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POSTER SESSION 1

1
DIFFUSE PRIMARY NEOPLASTIC PROCESSES OF THE LEPTOMENINGES. L Harms, A Bock, W Jänisch, J Valdueza, J Weber, I Link. *Berlin, Germany.*

The diagnosis of diffuse involvement of the leptomeninges by different processes is difficult. It is important to distinguish treatable processes such as meningitis, especially of tuberculous origin, sarcoidosis, carcinomatosis, or others, from the rare cases of primary leptomeningeal neoplasms (DPLN) which usually carry a poor prognosis. We present 3 cases of DPLN of different origin, including one case of gliomatosis, one of melanoblastosis and one of leiomyosarcomatosis. Eight cases of leptomeningeal gliomatosis have been reported in the literature. The incidence of leptomeningeal melanoblastosis is $1/10 \times 10^6$, but the diffuse leptomeningeal growth of a leiomyosarcoma has not been described before. All 3 cases produced similar symptoms. All patients had headaches, all developed hydrocephalus and involvement of the caudal cranial nerves, and visual disturbances of loss. The CT scan showed different signs including leptomeningeal calcification, contrast enhancement, hydrocephalus. The melanoblastosis could be diagnosed by the sediment of the CSF, the other diagnoses were done post mortem. Electron microscopic examination was necessary to confirm the diagnosis of leiomyosarcomatosis. The difficulties of diagnosis of DPLN and non specific clinical signs suggest the importance of a diagnostic algorithm with the early performance of leptomeningeal biopsy.

2
INSULIN-LIKE GROWTH FACTOR I RECEPTORS IN HUMAN FRONTAL CORTEX AND WHITE MATTER. J De Keyser; A Goossens, N Wilczak. *Brussels, Belgium*

The insulin-like growth factors (IGFs) have a pivotal role in the proliferation and differentiation of the developing nervous system, and they may remain important in the mature brain to maintain cell integrity. It is mainly the IGF-I receptor that mediates the proliferative effects of the IGFs. Using quantitative autoradiography with [125I]-IGF-I we have investigated IGF-I receptors in postmortem-obtained frontal cortex and white matter from 39 individuals without neurological disease, ranging in age from 0 to 95 years, and from 5 patients with Huntington's disease (HD) and 4 with Alzheimer's disease (AD). IGF-I receptor densities in white matter were significantly higher in neonates than in adults ($p<0.04$) during adulthood there was no further decline. The higher density of IGF-I receptors in white matter of neonates most likely reflects the myelination process which is extensive during this period of life. There was no significant decrease in IGF-I receptor densities in the cortical mantle with age, suggesting that the cells containing IGF-I receptors in frontal cortex are maintained during the entire life-span. There were no significant alterations in IGF-I receptor densities in frontal cortex and white matter from patients with HD and AD compared with controls from the same age groups.

3
THE EXPRESSION OF CD59 IN NORMAL NERVOUS TISSUE. C Vedeler, L Bjorge, E Uvestad, G Conti, K Williams. *Bergen, Norway; Milano, Italy & Montreal, Canada*

Complement activation with the formation of the membrane attack complex (MAC) contributes to demyelination in multiple sclerosis and Guillain- BarrÈ syndrome. Several membrane- associated proteins provide protection from damage by activated complement components, including CD59 which appears to be a major complement lysis restricting factor. We have demonstrated CD59 on neurons, Schwann cells, oligodendrocytes, astrocytes, microglia and endothelial cells in vivo and in vitro. Soluble CD59 was present in cerebrospinal fluid (CSF). Purified CD59 from nerve, brain and CSF was a 18–20 kDa glycosyl-phosphatidylinositol linked glycoprotein which inhibited complement mediated lysis. The presence of CD59 on various cells of the nervous system and in the CSF suggests that regulation of complement activation by this glycoprotein is important in neural host defence mechanisms.

4
BRAIN PLASMALOGEN CONTENT AND THE PATHOGENESIS OF NEURODEGENERATIVE DISEASE.L Ginsberg, S Rafique, SI Rapoport, NL Gershfeld, *London, UK & Bethesda, USA*

The post mortem membrane lipid content of the caudate nucleus was analysed with particular reference to ethanolamine phospholipids (PE) in patients with Huntington's disease (HD, n =5) and normal controls (n= 12). The proportion of phosphatidal ethanolamine (PE plasmalogen) expressed as mean mole % of the total ethanolamine phospholipid fraction (plasmalogen + non- plasmalogen (including lyso) PE) was 55% for HD patients with no significant difference from controls at 50% (Mann- Whitney U test). This finding contrasts with the previous observation of selective plasmalogen deficiency in affected brain regions (temporal cortex) in Alzheimer's disease (AD). Disease specificity for AD, along with anatomical specificity within the AD brain, support the view that the plasmalogen anomaly contributes to AD pathogenesis. A potential mechanism for this contribution would be by inducing membrane bilayer instability. Such instability has previously been detected in AD cerebral cortex, where it may lead to neurodegeneration directly, or synergistically with other processes e.g. by exposing the transmembrane amyloid precursor protein to aberrant amyloidogenic proteolytic attack (Ginsberg L et al., Brain Res 1993; 615:355).

5
TREATMENT OF UNILATERAL AND BILATERAL BENIGN PAROXYSMAL POSITIONAL VERTIGO. G De La Meilleure, L Crevits. *Gent, Belgium.*

Benign paroxysmal positional vertigo (BPPV) is a common cause of dizziness. Diagnosis is based on provoking a verticorotatory nystagmus, beating towards the undermost ear, by performing the Dix- Hallpike manoeuvre. The nystagmus has a short latency period, continues less than 1 minute and is fatiguable with repetitive provocation. Good results are described with physical therapy : liberation manoeuvres and exercises. We have treated 49 patients with BPPV over a period of 15 months : 31 with unilateral and 14 with bilateral BPPV of the posterior canal, 2 with unilateral and 1 with bilateral BPPV of the posterior canal combined with simultaneous involvement of the horizontal canal, and 1 with a purely horizontal canal BPPV. We have observed a clear distinction (significance level $P < 0.01$) between unilateral and bilateral forms of BPPV. 77% of the patients with unilateral BPPV are cured with one and another 19% with 2 liberation manoeuvres. Only 14% of patients with bilateral BPPV are cured with 1, and 60% with 2 liberation manoeuvres. Most patients with bilateral BPPV need repeated liberation and additional exercise therapy over a longer treatment period to become cured. Both vestibular organs seem to be pathologically involved in bilateral BPPV, as treatment of both sides is necessary to cure the patient.

6
SUPERFICIAL SIDEROSIS OF THE CENTRAL NERVOUS SYSTEM: REPORT OF FIVE CASES. JH. Faiss, N Heye, J Blanke, A Sackmann, O Kastrup. *Essen, Germany.*

Superficial siderosis (SS) of the CNS is characterised by hemosiderin deposits in superficial layers of the basal cortex, cerebellum, brain stem and spinal cord. It occurs after frequent subarachnoidal or intracisternal haemorrhages. In about half of the patients no etiology can be found. We report on five patients with SS. On the basis of our cases and a review of the literature neurological symptoms are rather consistent and characterised by progressive dementia, sensorineural hearing loss, cerebellar ataxia, pyramidal tract signs and sphincter disturbances. Differential diagnosis of SS should include normal pressure hydrocephalus (NPH). Neuropathological changes consist in superficial iron and hemosiderin deposits in the basal parts of the temporal lobes, the brain stem, the cerebellum and the spinal cord as well as the convexities of the cortex. In addition severe damage of the vestibulocochlear nerve with microglial metabolism of iron is present. MRI findings closely resemble neuropathological alterations. The rarity of SS at autopsy or on MRI, even in patients with recurrent subarachnoidal haemorrhages, is remarkable. Highfield spin- echo MRI is the most useful diagnostic tool to show superficial and/or subependymal hemosiderotic deposits.

7
NEUROPROTECTIVE EFFECTS OF RADICAL SCAVENGERS IN AN INTACT DRG HYPOXIA MODEL. R Doornbos, HB van der Worp, LJ Kappelle, PR Bar; *Utrecht. the Netherlands*

In order to study the potency of two different free radical scavengers in an intact dorsal root ganglion (DRG), we set up a system in which DRGs could be exposed to anoxia and used neurite outgrowth as index of neuronal function. Outgrowth was quantified with computerised image analysis. The effect of 30 to 180 min of anoxia was quantified by flushing N2/Co2 (95/5 %) through an incubator with 6–12 petri dishes, containing 4 DRGs per dish. Three hours anoxia resulted in 60- 80% reduction of cell growth and was chosen for further experiments. We tested EGTA, A23187 and nimodipine and established that calcium ions play a role (10- 6M nimodipine restored outgrowth from 35 to 65% of normal). Next we tested gluthathion to see whether free radicals were involved (0.3 mM GSH rescued about 20% of the neurons). Finally we tested two scavengers, U74389G, an 21-aminosteroid and MDL 73335A, a vit.E analogue. Both scavengers were capable of restoring outgrowth (U74389G 10^{-5} M and MDL73335A 10^{-8} M, 78 and 89% of controls, resp.). We conclude that 1. intact DRGs may serve as a model for hypoxia, displaying characteristic reactions seen in vivo. 2. the scavengers tested are capable of restoring neuron function significantly, but not, even when combined, completely.

8
PROTON MAGNETIC RESONNANCE SPECTROSCOPY (MRS) IN ADULT CASES OF PHENYLKETONURIA. CA Davie, GJ Barker, D Brenton, DH Miller, AJ Thompson. *London, UK.*

Neurological deterioration and MRI abnormalities may occur in adults with phenylketonuria (PKU) in whom diagnosis is delayed or who have poor dietary control. We have carried out Proton magnetic resonance spectroscopy (MRS) on five adult patients with PKU and abnormalities on MRI and in 8 healthy, age matched controls. MRI revealed diffuse high signal abnormalities on T2 weighted images in all patients. Spectra collected at echo times of 10 and 135ms showed normal NAA/creatine ratios (2.2 ±0.31) in areas of MRI abnormality and from areas of normal appearing white matter (NAWM) compared to controls (1.88±0.18). Choline/creatine ratios were increased in the MRI lesions (1.16±0.3) and in areas of NAWM (1.14±0.1) compared to control white matter (0.92±0.07). Inositol/creatine ratios were reduced in lesions (0.47±0.2) relative to control white matter (0.62±0.2). No abnormal peaks attributable to phenylalanine or myelin breakdown products were seen. The preservation of the NAA/creatine ratio suggests very little axonal loss is occurring within the MRI visible abnormalities in PKU while the elevated choline/creatine ratio suggests increased membrane synthesis. The absence of myelin breakdown products also suggests that active myelin breakdown is not prominent. The MRS findings in PKU support a non destructive pathological process with increased membrane/myelin turnover.

9
MUSCLE RELAXANT EFFECTS OF NMDA ANTAGONISTS. F Block, M Schwarz, *Aachen; Germany*

The present study examined whether the NMDA antagonists memantine and dextromethorphan exert in vivo muscle relaxant effects as tested on rat spinal reflexes. Systemic or intrathecal application of memantine (1.25–20 mg i.p.; 10–500 nmol i.th.) and dextromethorphan (4–100 mg i.p.; 10–100 nmol i.th.) dose- dependently reduced the magnitude of the polysynaptic flexor reflex without affecting the monosynaptic H- reflex. Intrathecal injection of AP7, a specific NMDA antagonist, (50 -500 nmol i.th.) decreased the flexor reflex without influencing the H- reflex. DNQX, a specific non- NMDA antagonist, given intrathecally (0.1–10 nmol i.th.) reduced the amplitude of the H- reflex without alteration of the flexor reflex. The depressant action of memantine and dextromethorphan on the flexor reflex was prevented by intrathecal coadministration of NMDA but not with the non- NMDA agonist AMPA. The present data suggest that the NMDA antagonists memantine and dextromethorphan exert a muscle relaxant effect via reduction of spinal polysynaptic transmission.

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SPINAL ARACHNOID CYSTS: NEURORADIOLOGICAL FINDINGS, CLINICAL PRESENTATION AND OUTCOME OF 11 CASES. L Delodovici, F Baruzzi, G Bonaldi, A Dario, A Marra, A Mercuri, *Varese, Italy*

A Variety of benign cystic lesions are known to occur at spinal, level, as arachnoid cysts, epithelial and teratogenous cysts. Signs of slowly progressive myelopathy are the most common clinical presentation, but symptoms may fluctuate in time and with postural change, leading to the wrong clinical diagnosis. Since 1972 we have observe 11 patients with spinal arachnoid cysts, intradural in 10 cases, extradural in 1; the topography was thoracic in 10 and lumbar in one, ventral in 1 case, dorsal in the remaining.The clinical onset was acute in the patient with the ventral lesion, while in the other cases there was a slowly progressive myelopathy of variable degree; in one patient ALS radicular impairment was observed, and 3 had disorders of sphincters. In 5 cases also neurophysiological tests (SEPs, MEPs) were performed. A11 had plain radiographs, 4 were studied only with conventional myelography and/or CT-myelography scan; the remaining had both CT and MRI imaging. Nobody had a previous hysteria of spinal trauma. Surgical management was performed in all. The clinical outcome was variable, and in some cases the improvement was only partial. We discuss our findings with the ones previously reported in literature.

11
CRAMPS: POSSIBLE IMPLICATIONS OF AUTOIMMUNE MECHANISMS F Dworzak, P Cavallari, P Confalonieri, M Zuffi, C Antozzi, F Cornelio, F Baldissera. *Milan, Italy.*

Etiology of cramps is multiple. Implication of autoimmune mechanisms has been shown in two different syndromes with muscle overactivity: the Stiff-man syndrome and neuromyotonia. This finding has led to immunosuppressive treatment, including plasma exchange, with dramatic improvement in some cases. We report a patient suffering in the last 10 years of muscle cramps, pain and sporadic sudden muscle atonia, unresponsive to any drug. An autoimmune etiology has been hypothesised. His cramps were investigated by electrophysiology before and after plasmapheresis and high dose intravenous immunoglobulin treatment. Before treatment cramps could be triggered in the triceps suralis by volleys in homonymous Ia afferents, and interrupted by antidromic stimulation and Renshaw inhibition, of motoneurones (F.Baldisse,a, P.Cavallari, F Dworzak: Neurosci Lett, 133,1991). After 2 plasma exchange courses, and after immunoglobulin treatment the patient had a dramatic improvement of his symptoms and no cramps could be elicited by the same tests. Conclusions: a) the mechanisms which generate cramps in this patient seem to be intrinsic to motoneurones, b) the efficacy of both plasmapheresis and immunoglobulin treatment suggests the implication of autoimmune mechanisms also in our patient..

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SUPERFICIAL HEMOSIDEROSIS OF THE CENTRAL NERVOUS SYSTEM. B Chassande, A Ameri, B Eymard, M Poisson, A Vérier, P Brunet, *Paris France*

Superficial Hemosiderosis of the Central Nervous System (SH) is a rare disease, which was chiefly diagnosed at autopsy by the rest- colored appearance of the involved structures. However Magnetic Resonance Imaging (MRI) have shown that the diagnosis is far more frequent than previously suspected. Therefore, we report a patient who suffered from SH for twenty years. The clinical picture was characterised by acute paroxysmal headaches, chronic cerebellum and pyramidal syndrom, hearing loss and insomnia. CSF was xanthochromic with increased protein content at 0,67 g/l, with 15200/mm3 red blood cells and siderophages on Perls coloration. MRI showed a hypointense superficial layer on T2 weighted images involving the spinal cord, cortex, brainstem and cerebellum due to hemosiderin deposits. The source of bleeding (MRI, CT, angiography and myelography) could not be detected. Repeated bleeding into CSF spaces without identified cause in half cases may cause superficial siderosis with progressive neurological impairment and the unique physical properties of MRI provide basis for the in vivo diagnosis of this entity.

