOS) sulci. One of the main problems in locating this area is represented by the high interindividual variability in the representation of sulci and gyri at level of the temporo-occipital cortex, and, moreover, most of previous studies were conducted using positron emission tomography, a technique with a low spatial resolution, in comparison to functional magnetic resonance imaging (fMRI). The aim of our study was to evaluate, using fMRI, the intersubject variability in the location of MT/V5. We studied fourteen healthy volunteers. FMRI was performed using EPI sequences. Visual stimuli were presented in the scanner through goggles and were constituted during the activation phases by a blue spot centered on the monitor screen surrounded by white dots moving clockwise or counterclockwise, during the rest phases, the dots were not moving. In each subject a T1-weighted magnetization prepared rapid acquisition gradient-echo (MP-Rage) sequence was also acquired. Image analysis was performed using SPM96. The data were motion corrected and smoothed with a 6 mm filter prior to statistical analysis. The MP-Rage sequence of each subjects was carefully matched with the mean image obtained from the realignment of EPI sequences and they were then used to obtain 3D reconstruction of the brain of each subject. On the left side MT/V5 was localized in the inferior part of the middle occipital gyrus (MOG), below the LOS in seven subjects, above the LOS in one subject, on both sides of the LOS in two subjects. In two other subjects it was in the MOG without relation with the LOS, while in the remaining two subjects it was located at the junction between the middle temporal gyrus (MTG) and the MOG. On the right side it was located in the MOG, above the LOS in five subjects, below the LOS in three subjects, at the posterior end of the LOS in one subject and on both sides of the LOS in one subject. In another subject it was in the MOG with no relation with the LOS, while in the last three subjects it was at the junction between the MOG and the MTG. Our study shows that there is a high intersubject variability in the location of MT/V5, more accentuated on the right side, nevertheless a good landmark for the localization of this area is represented by the LOS.

P852
MRI OF THE COMMON CRANIAL NEUROPATHIES. M. Semnic, R. Semnic, D. Kozic, K. Koprivsek, I. Vukadinovic, Z. Babic, Institute for Neurology and Psychiatry, Imaging Diagnostic Center (Novi Sad, Sremska Kamenica, YU)

Purpose of this study was to optimize Magnetic Resonance Imaging (MRI) protocols in order to visualise intracerebral segments of cranial nerves in the cerebellopontine angle (CPA) region: – trigeminal nerve (n. V), abducens nerve (n. VI), facial nerve (n. VII) and vestibulocochlear nerve (n. VIII) and to evaluate its pathology. Brain stem pathology was excluded. Material and methods: Brain MRI of the 126 patients with symptoms of different cranial neuropathies (30 with trigeminal neuralgia, 14 with abducens nerve palsy, 41 with facial palsy and 41 with lesion of vestibulocochlear nerve) was done. MR examination consisted of routine brain (6mm slice thickness scans) protocol and optimised sequences for cranial nerve imaging and pathological findings for each protocol were recorded. In optimised protocols we used submilimetric–0.781mm axial scans at the level of CPA with three-dimensional fast imaging steady-state procession (3D PSIF) sequence and 2mm axial scans with two-dimensional fast low-angle shot (FL2D) sequence before and after i. v. administration of contrast material (Magnevist). Results: Optimized MR protocol obtained excellent demonstration of cisternal segment of V-VIII cranial nerve and enabled differentiation fibers of VII out of VIII cranial nerve in the CP cistern and internal acoustic canal. Results of pathological findings in routine and optimised protocols are shown in following table:

MR protocol	n. V	VI palsy	VII palsy	n. VIII
Routine	10%	21%	24%	21%
Optimized	24%	40%	33%	43%

Discussion: Detection of discrete lesions such as tumors less than 5mm in diameter, neurovascular conflict (vertebral artery – n. V; posterior inferior cerebellar artery – n. VII) and postcontrast enhancement of particular cranial nerve due to inflammation, significantly increased percentage of pathological findings in optimised MRI protocols. Conclusion: Nowadays advanced MR technology is capable to reduce slice thickness preserving optimal spatial resolution, therefore visualisation of subtle structures as cranial nerves becomes reality. MR is the only in vivo diagnostic imaging tool for evaluation of infranuclear cranial nerve pathology which confirmed results of our study.

P853
PATTERN OF CORTICAL ACTIVATION IN LANGUAGE TASKS DEPENDS ON SEMANTIC CATEGORIES: AN FMRI STUDY. G. Fesl, J. Ilmberger, T. A. Yousry, Klinikum Grosshadern (Munich, D)

Anomias restricted to specific semantic categories in brain-injured patients (i. e. selective difficulty in naming living things) indicate that cortical areas are differentially involved in the naming process depending on semantic boundaries. In our study we used fMRI to identify in healthy subjects cortical sites involved in the processing of two semantic categories in two language tasks, naming and semantic fluency. Methods: MRI Acquisition: We examined 16 healthy right-handed volunteers. FMRI was performed using EPI sequences (128*128 matrix size, 26 slices/scan, 6 sec interscan interval) on a Siemens Vision 1.5T. Stimuli were presented through goggles. An examination consisted of 2 runs with 6 active and 6 baseline phases. In the active phase (60 sec) 10 drawings of animals and 10 drawings of tools were presented. In the baseline phase (30 sec) a random dot image was presented. During the first run the volunteers had to name aloud the objects presented (confrontation naming). During the second run the volunteers again named the drawings of animals and tools and had to add the name of another object from the same semantic category (confrontation naming plus semantic generation). During the baseline phase the volunteers just had to look at the random dot image. Postprocessing: For postprocessing SPM99 (Wellcome Dept. of Cognitive Neurology, London) was used. Group analysis (second level analysis: one sample t-test) was performed, defining an activation above T=7.66 (p-values corrected for the entire volume) as significant. Results: When contrasting the two semantic categories (animals/tools), group analysis showed the following corrected significant activations: naming tools: left cingulate gyrus; naming animals: inferior temporal gyrus bilateral; semantic generation tools: left inferior parietal lobule; semantic generation animals: inferior temporal gyrus bilateral. When subtracting the naming condition from the semantic condition, left sided activation was found in the medial frontal gyrus and in the inferior parietal gyrus for both, animals and tools. Discussion: Our results confirm that the patterns of cortical activation in language tasks depend on the semantic categories that are being processed. When in a simple naming task the knowledge about animals, as contrasted with tools, is processed, a temporo-occipital activation is found in both hemispheres. The activation is stronger in the right hemisphere possibly indicating that non-linguistic components such as knowledge about visual features of animals are involved in the specific task. A similar pattern of activation is seen for animal

items when contrasting the two semantic categories in a generation task where another member of the same category has to be produced in addition to naming. For tool items, however, there is left-sided activation only, demonstrating a strong verbal encoding of knowledge about these items. If the aspect of generating an additional response is highlighted by contrasting the naming task with the generation task, there is strong left-sided frontal activation irrespective of semantic category possibly indicating selection processes that are involved in any generation task.

Neuro-oncology

P854
NONDIAGNOSTIC STEREOTACTIC BIOPSIES IN A SERIES OF 158 PATIENTS: A FOLLOW-UP OF 23 CASES. LH Visser, G. Beute, M. Sluzewski, H. Teepen (Tilburg, NL)

In the period 1995–1997 158 stereotactic biopsies were performed at our department of neurosurgery. 103 (65%) of the 158 patients had an astrocytoma, 10 (6%) a metastasis,7 (4%) an oligodendroglioma, 8 (5%) a lymphoma, 6 patients with other pathology and 23 biopsies were non-diagnostic. The pathology of these biopies were: no abnormalities 8 (35%), possibly a lymphoma 3 (13%), necrosis 5 (22%), non-specific inflammation 4(17%) and granulomas in 3 (13%). These patients were followed and during follow-up for 8 patients no definite diagnosis could be found. By combining the clinical and neuroradiological pattern and sometimes performing a second biopsy a definite diagnosis could be made for the other 15 patients, resulting in a diagnostic yield of 95%. A conclusion from this study is that the definite diagnosis of lymphoma or non-neoplastic lesions like sarcoidosis can be difficult.

P855
A DOSE RELATED EFFECT OF A NOVEL ANTI-CANCER DRUG, HALOFUGINONE, IN A RAT BRAIN TUMOR MODEL. T. Siegal, I. Vlodavsky, Hadassah University Hospital (Jerusalem, IL)

Halofuginone, a low molecular weight (MW=495) quinazolinone alkaloid, is a potent specific inhibitor of collagen type alpha 1 (I) gene expression, extracellular matrix deposition and cell proliferation. It inhibits vascular tube formation and accordingly was found to be an inhibitor of both angiogenesis and tumor growth in in-vitro models. In-vivo it has a potent anti-tumor and anti-metastatic effect in systemic solid tumor models. As yet, its effect on the growth of brain tumors has never been evaluated in in-vivo models. Objective: To evaluate the ability of Halofuginone to inhibit tumor growth in a rat brain tumor model. Methods: Fischer rats were inoculated with 105 cells of malignant sarcoma into the right parietal hemisphere on day 0. Halofuginone was given p. o. once a day starting on day +6 (when a macroscopic tumor is already present) and continued until sacrificed on day 14. Three doses were evaluated: 0.1, 0.2 and 0.4 mg/kg/d. Visible tumor was excised and its 3-dimensions measured for calculation of tumor volume. Halofuginone plasma levels were determined on day 7 and 14. Animals were observed for signs of toxicity and for weight loss. Results: On day 14 mean tumor volume was 49.4±8.4 mm^3 in untreated control animals. Treatment with Halofuginone induced inhibition of tumor growth in all treatment groups: 49% inhibition of tumor growth in the 0.1 mg/kg/d dose (p=0.06), 88% inhibition in the 0.2 mg/kg/d dose (p=0.0005), 94% inhibition in the dose of 0.4 mg/kg/d dose (p=0.0001). Mean plasma levels on day 14 were: 1.32±0.4 ng/ml for the 0.1 mg/kg/d dose, 2.27±0.3 ng/ml for the 0.2 mg/kg dose and 4.53±1.02 ng/ml for the 0.4 mg/kg dose. All animals lost weight during the observation period. Weight loss ranged between 9–13% of initial body weight and did not differ significantly between untreated tumor bearing controls and Halofuginone treated animals. No drug related adverse reactions were observed. Conclusions: Halofuginone, as a novel inhibitor of angiogenesis and cell proliferation, is an effective anti-tumor drug. It is highly effective in inhibiting growth of a brain tumor even when treatment is given at a time that a macroscopic tumor mass has already developed. Its effectiveness is dose related and an oral daily dose equivalent to at least 0.2 mg/kg in rats is recommended for long term studies.

P856
SUBACUTE MYELOPATHY INDUCED BY INTRA-VENTRICULAR THERAPY WITH ARA-C: NEUROIMAGING FEATURES. F. Bokstein, J. M. Gomori, A. Lossos, E. Shalom, T. Siegal, Hadassah University Hospital (Jerusalem, IL)

Background: Intra-CSF therapy with Ara-C may cause myelopathy. The clinical presentation of Ara-C myelopathy includes back or leg pain, progressive weakness, diminished sensation and bowel/bladder dysfunction. The diagnosis of Ara-C myelopathy rests on the clinical history and neurological signs since most reports describe negative imaging findings and a few noted patchy enhancement of the affected spinal cord. The histopathologic appearance is characterized by demyelination. Objective: To describe MRI features of Ara-C myelopathy. Patients/Methods: 2 patients with brain parenchymal and leptomeningeal involvement of NHL were treated by different protocols that included cranial irradiation in one and high dose methotrexate in the other case. Following resolution of the parenchymal mass both continued treatment with intra-ventricular Ara-C injections (50 mg/treatment) for control of the known leptomeningeal seeding. The first patient, a 46 year-old female received monthly intra-ventricular Ara-C for residual positive CSF cytology for a period of > 12 months. To determine whether the persistent CSF cytology represents resistant disease, we studied the immunoglobulin (Ig) gene rearrangements in the CSF using PCR, analyzing the Ig heavy chain gene. We found a heavy chain rearrangement, indicating that the persistent positive cytology is related to a resistant disease. After treatment period of > 12 months she developed paraparesis and sensory loss which improved gradually following withdrawal of intraventricular therapy. The second patient, a 47 year-old female, developed lower extremities pain, progressive paraparesis, sensory and autonomic dysfunction following 2 mos of treatment with intra-ventricular Ara-C. No improvement was noted after withdrawal of therapy. Results: Axial T2-fast spin echo images of the thoracic cord demonstrated similar findings in both cases. It showed symmetric high intensity regions located postero-laterally and postero-medially. In addition, a midline linear high intensity region was noted in the antero-posterior direction. There was no gadolinium enhancement. Conclusions: The symmetric MRI features described in our patients probably reflect toxic demyelination as previously described on histopathologic evaluation of Ara-C myelopathy. Recognition of similar MRI pattern may serve to establish diagnosis of Ara-C myelopathy.