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MENINGEAL HEMORRHAGE: ETIOLOGICAL, CLINICAL, PRACLINICAL AND EVOLUTIVE FEATURES OF 226 SURGICAL AND NOT SURGICAL CASES. S Congia, PL Murgia,A Cannas, G Borghero, S Uselli, G Mellino, R Ferrai, R Lampis, R Massa, B Muzzetto, *Cagliari, Italy.*

The literature data report annual incidence rates of meningeal haemorrhages ranging from 6 to 24/100.000/inhabitants (AHO,1975), with a very high mortality rate. We examined 226 cases of meningeal hemorrhage collected in Neurological, Neurosurgery, General Medicine Departments and Intensive Care Units, to define the characteristics of this clinical entity, because of the majority of the studies concerned only the therapeutically as-

pects of surgical cases. The results of the study showed that 41.2 % were meningeal haemorrhages due to ruptured intracranial aneurysm, 7.1 % were related to ruptured arterio- venous malformation, 20.4 % were due to different causes, 11.9 were of unknown origin, 19.5 % were not studied because of early death. Our data were compared with those of the literature.

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ROLE OF NEUROPHYSIOLOGICAL ASSESSMENT OF PECTORALIS MAJOR MUSCLE AFTER PATEY AND MADDEN'S RADICAL MASTECTOMY. F Giannini, S Rossi, R Cioni, C d'Aniello, A Guarneri, N Battistini, *Siena, Italy*

The Medial Pectoral nerve (MPn) supplies the Pectoralis minor (Pm) as well as the lower Pectoralis Major (LPM) muscles. MPn is generally damaged during the resection of the Pm in Patey technique, but theorically preserved in Madden's surgical procedure. The anatomo- functional integrity of LPM is essential for a good outcome of the retromuscolar prosthesis implantation for plastic reconstruction after radical mastectomy. In order to evaluate the long- term effects of these surgical treatments, the following protocol was performed bilaterally - the intact side being taken as control- in two groups of patients (18 Patey="A" and 9 Madden="B"): clinical and electromyographic (EMG) evaluation of LPM and Upper Pectoralis major (UPM) muscles; measurament of the motor latency (from Erb's point) of the same muscles. EMG showed neurogenic patterns of the LPM in 72.2% of "A" group and 11.1% of "B" group, while lipoatrophy of LPM was clinically found only in 38.9% of "A" group. Mean values of motor latencies of LPM differed significantly ($p<0.01$) from the controlateral side only in patients treated by Patey technique. The UPM was always normal in both groups. These data indicate time the usefulness of the electrophysiological evaluation in detecting neurogenic, functionally relevant, abnormalities of the LPM muscle; furthermore, they suggest that - when oncologic conditions require a radical mastectomy-the Madden technique should be preferred if a plastic reconstruction is planned .

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HYPEREOSINOPHILIC ENCEPHALOPATHY. F Ceriani, A Del Santo, M Poloni, *Milano, Italy*

We describe the case of a 53 year old patient affected by idiopathic hypereosinophilia with slight peripheral nervous system impairment but severe CNS involvement. Hypereosinophilia without relation to allergic, parasitic or collagen diseases was diagnosed five years before this study; three months later following the onset of subacute left hemiparesis paresis he underwent brain CT scan (normal) and he had MR scan, which showed lesions compatible with demyelinization. The neurological deficit worsened gradually over the years and at present the neurological findings were: left hemiparesis, associated with ataxic disturbance of the movement, spastic hypertonia and brisk tendon reflexes. No sensory disturbance was clinically detected. CSF examination was normal (oligoclonal bands were absent). Visual evoked potentials were normal; somatosensory evoked response was absent for left tibial stimulation and markedly reduced for the right side stimulation. The cortical magnetic stimulation showed delayed and low amplitude response at the left leg. Brain CT scan was normal except for a slight enlargement of the ventricular cavities. Multiple lesions of hyperintense signal evident in T2 spin-echo sequences of the brain MR scan in both the hemispheres, but also of demyelination in the bilateral cortico-subcortical cerebellar and corpus callosum areas. The electromyographic study showed reduced sensory amplitude potentials with borderline conduction velocities at the lower limb.The ultimate mechanism responsible for nervous system impairment in idiopathic hypereosinophilia has not been established. Neurotoxicity might be due to direct infiltration of the nervous system but there are also date consistent with a toxic action of three proteins of the eosinophilic granules. In particular the so- called eosinophil- derived neurotoxin (EDN), responsible for myelinated axon damage in the CNS, could explain the atypical CNS involvement of our patient.

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BRUCELLAR SPONDYLITIS WITH EPIDURAL AND PARASPINAL ABSCESSES: SUCCESSFUL MEDICAL TREATMENT WITH MRI FOLLOW- UP. JF Campo, F Iglesias, MV Guitera, C Farinas, J Pascual, C Leno, J Berciano. *Santander, Spain.*

A 29 year- old- man developed fever, sweating and severe back pain over 10 days. He had a history of ingestion of unpasteurized milk. Examination revealed neck rigidity and resistance to movement of legs and back. There was tenderness on deep palpation of spinal process at T_6 and T_7 level. Neither paraparesis nor sensory loss in the lower limbs were found. Routine laboratory determinations were normal. Serum agglutination and Coombs tests for brucella showed titres of 1/80 and 1/640, respectively. CSF examination showed 12 lymphocytes per mm3, and normal glucose, IgG and protein content; brucella serology was negative. MR imaging of the spine revealed diffuse increased signal in T_5- T_7, T_6 disk collapse with endplates destruction and epidural and bilateral paraspinal abscesses. CT scan corroborated these findings. Bone scan with ^{99m}Tc- MDP showed increased activity at the T_5- T_7 vertebrae. He was treated with rifampicin and doxycycline for 24 weeks and streptomycin for 8 weeks. The patient's condition improved returning to normal five months after admission when MRI showed disappearance of the paraspinal and epidural masses. We conclude that MR imaging is the method of choice for the initial assessment and evaluation of the therapeutic response of patients with brucellar spondylitis.

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RAPID HIGH RESOLUTION AND DYNAMIC "BLOOD FLOW" MRI DETECTS SPINAL ARTERIOVENOU.S MALFORMATIONS. IW Thorpe, BE Kendall, WI McDonald, DH Miller, *London, UK*

Conventional MRI is relatively insensitive to spinal arteriovenous malformations (AVMs) and in particular dural fistulae (AVFs); diagnosis has required supine myelography followed by selective spinal angiography. We report on our findings using two recent advances: (i) rapid high resolution imaging with multi- array coils and fast spin echo; (ii) dynamic imaging during the passage of a gadolinium bolus. We have studied 6 patients (5 dural AVFs, 1 intramedullary AVM) and 2 controls. T_1-and T_2- weighted sagittal images of the whole cord were obtained by means of a multi- array receiver coil. Sagittal gradient echo images ($GE_{34/25}$ flip angle 10°) were then obtained at 3.5 second intervals following bolus injection of gadolinium-DTPA. Characteristic abnormalities were seen on high resolution images in all patients. In 5, dynamic scanning showed transient signal reduction within the perimedullary venous plexus during bolus passage. The MRI findings correlated well with those from selective spinal angiography, the site of the arteriovenous shunt being localised to within one vertebral body in 4 patients. With current MR imaging, myelography is probably unnecessary in the diagnosis of AVMs. Dynamic "blood flow" scanning is a useful adjunct to angiography as it may localise the site of an AVM.

18
MENINGOMYELORADICULITIS DUE TO CRYPTOCOCCUS CURVATUS: A. Moulignier, F Dromer, M Baudrimont, B Dupont, *Paris, France*

We report on the case of a 30 year- old bisexual man, HIV-1 positive (CDC stage II), who developped a febrile subacute meningomyeloradiculitis. The unique etiological agent identified was C. curvatus, usually described as a non pathogenic yeast. The CD4+ cell count was 15/mm3 (R=0.01). Despite antitoxoplasma, antimycobacteria, anti CMV and steroid therapies, the neurological status still worsened. Three weeks after its collection, the culture of the CSF was positive with a tiny yeast identified as *C. curvatus* (ID 32C, BioMerieux, France), whereas India ink staining was negative on direct examination. Immunosuppressed mice infected with the isolate had positive cultures in brain, lungs and spleen, with histological evidence of infection. A neuromuscular biopsy disclosed a lymphohistiocytic microvasculitis. Immunostaining for CMV and HIV was negative. A monoclonal antibody against C. curvatus antigens is now available and results of immunostaining on the neuromuscular biopsy will be shown. Clinical improvement was obvious a few days after Amphotericin B was administered. Four months after this therapy the patient was dramatically improved, but he refused to continue infusions and his neurological status deteriorated with the same pattern as the onset. Four other cases have been diagnosed after this patient. C. curvatus may thus be responsible for myeloradiculitis in AIDS.

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A PROSPECTIVE EVALUATION OF CLINICAL CRITERIA AND PCR ASSAY OF CSF FOR THE DIAGNOSIS OF CYTOMEGALOVIRUS RELATED NEUROLOGICAL DISEASES DURING AIDS. J Gozlan, M El Amrani, M Baudrimont, JC Petit, E. Roullet. *Paris, France*

Cytomegalovirus (CMV) causes several neurological diseases in the late stages of AIDS, but their ante- mortem diagnosis is problematic. Clinical criteria (defining a presumptive diagnosis) and polymerase chain reaction

(PCR) assay from cerebrospinal fluid (CSF) were blindly used to predict the involvement of CMV in neurological disorders of 164 consecutive AIDS patients undergoing a lumbar puncture. During the follow- up, a definite diagnosis based on viral culture of CSF, clinical outcome and/or CNS histology was allowed in 88 patients, 27 (16 %) of whom had a proven CMV related neurological disease. The concordance between the presumptive and definite diagnosis was of 60 %, inducing a moderate agreement kappa index of 0.40. In contrast, the sensitivity and specificity of PCR were respectively of 89 and 94 %, with a positive and negative predictive values of 86 and 95 %. Cytomegalovirus related neurological diseases appeared thus as a frequent complication of AIDS, and detection of viral DNA in CSF by means of PCR seems a reliable tool for their diagnosis, allowing its use for therapeutic decisions

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^{99m}TC- HMPAO LEUCOCYTE SCINTIGRAPHY IN DIAGNOSIS OF BRAIN ABCESSES. R.Sterzi; R Causaran, A Protti M Riva, F Erminio, 0 Arena, F Villa, E Maccagnano, M Miletta, F Spinelli, *Milano, Italy*

Aim: Brain abscess is a serious clinical condition demanding rapid diagnostic and therapeutic decisions. However, CI scan and MRI may be unable to differentiate an abscess from other types of lesions, tumoral or vascular. We assessed the sensitivity and the specificity of ^{99m}Tc- hexamethylpropylenamine oxime (HMPAO) leukocyte scintigraphy, a non invasive method for the detection of soft tissue infection that may be useful in the differential diagnosis of intracerebral mass lesions. Methods: We have studied an till now 18 patients with focal neurological signs and cystic masses, will contrast enhancement, on CT scan. WBC were extracted from 60 ml of venous blood sample and incubated with ^{99m}Tc-HMPAO. Doses of l85–222 mBq were injected and planar images were obtained 1,3,24 hs later by means of a maxi camera. Results: Seven leukocyte scintigraphy were positive and the final diagnosis turned out cerebral abscess in all these cases. Eleven patients obtained a negative results; their final diagnosis was glial or metastatic tumors, old hematoma or cysticercosis. No false positive or false negative cases were present at this phase of enrolment and therefore the sensibility and sensitivity are 100%. Conclusions: ^{99m}Tc-HMPAO leukocyte scintigraphy may add an useful dimension to the diagnosis of a brain abscess.

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EFFECTS OF HERPES SIMPLEX VIRUS TYPE 1 (HSV-l) INFECTION ON THE HYPOTHALAMIC- PITUITARY- ADRENOCORTICAL AXIS IN RATS T Ben.- Hur, J Weidenfeldl . *Jerusalem Israel*

Limbic structures (hippocampus and hypothalamus) are involved in the regulation of the hypothalamo- pituitary- adrenocortical (HPA) axis. HSV-1 is neurotropic and neurovirulent with preference to the limbic system. We therefore studied its effects on the HPA axis. Adult rats were injected with HSV-1 or saline by slereotactic injection to the hypothalamic paraventricular nucleus (PVN). The virus caused focal encephalitis associated with high basal serum corticosterone level, no response of corticosterone to stressful stimuli, lack of its suppression by low- dose dexamethasone and reduced corticotrophin- releasing- factor (CRF-41) content of the median eminence. These results are similiar to those obtained following hypothalamic or dorsal hippocampal lesions. When HSV- I was inoculated into the corneas it was traced during the first week post- infection through the trigeminal nerve to the brain stem (but not yet to the hypothalamus), causing subclinical infection without fever or systemic disease. T he virus induced high basal serum corticosterolle level, non- responding to stressful stimuli and resistant to dexamethasone, without any change in CRF-41 content of the median- eminence or PVN and without inflammation in the hypothalamus. Systemic infection with HSV- I (to the peritoneum) did not induce any change in the HPA axis. HSV-1 has, therefore, "remote" neural effects on the IIPA axis (i.e., not by local viral replication and not by systemic effect), possibly by specific neural connections between the brainstem and limbic system.

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CENTRAL NERVOUS SYSTEM TOXOPLASMOSIS IN AIDS. NS Rao, CC Chari, *Washington DC, USA*

Toxoplasmosis (TPM) of the central nervous system (CNS) is the commonest opportunistic infection in the acquired immune deficiency syndrome (AIDS). This is a report of 41 patients of TPM of CNS in AIDS, based on the criteria of Porter and Sande (N Engl J Med 1992; 327:1643–8), identified at D.C. General Hospital during the last 10 years. The mean age was 36.9 (range 22–57); there were 36 men and 5 women. Duration of known HIV+ ranged from 6 months to 8 years. Apart from systemic complaints of fever, vomiting, weight loss and diarrhoea, the commonest neurologic symptoms were headache, seizures, focal weakness and blurred vision. Neck rigidity was uncommon. Neurological signs consisted of cognitive impairment, hemiparesis, brisk DTRs and upgoing toes. Unusual findings were visual field impairment, ataxia, choreoathetoid movements and hemiballismus. CT or MRI showed multiple ring enhancing lesions with oedema in 33 patients (80.5%), solitary lesion in 3 (7.3%) and normal or cerebral atrophy in 5 (12.2%). T4 cell count ranged from 0–90 in almost all except 2 (141 and 190). T4, T8 ratio was less than 0.1 in most patients. Improvement in clinical status in 22 patients, though short lived, was evident in 10- 14 days on antitoxo treatment. CT improvement of disappearance or reduction in the size of lesions was evident in 2–4 weeks. Most patient died within weeks to months after admission with neurological presentation.

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PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY IN AIDS. TREATMENT WITH ALPHA-INTERFERON. P Laforet , S Matheron, D Adams, Ph Chemouilli, M Desi, G Said, *Paris, France*

We performed a retrospective study of 10 patients with AIDS and Progressive Multifocal Leucoencephalopathy (PML) treated with recombinant alpha interferon (αIFN).The diagnosis of PML was based on clinical, MRI and therapeutic criteria (lack of response to a 3 weeks course of antitoxoplasmic therapy) in all, plus brain biopsy findings and/or evidence of infection with JC virus by PCR in the CSF in 6 patients. The mean CD4 cell count was 57 per ml (3–194) αIFN was given (4 to 9 millions IU/day, subcutaneously or intramuscularly) without major side effects during 3 weeks to ll months Five patients died between 10 weeks and 4 months after the first manifestation of PML; in this suhgroup, the mean CD4 cell count at PML diagnosis was 26 per ml Five other patients survived an average 13.4 months; PML was the first AIDS defining event in 415 and mean CD4 cell count at onset was 88 per ml. Although this study is not conclusive on the efficacy of αIFN, unusual protracted course of PML in some patients is encouraging for further trials. We also found that a shorl duration of AIDS before onset of PML and a high CD4 cell count at diagnosis are associated with a slower progression of PML.

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VARICELLA- ZOSTER VIRUS MYELITIS AND ENCEPHALOMYELITIS AND AIDS. RECOVERY WITH ACYCLOVIR IN 2 PATIENTS. P Davous, F Lionnet, M Pulik, P Genet, F Rozenberg, *Argenteuil and Paris, France.*

We describe 2 AIDS patients affected by myelitis or encephalomyelitis associated with varicella- zoster virus (VZV) infection and successfully treated by acyclovir. One patient, a 35 year-old woman, had encephalomyelitis with Brown- Sequard syndrome, confusion, bilateral facial palsy and VIIIth nerve involvement. The other patient, a 29 year- old man had severe motor paraplegia with perianal sensory loss and urinary retention. In both cases, the CSF examined few days after onset contained a high protein level, lymphocytes, and showed a positive PCR for VZV. The MRI of the spinal cord was normal. The neurological syndrome progressed during 2 or 3 weeks after the introduction of treatment by acyclovir (30 mg/kg/day). Improvement began 20- 30 days after onset. Follow-up examination 6 and 10 months later showed near complete recovery. These cases suggest the following conclusions: 1. VZV can cause acute myelitis and encephalomyelitis in AIDS patients. 2. PcR assay of VZV in CSF is useful for early dlagnosis. 3. Early treatment with acyclovir is beneficial and should be promptly began when herpes virus infection is suspected.

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CHRONIC SIALOADENITIS AND HTLV-I ASSOCIATED MYELOPATHY/TROPICAL SPASTIC PARAPARESIS. LM Cartier, JL Castillo, JG Cea, R Villagra, *Santiago, Chile*

From 1988 to 1993 we studied 94 patients with HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP) in the Department of Neurology, Salvador Hospital, Santiago, Chile. There have been reports of Sjögren's syndrome associated with HAM/TSP. Some of our patients complained of xerophtalmia, 1993 we thus began to perform the Schirmer test on all available patients. To date we have tested 48 patients with HAM/TSP, of whom 14 (29.1%) 11 Women and 3 men, age of.50 years

(32–71) had a Schirmer test of less than 8 mm in both eyes. Evolution time of paraparesis ranged from 2 to 15 years and in all of them xerophthalmia developed after the onset of paraparesis. Biopsies of the small salivary glands in all these cases showed chronic sialoadenitis which was classified according to Chisholm and Mason. IgG levels above 1.500 mg/100 ml were found in 10 cases (71.4%); however tests for ANA, Ro, La were all negative and rheumatoid factor was negative, in all but one. The presence of leukemoid-like lobulated lymphocytes was shown in 9 cases (64,2%) and there was an increase in CD3 and CD4 in most of them. These results, together with the neurological findings associated with HTLV-I, differ from those found in classical Sjögren's syndrome.

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SILMULTAGNOSIA AS THE INITIAL SIGN OF AIDS-RELATED PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY. A Moulignier, L de Saint Martin, F Mahieux, MJ Manifacier, B Dupont, *Paris, France*

Simultagnosia is a disorder of visual perception characterised by the inability to see a picture as a whole, despite preserved recognition of single object. Progressive multifocal leukoencephalopathy (PML) is a subacute demyelinating opportunistic infection of the CNS that affects about 4% of patients with AIDS. No simultagnosia has been described in the 230 cases of PML reviewed by Brooks & Walker [Neurol. Clin. North Am., 1989, 87:299-313]. We report the case of a 27-year-old HIV-l-blood transfusion-infected man (CDC stage II) whose complaint was that his environment appeared fragmented. CD4+ cell count was 224/mm^3 (CD4/CD8 = .35). Neurologic examination only found simultagnosia. No general intellectual impairment was noted. He scored in the normal range on memory tests and insight was preserved. Detailed neuropsychological data will be shown. Simultagnosia is usually caused by bilateral lesions involving the parietal or the parieto-occipital areas. In our patient, this syndrome was associated with the demyelinating lesions in the bilateral posterior occipito-parietal white matter involving the splenium of the corpus callosum, as seen on the brain MRI. The diagnosis of PML was based on a characteristic MRI pattern and PCR for JC virus positive in the CSF. A month after onset, he developed a Balint's syndrome that persisted as the unique neurological feature until death. Serial MRI of the brain only showed occipito-parietal lesions. The patient died 4 months after onset. Autopsy was refused by the family. Clinicians should consider simultagnosia in AIDS patients who have slowly progressive monocular visual complaints.

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PULMONARY INVOLVMENT IN PATIENTS WITH HTLV-II/II ASSOCIATED MYELOPATHY. K Mattos, C Queiros, L Publio, V Vinhas, AC Peçanha-Martins, A Melo, *Salvador; Brazil.*

Following the initial description of HTLV-I associated myelopathy (HAM), significant attention has been paid to the relationship existing between HAM and non-neurologic diseases. Systemic manifestations associated with vasculitis, ichtiosis, CREST syndrome, polymyositis, Sjögren and other immunological diseases. Several authors have described lymphocytosis in the bronchoalveolar lavage fluid (BAL) in patients with HAM. The aim of this study was to determine pulmonary involvement in HAM patients compared to controls. Thirty five patients with non-traumatic and non-tumoral myelopathies were consecutively examined. Study and control cases fulfilled the diagnosis criteria for tropical spastic paraparesis. CSF was carried out in all patients in order to rule out cysticercosis, toxoplasmosis, syphilis and schistosomiasis. CSF and sera samples were collected and tested to HTLV-I with a commercially available enzyme immunoassay, the specimens were repeatedly reactive in this screening test, and underwent confirmatory testing by Western blot assay. Samples were considered positive when both p19 and p12E were present. BAL as well as other pulmonary function tests were performed in all patients. Transbronchial lung biopsy was carried out in one patients. We observed lymphocytosis in the BAL in 88% of 22 patients with HAM compared with 15.4% of the control group ($p<0.001$). Lung biopsy showed interstitial fibrosis.

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POLYMYOSITIS AND NEMALINE BODY MYOPATHY IN A PATIENT WITH AIDS. U Liska, U Zifko, H Budka, M Drlicek, W Grisold, *Vienna, Austria.*

Muscle involvement in HIV patients can be caused by inflammatory myopathy, the infectious agent or be related to therapy. A 33 year old male patient had been HIV positive for 7 years. 24 months before biopsy he noted weakness in his upper extremities. Within several months symmetric atrophy developed in his proximal arm muscles. He continued his sports activities and was able to do perform long distance bicycle rides. Proximal weakness in his lower extremities developed insidiously, with signs of severe sings of proximal myopathy. Upon admission he had a striking atrophy of the shoulder girdle with winging of the scapulae and atrophy of limb girdle muscles and thighs. A deltoid biopsy had already been performed elsewhere and showed normal findings, the presentation suggested a genetic form of neuromuscular disease. EMG revealed typical signs of myopathy with abundant spontaneous activity in proximal muscles. Despite the previously negative biopsy another biopsy was taken from the quadriceps femoris muscle revealing scattered inflammation suggesting polymyositis. Electron microscopy, however, showed additional evidence of nemaline body myopathy as described in HIV patients. Therapeutically the clinical course was rapidly downhill despite a steroid medication. Series of immunoglobulin in association with plasmapheresis had a marked influence on the progression and mild improvement was noted.

29
INTRATHECAL SYNTHESIS OF AUTOANTIBODIES IN LYME'S NEUROBORRELIOSIS. R Kaufmann, R Kaiser, M Czygan, *Freiburg, Germany*

Even after absorption of B. burdorferi- specific antibodies many patients with neuroborreliosis how an intrathecal synthesis of immunoglobulins in the CSF. Specificity of these immunoglobulins for central nervous system (CNS) antigens was investigated in 40 patients with neuroborreliosis. CSF and serum samples were tested for IgG-, IgM- and IgA-antibodies to proteins of the CNS by westernblot. Intrathecal synthesis of autoantibodies was judged from presence of unique bands or stronger staining of antibody bands in CSF. Of 33 patients who had an intrathecal synthesis of total IgM and IgG, as calculated by the Reiber formula, – 25 (76 %) had IgM-autoantibodies and 16 (48 %) had IgG- autoantibodies to CNS proteins, predominantly in CSF. IgA-autoantibodies in the CSF were detected in 6/16 patients (37 %) with an intrathecal synthesis of total IgA. Altogether, 32/40 patients (80 %) revealed an intrathecal immune response to some CNS protein. Less frequently (10 %), autoantibodies were also detected in the CSF of patients with viral meningoencephalitis (6/60). Conclusion: In neuroborreliosis a considerable proportion of intrathecally produced antibodies is specific for CNS antigens. Frequency of autoantibodies in the CSF is much higher in patients with neuroborreliosis than in those with viral meningoencephalitis.

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PURULENT MENINGITIS IN CHILDREN OF SALVADOR-BAHIA (NORTHEASTERN BRAZIL): A RETROSPECTIVE ANALYSIS. I Gomes, N Jones; S Cunha, E Katiane Embiruçu, V Vieira, I Araujo; M Alexandra, A Ferreira, J Goes, A Melo. *Salvador; Brazil.*

At the end of the 20th century, acute bacterial meningitis is still a public health challenge in developing countries. From 1990 to 1992, the Unit of Neuro-infectology of the Federal University if Bahia conducted a retrospective surveillance to review the etiology of and mortality from bacterial acute meningitis, in children less than thirteen years old, admitted at the Hospital Couto Maia in Salvador-Bahia (Northeastern Brazil). A case was defined as pyogenic meningitis if any of the following criteria were fulfilled: 1 positive CSF culture; 2 positive CSF gram stain; 3 CSF examination with > 1000 leukocytes/mm^3; (75% of neutrophils). Bacterial meningitis in children accounted for 26.3% of all meningitis admitted to this hospital during this period. The frequency of isolation of the meningeal pathogens was: H. influenzae (46.2%), N. meningitides (33.6%), S. pneumoniae (14.2%), Staphylococcus sp (2.4%), Streptococcus sp (2.0%), Enteroacteriaceae (1.6%). The case fatality rate was 19.7%. Among infants less than 1 year old the case fatality rate was 31.4%.

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REVERSIBLE MENTAL DETERIORATION AS A MANIFESTATION OF DIFFUSE TOXOPLASMIC ENCEPHALITIS IN AIDS. P Chemouilli, D Adams, M Desi, Israel-Biet, H Masson, G Said, *Poissy & Paris, France.*

Cerebral toxoplasmosis is easily recognised when a patient with HIV infection presents with unique or multiple brain abscesses. We report on 3 patients with unusual presentation as a diffuse encephalitis. Toxoplasmosis was the first opportunistic infection in one.CD4 count T cells ranged from 10 to 131 per ml. Two had an antiretroviral agent (AZT or DDI), and

one pyrimethamine for toxoplasmosis prevention. All patients had a progressive mental deterioration, with fever in one. Beside cognitive impairment, Patient 2 had a spastic paraparesis with urinary incontinence, Patient 3 had left ataxia. Brain CT scan showed diffuse white matter hypodensities in all patients without mass effect nor contrast enhancement. Brain MRI showed confluent areas of increased signal intensities in the white matter on T2-weighted images in all patients without Gadolinium enhancement on T1weighted images. The lesions were bilateral in 2. Serodiagnosis for Toxoplasmosis was negative in one patient, and CSF normal in all. Dramatic improvement of cognitive functions and apyrexia were obtained in all patients with pyrimethamine and sulfadiazine therapy. On brain MI, areas of increased signal intensity reduced in one patient and were stable in 2. The clinical and imaging pattern was that of PML in all patients. Diffuse Toxoplasma encephalitis should be suspected in subacute cognitive impairment in HIV patients, and a specific therapy should be started even in the absence of focal cerebral abscess.

32
DIFFERENT PATTERNS OF VASCULITIS IN MUSCLE AND NERVOUS SYSTEM OF PATIENTS WITH HIV INFECTION. C Lacroix, P Chemouilli, J Gasnault. *Le Kremlin Bicître. France.*

We observed 53 patients at all stages of HIV infection with different patterns of vasculitis in the muscle, the peripheral and the central nervous system. Necrotising arteritis (NA) was present in nerve and/or muscle specimens (NMS) of 9 patients including 6 with mononeuritis multiplex (MM) and 3 with distal neuropathy (DN); 1 had recent seroconversion and 2 had 50 CD4 Tcells/mm^3; others were not immunosuppressed. A NA associated with CMV ventriculitis in a patient who presented an acute coma and complex ophthalmoplegia. Two patients had in the nerve specimen old lesions of NA. A granulomatous angeitis (GA) was observed in the NMS of 7 patients, including 4 with DN, I with MM and 2 with myalgias, and in the brain of a child at autopsy. CD4 T- cells count of patients with GA was between 16 and 1 000/mm^3. Despite profound immunosuppression, some patients with NA or GA improved with steroids. A vasculitis was observed in 13 patients with cytomegalovirus (CMV) neuropathy: CMV inclusions were present in endothelial cells in 5; polymorphous cellular infiltrates of endo, peri and epineurial arteries were seen in 11 and associated with necrosis of the vessel wall in 2. A patient had a giant cell vasculitis in the muscle specimen. Microvasculitis was observed in 18 patients including 4 polyradiculoneuritis, 13 inflammatory neuropathy and 1 polymyositis.

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NEURO-BORRELIOSIS IN HIV INFECTION -FIRST CASE REPORT. B Hildebrandt-Müller, P Oschmann, P Krack, WR Willems, W Dorndorf. *Giessen, Germany*

We report a 32 year old man who suffered from diarrhea, weight loss (10 kg) as well as impotence. Two months later a bilateral facial palsy led to admission. In addition he showed further signs of a meningoradiculitis such as a moderate flaccid paraparesis of the legs with absent ankle jerks. The CSF contained 150 cells/µl and a total protein of 2.2 g/l. Peripheral motor conduction velocities were decreased and CMCT prolonged. In the immunoblot we found an intrathecal antibody response against borrelia burgdorferi specific antigens. The HIV- serology in the ELISA and western blot was positive. The patient was treated with 2 g ceftriaxon p.d. for a fortnight. The bilateral facial palsy disappeared, the paraparesis barelly changed. Impotence disappeared. Afterwards therapy with azidothymidin was initiated. Three months later the patient had gained 10 kg and the paraparesis further improved. CSF still showed 38 cells/µl and a total protein of 1.72 g/l. The T4/T8- quotient had increased from 0.1 to 0.2. In conclusion, this is the first report of an association of AIDS with neuro- borreliosis. As the patient's immune system is depressed we suggest that the pathogenetic mechanism of the neuro- borreliosis (stage II) is related to Bb itself rather than to a secondary autoimmune reaction.