P857
A PROSPECTIVE EVALUATION OF OCULAR TOXICITY INDUCED BY HIGH-DOSE TAMOXIFEN (HD-T) TREATMENT IN MALIGNANT GLIOMAS. S. Dotan, A. Lossos, H. Mechoulam, E. Banin, I. Chowers, F. Bokstein, T. Siegal, Hadassah University Hospital (Jerusalem, IL)

Objective: Prospective evaluation of ocular toxicity in malignant gliomas treated with high-dose Tamoxifen. Background: Tamoxifen is a nonselective protein kinase C inhibitor showing an in vitro activity against glioma cell lines. Clinically, HD-T has a modest efficacy in the treatment of recurrent high-grade astrocytomas. While generally well tolerated, HD-T may cause various systemic adverse effects. Ocular toxicity, including corneal opacities, retinopathy and optic neuritis, has been reported in less than 3% of patients treated with low doses for more than 12 months. However, no long-term follow up data are available in glioma patients maintained on HD-T and evaluated prospectively. Methods: 30 participants of a single institution randomized trial of either oral HD-T (240 mg/d) or HD-T combined with oral VP16 (100 mg/d, day 1–14 q 21 days) were prospectively monitored for potential adverse effects including ocular toxicity. Inclusion criteria required histologically verified and MR measurable recurrent malignant glioma, following previous therapy with surgery and radiotherapy. Median duration of treatment is currently 8 months for the combined treatment with VP16 and 9.5 months for HD-T alone. Patients underwent repeated ophthalmologic evaluation every 3 mos. When ophthalmologic examination revealed impaired visual acuity or refractile retinopathy, visual function was further assessed by static perimetry, full-field and focal electroretinogram (ERG), and color vision testing. Results: 5 patients on the protocol are followed for more than one year (17%), 4 of them (80%) had signs of ocular toxicity after a mean of 24 months (range 21–36) of treatment. Clinical findings included decreased visual acuity (4), changes in visual fields and color discrimination capacity (3), keratopathy (3), and macular refractile bodies (3). Full-field ERG revealed impaired rod function in 3 pts, and focal ERG showed decreased cone function in 4 patients. The toxicity was partially reversible following cessation of the treatment with some improvement in visual acuity, visual fields and ERG amplitudes.

Conclusions: HD-T is associated with high rate of ocular toxicity after treatment period of more than 18 months. Prospective ophthalmologic evaluation reveals intolerable rate of toxicity (80%) in the setting of long-term treatment with HD-T

P858
DELAYED OBJECTIVE RESPONSES OF ANAPLASTIC ASTROCYTOMAS (AA) TO TREATMENT WITH HIGH-DOSE TAMOXIFEN (HD-T). F. Bokstein, A. Lossos, E. Shalom, T. Siegal, Hadassah University Hospital (Jerusalem, IL)

Objective: To report unexpected delayed objective responses to treatment with HD-T in patients with AA. Background: HD-T is a biologic agent known to have a modest effectiveness in the treatment of high grade astrocytomas. Traditionally clinical and imaging progression are the endpoints for termination of treatment. A single case was previously described (Cloughesy, J. Neuro-Oncology 35:39,1997) with an objective delayed response documented after a period of initial tumor progression on HD-T. We observed 2 such patients with a delayed response observed after objective tumor progression in AA treated with HD-T. Methods: In our series of 101 patients with high grade astrocytomas (grade III and IV) treated with HD-T (240 mg/d) we noted 2 young female patients with AA who were initially considered as treatment failure on HD-T and showed an unexpected delayed response to this treatment.

Results: In the first patient, a 14 year old girl with an extensive thalamomesencephalic AA, a significant tumor shrinkage was first evident after 9 months of treatment, and 2 months after HD-T was discontinued because previous MRI showed tumor progression. The second patient, a 43 year old female had a right thalamic AA. She experienced marked improvement after 8 months of treatment despite initial tumor progression. Both patients completed radiotherapy 4 and 5 months prior to treatment with HD-T and both developed an ependymal spread of tumor before HD-T was introduced. Both patients were followed periodically by MRI (every 2 mo.) and had documented tumor progression before the unexpected tumor regression was noted. In the first patient improvement lasted 8 months before tumor progression occurred again. The second patient is doing well on HD-T treatment for more then 18 months.

Discussion: The traditional end point of tumor progression for termination of treatment prevents recognition of patients who benefit from the treatment by slowed growth or delayed response. A delayed response or slowed growth may be characteristic of biologic agents and therefore strong consideration should be given to prolonged treatment with this non-toxic agent in the design of future clinical trials.

P859
DOES STREAMING AFFECT DRUG DELIVERY DURING INTRA-CAROTID CHEMOTHERAPY OF BRAIN TUMORS? J. M. Gomori, R. Rubinstein, F. Bokstein, A. Lossos, E. Shalom, T. Siegal, Hadassah University Hospital (Jerusalem, IL)

Background: Streaming is the incomplete mixing of a substance injected into a flowing stream with the consequent formation of streamlines, downstream from the injection site. When intra-arterial chemotherapy is given for brain tumors streaming would cause different intravascular concentration of the injected drug in the capillary bed of the brain and the tumor. This would result in areas of higher and lower concentration than desired. The outcome can be areas of high exposure causing neurotoxicity or areas of sub exposure. Objective: To study whether significant streaming occurs when intra-carotid chemotherapy is given.

Methods: 4 patients with glioblastoma who relapsed after surgery and radiotherapy underwent monthly intra-carotid chemotherapy with carboplatin and etoposide phosphate. Immediately after the injection of chemotherapy they received intra-carotid injections of 0.5 mCu of Tc99mHMPAO in 50 cc of saline. Each patient received 2 injections, a month apart. Once over 10 min (slow injection) and once, a month later, over 8 sec (bolus). Patients were imaged by SPECT 3 hours later. The bolus images were assumed to be well mixed and without streaming and the slow injection images were assessed for streaming. The images were compared visually after normalization and co-registration. To eliminate the influence of blood flow heterogeneity within the brain, ratio images were computed by dividing the slow image by the bolus image. Heterogeneity of intravascular concentration is assessed visually and by measurement of the ratios in the ratio images.

Results: The SPECT images showed only the ipsilateral hemisphere with cortex highlighted due to the cortical blood flow. No uptake was visualized in the contralateral hemisphere. The first 4 pts showed no evidence for streaming in the slow injections. The slow injections are at the rate of less than 0.1 cc/sec compared to the normal internal carotid flow of about 6 cc/sec. Of note was the consistent decreased flow to the tumor relative to the adjacent normal brain even in regions of enhancing tumor on pretreatment MRI.

Conclusions: Our results fail to show any streaming on the slow injections meaning that incomplete mixing of the drug probably does not occur with slow vs. rapid intra-arterial injection of chemotherapy. This technique of 2 injections under different conditions with subsequent normalization and co-registration can be used for assessing maneuvers for increasing the relative blood flow to brain tumors undergoing intra-arterial chemotherapy.

P860
THE PROGNOSTIC SIGNIFICANCE OF FUNCTIONAL IMAGING AND RELATED IMMUNOHISTOCHEMICAL MARKERS IN ANAPLASTIC ASTROCYTOMAS (AA). O. Cohen, J. M. Gomori, D. Soffer, R. Rubinstein, T. Siegal, Hadassah University Hospital (Jerusalem, IL)

Objectives: To assess the prognostic significance of functional imaging studies performed after diagnosis of AA and of immunohistochemical markers. Background: AA has a better prognosis than GBM when response to treatment and overall survival are compared. About 30% of AA are non-enhancing tumors on MRI, a feature which may carry a prognostic significance and a relationship to the ability of some functional studies to detect abnormalities. The prognostic weight of standard and of functional imaging evaluations has not been studied before in AA. Methods: The inclusion of the 43 patients with AA was based upon availability of paraffin-embedded tissue obtained at primary surgery. Specimens were assessed for MIB–1 proliferation index and for microvessels' density by counting laminin immunostained vessels. Routine imaging studies included standard MRI (317 studies), relative cerebral blood volume mapping (rCBV, 208 studies) and 201Thallium SPECT scans (Tl-SPECT, 177 scans). rCBV maps were graded as 0 to 4, where 3 & 4 are indicative of high vascular density of well perfused or leaky vessels (Siegal, J Neurosurgery 86:22,1997). Tl-SPECT index above 1.4 is considered abnormal. Results: Initial treatment included surgery (6-biopsy only) and focal radiotherapy. 23 patients (53%) received chemotherapy at time of tumor progression. Median progression free survival (PFS) was 29.3 weeks (range:4.6–133) and median survival was 207.3 weeks. The median MIB–1 index was 8.3% (0.6–36%) and it did not correlate with survival for indices below or above 5 & 10%. Vascular density and PFS were negatively correlated ($r = -0.48$, $p=0.03$). Tl-SPECT indices obtained during the first 6&12 months after diagnosis correlated with PFS ($p=0.03$, $p=0.001$ respectively) and with overall survival. On standard MRI, 36% of the tumors were non-enhancing and the T2-weighted images obtained during the first 12 months showed that patients with stable/improved T2WI abnormalities lived longer than those with worsened T2WI ($p=0.02$), while presence/absence of enhancement did not correlate with survival. During the first 6 months rCBV was predictive of survival: those with grade 0–2 survived longer than those with grade 3–4 ($p=0.04$).

Conclusions: At diagnosis of AA vascular density has a prognostic significance. Similarly, functional imaging studies obtained after initial therapy carry significant prognostic weight and their routine use may help to stratify patients for controlled studies.

P861
MALIGNANT ACTIVITY OF BRAIN TUMORS AND ITS CORRELATION WITH MAGNETIZATION TRANSFER CONTRAST (MTC) AND DIFFUSION WEIGHTED CONTRAST (DWC) AS ASSESSED BY DYNAMIC MRI. J. M. Gomori, G. Golan, F. Bokstein, F. Gul-Aksoy, T. Siegal, Hadassah University Hospital (Jerusalem, IL)

Introduction: MRI based measures of relative cerebral blood volume (rCBV) correlate with clinical and malignant activity of brain tumors. There is interest in assessing the correlation of other MRI parameters with the malignant activity of brain tumors. However, this is an arduous process requiring accurate selection of anatomic sites for biopsy and clinical follow-up. It would be useful to screen first the potentially helpful MRI parameters by correlating them with rCBV, a known measure of malignant activity. This will also reduce variability as images with identical anatomic location are used for comparison. Purpose: to use rCBV as a surrogate for malignant activity of brain tumors in the initial screening of two other MRI parameters: relative MTC (rMTC) and rDWC. rMTC is indicator of macromolecular rigidity; e. g., myelinisation. rDWC indicates the mobility of free water molecules and is somewhat similar to viscosity. Method: 48 patients with histologically verified primary brain tumors were examined on a 2 Tesla MRI unit. There were 35 high-grade and 8 low-grade brain tumors. Standard spin-echo proton density (PD) and T2-weighted (T2) images were acquired. rMTC and rDWC images were obtained as previously described (MRM 37:716,1997) as well as rCBV (Siegal, J Neursurg 86:22,1997). Each pt had 1–4 follow up examinations and in each study 1–3 regions of interest (ROI's) were selected for measurement and correlation. In each study ROI's were selected so as to sample the spectrum of pathologic heterogeneity. Purely cystic regions or regions with normal white matter were excluded. A total of 161 ROI's were selected for this study. Results: The rCBV's correlated only and independently with the rMTC's; Kendall correlation (2 tailed) –0.1709, $p< 0.005$. There was no significant correlation with rDWC's, T2 or PD.

Conclusions: Our results show a negative correlation of rCBV with rMTC, independent of the tissue water content in the primary brain tumors, as indicated by the lack of correlation with T2 and rDWC. This finding suggests a decrease in macromolecular structure and rigidity with increasing malignant activity in brain tumors. Measures of rMTC may be useful as an additional parameter in the follow-up and the selection of biopsy sites since it may help to differentiate

between non-edematous, non-enhancing areas of tumor infiltration vs. predominantly edematous regions.

P862
CEREBROSPINAL FLUID (CSF) LACTATE DEHYDROGENASE (LDH) ISOENZYME PROFILE IN THE DIAGNOSIS OF THE CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT BY LYMPHOMA AND LEUKEMIA. A. Lossos, I. Lossos, O. Intrator, R. Breuer, F. Bokstein, T. Siegal, Hadassah University Hospital (Jerusalem, IL)

Objective: To determine the utility of CSF analysis for LDH isoenzymes in the diagnosis of lymphomatous and leukemic involvement of the CNS.