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ADULT T-CELL LEUKEMIA-LYMPHOMA IN A PATIENT WITH HTLV-I/II ASSOCIATED MYELOPATHY. V Freitas, A Bittencourt, D Fernandes, K Mattos, I Gomes, A Melo. *Salvador; Brazil.*

Although human T-cell leukemia virus type I (HTLV-I) has been etiologically implicated in a variety of systemic and neurologic diseases, few reports has described lymphoproliferative disorders associated with neurologic involvement in HTLV-I patients. We report the occurrence of adult T-cell leukemia-lymphoma (ATLL) mimicking mycosis fungoides/Sezary syndrome (MF/SS) in a patient with HTLV-I/II associated myelopathy. The patient is a 65 years old black man from Salvador (Northeastern Brazil) who presented with a ten year history of progressive spastic paraparesis (PSP). Four years later he developed clinical and laboratorial picture of cutaneous lymphoma. There was no history of blood transfusion and he denied intravenous drug use and homosexual activity. Magnetic ressonance imaging showed atrophy of thorocic spinal cord. CSF examination was normal. Bronchoalveolar lavage fluid showed 82% of lymphocites. Antibodies to HTLV-I/II were found in sera and CSF. Pathological findings: Skin biopsies showed an infiltration of medium sized neoplastic cells. The neoplastic cells exhibited round, cerebriform or convoluted nuclei. In the epidermis Pautrier microabscesses were observed. Immunohistochemistry: the neoplastic cells presented with a diffuse cytoplasmic staining for CD45RO and did not react with the B antibodies.

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ETIOLOGY MORBIDITY AND MORTALITY OF PURULENT MENINGITIS IN CHILDREN OF SALVADOR (NORTHEASTERN BRAZIL). MH Nascimento, M Severo, A Ferreira, S Cunha, D Moraes, I Gomes, A Melo. *Salvador; Brazil.*

Cases of purulent meningitis, which are frequent and serious, remain a cause of concern in delevoping world. Actualised informations of purulent meningitis in Brazil as well as in other nations of Latin Americz are scarce. Between April and November 1993, 259 patients with pyogenic meningitis were admitted in the Hospital Couto Maia in Salvador. A case was defined as pyogenic meningitis if any of the following criteria were fulfilled: 1 positive CSF culture; 2 positive CSF gram stain; 3 CSF examination with more than 1000 leukocytes/mm3 (>75% neutrophils). The majority of cases (73,4%) occurred in children less than 13 years of age, and 33,7% of cases were in children under 1 years. H. influenzae was the etiologic agent in 44.4% of the cases. N. meningitides caused 38.7% of cases; S. pneumoniae 13.7%, Streptococcus sp 1.6%, Staphylococcus sp 0.8% and Enterobacteriaceae 0.8%. Cultures or gram were not conclusive in 34.7% of cases with purulent CSF. Neurologic problems occurred in 25.3 % of patients. Seizures, subdural effusions and decreased level of consciousness were the main neurologic complications. The case fatality rate was 18.4%.

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MONITORING OF PATIENTS WITH NONPURULENT MENINGOENCEPHALITIS BY TRANSCRANIAL DOPPLER ULTRASONOGRAPHY. M Muller, K Hasert, S Merkelbach, K Schimrigk, *Homburg/Saar, Germany.*

Fourteen patients (9 male, 5 female, mean age ± SD: 36 ± 18 years) with nonpurulent meningoencephalitis diagnosed on the bases of headache, meningism, fever and an initial lymphocytic pleocytosis (100- 2800/3 cells with more than 90% lymphocytes) were followed up clinically and by means of Transcranial Doppler Ultrasound (TCD) recordings of the middle and anterior cerebral artery [MCA (n=28), ACA (n= 24)] on days 1, 3, 5, 8 after diagnosis. The patients were classified according to 1) the initial Glascow Coma Scale score into group I: score 13- 15 (n= 11) and Group II: score 12 or less (n= 3, two of them showed diffuse brain swelling on cranial computed tomography; and 2) the outcome on day 8 into well (Group A , n=12), and (Group B n=2, both were patients from Group II). Within each group and between the pairs of groups the mean blood velocity of the MCA and ACA and the ACA/MCA- ratio did not change significantly. The MCA pulsatility index (PI) was significantly ($p< 0.05$) increased in Group II on day 1 and 3 as compared to Group I (day 1: 1.17 ± 25 vs 0.87 ± 0.17, day 3: 1.32 ± .61 vs 0.85 ± 0.19), and in Group B on day 3- 8 as compared to Group A (day 3: 1.57 ± .31 vs .84 ± .18, day 8: 1.49 ± .37 vs.83 ± .17). We conclude from our small number of patients that monitoring of the MCA PI by TCD can prognostically indicate a complicated course of nonpurulent meningoencephalitis.

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MONITORING EXPERIMENTAL TREATMENT OF MULTIPLE SCLEROSIS: THE ANTI- CD4 TRIAL DESIGN. BW van Oosten , M Lai, CH Polman, FW Bertelsmann, DH Miller, WI McDonald, AJ Thompson, S Hodgkinson. *Amsterdam, The Netherlands; London, United Kingdom & Sidney, Australia.*

Trials investigating experimental treatments of multiple sclerosis will require fewer patients and less follow- up time than to phase three clinical trials if they use reduction in serial monthly gadolinium- enhanced brain

MRI activity as a measure of outcome. This is based on data from serial monthly gadolinium enhanced brain MRI of 23 patients with multiple sclerosis, from which it can be calculated that in a study of six months duration with parallel groups and placebo controlled design, a 70% reduction in the number of active lesions should be seen with a greater than 90% power in x 40 patients. With this study design, 72 patients with clinically active MS following either relapsing remitting or secondary progressive course have been randomly allocated to receive either 50 mgs. of chimaeric monoclonal anti- CD4 antibody (Centocor,cM T412) or placebo. Treatment with this monoclonal antibody has been demonstrated to result in a significant and rapid reduction in the peripheral blood CD4 count 9 which remains below the normal range for at least a number of months after treatment. MRI evaluation will be in the second half of 1994.

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UNCOMMON PRESENTATION OF MULTIPLE SCLEROSIS IN FRENCH ANTILLAS. PH Cabre, L Volpe, D Smadja, Ph Chemouilli, G Said & JP Vernant. *Fort de France & Bicltre, France*

Multiple sclerosis (MS) is uncommon in subtropical countries. We report on seven patients with a remitting-relapsing disease of the CNS, fulfilling the clinical criteria for diagnosis of MS. These young black women aged 16 to 53 years (average 30), from French West Indies had not travelled to Europe before the age of fifteen years . They all developed a severe, relapsing, bilateral optic neuritis and transverse myelitis following a subacute course. Three patients also manifested amenorrhea-galactorrhea with hyperprolactinemia. Serology for HTLV-1 was negative in all. CSF showed mild pleocytosis with intrathecal production of gamma-globulins but no oligoclonal bands. Brain MRI showed no white matter abnormalities of the type observed in MS. Three of the five spinal cord showed an intramedullary cyst with gadolinium enhancement in one, and a focal enlargement of the spinal cord in one. Despite transient improvement after treatment with corticosteroids, three patients died within five years, and three had a severe visual and/or motor impairment. All cases presented as chronic relapsing Devic's neuromyelitis. In contrast with European patients with MS, all had neuritis and myelitis with extreme severity of optical neuritis, absence of oligoclonal Ig bands in the CSF and of MRI abnormalities suggestive of MS after a course of several years. The relationship between the disease that affected these patients and MS remains questionable.

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TUMOR NECROSIS FACTOR (TNF-A) LEVELS IN THE SERUM AND CSF AFTER EAE (EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS) INDUCTION IN LEWIS RATS. H Villaroya, K Violleau, A Ben Younes-Chennoufi, N Baumann, *Paris, France*

EAE is the best characterized demyelinating disease of the CNS in animals. It serves as a useful model for MS (multiple sclerosis) since EAE and MS share many characteristics. EAE is an antigen-specific, T-cell mediated, autoimmune disease. Cytokines may play key roles in the regulation of myelin autoimmune responses. Soluble TNF activity, assessed by L 929 fibroblast bioassay, was determined in serum and CSF samples from Lewis rats after EAE induction with purified guinea pig myelin. We have also investigated the localization of TNF expression in the CNS by immunohistochemical methods. Results were expressed in U /ml in reference to the cytotoxic activity of a standardized (Genzyme) Preparation of recombinant human TNF. I unit representing about 50 pg human TNF. This cytotoxic method detects concentrations of above 0,5 U / ml. The data obtained showed that EAE induction results in detectable circulating levels of biologically active TNF. TNF release was well correlated with encephalitogenic effect. Our observations demonstrated that circulating TNF is detectable from the third day after EAE induction, before the onset of clinical responses. The higher concentrations of TNF bioactivity were obtained days 11-12, in relation to the clinical symptoms. Immunohistochemical studies showed production of TNF by monocytes and macrophages. Other CNS cellular components could be involved in the expression of TNF and are currently being investigated.

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CHRONIC SPASTIC PARAPARESIS AS CLINICAL PRESENTATION OF MULTIPLE SCLEROSIS. P Villanueva- Hernandez, J Ballabriga, E Basart, TX Arbizu, J Perez- Serra. *Barcelona; Spain.*

Spastic chronic paraparesis (SCP) is an infrequent presentation of multiple sclerosis (MS). We have reviewed the clinical, diagnostic and prognostic features of this entity. In a retrospective review of 300 patients with definite or probable MS (Poser's criteria), 10 patients had developed an insidious spastic paraparesis. Seven were males and three females. The onset ranged 17 to 48 years, with a mean of 38. The symptoms begin with spastic and paretic gait, usually asymmetrical. There were few or no sensibility and sphinteric symptoms. Other clinical signs of MS were uncommon, usually as optic neuritis (four cases). The course was slowly progressive with high disable standings. Cranial RMI showed plaques in all but two cases, while spinal RMI was positive in half of the patients. Evoked responses were delayed in all cases. The IgG index was elevated in seven cases. HTLV- I serology was negative in all. Conclusions: SCP represented the 3.3% of MS patients in our study. The disease has later onset (fourth decade) than in other forms of MS. The diagnosis needs to be supported by laboratory tests, development of other episodes suggestive of MS. Prognosis and response to steroid therapy are poor.

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CORRELATIONS BETWEEN CLINICAL AND PARACLINICAL DATA IN MULTIPLE SCLEROSIS. VALUE OF EVOKED POTENTIALS. F Vinuels, JM Giron, JM Castilla, L Redondo, G Izquierdo. *Sevilla, Spain.*

In this study we compared the clinical data with evoked potentials (EPs) findings in order to detect the more sensitive procedure to measure Multiple Sclerosis (MS) total lesion burden. Sixty- six clinically (or laboratory supported) definite MS (33 women and 33 men) were included in this study. Courses were relapsing- remitting in 41 patients, remitting- progressive and chronic- progressive in 14. The age was 39.8 ± 13 years and the duration of disease was 9,2 ± 9. Mean EDSS was 3.5 ± 2.Visual EPs are as sensitive as clinical examination (40 abnormal EPs out of 66 patients versus 39 out of 66) to detect lesions in optic nerve. Brainstem auditory EPs are clearly less sensitive than clinical examination (19/66 vs. 54/66, $p<0.05$). Somatosensorial EPs are as sensitive as neurologic examination of the sensorial system (44/66 vs. 45/66) and they are the only EPs that correlate with clinical functions ($p<0.05$). The clinical examination is as sensitive as visual and somatosensorial EPs, and more sensitive than Brainstem auditory EPs. Visual and Brainstem auditory EPs detect different lesions than clinical examination therefore they are very useful to detect silent lesions.

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THE FREQUENCY OF MULMTIPLE SCLEROSIS IN HIGH- RISK AREA: A POSSIBLE ASSOCIATION WITH PEAT. K Lauer, *Darmstadt, Germany*

In a number of studies of epidemiology of MS, higher morbidity rates were reed in regions characterized by marsh or peat soils. In order to substantiate this observation a systematic correlation analysis was made in four Northern and Western European high- risk countries. In two of them (Ireland and Finland) peat is still of considerable economic importance. In Ireland (26 counties) the MS prevalence 1971 (Brady et al 1977) was correlated with borderline significance with the out-put of turf drawn by farmers 1945- 1948 (rs 0.353; $0.05 < P < 0.1$); fourfold- table analysis confirmed the higher risk in counties above the mean exposure level vs. those below the mean (OR=5.06; 95% CI 0.96- 11.84; P=0.056). In Finland there was a steep gradient between the provinces Vaasa and Uusima for both the MS incidence (10- 13 vs. 5- 7 per 100,000; Wikstrom 1993) and the turf production (7.70 vs. 0.03 m3/inhabitant) and the density of power plants fueled by peat (41.8 vs.1.0 per 1,000,000 inhabitants) repectively. In the Netherlands the pension- based MS period prevalence 1946- 1955 (Dassel 1960; Kurtzke 1967) was higher in the provinces exhibiting raised or low- moor bogs in comparison to those showing no peat ($U = 4.5$; $m=5$; $n=6$; $0.05< P< 0.1$). No correlation between the MS risk and either peat soils or peat processing industry was found in Denmark. This moderate, but consistent association in countries where peat is a socio- cultural feature, but not in others, might point to an etiologic role of factors associated with peat per se, when used by man, rather more than to a more indicator role or geological factors in MS, at least in countries showing a high frequency of both features.

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ANTIBRAIN ANTIBODIES IN MULTIPLE SCLEROSIS (MS) PATIENTS. A Henneberg, N Bittmann, D Link, KH Wollinsky. *Ulm, Germany*

We have described antibodies against white matter of human pons tissue in sera of MS patients before (Henneberg et al., 1991). They were mostly

of IgM-and IgG- subtype and were present in chronic progressive, but not in relapsing- remitting MS patients. Testing concentrated cerebrospinal fluids (CSFs) obtained by lumbar puncture from 25 MS patients with relapsing- remitting or chronic progressive course versus CSF's from 25 pairwise age-and sex- matched controls we found again prevalence of antibodies in the MS group, but with different presentation than in the sera: most of the antibody- binding was by IgGantibodies, there were no differences between the two courses of the disease. Therefore we examined sera and CSFs of the same MS patients in parallel using again an indirect immunofluorescence assay on frozen slices of human pons tissue. In most of the seropositive patients we could find no binding in the CSFs, while the binding often was seen in the former CSF- negative patients after a therapeutic course of 30 filtrations of their CSFs in vivo (liquorpheresis). Therefore we think, that CSFs of MS patients won by lumbar puncture might not be a reliable tool for further immunological studies.

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THE LYMPHOCYTE HOMING RECEPTOR THAT CONTROLS INTO INFLAMMATORY LESIONS IS ELEVATED IN SERUM OF MS PATIENTS WITH ACTIVE MRI PLAQUES. R Mobner, K Fassbender, J Kuhnen, A Schwartz, M Hennerici, *Mannheim, Germany*

Perivascular plaques of MS patients are characterised by dense infiltrates of mononuclear cells. Lymphocytes leave the circulation at inflammatory sites by means of adhesion molecules. Central among these is the lymphocyte homing receptor, termed L- selection. It is found on leukocytes and is responsible for the initial adhesion event at sites of inflammation. It is subsequently shed from the cell surface. This shed form of the lymphocyte homing receptor, soluble L- selecting (sL- selecting), may be measured in the circulation. We therefore determined serum levels of sL- selecting in 20 patients with definite MS, using an enzyme- linked immunosorbent assay. Inflammatory activity of MS patients was determined by Gadolinium-DTPA- enhanced MR imaging. sL- selecting was also measured in patients presenting with viral encephalitis, and in controls. MS patients with active, Gadolinium- DTPA- enhancing lesions had significantly higher sL-selecting (mean of 1382 ng/ml) than either unenhancing MS patients (mean of 989, P<0.02) or controls (972, P<0.02). Mean levels in viral encephalitis were only 1067 ng/ml. We conclude that elevated levels of the lymphocyte homing receptor responsible for the initial adhesion can be demonstrated in MS patients with active lesions. This indicates that excessive adhesive events may be occurring in such patients, especially when compared to the lower levels in viral encephalitis.

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ORALLY ADMINISTERED MYELIN BASIC PROTEIN IN NEONATES PRIMES FOR IMMUNE RESPONSES AND ENHANCES SUSCEPTIBILITY TO EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS IN ADULTS. A Miller; O Lider, O Abramsky, HL.Weiner, Haifa, Rehovot, *Jerusalem, Israel & Boston, USA.*

To determine the role of the particular route of antigen administration in neonates, and the associated antigen- driven tolerance or immunity to myelin basic protein (MBP). Background: Antigen- driven tolerance may involve various immunological mechanisms including clonal deletion, clonal anergy and active suppression depending on the route, concentration and physical state of the antigen administered. While oral administration of MBP in adults induces systemic tolerance its effect has not been studied in neonates. Methods: Oral, intraperitoneal and subcutaneous administration of MBP in neonatal and adult rats were tested for both in-vitro and invivo effects. Results: Proliferative responses of spleen cells (SPC) to MBP were significantly elevated in animals neonatally fed, but not s.c. or i.p administered MBP and injected with MBP/CFA when grownup. While irradiated SPC of adult fed MBP suppressed proliferative responses of MBP- specific encephalitogenic T cell line, in- vitro coculture of this line with irradiated SPC of rats fed MBP in the neonatal period, was associated with enhancement rather then suppression of proliferative responses. Neonates fed MBP and induced 6w later for EAE demonstrated marked enhancement of disease seventy, and were not protected from a second attack upon active reinduction of EAE. Immunologic priming gradually disappeared in animals fed MNP at the age of 3- 4w and systemic tolerance gradually appeared feeding MBP at 5w of age. Conclusions: It is suggested that antigen- driven tolerance or immunity to MBP are route and agedependent. Additionally, the modulatory network associated with oral tolerance may play a role among the natural counter- autoimmune mechanisms, and immaturity or impairment of this immunoregolatory system may contribute to the pathogenesis of MS.

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ANERGY INDUCED IN VITRO BY TCR VB8.2(39- 29) PEPTIDE SPECIFIC T CELLS IN EAE. H Offner, AA Vanderbark, *Portland, Oregon, USA*

T cell receptor peptide immunization in Lewis rats Prevents induction of EAE. To address the mechanism of this immuno- regulation CD4 + TCR VB8.2 (39- 59) specific T cells were co- cultured with GPBP specific T cell lines in vitro and responses measured by proliferation and passive transfer of EAE. Co- stimulation of mixed TCR and BP reactive lines resulted in significant reduction of the response to GPBP and loss of proliferation to the major encephalitogenic epitope 72- 89 but had little effect on response to TCR peptide or on expression of VB8.2. Passive transfer of equivalent numbers of VB8.2 (as detected by staining with antibody to VB8.2) dramatically reduced EAE induction with co- cultured cells as compared to a BP line. These data demonstrate that TCR peptide specific T cells or their lymphokines directly inhibit but do not delete VB8.2+ BP specific T cells and thus provide a plausible mechanism for their regulation of EAE in vitro. Supported by NIH grants NS23444 NS23221 Dept. of Veterans Affairs and XOMA Corp.

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CSF FREE LIGHT CHAINS IN MULTIPLE SCLEROSIS AND IN OTHER NEUROLOGICAL DISCORDERS. E Paoino, E Fainardi, MC Addonizio, P Ruppi, MR Tola, E Granieri, M Carreras. *Ferrara, Italy.*

Intrathecal IgG production is common in Multiple Sclerosis (MS) and the occurrence of CSF Free Light Chains (FLC), Kappa (FLKC) and Lambda (FLLC),has al so been documented. CSF FLC in MS seem to indicate a recent immunological stimulation leading to a CNS increased synthesis. We assayed CSF and Serum Albumin, IgG, FLKC and FLLC in 244 subjects (52 Clinically Definite/Probable MS -CD/PMS; 26 Possible/Suspected MS -CP/SMS; 129 Other neurological Disorders -OND; 37 Healthy Subjects -HS). Thus, we estimated the IgG Index (normal values<0.70), and the Kappa (normal values<0.65) and Lambda (normal values< 1.96) Indexes by using the Link's Formula. A positivity of IgG, Kappa and Lambda Indexes was found in 71.1%, 80.7% and 36.5% of CD/PMS, 61.5%, 65.4% and 19.2% of CP/SMS 6.2%, 15.5% and 11.6% of OND. IgG Index resulted positive in 5.4% of HS, while Kappa and Lambda Indexes were negative. The positivity of at least one Index was observed in 88.5% of CD/PMS and in 76.9% of CP/SMS. Kappa and Lambda Indexes showed a Specificity of 84.5% and 88.4%, respectively. The Positive and Negative Predictive Values also resulted to be high in both MS groups. No difference emerged when we compared MS course, activity and disability. These findings suggest that CSF FLC originate in intrathecal plasma cells, not exclusively from degradation of whole IgG, and that their assay may be useful for the improvement of MS diagnosis.

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PREVALENCE OF MULTIPLE SCLEROSIS (MS) and auto-IMMUNE DISEASES IN FAMILIES OF FRENCH MS PATIENTS: A PROSPECTIVE STUDY. V Sazdovitch, A Joutel, MH Verdier-taillefer, O Heinzlef, C Radder, E Tournier-Lasserve, E Roullet, *Paris, Villejuif, France*

Differences in population frequencies of the putative gene(s) involved in the susceptibility to MS Could explain the discrepancies between twin studies conducted in France and in other (Mc Farland, An Neurol, 1992). Auto-immune diseases (AID) are occasionally found in the families of MS patients but have not been the subject of any systematic evaluation. To determine the prevalence, type and distribution of MS and other putative AID in the families of French MS patients. Family history was taken from unselected French MS patients followed at our clinic. A semi-standardised questionnaire was administered by phone or direct interview to the patient and to a second informant when appropriate. Medical information was checked through the corresponding physicians. Extended pedigrees could be determined from 306 definite MS patients. Familial MS was present in 11.7% (36 patients, first degree:28, second and third degree: 8, multiplex families (>3 affected members): 6). Forty-two patients(13.7%) had a first-degree AID-affected member and 25 belonged to a multiplex AID family including MS. Pedigrees and detailed data on type and frequency of AID will be presented.The MS genetic load is lower in France than in countries with a higher MS prevalence. The occurrence of multiples MS+AID families could offer new insights into the genetic aspects of MS

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THE RELATIONSHIP BETWEEN Gd- DTPA ENHANCEMENT AND THE ONSET OF PROTON NMR SPECTRAL CHANES IN ACUTE EXPERIMENTAL ALLERGIC ENCEPHALITIS (EAE). RE Brenner, PMG Munro, SCR Williams, JD Bell, GJ Barker, CP Hawkins, WI McDonald, *London, UK.*

The earliest detectable event in the development of the new lesion in MS, as in experimental allergic encephalomyelitis (EAE),is a breakdown in the blood- brain barrier in association with inflammation. The precise sequence of events is however uncertain. We have attempted to elucidate them in acute EAE in guinea pigs. In acute EAE as in MS magnetic resonance spectroscopy (MRS) reveals an elevation of the choline:creatine ratio which at least in the former is associated with inflammation, reflecting increased metabolic turnover in the cellular infiltrate. In sequential studies in 14 animals with EAE compared with controls, we observed an increase in choline:creatine before the onset of Gd- enhancement. This suggests at perivenous inflammation precedes blood- brain barrier breakdown to solutes. Whether the same is true in MS awaits the results of serial MRS studies in patients with much ongoing disease activity.

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MAGNETISATION TRANSFER IN MULTIPLE SCLEROSIS ENHANCING AND NON-ENHANCING LESIONS. M Filippi, A Campi, V Dousset, N Canal, G Comi, *Bordeaux, France & Milan, Italy.*

The aim of this study was the evaluation of the magnetisation transfer (MT) characteristics of MS gadolinium- enhancing and non- enhancing lesions in multiple sclerosis. MT studies were performed with a 1.5 T machine (TR=600ms, TE=12ms, flip angle=20°, matrix size=192X256, section thickness=5mm, interslice gap=0.4 mm, saturation off resonance pulse=1.5 kHz pulse bandwidth=250 Hz) in 21 MS patients and nine sex- and age- matched controls. The MT ratio was calculated according to the formula published by Dousset et al. (Radiology 182: 483- 491, 1992). Thirty- eight enhancing lesions, 219 non- enhancing lesions, and 46 areas of normal appearing white matter (NAWM) were studied. Lesions had significantly lower MT ratio than the NAWM of the patients and the normal white matter of the controls. ($p<0.0001$). No difference was found between MT ratio in enhancing and non enhancing lesions. In 4 patients with 10 isolated non- enhancing lesions, a progressive increase of MT ratio from the nearest to the furthest NAWM was observed. Our results suggest a large variability of both enhancing and non- enhancing MS lesions and a microscopic pathological involvement of the adjacent NAWM.

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A FIRST STEP IN DEVELOPMENT OF GENE THERAPY FOR BRAIN TUMOURS: GENE TRANSFER AND EXPRESSION IN VITRO AND IN VIVO. J Zhu, F Weber, R Retska, J List, L Zhang, M Brock, *Berlin, Germany*

We tested the efficiency of two cationic liposomes (Lipofectin, DC- chol) for transfection of a report gene, (- galactosidase gene, into human and rat malignant glioma cells in monolayer culture, multicellular tumour spheroids(MTS), and in vivo. The two different cationic liposomes could mediate (β- galactosidase gene expression in both rat and human cell lines. However, the level of observed expression was dependent upon the cell lines. In rat glioblastoma cell lines(C6 and F98), lipofectin mediated a highest transfer efficiency; but transfection activity of DC- chol liposomes was four times greater than that of lipofectin in N64 human glioblastoma cell line. We determined that ratio of 20 nmol lipids of DC- chol liposome to 1 μg of DNA produced maximal Lac- Z gene expression in human cell lines MTS model system, in which cells grow in vitro as 3- dimensional aggregates, represents an intermediate level of growing as monolayer in vitro and solid tumour in experimental animals in vivo. After transfection with DNA- liposome complex, some positively stained cells were seen in MTS. At 4 h-transfection experiment. the positive cells were superficial tumour cells; but at 24 h- transfection positive cells were apparent in deep layers. This finding suggests that DNA- liposome complex can penetrate spheroid tissue slowly. For in vivo transfection of brain tumours, rats inoculated with rat glioblastoma cells into the right caudate nucleus were given one week later an intra- tumour stereotaxic injection of DNA- liposome (Dc- chol) complex. Seven days post- transfection, many cells positively stained for (β- galactosidase were seen within the tumour mass. 10-20% of tumour cells in the point of injection expressed the Lac- Z gene in animals. These results suggest that cationic liposomes will be useful in facilitating delivery of DNA into tumour cells in brain tumour gene therapy

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HYPOTHALAMIC- PITUITARY FUNCTION TESTS AFTER RADIOTHERAPY OF LOW- GRADE GLIOMA. MJB TAPHOORN, JJ HEIMANS, EA van der Veen, ABMF. Karim, *Amsterdam, The Netherlands.*

We studied endocrine functions in adult low- grade glioma survivors with complaints which could be suggestive of hypothalamic- pituitary dysfunction. A high prevalence of hypothalamic- pituitary dysfunction is reported in patients treated with radiotherapy for brain tumours. Evaluation of endocrine functions in these patients is important, because this is a treatable condition. Fifteen brain- tumour patients (9 male, 6 female, age 24- 66 years) with complaints of tiredness, lethargy, decreased libido and sleep disturbances were studied. They had received radiotherapy for supratentorial low- grade glioma at least one year before (range 1- 11.5 years) and were without clinical or CT signs of tumour recurrence. The total radiation dose (4 or 6 MeV photons, 1.8 Gy/fraction) varied between 30 and 61.2 Gy. The calculated doses delivered to the hypothalamus and pituitary varied from 5 to 54 Gy (mean 40.5). Endocrine testing included measurements of serum pituitary hormones, cortisol and thyroid hormones before, and 20 and 60 min after injection of 4 hypothalamic hormones (thyrotropin-and gonadotropin- releasing hormones, corticotropin-and growth hormone- releasing factor). In all patients all hormonal assays were normal. Conclusion: These patients had undisturbed endocrine functions. Their complaints should therefore be attributed to disturbances caused by the tumour or by the radiotherapy.

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PRIMARY MALIGNANT LYMPHOMA OF THE CENTRAL NERVOUS SYSTEM: RESULTS OF TREATMENT OF 12 CASES WITH CHEMOTHERAPY AND RADIOTHERAPY. M Sarazin, A Ameri, N Argentino, M Poisson, JY Delattre, *Paris, France*

There is some evidence that chemotherapy (CT) is of value for primary CNS lymphomas (PCNSL). We retrospectively studied 12 HIV negative patients with PCNSL who received combined CT and radiotherapy (RT). None had occult systemic lymphoma, but 16% had ocular and 41% had definite or probable Leptomeningeal lymphoma. Two groups were identified. In group A, 8 patients received a combined regimen using pre- RT intravenous methotrexate (MTX) (lg/m2) and intra- thecal MTX, followed by 4,OOO cGy whole- brain RT with a 1,44O cGy boost on the tumor bed, and 3 courses of post- RT CT with Thiotepa (4O mg/m2) and Procarbazine (lOO mg/m2/15 days), repeated every 4 weeks. Four other patients (group B) received an identical regimen after RT. In group A, median time to tumor progression (MTP) (ocular or CNS) was 35 week, and median survival (MS) was 178 week. In group B, MTP was 16 weeks and MS was 7O weeks. Grade 2 and 3 blood toxicity occurred in 6 patients (50%). Unfortunately all surviving patients developed a leucoencephalopathy with mental deterioration. Our study suggests that the addition of CT administered before and after RT is useful for PCNSL. However, late CNS toxicity appears to be a major side effect of this approach.