Background: Definite diagnosis of leptomeningeal seeding by lymphomas or leukemias requires cytological analysis of the CSF. However, CSF samples often contain only a few identifiable malignant cells and therefore the sensitivity of a single cytological examination is less than 70%. Since tumor cells of hematological origin employ anaerobically active LDH isoenzymes, we assumed that LDH analysis might serve as an indicator for the presence of neoplastic activity in the CSF. Therefore, CSF analysis for isoenzymes LDH 4 and 5 may prove helpful in the diagnosis of leptomeningeal seeding by neoplasms of hematological origin. Design/Methods: 93 consecutive patients with systemic lymphoma or leukemia underwent CSF examination as part of their initial staging or for evaluation of newly developed neurological symptoms. The profile of LDH isoenzyme 1 to 5 was evaluated in all the samples and its pattern was analyzed by the classification and regression trees (CART) method in order to construct a decision tree for prediction of CNS involvement. A group of 63 patients with no previous CNS disease formed the derivation group. In this group 15/63 patients had CNS involvement by leukemia or lymphoma as diagnosed by positive CSF cytology and/or by positive neuroimaging findings. An additional group of 30 patients comprised a validation set that was used for cross-validation of the CART-derived decision tree. Results: The mean±SD measure of LDH 5 was 0.1±0.5 units for patients without CNS involvement in the derivation group and was 12.4±8.6 for patients with CNS spread. For prediction of CNS involvement, a decision tree with a single split at 2.8 units of LDH 5 was constructed and validated by data in the validation set of patients. The decision tree had a sensitivity of 93% and a negative predictive value of 98%. One (1.6%) and two (6.6%) patients were misclassified in the derivation and the validation sets respectively. Overall, in the combined derivation and validation population the decision tree misclassified 3.2% of patients, while CSF cytological examination misclassified 4.3% of patients who had parenchymal rather than leptomeningeal involvement of the CNS. Conclusions: The analysis of the CSF LDH isoenzyme profile may serve as an adjunctive tool in the evaluation of patients with suspected CNS involvement by lymphoma or leukemia. When compared with either the CSF or with neuroimaging, it may significantly improve the yield of a single diagnostic evaluation.

P863
ANALYSIS OF ICAM-1, -3 AND E-SELECTIN IN SERUM, CSF, AND DORSAL ROOT GANGLIA (DRG) OF PATIENTS WITH ANTI-HU-ASSOCIATED PARANEOPLASTIC ENCEPHALOMYELITIS (PEM). A. Saiz, C. Vilardell, A. Pifarré, T. Ribalta, J. Yagüe, F. Graus, Hospital Clinic (Barcelona, E)

Brain inflammation requires the adhesion and migration of lymphocytes across the blood vessels that are regulated by adhesion molecules and cytokines. The expression of ICAM-1, -3 and E-selectin in anti-Hu-associated PEM is unknown. We analyzed by ELISA the index (CSF/serum molecule/CSF/serum albumin) of ICAM-1, -3 and E-Selectin in paired serum/CSF samples of 26 patients with PEM, 28 with multiple sclerosis (MS) in relapse, and 22 with degenerative cerebellar disease (DCD).The expression of these molecules was also analyzed by an avidin-biotin technique in pathologic DRG from three patients with PEM and normal DRG from 10 patients with no neurologic disease and one with Lambert-Eaton myasthenic syndrome. PEM group had an ICAM-1 index higher than the DCD ($p=0.001$) but lower than that of MS ($p< 0.001$). ICAM-3 index of PEM group was similar to that of DCD and MS groups. E-selectin index could not be calculated because the molecule was undetectable in the majority of CSF samples. ICAM-1 but not E-selectin was found in the endothelial cells of normal and pathologic DRG. However, satellite cells of DRG from PEM patients had an increased expression of ICAM-1. ICAM-3 was only detected in the majority of infiltrating lymphocytes in the pathologic DRG. These results suggest a role for ICAM-1 in the migration of lymphocytes to the nervous system in PEM patients similar to that described in MS. The upregulation of ICAM-1 in satellite cells of DRG from PEM patients may be relevant in the attraction of lymphocytes to the sensory neurons, one of the main targets of the immune response in PEM.

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P864
NERVOUS SYSTEM LYMPHOID INFILTRATION IN WALDENSTROM'S MACROGLOBULINAEMIA: UNUSUAL CLINICAL AND RADIOLOGICAL FEATURES. S. Massengo, L. Riffaud, M. Bernard, X. Morandi, G. Edan, M. Vérin, CHU Rennes, CHU Rennes Hôpital Pontchaillou (Rennes, F)

We report a case of a 77 year old woman suffering from Waldenstrom's Macroglobulinaemia (WM) with lambda light chain-type for ten years. The only features found were mild anemia and fatigue. After ten years of very good follow-up without treatment, she experienced progressively gait ataxia, lower limbs spasticity and vesico-urethral disturbances (urgency and periodic incontinence). These symptoms were related to MRI demonstrated cauda equina roots and lumbar perimedullary infiltration. Tumoral and lymphoid nature of it had been proven by cerebrospinal fluid (CSF) electrophoresis and immunophenotypical studies in demonstrating lymphocytosis with abnormal B monoclonal lymphoid cells and IgM monoclonal peak in CSF, consistent with specific complications of WM. Moreover, MRI showed a long intraspinal lesion extending from C2 to L2, isointense in T1 and hyperintense in T2 weighted spin echo images, with light and heterogeneous enhancement after contrast at cervical region, suggesting lymphoid infiltration or ischemic lesion. Intrathecal therapy by Methotrexate and Cytarabine allowed CSF normalization, disappearance of cauda equina and perimedullary infiltration on MRI and clinical improvement. On the other hand, intraspinal lesion was still present after one year of follow-up. Reported cases of spinal infiltration in WM are very rare. Radiological features of it are not well known mainly because of the rarity of cases. We can not find any earlier report about MRI demonstration of lymphoid infiltration in spinal cord and peripheral nerves. It must be emphasized that some aspects are unusual in our report: 1) the special localization of the lymphoid infiltration in cauda roots and perimedullary region never mentioned up to now; 2) the demonstration of lymphoid infiltration by non-invasive tests (IRM and CSF immunophenotypical study); 3) the spectacular response to intrathecal chemotherapy and 4) the probably first reported spinal tumoral or ischemic lesion secondary to lymphoid infiltration in WM.

P865
A CASE OF ANGIOTROPIC LYMPHOMA SECONDARY TO SYSTEMIC LYMPHOMA. N. C. Silver, C. Crawley, A. J. Norton, J. F. Geddes, T. O. Kumaran, J. Gawler, Royal London Hospital, North Middlesex Hospital, St Bartholomew's Hospital (London, UK)

Angiotropic lymphoma is a rare presentation of a malignant lymphoma which carries a poor prognosis. It is characterised by an intra-lumenal accumulation of clonal lymphoid cells within small blood vessels. It frequently involves the central nervous system and/or skin although any organ can be affected; marrow replacement is uncommon. Disseminated disease has been observed concurrently with angiotropic lymphoma, and probably represents disease progression. We present a case of Burkitt-like lymphoma that recurred secondary as an angiotropic lymphoma; to our knowledge, such secondary presentation has not been reported.

A 57 year patient presented initially with weight loss, sweats, dysphagia, and hoarse voice.

No cause was found and the illness spontaneously remitted. Eighteen months later, he represented with a solitary, rapidly growing cervical mass that was biopsied and diagnosed as Burkitt-like non-Hodgkin's lymphoma; this was successfully treated with radiotherapy and combination chemotherapy. A year following treatment, he re-presented with pyrexia, sweats, and progressive neurological disturbance (fluctuating conscious level, extrapyramidal rigidity, limb weakness, vague affect and incontinence). Extensive investigations were negative except for a raised lactate dehydrogenase (LDH) and magnetic resonance imaging (MRI) which showed a benign-appearing mass in the right lateral ventricle. A short-lived response was seen with high-dose steroids (48 hour improvement in mental status and resolution of fever). Other therapeutic trials were ineffective (antibiotic, antituberculous, antifungal, limited chemotherapy). He deteriorated pending a brain biopsy, with myoclonus, focal and generalised seizures and subsequent respiratory infection leading to death.

Autopsy revealed no macroscopic abnormalities. The intraventricular mass seen on MRI was a central neurocytoma. Extensive intravascular lymphoma was observed in arterial vessels and capillaries throughout the brain, with no perivascular sheathing in the Virchow-Robin spaces.

No evidence of cerebral infarction was noted, although groups of neurons showed acute ischaemic-type change throughout the brain. Bone marrow and systemic organ examination revealed no lymphoma, with the exception of tumour cells in the renal vessels. Morphological appearance of the tumour cells was identical to that of the previous lymphoma, suggesting secondary recurrence as an angiotropic lymphoma.

Angiotropic lymphoma is a rare cause of progressive neurological decline associated with pyrexia and occasionally has been reported to show some re-

sponse to chemotherapy. It is unclear whether angiotrophic lymphoma represents a discrete lymphoma entity or whether it simply represents an unusual pattern of spread of aggressive lymphomas. The progression of a Burkitt-like lymphoma to an angiotropic lymphoma would support the latter explanation. Brain biopsy might be the only investigation to allow diagnosis, and should be considered in cases of pyrexia associated with progressive neurological disturbance, even in the absence of focal MRI lesions.

P866
ALTERNATIVE 5′-REGULATORY SEQUENCES OF THE EAAT2 MRNA ARE DIFFERENTIALLY EXPRESSED IN ASTROCYTOMA. C. Münch, B. Schwalenstöcker, A. Penndorf, A. C. Ludolph, T. Meyer, P. Ince, University of Ulm, Newcastle General Hospital (Ulm, D; Newcastle, UK)

The excitatory amino acid transporter 2 (EAAT2) is the major protein of glutamate uptake from the synaptic cleft. A defective expression of the EAAT2 protein has been reported in acute and chronic neurodegeneration. Furthermore EAAT2 has been found to be reduced in human glioma cell lines. Compromised glutamate transporter has been discussed to be related to neuronal necrosis and seizures associated with malignant gliomas.

We have recently cloned three 5′-splice forms of the EAAT2 RNA encoding alternative 5′-untranslated and N-terminal coding sequences, named EAAT2–5UT1–3. The highly variable 5′-sequences predict a complex regulation of EAAT2 protein translation. The aim of this study was to analyze the expression of the EAAT2 RNA and its 5′-splice forms in human astrocytic tumors using quantitative RT-PCR. We investigated tumor tissue of 20 patients with low-grade astrocytomas, anaplastic astrocytomas and glioblastoma multiforme. The main EAAT2 RNA was abundantly expressed in all astrocytoma and glioblastoma samples. The splice form EAAT2/5UT1 showed a variable expression in the investigated series of tumors, whereas EAAT2/5UT2 and EAAT2/5UT3 were diminished in all specimen.

The EAAT2 splice forms EAAT2/5UT1–3 encode variable N-termini of the EAAT2/5UT1–3 polypeptides. Sequence analysis of EAAT2/5UT1–3 using the PSORTII algorithm predicted a different cellular sorting of distinct EAAT2 isoforms. This mechanism of posttranscriptional EAAT2 gene regulation may account for the reported reduction of the transporter in neoplastic transformation of human astrocytes.

T. Meyer and P. Ince were contributing equally

P867
FOCAL DEMYELINATING LESIONS OF THE BRAIN ASSOCIATED TO SEMINOMA: CLINICAL AND MRI RESOLUTION AFTER TUMOUR TREATMENT. S. Galgani, C. Gasperini, C. Gerace, A. Pingi, C. Colacecchi, M.R Fele, G. Piazza, S Camillo-Forlanini Hospital (Rome, I)

We present the case of a 35 year old man who developed a sudden visual loss in the left eye. His neurological evaluation revealed gait ataxia, a deep propiocettive sensation deficit in the hand and feet. Visual acuity was 1/10 in the left eye and 10/10 in the right one. Brain MRI showed two large focal lesions in the gray matter and subcortical white matter of the right fronto-parietal and temporal lobes markedly hypointense on T1WI, hyperintense on PD and T2WI, with enhancement after gadolinium injection. Serum was negative for tumoural markers, autoantibodies, HIV antibodies. Cytological and serological exam of CSF were negative. CT of chest and abdomen revealed no evidence of primary or metastatic tumors. EMG was suggestive of a demyelinating neuropathy. Cerebral biopsy was consisting of demyelinating lesion. In the following months the patient experienced recurrent optic neuritis responsive to steroid theraphy. After 14 months period from the neurological onset a diagnosis of testicular seminoma was performed. After orchiectomy, radiation therapy and chemotherapy the patient continues to be free from neurological symptoms and signs up to now (18 months since tumour treatment) with normal EMG findings and only mild signal abnormalities on MRI.