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TREATMENT OF SUPRATENTORIAL GLIOMAS WITH ASSOCIATION OF CYCLOPHOSPHAMIDE AND METHOTREXATE : A PHASE II STUDY. P Derkinderen, A Ameri, M Poisson, JY. Delattre, *Paris, France*

Objective and Background: Treatment of recurrent malignant supratentorial gliomas (RMSG) is disappointing and needs the use of new association of chemotherapeutic drugs. Methods: 21 patients previously treated with surgery, radiation therapy and chemotherapy with nitrosurea for recurrent malignant supratentorial gliomas (13 glioblastomas multiform, 5 anaplastic astrocytomas, 4 anaplastic oligodendrogliomas) received a combination of cyclophosphamide and methotrexate at tumor progression. Cyclophosphamide was administered at a dose of 12 to 20 mg/kg at day 1 and day 2, methotrexate at a dose of $1 g/m^2$ at day 1. Courses of therapy were repeated every four weeks. The umber of courses per patient ranged from 1 to 7 (mean 2). Results: Tolerance was evaluated in 21 patients. Blood toxicity Grade III and IV occurred in 6 patients (29%). All 21 patients could be evaluated for therapeutic response. No patient had partial or compact response. Stabilisation lasting 2+ to 9 months was observed in 6/21 patients ('9%). Estimated median duration of survival for the entire group was 24,3 weeks following the onset old methotrexate and cyclophosphamide (67 weeks following the date of histology). Conclusion: This study suggests a modest benefit of cyclophosphamide and methotrexate a second chemotherapy for RMSG.

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DIFFERENTIAL DIAGNOSIS IN BRAIN TUMOURS USING PROTON SPECTROSCOPY. B Buchwald, G Schroter, G Serve, CH Franke, B Conrad, *Munich, Germany*

Proton NMR spectroscopy (1 H- MRS) allows to identify resonance for N-acetyl- aspartate (NAA), a neuronal marker, phospho/creatine (PCr/Cr), choline (Cho), which reflects cellular membrane metabolism and mobile lipids. In some cases it is also possible to monitor lactate (Lac), indicating anaerobic glycolysis. We investigated 16 patients and 9 healthy volunteers by 1 H- MRS. 1 H- MRS was performed at 1.5 Tesla. Magnetic field homogeneity was shimmed to 9 (2 Hz. The average volume of interest was 9.4 ml. 128 -512 measurements were summed up with an interpulse delay of 3 seconds. Measurements were performed at echo times of 272 and 136 ms. Peaks were fitted to Lorenzian lines. All spectra of malign intracerebral tumors showed elevated Cho peaks. All astrocytomas showed relatively moderate elevations of Cho and reductions of NAA. The increase of Cho was the strongest in the breast cancer metastasis. Increase of Cho was very high in glioblastomas and in the patient with the tumor of unknown histology. Conclusion: 1. 1 H- MRS at 1.5 Tesla is a helpful means in differentiating intracerebral tumors due to their metabolic profiles and can fairly exclude malign intracerebral lesions. 2. Cho increase and NAA decrease seem to reflect malignancy of different tumors. 3. 1H- MRS reveals anaerobic glycolysis and so far can give additional information to studies of energy metabolism as assessed by 31 P- MRS and glucose consumption assessed by FDG- PET.

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NMR PROTON SPECTROSCOPY OF MENINGIOMAS. RE Brenner, CA Davie, ND Kitchen, DGT Thomas, DH Miller, WI McDonald, *London, UK*

The pre- operative identification of cerebral tumours remains a challenge. Proton magnetic resonance spectroscopy (MRS) detects at least nine cerebral metabolites, and is being increasingly utilised to investigate the biochemical changes accompanying neurological disease. However, the information obtained is often non- specific, providing perhaps prognostic data but rarely a diagnosis. In vivo short echo proton spectra (TE = 10ms) obtained at 1.5 T from two patients with cerebral meningiomas revealed an elevation of the peak assigned to choline containing compounds, a reduction in that assigned to N- acetyl containing compounds as well as a prominent resonance assigned to alanine, as has previously been described. In addition, a marked increase was seen in the peaks assigned to glutamate and glutamine. This was confirmed by high field spectra (11.5 T) obtained from tumour extracts. High levels of glutamate and glutamine have not previously been reported in cerebral tumours. While this observation clearly requires confirmation, it raises the possibility that MRS may provide a "metabolic fingerprint" and thus aid in the non- invasive diagnosis of cerebral space occupying lesions.

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SOMATOSENSORY EVOKED POTENTIALS SERIA IN STUDIED IN RADIATION MYELOPATHY . IN THE RHESUS MONKEY. AD Forman, Kie- Kian Ang, R Price, C Stephens, *Houston, U.S.A.*

Radiation injury remains the main limit of therapeutic radiation for malignancy in or near the central nervous system, yet the mechanisms of radiation injury are still poorly understood, with debate as to whether the early damage is to endothelium, myelin or axons. We studied 48 adult Rhesus monkeys following radiation to the spinal cord in doses ranging from 89.4 Gray in 82 fractions to 44.0 Gray in 20 fractions with clinical evaluation, somatosensory evoked potentials and neuropathology. Spinal cord magnetic resonance imaging was done in selected animals. The minimal period of study was 150 days with 17 animals studied for 600 days or longer. No significant change was found in the latency of the somatosensory cervical response (12.39 ms (5.8), P1 (18.08 ms (4.22) or N1 (23.32 ms (5.31) throughout the study. The cortical amplitude was significantly diminished at 500 days (baseline 3.84 mV (2.59 versus 3.07 mV (2.42 with a two tailed paired t test having a p value of 0.015, t=2.59 with 28 degrees of freedom.) The amplitude continued to diminish at 600 days study (2.87 mV (1.98) although the numbers are not yet significant (17 animals studied.) These findings strongly support the hypothesis that the earliest damage in radiation injury is not to myelin, but rather to the axon. neuropathologic and magnetic resonance imaging support these findings.

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AN ANTINEURONAL ANTIBODY IN A CASE OF NEUROBLASTOMA AND OPSOCLONUS- MYOCLONUS- ATAXIA. A Salmaggi, R Nermni, A Silvani, MG Forno, R Luksch, P Confalonieri, A Boiardi; *Milan Italy.*

The association between neuroblastoma and opsoclonus- myoclonus-ataxia is well- known, but the presence of serum and CSF anti- neuronal nuclear antibodies has been reported only in one case. A 19- year old male was diagnosed as affected by retroperitoneal neuroblastoma and treated by polychemotherapy; after chemotherapy the patient developed vertigo, diplopia and dizziness, with subsequent spontaneous regression. Partial surgery was performed on the tumour. After 2 cycles of metabolic radiotherapy the patient developed gait ataxia, opsoclonus, dysarthria, head and limb myoclonus with progressive evolution. CSF showed increased IgG-index and oligoclonal bands at isoelectric focusing. Immunocytochemistry performed on rat cerebellum showed that both serum and CSF stained the nuclei of all neurons in a diffuse homogeneous pattern. Western blot revealed the presence in serum and CSF of IgG reacting with a protein band of 40 kD. Immunocytochemistry performed on the patient's tumour showed that, although no in vivo binding of immunoglobulins to the tumour was present, incubation of tumour with CSF and serum (followed by anti- IgG antibody) produced a staining pattern of the tumour cell nuclei similar to the one seen in cerebellum neurons. This further supports the pathogenetic role of ANNA in the neurological syndrome.

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THE F WAVE IN ASSESSMENT OF INFLUENCE OF INTRATHECAL METHOTREXATE (IT- MTX) ADMINISTRATION ON PERIPHERAL NERVOUS SYSTEM FUNCTION. H Grzelec, C Fryze, P Nowacki, B Zdziarska, *Szczecin, Poland*

Electrophysiological examination was performed in 20 patients aged 40-71 years (mean age 56 yrs) with non- Hodgkin's lymphomas of high malignancy. Patients were treated with general chemotherapy according to CHOP, COP- BLAM and CEVEP schedules. on first day of chemotherapeutic cycle they received IT- MTX (12 mg/m^2) and prednisolone (2S mg) intrathecally as a prophylaxis of central nervous system involvement. Electrophysiological study was carried out twice in each patient: before and day after IT- MTX injection. The study procedure included: conventional nerve conduction examination (peripheral conduction velocity and compound muscle action potential), the F wave latency measurement and F ratio: F- M- l/2M calculation for each peroneal and tibial nerve. Results of the first and second examination were statistically compared by t- Student' s test. No significant differences between values of estimated parameters were found. Proximal, paraspinal motor conduction velocity as well as motor neuron excitability due to antidromical electrical activation were not diminished day after IT- MTX administration. The study revealed no direct negative influence of MTX given intrathecally on peripheral nervous system function.

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EVIDENCE OF AT LEAST TWO DIFFERENT MOLECULAR PATHWAYS IN MENINGIOMAS TUMORIGENESIS. M Sanson, P Merel, S Richard, G Rouleau, G. Thomas. *Paris, France & Montreal, Canada.*

Loss of one chromosome 22 is the most frequent genetic abnormality in meningiomas. The gene of the neurofibromatosis type II, which predisposes to multiple meningiomas and schwannomas, has been located on chromosome 22. We recently isolated the NF2 gene, which codes for a protein called schwannomin. DNA from 38 meningiomas were investigated for mutations in the 16 coding exons of the NF2 gene using DGGE technique. Loss of a chromosome 22 alleles using different polymorphic loci, and histopronostic grading were also monitored for each tumor. Evidence of allelic loss of one chromosome 22 was found in 21 tumors. Mutations resulting in a truncated, presumably inactive schwannomin were found in 6 tumors: all of them displayed evidence for the loss of the non mutated chromosome 22, confirming complete inactivation of the schwannomin in this subset of tumors. However the 18 tumors without loss of chromosome 22 did not display any mutation ($p<0.02$). Furthermore, histopronostic grading was significantly higher in the tumors involving loss of chromosome 22 ($p<0.01$). This results suggest at least two different molecular pathways in meningiomas tumorigenesis: one subset of tumors (approximately 50%) involves functional inactivation of the NF2 gene; the other includes less aggressive tumors but their mechanism of tumorigenesis is unknown.

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CLINICAL, ELECTRODIAGNOSTIC AND MAGNETIC RESONANCE CHARACTERISTICS IN RADIATION INDUCED BRACHIAL PLEXOPATHY. NK Olsen, P Pfeiffer, N Egund, SM Bentzen, L Johannesen, K Mondrup, C Rose, *Odense, Denmark*

To characterize brachial plexopathy (RBP) induced by radiation therapy (RT), we performed a thorough neurological follow- up examination in 207 recurrence- free breast cancer patients. Group 1 (DBCG 77): 79 patients received 36.60 Gray (Gy) in 12 fractions, twice a week. In addition 48 patients received chemotherapy. Median follow- up 60 months. Group 2 (DBCG 82): 128 patients received 50.00 Gy in 25 fractions, five times weekly. In addition 82 patients received chemotherapy. Median follow- up 50 months. Results: The clinical manifestations were similar in both groups. However, in DBCG 77, disabling and mild brachial plexopathy (RBP) was found in 19 and 16%, respectively, as compared to DBCG 82 where the corresponding figures were 5 and 9%, respectively (p=0.001). RBP was more frequent in younger patients (p=0.001) and patients receiving chemotherapy (p=0.01). Multivariate logistic regression showed that RBP strongly depended on age and dose per fraction. Neurophysiological investigation in 46 patients showed chronic partial denervation. MRI showed disintegration of the normal anatomy with shrinking of the brachial plexus branches in 6 out 10 patients with clinical RBP. Histological evaluation revealed attenuation of sensory nerve fibres. Conclusion: The brachial plexus is more vulnerable to large dose per fraction and more frequent in younger patients.

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EFFECTIVENESS OF INTRATHECAL METHOTREXATE ADMINISTRATION IN PROPHYLAXIS OF CENTRAL NERVOUS SYSTEM INFILTRATES IN PATIENTS WITH NON- HODGKIN'S LYMPHOMAS. B Zyluk, P Nowacki, *Szczecin, Poland*

Clinical and neuropathological examinations were carried out in 43 patients deceased due to non Hodgkin's lymphomas of high malignancy, aged 18 -78 years (mean age 44.5 years). The patients were divided into two groups: with intrathecal methotrexate administration as a prophylaxis of central nervous system infiltrates (CNS infiltrates) (18 patients) and without intrathecal methotrexate administration (2S patients). In all patients general chemotherapy according to appropriate protocols has to be given. It was found that in patients with intrathecal prophylaxis neurological manifestations of CNS infiltrates appeared a little rarely than in cases without prophylaxis (28.5 and 34 % respectively). Lymphomatous infiltrates in neuropathological examinations were observed in patients with- and without intrathecal prophylaxis. In cases with intrathecal prophylaxis the lymphomatous infiltrates were usually observed in deep parts of cerebellum -region difficult access for methotrexate given inkathecally. They were also found in the spinal meninges and roots, in the vicinity of intrathecal methotrexate administration. These investigations suggest that intrathecal prophylaxis with methotrexates reduces the clinical risk of CNS lymphoma, but it isn't able to prevent the lymphomatous infiltrates in CNS -potential reservoirs for CNS lymphoma with clinical manifestations. The infiltrates probably develop within the periods between intrathecal methotrexate administrations, especially during leukemic conversion of lymphoma (periods with hyperleukocytosis in peripheral blood).

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NEUROLOGIC FINDINGS IN CANCER PATIENTS; A RETROSPECTIVE EVALUATION OF A NEURO- ONCOLOGIC OUTPATIENT DEPARTMENT. E Wondrusch, O Berger, M Drlicek, N Fast, K Jellinger, K Lindner, A Urman, U Zifko, W Grisold, *Vienna, Austria*

Neurologic deficits in cancer patients may be caused by metastasis, metabolic, paraneoplastic and non tumour related disorders. A series of 400 consecutive tumour patients with solid tumours was retrospectively evaluated. The tumours were unselected reflecting the specialisation of the referring oncologic centre. Most frequently lung cancer, followed by breast cancer was seen. Neurologic symptoms were classified into central nervous lesions (CNS), spinal cord lesions, cranial nerve involvement, neuromuscular symptoms. CNS symptoms occurred most frequently; focal signs (23 %), altered mental status (15 %) and seizures (9 %): 39 % of CNS symptoms were not tumour related. Transverse spinal lesion occurred in 5% and were cancer related. Peripheral cranial nerve lesions were caused by meningeal carcinomatosis or metastasis to the base of the skull. Caudal cranial nerve lesions were observed as a complication of neck surgery. The peripheral nervous system was affected most often by symmetric subclinical neuropathy (15%). Other types of neuropathy included sensorimotor types (10 %) only one case of subacute sensory neuronopathy was observed (0.2%). The Lambert Eaton myasthenic syndrome was seen in 2 cases (0.5%). Definite paraneoplastic neurologic syndromes occurred in 4 patients (1 %) and comprised a seronegative case of paraneoplastic cerebellar degeneration in 3 patients with neuromuscular symptoms.