Paraneoplastic focal demyelinating disorder associated to seminoma have been rarely reported. No significant neurological improvement was observed in most of the patients with paraneoplastic syndrome associated to testicular cancer while in some cases MRI showed a regression or a significant reduction of the abnormalities.

In our case the eradication of the tumour favorably affected the neurological course in spite of the long period between neurological symptoms onset and seminoma diagnosis.

P868
EIGHT YEARS FOLLOW-UP OF A PATIENT WITH MULTIPLE BRAIN CALCIFIED METASTASES FROM OVARIAN CARCINOMA. F. Le Doze, C. Schupp, J.-Y. Genot, G.-L. Defer, Service de Neurologie Dejerine – CHU Caen, Centre François Baclesse – Caen, Fr

Background: Calcifications of the brain can be physiological or secondary to a pathological process but neoplastic mechanism is rarely reported. Multiple brain metastases are of poor prognosis. We report the case of a patient with calcified brain metastases from ovarian carcinoma and still alive 8 years after the first symptoms of the neoplasm. Case report: A 39-year-old woman presented with dyspnea in 1992. At this time, a metastatic pleuritis was diagnosed and histological examination showed signs of colloidal adenocarcinoma. In May 1997, she presented partial epilepsy related to multiple brain lesions and received carbamazepine (400 mg/d). CT scan revealed multiple infra and supratentorial lesions. Some of them were surrounded by perifocal oedema and others were enhanced by contrast. Most of them were circled by ringlike hyperdensities indicating calcium deposition. These lesions tended to be hypointense on T2-weighted MRI. They were of small to medium size with no mass effect. Neurological examination was normal. Craniotomy allowed direct biopsy, which confirmed the same histological diagnosis as mentioned above. One year after in 1998, a laparotomy showed a left ovarian tumor, which was histologically identified as an adenocarcinoma associated with asymptomatic peritoneal metastases. No ovariectomy was performed. She received cis-platin and paclitaxel in September 1998. Since then, the evolution was marked in November 1999 by an episode of intracranial hypertension regressive under corticosteroids, associated with an hemiparesis still present in January 2000. Discussion: Calcifications are rarely observed in malignant lesions due to the long time necessary to calcium deposits. Nevertheless calcified metastases are reported in sarcoma and carcinoma from different organs particularly from ovary. Only one case of prolonged survival in a patient with calcified metastases from ovarian carcinoma (but not exceeding 2 years and 9 months) has been published (Hwang et al.). These cases raise the still unresolved questions, of the mechanism of calcium deposits in neoplastic lesions. The exceptional survival in our case of generalised ovarian adenocarcinoma needs to be underlined.

P869
THALIDOMIDE TREATMENT IN RECURRENT GLIOBLASTOMA PATIENTS AND MONITORING OF TNF, TM, IL12, MMP9 SERUM LEVELS. A. Boiardi, E. Corsini, M. Gelati, E. Ciusani, A. Silvani, A. Salmaggi, M. Eoli, Besta (Milan, I)

Malignant tumors are angiogenesis dependent diseases: the formation of new blood vessels is considered a crucial process for tumor growth and spreading. Thalidomide has been shown to inhibit of angiogenesis induced by basic fibroblast growth factor and to decrease in vitro endothelial cell proliferation. For this property the drug is under investigation as antitumor agent, unless its mechanism of action as an angiogenesis inhibitor has not been established. To evaluate safety and potential effectiveness of thalidomide, we conducted a pilot study on 15 patients (9 M and 6 F) with recurrent glioblastoma multiforme, already treated also with chemotherapy with a KPS >/= 60. Serial serum or blood samples were obtained in the patients and in 11 healthy controls to analysize possible variations in TNF alpha, Interleukin 12, soluble thrombomodulin and metalloproteinase 9, factors involved in different phases of angiogenesis. 7 patients (47%) died within two months from treatment onset. 8 patients (53%) responded: 5 (33%) achieved stable disease and 3 (20%) partial response (3) lasting from 2 to 5 months. In the last three patients CT scans after two months of treatment showed a shrinking of tumor enhancing area.All patients could tolerate the drug. No significant variations of soluble trombomodulin and IL12 were detected, while a decrease of TNF a and MMP–9 levels occurred during thalidomide treatment. According to our results the drug should be considered worthy of futher investigation in the treatment of high grade gliomas.

P870
VINCRISTINE-INDUCED PERIPHERAL NEUROPATHY, RELATED TO DOSE-INTENSITY. CCP Verstappen, S. Koeppen, TJ. Postma, J. Heimans, Azvu, Klinikum Essen (Amsterdam, NL; Essen, D)

Introduction: Vincristine (VCR) has anti-tumor activity against lymphoproliferative diseases. The most frequent side effect of VCR is peripheral neuropathy. We describe a prospective study, in which VCR-induced peripheral neuropathy was evaluated in patients with non-Hodgkin's lymphoma and Hodgkin's disease.

Patients and methods: Two dose intensity groups were evaluated. One group of patients (n=47) received 2 mg of VCR at 3-weekly intervals (0.67 mg/week, low-dose intensity group). The other group of patients (n=74) received 4 mg of VCR at 3-weekly intervals (1.33 mg/week, high-dose intensity group). Neuro-

logical assessments, including a questionnaire on symptoms and a neurological examination, were performed after 4 and 8 mg of VCR, and 4 and 8 weeks after the last dose of VCR.

Results: In the high-dose intensity group more symptoms were reported during therapy ($p< 0.001$). Furthermore, off-therapy worsening was observed predominantly in the high-dose intensity group (64 % of patients). During vincristine therapy there were no significant differences in neurological signs between the two dose intensity groups. After the last dose, both groups showed a deterioration, which was significantly more pronounced in the high-dose intensity group (70 % of patients) compared to the low-dose intensity group (33 % of patients) ($p< 0.007$).

Conclusion: Symptoms, but not signs, occurred significantly more often in the high-dose intensity group during therapy. Off-therapy worsening occurred in a considerable number of patients, particularly in the high-dose intensity group. This phenomenon has not been described in earlier studies.

P871
REJECTION OF RAT GLIOMAS BY INTRA-TUMORAL INJECTIONS OF CPG OLIGODEOXYNUCLEOTIDES. G Auf, J Xie, JY Delattre, AF Carpentier, Salpêtrière Hospital (Paris, F)

Phosphorothioate oligodeoxynucleotides (ODN) containing a CpG motif activate various immune cell subsets and induce production of a wide variety of pro-inflammatory cytokines. We evaluate whether established 9L gliomas can be rejected in immunocompetent rats by intra-tumoral injections of ODN with (CpG-ODN) or without (IMM-ODN) CpG motifs. Fisher rats were inoculated with 9L cells into the right cerebral hemisphere or subcutaneously, and subsequently injected into the tumor bed with isotonic sodium chloride or CpG-ODN or IMM-ODN.

When 9L cells were implanted subcutaneously, all rats treated with saline developed tumors. Treatment with 100µg CpG-ODN on day 2, 5 and 9 after tumor inoculation resulted in a 93 % inhibition of the tumor volumes when compared to controls injected with saline (mean tumor volumes ± SEM on day 26: 1729 ± 261 mm^3 for controls, vs 45 ± 19 mm^3 for CpG-ODN treated rats, n=4 per group, $p< 0.001$). On opposite, treatment with IMM-ODN was inefficient, showing that CpG motifs are critical for the antitumoral effect.

When 9L cells were implanted intracerebrally, although no significant effect on survival was seen, CpG-ODN treatment induced 48 hours after the injections a 25 fold increase of CD8 positive cells and a 2 fold increase of NK cells within the tumor, when compared to controls injected with saline (mean of positive cells per 0.135 mm^2 field ± SEM: 101±41 vs 4±1 for CD8+ cells, $p=0.02$; 12±4 vs 6±4 for NK cells, p =n. s.). No significant infiltration with ED1+ cells (macrophages and microglial cells) were seen in controls or CpG-ODN treated animals.

In conclusion, immunostimulatory CpG-ODN can induce rejection of subcutaneous established gliomas and warrant further evaluation as a potential immunotherapeutic agent in glial tumors.

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CAN INTRATUMORAL DELIVERY OF MITOXANTRONE IMPROVE SURVIVAL IN RECURRENT GLIOBLASTOMA PATIENTS. A. Boiardi, M. Eoli, A. Salmaggi, B. Zappacosta, G. Broggi, A. Silvani, Besta (Milan, I)

We managed a group of 45 malignant recurrent GBM patients in an effort to improve survival by delivering mitoxantrone through an Ommaya reservoir (4 mg with 4 mg desamethasone as single local injection) twice monthly until tumour progression, in combination with a second line chemotherapy (PCV) systematically delivered for a mean of 5 cycles.

The choice of Mitoxantrone that kills both proliferating and non-proliferating cells was based on its potency and excellent antitumour activity. 25 patients had a second surgery before starting local treatment (group A), 20 patients (group B) were locally treated after tumour recurrence diagnosed by RM, without tumour debulking, and 27 (group C) did not receive local chemotherapy treatment but only PCV as all patients. The ST after tumour recurrence was 16.8, 9.2, and 5.8 in group A, B and C respectively {logrank 0.001 (A vs. C) and 0.02 (B vs. C)} Overall survival percentage at 24th month was 48 %, 30 %, and 5 % for group A, B, and C respectively. Locoregional mitoxantrone treatment, except for a mild to moderate increased local brain oedema, no other major side effect produced. Ommaya reservoir had to be removed in 5 patients, each managed with more than 20 injections, due to infection in one and to decubit of Ommaya in 4 cases occurred owing to drug linkage out of the reservoir. Association of locoregional mitoxantrone to systemic PCV did not increase haematological or liver toxicities. In view of both good tolerability and encouraging results, a therapeutic approach with concurrent local and systemic chemotherapy seems worthwhile pursuing in the treatment of recurrent GBM.

P873
BRAIN METASTATIC LESIONS IN CHILDREN WITH EWING'S SARCOMA. I. Shchurovska, A. Abramyuk, Regional Specialized Children's Hospital (LVIV, UKR)

In literature brain metastatic lesions (BML) are rarely reported in children with Ewing's Sarcoma (ES). The aim of study is to show the frequency of BML in ES patients, as well as its dependence of the primary locations. From January 1993 till January 2000 there were 16 patients with ES treated (10 boys and 6 girls). The age range was from 3 to 17 years (mean – 11,2). Eight patients had 15 metastases in different locations, where brain locations make 33 % of them. All BM were imaging modality identified, 3 were histologically confirmed. At the time BM were diagnosed all the patients had some neurological symptoms: headache (n=3), headache and hemiparesis (n=2). Location of primary lesions (PL) with metastatic involvement (MI) respectively were the following: PL Pelvis (n=6) with MI Brain (n=4), Spine (n=3), Lung (n=1), Bone Marrow (n=1), Rib (n=1); PL Rib (n=1) with MI Rib (n=1); PL Femur (n=4) with MI Spine (n=1); PL Humerus (n=1) without MI; PL Tibia (n=2) with MI Brain (n=1), Lung (n=1); PL Fibula (n=2) with MI Lung (n=1).

BM more often occur in cases of central, especially pelvis location of primary lesions (in 4 children of 6) than cases of peripherally located primary tumor, but this difference is not statistically significant (chi=2,01 p=0,18). It is our opinion oncologists must be more aware of the possibility of BM in ES patients (especially of central location) and should conduct the appropriate diagnostic procedure to exclude it.

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EPILEPSIA PARTIALIS CONTINUA AND FRONTAL FEATURES AS A DEBUT OF ANTI-HU PARANEOPLASTIC ENCEPHALOMYELITIS WITH FOCAL FRONTAL ENCEPHALITIS. J. Porta-Etessam, J. Benito-León, J. Ruiz-Morales, J.M Millán, A. Ramos, F. Bermejo P, Hospital "12 de octubre", Hospital Móstoles (Madrid, E)

Paraneoplastic limbic encephalitis (LE) is a particular manifestation of paraneoplastic encephalomyelitis. LE presents with a diversity of symptoms, like dementia, anxiety, amnesia, and confusion. The clinical picture is a subacute onset of confusion and reduction of short-term memory. The MRI study may be abnormal with increased signal on T2 weighted images involving the temporal lobes and the brain stem. The most important test is the detection of the anti-Hu antibodies in the serum and CSF. Shavit et al. described 3 anti-Hu positive patients who presented with clinical and electroencephalographic features of epilepsia partialis continua. The magnetic resonance imaging (MRI) of two of them showed a hyperintense nonenhacing focal lesion in T2 weighted images in sensorimotor area. We report a patient who presented with epilepsia partialis continua, a frontal syndrome and two focal lesions in the MRI.

A 66 year-old man was admitted due to a continuous involuntary clonic muscular twitching of the muscle of the left side of the face that he was suffering for 5 days. He also presented depression, personality changes with perseverance and inhibition in the month before admission. The examination demonstrated, beside the EPC, left grasping and palmomentonian sign and abnormal performance of Luria's manoeuvre (striking the table with palm, edge and fist successively). The EEG demonstrated periodic epileptiform discharges in the right frontal lobe. The head CT scan presented a right frontal, noncontrast enhancing, hypodense lesion without mass effect. MRI showed nonenhancing lesions involving gray and white matter in right frontal and medial bitemporal lobes in T2-weighted images (figure 1a & 1b). A chest CT showed a nodule in inferior lung lobe and the biopsy confirmed a small cell lung cancer. Anti-Hu antibodies were positive in the range seen in patients with paraneoplastic encephalomyelitis.

This patient presented with EPC and a frontal syndrome due to frontal focal encephalitis. The MRI findings, positive anti-Hu antibodies and clinical evolution of the patient support the paraneoplastic origin of the central nervous system lesions. Besides, a cranial CT scan performed a month later did not show any enhancement in the frontal lesion and there were no other signs to suggest the lesions had a metastatic origin. Unlike the previously reported cases our patient shows that multifocal T2-weighted images involving gray and white matter do not rule out possibility of PEM.

P875
LOW-GRADE GLIOMAS: CAN WE PREDICT THE SPREAD DIRECTION USING PROTON MR SPECTROSCOPY? K. Koprivsek, M. Lucic, V. Ivanovic, R. Semnic, V. Diklic, V. Baltic, Institute of Oncology (Sremska Kamenica, YU)

Purpose: Pathological studies have confirmed that the spread direction of intracranial gliomas is not random. Frontal lobe gliomas can extend via corpus callosum or via capsula interna. The aim of our study was: 1) to assess possible

differences in biochemical profiles within different parts of a glioma and 2) to determine spectral parameters of glioma part of which actually infiltrates into brain parenchyma.

Materials and methods: We performed a prospective study on twenty patients with untreated gliomas in frontal lobe. MRI at 1.5 T (SP 63 Siemens Magnetom) confirmed the low-grade of tumors after Gd-DTPA administration. MRS was performed using two sequences: STEAM 20 and SE 135. With two voxels (size 1.25 X 1.25 X 1.25) we covered the medial and posterior aspects of tumor (oriented towards corpus callosum and capsula interna). In the follow-up period, MRI was performed two times and in 16 patients tumor progression was found.

Results: All tumors exhibited abnormal 1H MR spectra, typical for low-grade gliomas. In 16/20 cases we found differences between biochemical profiles in different parts of tumor. The main difference was noted in levels of choline containing compounds and choline related ratios (Cho/tCr). In 9/16 gliomas the choline levels were higher in parts of tumor oriented towards corpus callosum; and in this group the MRI follow-up confirmed the extent of tumor to this structure. In 7/16 cases the choline levels were more elevated in posterior tumor parts; in this group the MRI follow-up showed tumor infiltration of capsula interna region in five cases. In 4/16 cases the gliom extends in both directions. In 4 cases neuroradiologists did not notice progression.

Conclusion: The parts of low-grade glioma with highest choline levels could be the parts with most intensive membrane metabolism, hence we can assume that those are the tumor parts that actually infiltrate into brain parenchyma. Therefore, choline levels could be taken as a predictor for infiltrative growth of low-grade gliomas and choline levels tracking could help in planning of guided biopsies, subsequent therapy and monitoring of tumor response.

P876
MORPHOLOGICAL AND CLINICAL STUDY OF BIOPSY AND AUTOPSY CASES OF THE PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL). V. Jovanovic, S. Dozic, V. Govedarovic, M. Skender-Gazibara, D. Cvetkovic-Dozic, M. Nagulic, Institute of Pathology (Belgrad, YU)

Aim: Anatomo-clinical features of the PCNSL will be presented. Extreme rarity of these tumors in the examined series remains to be explained.

Methods: Retrospective analysis of 29 biopsy and 2 autopsy cases of PCNSL was performed using standard histological and immunohistochemical methods. The following DAKO monoclonal antibodies were applied: LCA, CD45RA, CD20, CD3, Cytokeratin, Vimentin, Desmin, Neurofilament and GFAP. Clinical data were also available.

Results: In our biopsy series of 8386 primary tumors of central nervous system (CNS) there were 29 cases of PCNSL (0,34%). They were located in the cerebral hemispheres (28) and cerebellum (1). The mean age of the patients was 53.05 years and female to male ratio was 1.6:1. No patient was immunocompromised, without AIDS or HIV positivity. Phenotypic determination in all cases was of B-cell type. Histological subtypes (modified REAL classification) included follicular (19 cases), diffuse large B-cell lymphoma (DLBCL) (6), Burkitt-like (2), small lymphocytic B-cell (1) and lymphoplasmocytic lymphoma (1). Among follicular lymphomas predominated large cell proliferations (10 cases), then tumors with mixed small and large cells (6) and at last mostly small cell tumors (3). DLBCL were identified in 6 cases and one of them was of angiotropic type (intravascular lymphoma). Almost half of the PCNSL (14) represented large cell proliferations. All these neoplasms were of high grade malignancy including two cases of Burkitt-like lymphoma. The patients were treated with combined radio-chemotherapy. A 58-year old male and 69-year old female with follicular small cell lymphoma were alive three and two years respectively after surgery. Sixteen patients died during next two months, while 9 were with no data.

In autopsy cases (2) the PCNSL was diagnosed in 32-years old man and 30-years old female with location in the cervical spinal cord and medulla oblongata respectively. Histological analysis in both cases showed low grade lymphoma of lymphoplasmocytoid type.

Conclusion: According to our investigation the PCNSL with location in cerebral hemispheres were in the majority of cases of follicular and DLBCL type and favoured the relatively older age group. PCNSL of the cervical spinal cord and medulla oblongata (rare location) were small cell lymphomas, otherwise of low grade risk and were found in obviously younger age group. The biopsy cases of PCNSL are characterized by particularly extreme rarity (0.34% of the analysed primary CNS neoplasms) possibly because the examined series consisted only of immunocompetent patients. These tumors are of high grade malignancy, most frequent of follicular type, with poor prognosis regardless of the histological type of lymphoma.

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MOLECULAR ANALYSIS OF GLIOBLASTOMAS WITH OLIGODENDROGLIAL COMPONENT. J. A. Kraus, G. Reifenberger, K. Lamszus, U. Schlegel, Neurology, University Hospital, Neuropathology, University Hospital (Bonn, Hamburg, D)

Objective: This study aimed to characterize the molecular genetic alterations in "glioblastomas with oligodendroglial component."

Background: Glioblastoma (WHO grade IV) is usually associated with a poor prognosis despite multimodal therapy with radiation and chemotherapy. A small subset of malignant gliomas classified as glioblastomas according to WHO criteria, however, may contain regions with histological features of oligodendroglial differentiation. The molecular characteristics of these tumors are not known.

Methods: Fifteen of these tumors were analyzed for genetic alterations and/or expression of the TP53, CDKN2A, PTEN and EGFR genes. A subset of 11 tumors was additionally investigated for loss of heterozygosity (LOH) on chromosome 1p, 19q and 10q.

Results: Four of the 11 tumors investigated for LOH had allelic loss on 1p. One of these 4 tumors showed additional LOH on 19q. The tumors with LOH on 1p showed no LOH on 10q, lacked detectable PTEN and TP53 mutations, and demonstrated no EGFR overexpression. In contrast, the remaining 11 tumors showed alterations typically seen in high-grade astrocytic tumors, including TP53 mutation associated with p53 accumulation (3/11), nuclear p53 accumulation without TP53 mutation (5/11), EGFR overexpression (5/11), LOH on 10q (1/7), and PTEN mutation (1/11). Six of the 15 gliomas showed homozygous deletion of the CDKN2A gene, including 1 of the 4 tumors with LOH on 1p. The median survival time of the patients was 20.7 months.

Conclusion: Glioblastomas with oligodendroglial component share many genetic characteristics with classical glioblastomas, including frequent homozygous CDKN2A deletions, TP53 mutation/accumulation, and EGFR overexpression. However, LOH on 10q and PTEN mutation appear to be less common. Furthermore, a fraction of these gliomas shows allelic loss on 1p, a genetic alteration found to be associated with chemosensitivity and good prognosis in anaplastic oligodendrogliomas.

Neuro-ophthalmology

P878
THE DIAGNOSTIC ROLE OF VISUAL FIELDS IN OPTIC NEURITIS. M. Paschalidou, Ch. Terzidou, N. Georgiadis, T. Doskas, N. Halvatzis, I. Milonas, Ahepa Hospital Univ. of Thessaloniki (Thessaloniki, GR)

Background: To compare visual fields (VF) results and magnetic resonance imaging (MRI) results in patients presenting with optic neuritis (ON) in order to consider the ON as the first manifestation of multiple sclerosis (MS). Material and methods: We studied 22 patients, 17 women with age 19–49 years (mean 32.8) and 5 men with age 31–35 years (mean 31.6), with the diagnosis of ON during the last year. Seven patients with recurrent ON (5 bi and 2 unilateral) suffered from MS. All these patients presented with abnormal VF in both eyes. Fifteen patients presented with ON as the only clinical symptom. In 13 of them the ON was unilateral and in 2 patients bilateral. Nine out of 13 patients with unilateral ON presented with demyelinating lesions in MRI and abnormal visual fields in both eyes. In 6 out of 13 patients MRI results were negative for any lesion. Two of these patients with bilateral clinical indication presented with abnormal visual fields in both eyes. From the 4 patients with unilateral optic neuritis and negative MRI the VF were bilaterally affected in two patients. Conclusion: The MRI findings provide a strong indication for the characterization of ON as a first symptom of MS. The VF presenting bilaterally abnormal results in unilateral ON may increase the suspicion of MS.

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LEBER'S HEREDITARY OPTIC NEUROPATHY, HYDROCEPHALUS AND MULTIPLE SCLEROSIS-LIKE ILLNESS IN A MAN HARBORING THE 14 484 AND 15 257 MITOCHONDRIAL DNA MUTATIONS. Y. Boukriche, P. Aubert, H. Dehen, Beaujon Hospital (Clichy, F)

Leber's hereditary optic neuropathy (LHON) is a maternally inherited disease in which visual dysfunction is the only significant manifestation. A multiple sclerosis-like illness (MS like) has been infrequently described in association with LHON, mostly in women carrying the 11778 mitochondrial DNA (mt DNA) mutation. We report on a man harbouring both 14484 and 15257 mt DNA mutations with a MS-like illness and hydrocephalus.

Case report: A previously healthy 33 year-old man experienced painless vi-

sual loss in the right eye to 1/10 at age 28. Few weeks later, the left eye was similarly affected. At that time a CT scan and a brain MRI showed a tetraventricular hydrocephalus. A ventriculoperitoneal shunting was then performed, without any improvement. At age 31, he developed unsteadiness, numbness and weakness in both legs. Two years later, he was admitted to our hospital. On examination, visual acuity was 1/20 in both eyes. Both optic discs were pale and there were large bilateral central scotoma. The pupillary reflexes to light were slow. Neurological examination showed a spastic paraparesis with bilateral Babinski sign, brisk reflexes, sustained knee and ankle clonus. There was a wide-based ataxic gait with rombergism, impaired cutaneous sensation below T10. He also had urgency of micturition and impotence. MRI of the spinal cord was normal on two occasions. A lumbar puncture revealed 2 lymphocytes/mm^3, increased protein level to 0,6 g/L, increased Ig G production to 200 mg/L (normal: 10–45) with oligoclonal band. Brainstem auditory evoked potentials showed an increased latency for the left wave V. Pattern evoked visual potentials could not be recorded. There was no family history of neurological or ophthalmological disease. MRI of the brain again showed a tetraventricular hydrocephalus and a hyperintense signal in the left centrum semiovale. His final visual acuity was counting fingers. The patient was found to harbour the 14484 and the 15257 mt DNA mutations.

Discussion: it seems to be the second report of LHON with a MS-like illness associated with the 14484 mt DNA mutation. Hydrocephalus has never been reported in LHON. We suggest that LHON may account for hydrocephalus.