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CLINICAL, RADIOLOGICAL AND HISTOLOGICAL FINDINGS IN GLIOMATOSIS CEREBRI. JL THIBAULT, M Sanson, Ch Duyckaerts, JY Delattre, M Poisson. *Paris, France.*

Gliomatosis Cerebri (GC), characterized by extensive proliferation of tumor cells resulting in diffuse overgrowth of the neuraxis is rare, with less than a hundred cases reported . We report here four cases of GC. Clinical observations included: elevated intracranial pressure, behavioural changes, cognitive dysfunction, seizures, focal neurological deficit. Nonspecific results of laboratory and radiological investigation made the diagnosis quite difficult. On CT scan, 2 patients had normal findings, one had diffuse enlargement of the brain and one had white matter hypodensities. On MRI, diffusely increased signal on T2 weighted images was found in all patients. Histological diagnosis was obtained in all cases. As found in most published patients, diffuse anaplastic astrocytic proliferation was present in 3/4 patients. In the fourth case, neoplastic cells were oligodendrocytes. Only one case of pure oligodendroglial GC, and three cases of mixt proliferation have been published to date. One patient was not treated and died within 4 months. The three other patients received a combination of whole brain radiotherapy and nitrosourea-based chemotherapy. One died within 2 months but 2 other are still alive at 3 and 14 months. Clinical and radiological diagnosis of GC is impossible and biopsy should be considered in case of subacute unexplained diffuse leukoencephalopathy. Treatment with radiotherapy and chemotherapy may be of benefit in some patients.

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MANAGEMENT OF PRIMARY CEREBRAL LYMPHOMA. H Strik, B Muller, E Richter, P Krauseneck, *Dresden, Lubeck & Bamberg, Germany.*

We reviewed 40 HIV-negative patients treated since 1978. Patient characteristics: 23 female, 17 male; mean age 53 (19-77); Clinical features: focal signs 28 pts.; psychiatric sympt. 22 (!); seizures 6; leptomeningeal seeding initially over 50%, during total course 87%; typical symptoms of CSF seeding only in one patient. Diagnosis: resection 12, biopsy 19, CSF cytology 6, autopsy 3. Histology: 13 low-, 15 high grade, 12 unclassifiable, all B-cell. Treatment: no specific therapy 7 pts., radiation only 16 pts., radiation and (low-dose-) chemotherapy 17 pts.; in the last years CSF monitoring and intrathecal chemotherapy became standard. Results: 10 pts. still alive, survival over 2 years 17 pts., over 5 years 7 pts.; median survival: 22 m. with radiation (16 pts.), 26 m. with radiation and initial low-dose chemotherapy (8 pts.). In three pts. detection of CSF seeding pointed to a clinically in apparent solid relapse; Conclusions: Quick diagnosis and onset of therapy is essential. Survival times are best for pts. with initial combined radio- and chemotherapy. Regular CSF cytology and intrathecal chemotherapy are important. The advantage of high-dose chemotherapy has to be discussed and therapeutic concepts should be evaluated in interdisciplinary concepts.

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ADJUVANT CHEMOTHERAPY FOR MEDULLOBLASTOMA IN ADULTS. A Steinbrecher, M Schabet, C Hess, M Bamberg, J Dichgans. *Tubingen, Germany*

Standard therapy of medulloblastoma in adults includes postoperative irradiation of the craniospinal axis with a boost to the tumor. The role of adjuvant chemotherapy (aCH) is not defined. To investigate the value of aCH for medulloblastoma in adults we performed a retrospective analysis of original data and follow- up of 14 patients (pts) treated at our institutions between 1976 and 1993. Median age at diagnosis was 22 years (range 17- 45). All pts received rather uniform postoperative radiotherapy with median doses of 52 Gy to the posterior fossa and of 35 to the craniospinal axis. Seven pts underwent aCH consisting of methotrexate, vincristine, CCNU and procarbazine in various combinations. Among these 3/7 had subtotal resection (SR) of tumor and 4/7 initially had leptomenigeal dissemination (LMD). At 5 years 5/6 of the evaluable pts were recurrence- free, at 7 years 4/4. Among pts without aCH 4/7 had SR, none had initial LMD. At 5 years 1/4 of the evaluable pts was recurrence- free. While extent of surgery was about the same in both groups, treatment

evaluation is biased by the fact that initial LMD as a bad prognostic factor only occurred in the aCH group. Nevertheless pts treated with aCH were more likely to be recurrence- free at 5 years. Therefore we suggest that aCH may be useful at least for pts with SR or primary LMD.

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REVERSAL OF SUBACUTE PARANEOPLASTIC CEREBELLAR SYNDROME WITH INTRAVENOUS IMMUNOGLOBULIN. C E Counsell, M McLeod, R Grant. *Edinburgh, UK*

A patient with known Lambert-Eaton Myasthenic Syndrome subsequently developed a rapidly progressive, disabling paraneoplastic cerebellar syndrome associated with a small cell lung carcinoma and anti-neuronal nuclear antibody type 1 (anti-Hu). The ataxia rendered him bedridden. He was treated at an early stage with intravenous immunoglobulin (2g/kg over 5 days) and also received a course of radiotherapy for his lung carcinoma (30 Gray in 10 fractions). Within two weeks of receiving the immunoglobulin there was a significant improvement in his condition such that he was able to walk again. The speed of this recovery made it unlikely to be due to the radiotherapy. The improvement was sustained and on review at three months there were no cerebellar signs.

68
LYMPHOMA AND ENIGMATIC LEUKOENCEPHALOPATHY. GB Creel, *Pittsburgh, USA*

In order to increase the awareness of clinicians to the possibility of primary central nervous system (CNS) lymphoma in enigmatic patients with cognitive decline, motor neuropathy, and progressive leukoencephalopathy, we report on three cases of progressive leukoencephalopathy seen in one year by the neurology teaching service. Patient 1, a 37 year old man with hemophilia A and HIV, had a 6- 8 month decline with muscle atrophy and fasciculations, ending in an intracerebral hemorrhage. Autopsy revealed intracerebral T- cell lymphoma and loss of anterior horn cells. Patient 2 was a 65 year old woman with 13 months of progressive dementia, motor neuropathy, and intrathecal monoclonal IgG synthesis. Autopsy showed B- cell lymphoma infiltrating the brain and spinal cord with corticospinal tract degeneration. Patient 3 was a 23 year old man with a long standing immunodeficient state and 8 months of progressive spastic quadriparesis, sensorimotor polyneuropathy with fasciculations, and dementia. Autopsy found T- cell lymphoma in the brain and spinal cord. Conclusions: Despite extensive workup, including brain biopsy in patient 2, lymphoma was not diagnosed in these patients during life. As treatment exists for CNS lymphoma, early diagnosis is essential. Aggressive diagnostic procedures such as brain biopsy should be considered.

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ASCENDING CENTRAL NERVOUS SPREADING OF A SPINAL ASTROCYTOMA. D Claus, E Sieber, A Engelhardt, T Rechlin, P Thierauf, U Neubauer. *Erlangen, Germany*

A 43-year-old man died from the complications of a metastasising astrocytoma. In 1979 he had symptoms of a lumbar disc prolapse. In 1986 a pilocytic astrocytoma (grade 1) of the spinal cauda was removed. In 1989 residual tumour at the same site was partially removed. Histology showed a grade I I astrocytoma. Two months later the patient developed symptoms of increased intracerebral pressure. CSF cytology showed polymorphic giant tumour cells with hyperchromatic nuclei and a glioblastoma of the cerebral ventricles was diagnosed. The patient died from cardiovascular complications. Post-mortem investigation revealed an astrocytoma of the conus medullaris with an anaplastic ventral area (grade 4). This area had not been seen in the biopsy. It is believed that anaplastic parts of the tumour metastasised along the spinal cord and brain stem and finally invaded the brain and cerebral ventricles.

70
NEUROPHYSIOLOGICAL EVALUATION OF SACRAL REFLEX IN UROLOGICAL PATIENTS. M Peresson, G Di Giovacchino, GL Romani, and F Di Silverio. *Chieti and Rome- Italy*

The neurophysiological investigation of the afferent/efferent somatic pathways in the pelvic structures has proved useful in the functional detection and classification of a variety of urological diseases. The rationale for the present work was to evaluate both the neurophysiological and urological parameters and to predict the outcome of rehabilitative therapy . In this study 1 50 patients with various urological and neurological problems, all presenting altered micturition, were evaluated. In all patients a complete neurophysiological screening was carried out that consisted of: 1. Somatosensory evoked potential (SEP) in response to electrical stimulation at the dorsal nerve of penis/clitoris; 2. Recording of the reflex response of the bulbocavernous (BC) muscle; 3. Sympathetic skin response (SSR). A parallel urological screening was performed that included morphological and dynamic sonography and urodynamic tests. Out of 1 50 patients, 60% presented no alterations of the neurophysiological parameters as measured, while the rest had various degrees of alteration. All the patients underwent rehabilitative therapy. As expected the patients with no neurophysiological alterations were able to restore a normal functionality (83%), while the remaining population ca 40% obtained a partial rehabilitation. Our results show that neurophysiological screening represents a suitable tool to predict the prognosis in case of micturition disturbances.

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NEUROLOGICAL FINDINGS IN KALLMANN SYNDROME. A Danek, M Kuffner, R Hoermann, J Schopohl, M Laska, B Heye, *Munich, Germany*

Defect of the X-linked KALIG-1 gene cell adhesion molecule impairs migration of olfactory and gonadotropic cells in Kallmann syndrome (hypogonadotropic hypogonadism with anosmia; KS). In autosomal KS, the defect is yet unknown. Mirror movements (MM) and bilateral cortically evoked motor responses (CEMRs) may occur in KS. To elucidate the genetic basis of MM we examined 21 males with KS and elicited CEMRs by focal transcranial magnetic stimulation of hand motor cortex. Six patients showed pronounced MM. Only in these CEMRs occurred bilaterally, in all others contralaterally. In the latter, MM were either absent or not different from those of normals. One patient had congenital facial palsy, nystagmus, and gait ataxia, yet no MM. Heterogeneous mechanisms for KS are suggested by these patterns of neurological findings. MM with bilateral CEMRs were found in a patient with KALIG-1 deletion, in three brothers with X-linked KS and in a patient with an anosmic mother. Therefore, pathologic mirror movements seem specific for defects of KALIG-1, thus guiding also motor axons.

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AUDITORY BRAINSTEM RESPONSES IN ACOUSTIC NEURONS PATIENTS. AT Zangaladze. *Tbilisi, Rep. of Georgia*

The auditory brainstem responses (APPs) were averaged in 24 patients with acoustic neuroma. ABR Wave V abnormality occurred most frequently at initial stages of the disease. The structure of Wave V, generation unlike earlier ABR components, is separated by more synapses from the principal lesion. Therefore, synaptic dispersion is distinctly revealed in Wave V parameters. a sensitive index of acoustic neuroma as well as of other retrocochlear lesions may be the difference between the interpeak intervals (IPIs) of III-V and I-III. The IPI III-V could be increased relative to the IPI I-III and this increase can be the only electrophysiological sign of the pathology. In case of minimal compression of the brainstem by tumour, in response of stimulation of unaffected ear the abnormality was pathological alteration of Wave V. Since the superior auditory complex is a first auditory structure which is characterized by contralateral projections, it might be the principal source of APP Wave V

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FACILITATION OF THE BLINK REFLEX RESPONSES TO AUDITORY STIMULUS BY AN IMPENDING SUPRAORBITAL NERVE ELECTRICAL STIMULUS. J Valls-SolÈ, A Cammarota, R Alvarez, E Tolosa, M Hallett. *Barcelona, Spain & Bethesda, USA.*

In human neurophysiologic studies carried out with pairs of time-locked stimuli, only the "pre-pulse" effects induced by the first stimulus of the pair upon the response to the second stimulus are usually considered. We have investigated the occurrence of "post- pulse" effects, induced by the second stimulus of the pair upon the response to the first stimulus, using the blink reflex responses to auditory and electrical stimuli. The auditory stimulus was applied alone in control trials, and preceding the electrical stimulus, at intervals of 100 or 500 ms, in test trials. Series of 5 trials, either control or test, were applied in alternation. We measured the duration and amplitude of the responses induced in the orbicularis oculi by the auditory stimulus (auditory blink reflex = ABR) in control and test trials, and the results were statistically compared with the t test. At any given stimulus intensity or duration, ABRs were larger in test trials than in control tri-

als. Also, ABRs appeared in a larger number of trials in the series containing test trials than in those containing control trials. The postpulse facilitation documented here maybe related to an enhancement in the excitability of the brainstem neuronal systems involved in processing sensory information.

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552. PLANNING OF TUMOUR OPERATIONS BY LOCALIZATION OF SENSORY BRAIN AREAS USING EVOKED MAGNETIC RESPONSES. D Ulbricht, O Ganslandt, H Kober, J Vieth, P Grummich, H Pongratz, C Brigel, R Fahlbusch, *Erlangen, Germany*

In neurosurgical operations near the central or Sylvian fissure the exact position of the somatosensory and auditory cortex usually is localised by electrocorticography. We asked, whether the non-invasive source localization of evoked magnetic somatosensory (SEF) or auditory (AEF) evoked fields can be used instead. The magnetic brain activity of 9 patients with temporal or central tumours was recorded using a 37-channel-biomagnetic system (Siemens KRENIEKONr). The SEF was elicited in 6 patients, the AEF in 2, and both in 1. At the peaks of the averaged response single dipoles were localised. The results were fitted exactly with the MRI by a contour-fit of the digitally scanned head surface and the surface reconstructed from a 3-D-MRI set. In all patients the evoked magnetic activity was found in the corresponding sensor area even if the position was dislocated by the tumour. In 8 surgically treated patients the position of the intraoperatively obtained electrocorticographical evoked response agreed completely with the SEF and AEF location. The results show, that the non-invasive localization of the magnetic somatosensory and auditory evoked response can be used for planning operations in the central or Sylvian region.

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ORGANOGENESIS OF COMPULSIVE OBSESSIONAL DISORDERS: A NEUROPHYSIOLOGICAL CONTRIBUTION. FP Serra, V Palma, G Nolfe, GA Buscaino, *Naples, Italy.*

To assess the possible relation between obsessional compulsive disorders (OCD) and some brain damages, like frontolenticular lesions, basal ganglia cavitations and local glucose metabolism impairment referred in recent Literature, an electrophysiological approach has been performed in 100 consecutive nevrotic patients, screened with various neuropsychological tests and distinguished into two groups, 50 with OCD and 50 with anxious neurosis. Patients were submitted to EEG spectral analysis and BAEP studies and compared with 25 age-matched normal controls. Highly significant increase in absolute latency of V wave and I-V and III-V interpeak latency has been observed in whole nevrotic populations as compared with control group. A statistically significant increase in absolute latency of V wave and I-V and III-V interpeak latency has been observed in OCD patients, whereas a statistically significant increase in I wave has been observed in anxious patients. A significant increase in main alpha power in occipital regions was found in 15 OCD patients, whereas a significant decrease in alpha power was recorded in anxious patients. A significant reduction in frontal beta activity has been observed in both nevrotic groups. The above findings seem to corroborate both a frontotemporal and brainstem dysfunctions with a probable involvement of serotoninergic central pathways, leading to two distinct electrophysiological features with a significant impairment of pontine segments in anxious patients and of mesencephalic regions in OCD patients.