P880
REVERSIBLE BLINDNESS AFTER BILATERAL OCCIPITAL ABSCESSES. M. Dupuis, J. Fakih, G. Dardenne, F. Coche, Clin. Saint-Pierre (Ottignies, B)

A 28-year-old cook was referred to our hospital on April 26, 1997 with nausea and visual loss. Despite numerous diets, his weight was 153 kg for 183 cm and he had undergone a gastroplasty two months before. Muscle dehiscence and wound sepsis occurred after surgery, as well as lasting nausea, gastric ulcus and slimming of 46kg. On April 23, headaches and visual loss were noted. On April 26, bilateral visual acuity was 2/10 with central scotoma, colours perception disturbances, normal photomotor reflex and fundus. Notwithstanding vitamins B complexes prescription, he discerned only hand movements on April 29. He complained of headaches and blindness. No other neurologic deficit was demonstrated. He had no fever. Leucocytosis was $11,650x10^3$/L with a normal differential count. C-Reactive Protein was 154,000 mg/L. Cerebral Ct-scan and MRI showed bilateral lesions measuring 42x34x33mm on the right and 37x30x40mm on the left, with central hypodensity surrounded by a thick irregular contrast enhancement and oedema suggesting abscesses. On April 30, yellow odourless pus was collected through a bilateral external drainage. Streptococcus viridans grew from the culture of both cerebral and abdominal samples. Post-operative leucocytes scintigraphy detected only a small hyperactive area at the abdominal wound. Transthoracic and transesophageal echocardiography was normal. Under external drainage and adequate antibiotherapy, the patient's vision improved. After 3 days, he was able to distinguish colours. Visual acuity was 1/10 on May 6 and 10/10 on May 29. On November 5, only a small bilateral inferior paracentral scotoma remained. He resumed work on July 15 and drove his car.

In this case, the history of severe weight loss after diet and gastroplasty led at first to incriminate a vitamin deficiency with optic neuropathy. Actually, the almost total blindness with preserved photomotor reflexes proved to be due to bilateral occipital abscesses. Cortical or cerebral blindness (CB) refers to loss of vision produced by lesions affecting geniculocalcarine visual pathways. In this case report, mass effect on these visual pathways explains as well the visual symptoms, including colour agnosia, as the quality of recovery. No fever was noted as usual with brain abscesses. We found in the literature reports of hemianopia due to contralateral abscess but no other case of bilateral abscesses inducing CB. CB is reported mainly after bilateral occipital strokes and less often after various conditions including eclampsia, angiography, trauma, neoplasm, toxics, porphyria, adrenoleukodystrophy, Krabbe's disease, subacute sclerosing panencephalitis, progressive multifocal leukoencephalopathy and acquired immunodeficiency syndrome, bacterial meningitis. Bilateral occipital abscesses have to be added to this list. According to this first case report a good recovery of CB is possible despite severe visual loss and voluminous mass effect on Ct-scan.

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EALES DISEASE AND CENTRAL NERVOUS SYSTEM INVOLVEMENT: A CASE REPORT. S. Zoccolella, G. Palagano, G. Durante, P. Tronci, C. Andreula, G. Iliceto, L. Serlenga, P. Lamberti, University Of Bari, Dept Of Neurological Sciences, University Of Bari Ospedale Policlinico (Bari, I)

Eales Disease (ED) is an uncommon idiopathic disorder characterized by retinal perivasculitis and recurrent vitreous hemorrhages. ED is more common in India and Middle East. Extraocular involvement is rare and usually confined to Central Nervous System (CNS); acute\subacute myelopathy is the most frequent neurological manifestation. The diagnosis is based on clinical grounds, Ocular Fundus Examination (OFE) and Fluorescein Angiography (FA). We report the case of a young woman with ED and CNS involvement. CASE DESCRIPTION: A 26 year old female presented acute visual loss in the right eye; OFE revealed bilateral retinal vasculitis with vasal sheathing and vitreal torpidity. The FA showed vasal staining and leakage, micro and macro aneurisms and retinal ischemia. 15 days later she began to complain of headache, vomiting, ataxia. After one week she became confused, dysphagic, anarthric; deep tendon reflexes were increased with bilateral Babinski sign. On blood investigations there was a neutrophilic leukocytosis; in addition, immunocomplexes were increased. CSF analysis showed a high content of proteins (80 mg/dl), without intrathecal oligoclonal bands. Diffuse theta-delta activity was evident on EEG. MRI of the brain revealed multifocal hemispheric and brainstem abnormalities and, one week later, a diffuse leptomeningeal impregnation. Neurological features and EEG abnormalities improved after one week of corticosteroid treatment with Dexamethazone (12 mg daily). In addition, CSF protein content and blood immunocomplexes returned to normal values and MRI multifocal abnormalities were reduced. An OFE and FA control revealed an increase of retinal ischemia and showed neovascularization, therefore laser retinal photocoagulation was carried out. On discharge, the clinical picture of the patient was characterized by a cerebellar-piramidal syndrome. One year later, the FA showed further ischemic retinal areas with neovascularization, therefore laser photocoagulation was again necessary. In addition, the patient developed secundary generalized partial seizures. EEG revealed focal slow abnormalities on the right temporal region, while cortical and cerebellar atrophy was detected on MRI. Treatment with carbamazepine (800 mg daily) was then started with a complete control of epileptic seizures. CONCLUSIONS: Clinical and MRI features of this case suggest that ED, although rare, should be considered in the differential diagnosis of Multiple Sclerosis.

P882
BILATERAL PERIPHERAL RETINAL NEOVASCULARIZATION IN A PATIENT WITH MULTIPLE SCLEROSIS. J Katsimpris, K. Flampouriary (Genève, CH)

A 32 year-old man was admitted to our clinic for evaluation of a sudden onset decrease of vision in the left eye. Patient's medical history revealed the presence of multiple sclerosis. The disease had started 10 years ago, and has been characterized as relapsing remitting. Also from the ophthalmological history there was a reference of an attack of retrobulbar neuritis in the left eye three years ago. On examination the visual acuity was 20/20 in the right eye and 2/20 in the left eye. The intraocular pressure was 15 mmHg and 17 mmHg for the right and left eye respectively. Slit lamp biomicroscopy did not reveal any abnormality in the anterior segment in both eyes. Pupil responses to light stimulation were elicited normally. Fundoscopy in the left eye showed the presence of intravitreal hemorrhage and the presence of peripheral neovascularization. Additionally we were able to observe the occlusion of the peripheral retinal vein and the obstruction of the capillary bed distal to the site of the neovascularization. Also during fundoscopy of the right eye peripheral neovascularization without signs of intravitreal hemorrhage was observed. After the initial ophthalmological evaluation fluorescein angiography and color fundus photography were done. In the arteriovenous phase of the left angiogram there was hyperfluorescence of the peripheral neovascularization while in the later phase there was a marked leakage of the fluorescein associated with venous wall staining. The presence of peripheral neovascularization was also evident in the retinal periphery of the right eye. Besides the ocular and neurological examination a thorough systemic and laboratory examination was done in an effort to exclude other ophthalmic and systemic diseases that probably coexisted with multiple sclerosis and provoked peripheral retinal neovascularization. All these tests and examinations were negative. Retinal vasculitis may be occasionally observed in patients with multiple sclerosis in the general context of immunological mediated vasculitis. This vasculitis is particularly affecting the retinal venous system causing retinal capillary ischemia that subsequently leads to peripheral retinal neovascularization.

P883
POST LUMBAR PUNCTURE HEADACHE IN PATIENTS WITH PSEUDOTUMOR CEREBRI. I. Biran, O. Abramsky, Hadassah Medical Center Ein-Kerem (Jerusalem, IL)

Objective: To investigate the occurrence of post lumbar puncture (LP) headache in patients with pseudotumor cerebri (PTC).

Background: PTC is characterized by headache, papilledema, normal CSF composition and normal imaging. The intracranial pressure is elevated and one of the suggested therapeutic modalities is repeated lumbar punctures. The occurrence of post LP headache is regarded as a rare and unexpected phenomenon.

Methods: We retrospectively analyzed the records of patients with PTC and extracted demographic and clinical data. The diagnosis of PTC was based on the clinical course, elevated intracranial pressure with normal CSF composition and normal brain imaging. The occurrence of post LP headache was recorded. Post LP headaches were defined as headaches following LP, differing from the patients' preceding headaches and accompanied by vomiting, nausea or aggravation on standing and sitting.

Results: There were 52 patients with PTC, 48 women and 4 men. Their average age was 29.3 (range 12–70). Post LP headache occurred in 19 of the patients (33%), and in 4 of them it occurred more than once. The patients had a total of 109 LPs, out of which 26 were followed by post LP headache (23%). The occurrence of post LP headache did not correlate with the opening pressure (31.9 cm H_2O for LPs followed by post LP headache as compared to 32.7 cm H_2O for LPs without post LP headache), age, initiation of acetazolamide therapy, drainage of large quantities of CSF (done in 3 patients) and the interval from preceding LPs. The patients were usually treated with analgetics and in some cases with blood patch, prednisone or reduction in the dose of acetazolamide.

Conclusion: Post LP headache are more common in PTC patients than previously reported and their prevalence in this population is as high as their prevalence in patients without PTC. It seems that the elevated intracranial pressure does not protect PTC patients from the development of this headache and that the occurrence of post LP headache does not preclude the diagnosis of PTC.

P884
CAN PUPILLOGRAPHY DIFFERENTIATE OPTIC NEURITIS FROM ISCHEMIC OPTIC NEUROPATHY? D. M. Bittner, B. Wilhelm, H. Luedtke, H. Wilhelm, University of Ulm, University of Tuebingen (Neuro-ophthalmology) (Ulm, Tuebingen, D)

OBJECTIVE The goal of the current study was to examine whether pupillography can differentiate between optic neuritis (ON) and anterior ischemic optic neuropathy (AION).

BACKGROUND Frequently ON and AION can be distinguished clinically. However in a number of cases diagnosis remains uncertain mainly because there is no objective method that reliably allows a differentiation. One study showed a prolonged pupillary light reflex (PLR) latency in ON compared to AION. Our aim was to evaluate if this difference allows increased diagnostic certainty for diagnosis finding.

DESIGN/METHODS 14 Patients with clinically confirmed unilateral AION (age 46–81y) and 29 with unilateral ON (age 13–54y) initially seen in the out-patient clinic of the neuro-ophthalmology department at the University Eye Hospital Tuebingen were studied. The relative afferent pupillary defect (RAPD) and the pupillary light reflex (Compact Integrated Pupillograph, AMTech, Weinheim) were measured. In pupillography a dim (basic) stimulus was applied in the healthy eye of the patients while in the affected eye according to the initially measured RAPD a brighter light intensity was applied. This situation was defined as compensation constellation.

RESULTS In the affected compared to the healthy eye amplitude, latency and quotient of amplitude divided by latency of the pupillary light reflex were impaired in 85 to 100% of the cases (mean difference in latency: 16–27 ms; in amplitude: 0.2–0.35 mm). The approach of the pupillary response in the affected compared to the healthy eye succeeded almost perfect for AION while in ON a substantial difference remained such that now in the affected eye a much more intense response was present (in amplitude 0.14 mm and in latency 16.7 ms; $p< 0.01$). These differences between AION and ON became significant for amplitude ($F=1.22$; $p=0.026$) and the quotient of amplitude and latency ($F=1.69$; $p=0,022$). Depending on the parameter ON could be separated from AION with a maximum sensitivity of 78.6% and specificity of 85.7%.

CONCLUSION We can conclude that 1. the pupillary light reflex seems to be a reliable measure in detecting demyelinating optic neuritis and non-arteritic anterior ischemic optic neuropathy, that 2. using a special design (compensation constellation) there are clear differences in amplitude and quotient of amplitude divided by latency between both entities.

P885
CORRELATION BETWEEN HEAD-SHAKING NYSTAGMUS AND NICOTINE-INDUCED NYSTAGMUS: DO BOTH INDICATE A LATENT VESTIBULAR TONE IMBALANCE? S. von Stuckrad-Barre, M. Strupp, K. Jahn, O. Kolev, T. Brandt, Ludwig-Maximilians University Klinikum Grosshadern (Munich, D)

There is good evidence that the direction of head-shaking nystagmus reflects a latent central or peripheral imbalance of the vestibulo-ocular reflex (VOR). We hypothesize that the interindividually varying, but intraindividually consistent directions of the nicotine-induced nystagmus are also due to a latent tone imbalance of the VOR. Therefore, we examined the separate and combined effects of the head-shaking maneuver and nicotine to evaluate differential effects of both stimuli on the occurrence and the direction of induced nystagmus. Two-dimensional video-oculography with an infrared camera (integrated in a mask to prevent any perception of ambient light) was used to record eye movements in the horizontal and vertical directions in 12 healthy subjects (non or occasional smokers) (a) prior to, (b) 1, 5, and 10 minutes after smoking a cigarette, and/or (c) before, and (d) after horizontal head-shaking at 3 Hz for 20 sec. Five of the 12 subjects showed neither head-shaking nor nicotine-induced nystagmus. All subjects with a head-shaking nystagmus (6 of 12) exhibited a nicotine-induced nystagmus (1 or 5 min after smoking). One additional subject had nicotine-induced nystagmus but no head-shaking nystagmus. The combination of both stimuli caused an increase of the peak slow phase velocity of the nystagmus in 6 of the 7 subjects. The direction of the head-shaking and the nicotine-induced nystagmus was identical in 6 of 7 subjects. Conclusion: The hypothesis that nicotine – like the head-shaking maneuver – discloses a latent individual tone imbalance is supported by three observations: (1) the strong intraindividual correlation of the occurrence, (2) the identical directions of both nystagmus forms, and (3) the additive effects when both stimuli were combined.

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VESTIBULAR IMBALANCE ELICITED BY UNILATERAL LESIONS OF THE INTERSTITIAL NUCLEUS OF CAJAL (IC) IN THE ALERT MONKEY. C. Helmchen, H. Rambold, U. Büttner, Medical University of Lübeck, University of Munich (Lübeck, München, D)

The midbrain interstitial nucleus of Cajal (iC) is part of the neural integrator for vertical and torsional eye movements. Vertical-torsional nystagmus after iC lesions is thought to be a result of the failure of the neural integrator. In this case, nystagmus components are expected to be conjugate in both eyes with parallel rotation axes. In contrast, in the case of a vestibular imbalance of the vestibular projections to/from iC, nystagmus on both eyes may be asymmetric, with disconjugate rotation axes.

To test both hypotheses, we investigated the conjugacy of vertical-torsional nystagmus after unilateral reversible iC inactivations (Muscimol) in the alert monkey using binocular three-dimensional search coil recordings. Rotation axes of spontaneous nystagmus in gaze straight ahead position were compared with the eye muscle rotation axes, which were corrected for the tonic ocular torsion on both eyes elicited by the iC inactivation. All injections in the region of iC elicited vertical-torsional spontaneous nystagmus in both eyes. Amplitudes of quick phases of nystagmus in both eyes and their rotation axes differed between both eyes on gaze straight ahead. Thus, the rotation axis of the contralesional eye was always vertical whereas the ipsilesional eye had a vertical-torsional rotation axis. It resembles the stimulation effects of the anterior canal afferents in the animal experiment (Tokumasu et al. 1971).

We propose that a failure of the descending projections from iC to the vestibular nuclei might functionally lead to an excitation of the ipsilesional anterior semicircular canal. Thus, in addition to the deficient neural integrator, a vestibular imbalance may contribute to the vertical-torsional nystagmus after iC inactivations.

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PTOSIS IN PATIENTS WITH HEMISPHERIC STROKES. L. Averbuch-Heller, V. Mermelstein, L. Zagalsky, J. Streifler, Rabin Medical Center (Tel Aviv, IL)

Objectives: To study eyelid dysfunction in patients with hemispheric cerebrovascular events.

Background: Cerebral ptosis is considered rare; it has been reported with unilateral, usually right, hemispheric lesions. However, the frequency of cerebral ptosis is unknown; it may be underestimated since patients' inability to open their eyes can be mistakenly ascribed to drowsiness. To date, eyelid dysfunction in stroke patients did not receive systematic study.

Design/Methods: We studied 50 consecutive patients with acute hemispheric stroke. Their eyelid function was assessed within 48 hours of admis-

sion, including palpebral fissures (PF), marginal reflex distance (MRD) and levator excursion. Patients underwent neuro-ophthalmologic evaluation of pupils, ocular motility, visual fields, and visuo-spatial neglect, using standardized testing paradigms. Brain CT was obtained in all patients. Patients with lack of cooperation, signs of brainstem dysfunction, levator dehiscence, and dermatochalasis were excluded. As a control group, 50 age-matched patients admitted to internal medicine ward without known neurological disease underwent evaluation of their eyelid function.

Results: Twenty-three patients (46%) had neurogenic ptosis, as reflected by PF 8 mm and MRD 1.5 mm. CT demonstrated right-sided lesions in 10 patients and left-sided in 11; in two, no focal lesion was observed. Two types of CT findings were consistently associated with ptosis: (1) unilateral, extensive MCA infarctions or hemorrhages; (2) bilateral lacunar lesions involving the basal ganglia and internal capsule. Complete ptosis, with PF 3 mm, was found in seven patients, mostly with right hemispheric events (5/7). In 15 patients, ptosis was bilateral and symmetric; it was usually associated with right hemispheric events (9/15). In eight patients, ptosis was unilateral or highly asymmetric, worse ipsilesionally (6/8); this was usually associated with left hemispheric events (7/8). Ptosis was accompanied by horizontal gaze deviation in 11 patients, and upgaze limitation in ten. On the other hand, of non-ptotic patients only four had gaze deviation, and two – upgaze limitation. In four patients with massive MCA infarction, complete bilateral ptosis was the first sign of imminent herniation, preceding pupillary dilation and ocular motor deficits. One patient developed blepharospasm, two patients – apraxia of eyelid opening. None of the control subjects had neurogenic ptosis; three had mechanical ptosis due to levator dehiscence (2) or dermatochalasis (1).

Conclusions: Ptosis occurs frequently in patients with hemispheric strokes. Complete bilateral ptosis is usually caused by massive right-sided lesions and may be a premonitory sign of an impending herniation. Association with horizontal gaze deviations implicates abnormal visuo-spatial attention in the pathogenesis of cerebral ptosis. Concurrent deficits of eye opening and upgaze argue for common control of the eyelids and the eyes on the cortical level.

P888
JUVENILE NEURONAL CEROID LIPOFUSCINOSIS – OPHTHALMOLOGICAL FINDINGS. J. Katsimpris, K. Flampouriari (Genève, CH)

The neuronal ceroid lipofuscinoses are a group of inherited neurodegenerative disorders. These disorders are characterized by the accumulation of storage material in the neurons and also in other cell types. The diseases can be differentiated into several subgroups according to age of onset, the clinical picture, neurophysiological and neuropathological abnormalities and special ultrastructural studies with regard to the different types of the storage material.

We present a 5-year-old girl that progressively developed a diminution in her visual acuity affecting both of the eyes. Gradually the visual field and the colour perception were affected also. After two years follow up the visual acuity was diminished only to light perception. During this period of observation seizures appeared that were medically treated together with a slow psychomotor and intellectual deterioration. EEG was pathological while the MRI examination of the brain was normal. Fundoscopy with colour photography and fluorescein angiography were done showing major alterations in the posterior pole affecting especially the macula. The clinical picture resembled bull's eye maculopathy. The ERG was abolished in both eyes.

The final diagnosis was made from the neuropediatric and cytologic examination. Electron microscopy of the peripheral lymphocytes was positive.

Although there is no therapy for this disease the ophthalmologist should be aware of this rare disease. The combination of the fundoscopic findings with the neurological findings usually leads to the definite diagnosis.

P889
AGE-DEPENDENT DISTRIBUTION OF HSV-1 IN HUMAN GENICULATE, VESTIBULAR, AND SPIRAL GANGLIA. V. Arbusow, M. Strupp, P. Schulz, T. Brandt, Klinikum Grosshadern (Munich, D)

A reactivation of herpes simplex virus type 1 (HSV-1) in human temporal bone ganglia is suspected to cause Bell's palsy, vestibular neuritis, and sudden hearing loss. Using the nested polymerase chain reaction we examined the age-dependent distribution of HSV-1 in 40 human temporal bones in three groups: five young children (3 months to 7 years; 10 temporal bones), seven young adults (14–40 years; 14 temporal bones), and eight older adults (41–85 years; 16 temporal bones).

HSV-1 was found in 60% of the geniculate ganglia (GG) of the children, indicating that infection occurs early in life. If the vestibular ganglia (VG) were infected in this age group (20%) there was regularly an infection of the GG of the same temporal bone. This finding is compatible with primary infection of the GG (via chorda tympani) and secondary viral migration along preformed facio-vestibular and vestibulo-cochlear anastomoses.

In the two adult groups the frequency of HSV-1 latency in the GG was about the same (57%), indicating no relevant infections of this ganglion during adulthood. The frequency of HSV-1 infection in VG and spiral ganglia (SG) was significantly higher in the adults (VG 50–57%, SG 50–56%) than in the children (VG 20%, SG 0%), indicating involvement of these ganglia during adolescence and young adulthood. Four possible mechanisms are proposed to explain this pattern of viral distribution: (1) viral migration along anastomoses, (2) direct infection of the VG and SG, (3) viral migration from one temporal bone to the other via central vestibular commissural fibers, and (4) hematogenic infection by HSV-1 infected T-lymphocytes.

P890
PHOBIC POSTURAL VERTIGO: BODY SWAY DURING OPTOKINETICALLY INDUCED ROLL VECTION. V. Querner, S. Krafczyk, M. Dieterich, T. Brandt, Kinikum Grosshadern, Univ. of Munich (Munich, D)

Phobic postural vertigo (PPV) is a frequent somatoform condition, characterized by a dissociation of subjective postural instability and objectively maintained balance skills. Patients with PPV typically report feeling off balance when looking at moving scenes, such as flowing traffic or crowds of people; however, they do not fall. Therefore, we measured body sway during normal upright stance in 22 patients with PPV (m: f = 16: 6; mean age 40 years) while looking into a half-hemispheric, rotating dome (60 cm in diameter), whose inner surface was covered with randomly distributed colored dots (rotation around the line of sight at 4°/s). Fifteen normal subjects (m: f = 10: 5; mean age 33 years) served as controls. Body sway was determined in fore-aft and lateral directions, and total displacement of the center of foot pressure (COP) was calculated for periods of 22 s a) at the beginning of large-field roll motion stimulation and b) one minute later after the end of stimulation. Normal subjects exhibited an increased body sway and a mean displacement of COP of 1.82 cm (± 1.73; range 0 to 5.1 cm) in the direction of stimulus motion. This displacement occurred about 10 s after stimulus onset and was associated with the perception of apparent counterclockwise self-rotation (roll vection). Following termination of the stimulus, body sway and COP returned to normal pre-stimulus values within about 20 s. Patients with PPV also experienced roll vection after about 10 s of stimulation. Their body sway also increased, however without a relevant direction-specific deviation of COP (0.25 cm ± 0.83 in stimulus direction; range 0 to 2 cm; Student's t-test between both groups: $p < 0.001$). The smaller deviation of upright stance during roll vection stimulation in the patients might have two possible explanations: a) the balance control of PPV patients is less dependent on visual input or b) under stimulus conditions that create a mismatch between multisensory inputs the misleading visual stimulus is largely disregarded in favor of the more reliable proprioceptive (muscle spindle input) and vestibular signals.

Peripheral neuropathy

P891
CHRONIC MILLER-FISHER SYNDROME ASSOCIATED WITH SEVERE DYSAUTONOMIA AND IGG MONOCLONAL GAMMOPATHY. P. Meynieu, P. Krystkowiak, T. Stojkovic, J. F. Hurtevent, J. D. Guieu, A. Destee, University of Lille Hôpital Roger Salengro (Lille, F)

Miller-Fisher syndrome is a form of acute inflammatory polyneuritis. Chronic forms are rarely described. We report the rare case presenting with a chronic form of Miller-Fisher syndrome associated with severe dysautonomia and benign monoclonal gammopathy of IgG Kappa type. Case report: A 40 year-old woman presented with a subacute distal lower and upper limb sensory impairment associated with pain and dysesthesia. Later on, abducens oculomotor palsy causing diplopia, loss of proprioception, deep tendon reflexes abolition and severe orthostatic hypotension progressively appeared. Serum immunoelectrophoresis revealed a monoclonal IgG Kappa paraprotein. Antisulfatide antibodies were positive. Antiglycolipids antibodies were negative. Motor, sensory nerve conduction study and F wave latencies were normal. H reflexes were absent. Needle EMG study was normal. Cutaneous sympathic reflex was normal but anal and urethral electromyogram showed neurogenic pattern. Sensory evoked potentials produced by stimulation of the median nerve showed proximal conduction blocks. Intravenous human immunoglobulin treatment (IgIV) improved the symptoms within one week. However, she had to be treated by IgIV every six weeks during two years. Discussion: Dysautonomia is rarely reported in chronic form of polyradiculoneuritis. Pathogenicity of the monoclonal immunoglobulin may be discussed, but the presence of anti-sulfatide antibodies suggests that the association with polyneuropathy may be not fortuitous. The clinical presentation may suggest that the monoclonal gammopathy could impair the function of ion channels. Conclusion: Chronic Miller-Fisher syndrome

associated with dysautonomia may be a new variant of polyneuropathy associated with IgG Kappa gammopathy.

P892
COMPARISON OF DIFFERENT THERAPEUTIC APPROACHES IN CIDP. V. M. Martic, Military Medical Academy (Belgrade, YU). Vesna Martic[1], Danilo Vojvodic[2], Stevan Petkovic[1], Toplica Lepic[1], Aco Jovicic[1] – Dept. of Neurology 1, In. med. res. 2 Military Medical Academy, Belgrade, Yugoslavia

The term autoimmune would be ideally applied to those diseases where it is possible to demonstrate the pathogenic role of the autoimmune process, excluding those situations where the production of autoantibodies is an epiphenomenon occurring after tissue damage. As the role of autoantibody synthesis in some chronic inflammatory demyelinating polyradiculoneuropathies (CIDP) is still unclear, we prefer to define it as immune related rather than autoimmune neuropathies. Because of that, it is a difficult question which therapy is the best for the CIDP.

Patients and methods: Of the patients with chronic polyneuropathy, 35 CIDP patients who fulfilled the diagnostic criteria proposed by the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force (1990) were evaluated. Serum samples from all CIDP patients were tested for anti-GM1, anti-MAG and anti-sulfatide antibodies. On the initial and all subsequent (1,5 months) patient controls, Manual Muscle Strength testing and Medical Research Council scale were used to grade muscle weakness for a period of one year. Objective sensory loss and loss of tendon reflexes was evaluated too.

Patients were divided in four groups: the first group was treated with intravenous 5S human immunoglobulins (10 patients), the second was treated with corticosteroids and azatioprine (10 patients), the third with plasma exchange and corticosteroids (10 patients) and fourth with intravenous 7S human immunoglobulins (5 patients).

Conclusion: In patients treated with plasma exchange and corticosteroids the most rapid improvement occurred. This observation cannot distinguish whether the responsible agents are antibodies or other soluble factors with immunoregulatory activity.

P893
AUTONOMIC DYSFUNCTION IN EXPERIMENTAL AUTOIMMUNE NEURITIS: HEART RATE. N.-S. Wang, J. Chapman, R. Rabinowitz, S. Viskin, A. D. Korczyn, Tel Aviv University (Tel Aviv, IL)

Autonomic nervous system (ANS) dysfunction occurs in about 50% of Guillain-Barre syndrome (GBS) patients and is an important cause of death in the disease. In this longitudinal study we examined heart rate (HR) changes in an animal model of GBS, experimental autoimmune neuritis (EAN) induced by immunization with myelin extracted from bovine spinal roots. The animals developed various degrees of motor weakness that coincided with significant weight loss and hypothermia. HR was measured in 33 EAN rats at rest (rHR) and following stressful stimulation (sHR). Average pre-immunization rHR was 341±28 beats per minute (bpm) and sHR was 486±21 bpm ($p< 0.001$). Although the mean rHR in rats with EAN was not significantly different compared to their baseline, there was a significant increase of variation of rHR with some rats demonstrating extreme bradycardia (2/33) or tachycardia (10/33). During the disease course sHR was significantly lower ($p< 0.01$) and especially in rats with clinical degree 5–7 (on a scale of 0–8, $p< 0.01$) than in pre-immunization, suggesting a specific impairment of the sympathetic system. These findings may serve as a basis for testing treatments of ANS dysfunction in EAN.

P894
MILLER FISHER SYNDROME ASSOCIATED WITH DENTATE NUCLEI LESION ON MRI. M. Coustans, V. Golfier, S. Drapier, X. Morandi, M. Vérin, G. Edan, University Hospital Pontchaillou (Rennes, F)

OBJECTIVE: To report a patient with symptoms and signs meeting the criteria of the Miller-Fisher syndrome where ataxia might be explained by a central nervous involvement of cerebellum.

BACKGROUND: The mechanisms of this syndrome have been controversial especially for ataxia. Whether ataxia is due to dysfunction of the central or peripheral nervous system is not known. MRI are usually normal, but some authors described abnormalities of central nervous system.

CASE REPORT: A 63-year-old man awakened with gait ataxia and bilateral upper limb paresthesia, 8 days after a regressive bilateral otalgia. On admission to Rennes hospital two days later, neurological examination disclosed severe limb and gait ataxia, areflexia, without limb weakness. No sensory dysfunction was detected on clinical examination. On the third day his condition worsened, with major static and kinetic cerebellar ataxia, proximal upper limb weakness, and oculomotor disability with left external ophthalmoplegia and bilateral ptosis. Lumbar puncture produced clear acellular cerebrospinal fluid (CSF) with protein content of 0.4 g/l. A second lumbar puncture (ten days after admission) produced 3 normal lymphocytes and raised protein (1,13 g/l). Electrophysiological study revealed normal nerve conductions, reduced sensory potentials and axonal damage on electromyography. MRI of the brain showed in axial T2 weighted symmetric hyperintensity of both dentelate nuclei. He was treated with intravenous immunoglobulins and recovery started shortly after. Three months later no neurological abnormality was evident, except areflexia. MRI controls three and six months later showed regression of dentelate nuclei lesions.

CONCLUSION: This patient presented an acute illness characterised by ataxia, ophthalmoplegia and areflexia, according to Miller Fisher syndrome. Ataxia was the predominant feature, with inability to walk, dysmetry, despite normal sensory modalities on clinical examination. Our MRI findings indicate that the origin of ataxia might be explained by a central nervous system involvement, especially the dentelate nuclei.

P895
CHARCOT-MARIE-TOOTH PROJECT IN CZECH REPUBLIC – RESULTS OF 3 YEAR CLINICAL, ELECTROPHYSIOLOGICAL AND MOLECULAR GENETIC STUDY. COOPERATION WITH CZECH C-M-T ASSOCIATION. P. Seeman, R. Mazanec, M. Ctvrteckova, S. Hrusakova, B. Rautenstrauss, Charles University Prague 2nd School of Medicine, University Erlangen (Praha 5, CZ; Erlangen, D)

Charcot-Marie-Tooth (CMT) diseases are with the reported incidence of 1: 2500–5000 a common hereditary peripheral nerve disorder. A similar phenotype is genetically heterogeneous with more than 18 known different responsible chromosomal localisations. Up to now four responsible genes including peripheral myelin protein 22 (PMP22), connexin 32 (Cx32), myelin protein zero (MPZ) and early growth response 2 (EGR2) are known.

Since 1997 molecular genetic tests for CMT are available in Czech Republic (CR). We use our own detection method for the most common mutation on 17p11.2–12 based on microsatellite markers from the critical region. Our department is the only one performing DNA testing for CMT in all the Czech Republic with 10000000 inhabitants. Vast majority of CMT patients is therefore concentrated in our department. More than 400 patients from more than 150 families were tested for the 17p rearrangement and for mutations in connexin 32 (Cx32) and myelin protein zero (MPZ) genes during the three years period. Due to a close cooperation with clinical neurologists and geneticians a CMT mutation could be found in more than 50% patients. Direct sequencing of Cx32 gene is used in families, without male to male transmission after exclusion of 17p rearrangement. Direct sequencing of coding region of MPZ is used in severely affected patients with Dejerine-Sottas syndrome (DSS). All DNA confirmed CMT1A, HNPP and Cx32 patients are reexamined clinically and electrophysiologically by one neurologist. Resulted data and experiences are used for improvement of clinical and electrophysiological criteria for CMT and its subtypes before molecular genetic tests.

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Abstracts arrived after the editorial deadline

HEREDITARY DEMYELINATING DISORDERS OF THE CENTRAL NERVOUS SYSTEM. O. Boespflug-Tanguy (Clermont-Ferrand, F)

Introduction of magnetic resonance imaging (MRI) techniques has completely changed the recognition of white matter diseases and of its main component, the myelin. However affections of the white matter including myelin, glia, blood vessels and axons are common in diseases of the central nervous system (CNS). Therefore numerous abnormal signals of the white matter on MRI are not related to primary myelin disorders. In the acquired myelin disorders, normal formed myelin is destroyed by endogenous or exogenous noxious agent leading to a demyelination process. The most important representative of this group is multiple sclerosis. In the hereditary forms we are dealing with inborn errors of myelin synthesis, maintenance or breakdown leading to a mix of hypo-, dys- or de-myelination. Deterioration of motor function is the most common presentation but cognitive decline or psychiatric features are frequently observed as the first and isolated symptoms in myelin disorders with an onset after childhood. Analysis of disease progression as well as the pattern of abnormalities in MRI, magnetic resonance spectroscopy (MRS) and central evoked potentials can be helpful to characterise the predominantly pathological process but when maintenance of normal myelin is no longer possible a stereotyped route to progressive destruction occurs, largely irrespective of the initiating cause. Classifications of inherited myelin disorders have changed with the state of scientific development. Based in the past on neuropathological aspects, they are now classify according to their underlying causes identified by specific metabolic markers and more recently by identification of genetic defects. They have been described as resulting from nuclear, lysosomal, mitochondrial, peroxisomal and cytoplasmic enzyme dysfunctions. More recently, defects in gene encoding myelin proteins, as the proteoliprotein gene (PLP), have been found in patients with early and severe impairment of motor development (Pelizaeus Merzbacher) as well as in less severe forms with an early onset spastic paraplegia (SPG2). In addition, patients heterozygous for certain mutations can express a lat onset spastic paraplegia with progressive dementia but without abnormal signal of the white matter on MRI, emphasising importance of axonal dysfunction in primitive CNS myelin disorders. Identically, primitive alteration of astrocytes is able to induce a severe demyelination. Despite extensive biochemical and genetic analysis, a large number of inherited myelin disorders remains of undetermined origin. Efforts to classify them in homogenous groups of patients have lead to the description of new entities accessible to genetic analysis.

EFFECTS OF INTERFERON BETA-1A (REBI®) IN PATIENTS WITH ACUTE NEUROLOGICAL SYNDROMES AT HIGH RISK OF DEVELOPING CLINICALLY DEFINITE MULTIPLE SCLEROSIS: A DOUBLE-BLIND, MULTICENTRE EUROPEAN, RANDOMISED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY (ETOMS). G. Comi, M. Filippi, F. Barkhof, L. Durelli, G. Edan, O. Fernandez, H. P. Hartung, P. Seeldrayers, P. Soelberg-Sorensen, M. Rovaris, F. Martinelli, V. Martinelli, M. Rodegher, G. Francis, O. R. Hommes and the ETOMS study group (Milan, I; Amsterdam, NL; Turin, I; Rennes, F; Malaga, E; Graz, A; Charleroi, B; Copenhagen, DK; Geneva, CH; Nijmegen, NL).

Class 1 clinical trials have demonstrated that interferon beta-1a (Rebif®, Serono) is effective in reducing clinical and MRI disease activity in relapsing-remitting multiple sclerosis. This effect seems to be dose dependent; in fact very low doses (22 mcg once a week) did not reduce the relapse rate in a 48-week study. Evidence is accumulating that early treatment may result in optimum benefit for MS patients. It is also known that patients with a acute neurological syndrome suggestive of demyelination and abnormal brain magnetic resonance imaging (MRI) findings have a high risk of developing clinically definite multiple sclerosis (CDMS). The aim of the present multicentre, randomised, double blind, placebo controlled 2-year study was to evaluate the efficacy of interferon beta-1a (Rebif®, Serono), 22 mcg once a week, administered subcutaneously, in reducing the risk of conversion to CDMS in this category of patients. Clinical evaluation was performed at baseline, month 1 and then every 6 months; brain MRI was performed annually. Three hundred and eight patients were randomised to Rebif (154) or placebo (154). Mean age was 28.4 years (range 18–45); 112 were male and 197 female. According to the Poser criteria, 134 patients were CPMS and 174 were LSDMS. Treatment discontinuation occurred in 26 % of placebo patients and 18 % of patients taking interferon beta-1a; however, 79 % of discontinuations were related to the occurrence of a second relapse, which was an option defined in the protocol. The proportion of patients converting to CDMS was significantly reduced by interferon beta-1a (34 %, compared with 45 % in the placebo group; –24 %, p=0.047, Chi square). Time to conversion to CDMS was also significantly delayed by 282 days (p=0.034, log rank test). The annualised exacerbation rate was 0.43 in the placebo group and 0.33 in the interferon beta-1a group (–23 %, p=0.026). Six percent of patients in the placebo group had no evidence of MRI activity at the end of the study, compared with 16 % in the interferon beta-1a group (p=0.014). The mean number of new T2 lesions during the 2 years of follow-up was significantly reduced by interferon beta-1a ($p< 0.001$). The mean number of enhancing lesions was only modestly reduced by active treatment compared with placebo. At the end of the study, the volume of T2 lesions had increased by 7.2 % in the placebo group and decreased by 13 % in the interferon beta-1a group. Treatment was very well tolerated; as expected, fatigue and local injection site reactions occurred more frequently in the active treatment group. The study provides evidence that patients at high risk of conversion to CDMS benefit from treatment with interferon beta-1a, which is very well tolerated. Low doses are active, but in view of mounting evidence that high doses of interferon beta-1a provide more benefit for MS patients, the optimal dose for this category of patients remains to be determined.