76
REVISITING THE DEFINITION OF BRAIN DEATH IN HYPOXIC COMA. TL Rothstein, *Seattle, Washington, USA*

Approximately 350,000 Americans experience cardiac arrest each year. Most predictive scales rely upon the preservation of brain stem activity to establish prognosis. However, many of these patients will die without awakening despite preserved brain stem function because they have sustained irreversible destruction of the cerebral cortex. This reflects the selective vulnerability of adult cerebral cortex to anoxia. In a prospective analysis of 40 patients with cardiac arrest in whom coma exceeded 6 hours duration, median nerve somatosensory evoked potentials were the most useful guide for predicting outcome. Every patient with bilaterally absent cortical evoked potentials died without awakening. Neuropathological study was obtained in eight patients. The absence of cortical potentials correlated with global cortical necrosis. This study, and others, establish the sensitivity of absent cortical evoked potential in predicting death without awakening in every patient afflicted with hypoxic coma. Patients who are cortically dead will never again regain those basic qualities of thought and awareness that are necessary for a decent life and meaningful existence, and should be regarded as brain dead. Such a redefinition of brain death would avoid costly and dehumanizing medical care that is ultimately to no avail.

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VOLITIONAL AND REFLEXIVE SACCADES IN HUNTINGTON'S DISEASE: A STUDY IN EARLY AFFECTED PATIENTS AND AT RISK RELATIVES. Gibson J.M., Morrison P.M., Collins A.D., *Belfast, Ireland*

Ocular motor abnormalities are common in Huntington's disease (HD). Recent studies have reported that so called, "volitional saccades " (VS), which depend upon frontal lobe and basal ganglia function are abnormal in HD. Our purpose was to establish if study of VS in "at risk" relatives could identify pre-clinical abnormalities. Infrared oculography was used to record horizontal saccades using both reflexive (RS) and 3 volitional, [Anti (AS), Remembered (RmS) and Predictive (PS)] paradigms, evoked using LEDs and analysed by computer. 25 early HD patients and 45 "at risk" relatives were studied. 70% of HD had abnormal AS. Only 40% could perform VS and these were all abnormal. In the "at risk" group, trinucleotide repeat testing showed 1 6/42 to be asymptomatic gene carriers. Only 1 subject had abnormal RS. 80% of the gene carriers and 36% of non-carriers had abnormal VS. Conclusions: VS are affected earlier than RS in HD, however, there are many false positive results and, follow-up will be required to establish the natural history of these changes.

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LOCALISATION AND DESCRIPTION OF PENICILLIN-INDUCED SPIKES BY DETECTED ELECTRIC AND MAGNETIC FIELDS. M Eiselt, H Wagnur, U Zwiener, T Schindler, *Jena, Germany*

Localisation and description of neuronal processes underlying seizure activity can be improved by comparing of electric and magnetic fields. Neuroelectric processes: The involvement of cortical areas surrounding spike focus was investigated in 6 rabbits through 2-dimensional intracortical Current Source Density analysis (CSD). Spikes were initiated by focal application of 50 I.E. penicillin (layer II/III). The electric field was measured with two 16-channel micro-electrodes, one within the focus and the second in decreasing distance from the focus starting at S mm. Results: During the negative deflection of the spike within the focus, a sink was detected at 300 µm (boundary between layer I/II) and a source at 600 µm (layer IV). After a time delay of 30-50 ms, a source could be detected at 300 µm and a sink at 600 µm. Within the surrounding area, a source occurred at 300 µm and a sink at 600 µm during the negative deflection of the spike. Inverse distribution of sinks and sources could also be found. At distance of 5 mm from the focus the occurrence of sinks and sources related to the spikes was infrequent. Neuromagnetic processes: A 3-dimensional model of intracortical current density distribution was developed and the magnetic field was calculated on the basis of CSD-analysis. Localisation, orientation and strength of the current dipoles were estimated. The accuracy of the localisation was about 1 mm (signal to noise ratio of 100:1). Conclusion: Penicillin-induced spikes are accompanied by a complex current density distribution of up to 4 mm in the surrounding area. Selective spike averaging seems to be necessary to distinguish between different processes and to improve accuracy of localisation by the detected magnetic field.

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240. A STABLE LATE SOLEUS EMG RESPONSE ELICITED BY CORTICAL STIMULATION DURING VOLUNTARY ANKLE DORSIFLEXION. H Efendi, C Ertekin M Erfas, LE Larsson, H Sirin, N Araç, A Toygar, Y Demir, *Izmir, Turkey.*

In this study 47 experiments were made on 42 normal subjects (13 males, 29 females) aged 19-62 years. We used a Digitimer electrical stimulator (D180) and magnetic stimulator (MAG STIM 200). In all subjects three experimental paradigms were performed.1. Each subject was asked to lie on an examination table with full relaxation. 2. the Ankle was voluntary dorsiflexed at about 90° with mild voluntary contraction of the anterior tibial muscle. 3.the Ankle was voluntarily flexed in the planter direction at about 130° angle. Different kinds of manoeuvre and tests including passive dorsiflexion Jendrassik manoeuvre, vibration, ischemia were performed in all three paradigms. A stable late response recorded from soleus

muscle while voluntary activation of the antagonist anterior tibial muscle is called Soleus MEP-80. This response was elicited all normal subject in (86.9 (6.4) latency. In conclusion, the Soleus MEP-80 is a polysynaptic extensor response related to postural mechanism and originated through convergence of descending motor commands and peripheral sensory feedback.

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ELECTRODIAGNOSTIC PARAMETERS OF CARPAL TUNNEL SYNDROM IN POLYNEUROPATHY. S Seddigh; TH Vogt, H Hundemer, A Visbeck. *Mainz; Germany.*

Our goal was to see, which electrophysiological parameter of carpaltunnel syndrome (CTS) is most valuable in Patients with polyneuropathy (PNP). Electrodiagnosis of CTS is based on measurement of the distal motor latency, sensory nerve conduction velocity and amplitude of the sensory nerve action potential of the median nerve. In many PNPs, these parameters show pathological values. It is however important to determine, wether a local compression of the nerve has to be treated surgically. We studied motor sensory conduction in the median and ulnar nerve and measured the difference of motor latency to the second lumbrical and interosseus muscle stimulationg the median end ulnar nerve at the wrist. Studies were performed in 20 controls, 20 patients wich CTS, and 20 PNP patients with and without complaints of CTS. In controls, the latency difference was 0.6 (0.3) ms, this value is increased in 90% of patients with CTS. In patients with slowing of conduction velocity due to PNP, the latency difference was within the normal range, whereas patients with complaint of CTS show significant increase. Conclusion; Median/ulnar latency difference is a helpful tool to determine a CTS in patients with PNP. It is moreover easily to perform.

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THE INCREASE OF THE ENVIRONMENTAL PRESSURE AND EEG BRAIN MAPPING. L Pastena, F Faralli, G Mainardi R Gagliardi, *Roma, Le Grazie ,La Spezia, Italy.*

We studied the EEG of three subjects during the compression's time of a saturation diving session in a hyperbaric chamber until -250 m, for twenty minutes at different environmental pressure (+11 absolute atmosphere (ATA) equivalent at 100 m depth and +26 ATA equivalent at 250 m depth) . The goal of this study was to show the adaptation's mechanisms of the brain to the high pressure. The EEG, without movement's artefacts, was analysed by a Fast Fourier Transform (F.F.T.). A power spectra's statistical comparison between different conditions was performed. The percentages of significant EEG spectra variations for each pressure respect to basal conditions are plotted, for each subject, with a straight line's function. A decrease of alpha activity was noted and a reliable increase of theta and beta activities was observed especially in precentral regions (Fz) . A power spectra's correlation program between Fz and the other EEG derivations was performed and the results were plotted on a colour map in order to study the active area's development. A bigger active area for theta activity was noted.

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INNERVATION VARIANTS OF THE INTRINSIC FOOT MUSCLES. D. Linden, P. Berlit, *Essen, Germany.*

Recently, we described a patient with exclusive tibial nerve supply of the intrinsic foot muscles, including the extensor digitorum brevis (EDB), which is believed to be purely innervated by the peroneal nerve. In order to evaluate the innervation of the EDB and the abductor hallucis (AH) muscle, we performed motor nerve conduction studies of the peroneal and tibial nerve with simultaneous 2-channel recordings. Near nerve stimulation techniques were used, and compound muscle action potentials (CMAP's) were recorded both with surface and bipolar needle electrodes in thirty volunteers. In 19 subjects (63.3%) peroneal and tibial nerve stimulation elicited a CMAP with positive initial deflection of the AH and EDB, respectively. However, CMAP s greater than 2 mV were only recorded over the EDB after tibial nerve stimulation. Only in these 8 subjects (26.7%) needle recordings of the EDB showed a polyphasic potential with abrupt onset. CMAP s were nearly identical after proximal and distal stimulation in all but 4 subjects with an accessory deep peroneal nerve. Co-innervation of the EDB by the tibial nerve is common and may reach a relevant degree. Low CMAP s of the EDB and AH after tibial and peroneal nerve stimulation, respectively, are frequently recorded but probably volume conducted in most cases.

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ELECTROENCEPHALOGRAPHIC CORRELATES OF PERIVENTRICULAR WHITE-MATTER LESIONS IN PROBABLE ALZHEIMER'S DISEASE. OL Lopez, JT Becker, C Jungreis, R Brenner, D Rezek ST Dekesky, C Estol, F Boller, *Pittsburgh, PA, USA, & Paris, France.*

We evaluated the relationship between periventricular white-matter lesions (PWMLs) and EEG abnormalities in probable Alzheimer's disease (AD). Although EEG can be normal in early stages of AD, there is a strong correlation between the degree of EEG abnormalities and cognitive impairment. Importantly, there are no data concerning the impact of PWMLs in EEGs of demented subjects. We visually analyzed the EEG of 27 probable AD patients with mild-moderate degree of dementia participating in a longitudinally study of dementia. Patients had both CT and MRI at the moment of the initial examination, which also included a sixteenchannel EEG. The EEGs were classified according to the Mayo Clinic Classification System. PWMLs were rated using a semi-quantitative scoring method in CT and MRI films. PWMLs scores in CT and MRI correlated with the degree of EEG abnormalities. PWMLs in frontal, parietal and occipital lobes correlated with abnormal EEG, but not when they occurred only in the temporal lobes. The development of seizures (3 patients) in follow-up examinations correlated with the severity of PWMLs in CT at baseline. The presence of PWMLs appeared to contribute to the abnormal EEGs observed in AD patients.

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BOTOX IN POSTPARALYTIC FACIAL SYKINESIS (PSF) CLINICAL AND EMG EVALUATION OF 40 PATIENTS. JM Fernandez, S Mederer, J Batlle, A Turon, A Codina, *Barcelona, Spain*

Forty patients (24 women, 16 men), age range 25 to 75 years (mean 45), were included in the study designed to evaluate the effect of the Botox in PSF. All had sequelae of severe peripheral facial palsy as assessed electroneurographically (initial degree of axonotmesis > 90%). Ten patients were treated once, the remainder two or more. The initial doses ranged from 10 to 20 Units being injected in four different sites of the orbicularis oculi (OO). Because of the poor results, lower facial muscles were not injected. Facial contracture and synkinesis was assessed following the Zander Olsen score (Acta Neurol Scand 1975). The degree of Botoxinduced blocking was calculated by comparing the compound muscle action potential (CMAPs) of the orbicularis oculi before and treatment. Twenty per cent of the patients found the results "excellent", 60% "good" and 20% "negligible" or "poor". Facial paresis increased by 20% after Botox. Contracture and synkinesis diminished by 30% and 70%, respectively. The mean amplitude of the CMAPs of the OO pre-Botox was 1380 microvolts (SD, 825) and fell to 498 microvolts (SD, 298) after Botox, indicating that about 60% of the motor end-plates become blocked. We conclude that Botox is the treatment of choice for patients with severe PFS, particularly those with only mild residual facial paresis.

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THE VALUE OF THE OPTICALLY EVOKED BLINK REFLEX IN THE NEUROPHYSIOLOGICAL DIAGNOSIS OF BRAINSTEM ISCHEMIA. U Zifko, K Lindner, O Berger, P Hitzenberger, W Grisold, *Vienna, Austria.*

The establishment of normal values for the optically evoked blink reflex (OEB) is an important contribution to the assessment of brainstem reflexes, particularly at the mesencephalic level. Our laboratory examined the OEB in 60 healthy persons (37 between 20-40 yrs old, 23 between 40-70 yrs old) and in 28 patients with ischemic brainstem lesions. Examinations were performed in a darkened, silent room in horizontal position. For stimulation a flash light with 1 Joule per flash and a flashtime of 10 microseconds was used. Registration was done with surface electrodes from each side of orbicularis oculi muscle. Due to habituation of OEB a latency of 30-60 seconds between each flash light was allowed. The blink response occurs after 47,2 ms (SD: 7,1) in the 20-40 yrs old and alter 49,0 ms (SD: 8,0) in the 40-70 yrs old. The reproducibility was constant. The diagnostic value of the OEB was compared with the electrically evoked blink reflex in MRI confirmed brainstem and thalamic ischemia. In 22 patients with pontine or medullar brainstem ischemia the OEB was in 7 pathological cases. In 6 patients with mesencephalic or thalamic lesions the OEB was delayed despite normal EEB findings. The OEB is of diagnostic value for thalamic region or mesencephalic level of brainstem, if sensitive neuroimaging methods are not available.

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SHORT TERM AND FOLLOW UP STUDY OF THE BLINK REFLEX IN PATIENTS WITH WALLENBERG'S SYNDROME. N Vila, J Valls-SolÇ, R. Alvarez, A. Chamorro. *Barcelona, Spain*

We have studied the blink reflex to supraorbital nerve electrical stimuli in 7 patients with WS, confirmed with MRI. In 6, the infarct was limited to the dorsolateral medulla, and in one, it also extended to the cerebellum. In 4 patients the study was carried out in the acute phase. In 3 of these 4 there were absent or significantly delayed bilateral R2 responses, with normal R1 response, to stimulation of the supraorbital nerve ipsilateral to the lesion. Responses to stimulation of the contralateral nerve were normal. In follow-up examinations, similar abnormal findings were observed after the 1 month, but the results were normal after 4 months in all 3 patients. In The patient with cerebellar infarction, the R2 response was also absent on the side of the lesion after stimulation of the contralateral supraorbital nerve. This patient died from a cardiorespiratory arrest. Three patients, examined 1 year after stroke, had normal blink reflexes. We concluded that blink reflexes are abnormal in patients with WS shortly after the onset, and that they normalise after a few months in most patients.

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COMPARISON OF SINGLE MOTOR UNITS ELECTRICAL AND MECHANICAL PROPERTIES IN AMYOTROPHIC LATERAL SCLEROSIS. J Pouget, A Schmied, D Morin, JPh Azulay, JP Vedel, *Marseille, France*

In amyotrophic lateral sclerosis (ALS), the compensatory reinnervation process increased the size of the surviving motor units (MU) but the relationship between mechanical and electrical properties of single MU has been seldom studied and contradictory results have been obtained. During voluntary contraction, 148 single MU were recorded from the extensor carpi radialis muscle in 7 patients with ALS. The ages ranged from 52 to 72 yrs and the symptoms duration from 8 to 72 months. The single motor unit potentials (MUP) were recorded using macro-EMG and MU twitch contractions were obtained from an isometric strain-gauge using spike-triggered averaging. In patients, macro-MUP area distribution showed an enlargement compared to controls whereas MU twitch amplitudes revealed a combination of smaller and larger twitches. The ratio between mechanical and electrical properties of the MU (twitch amplitude/ macro-MUP area) was significantly decreased in ALS patients. Conclusion: In ALS the enlarged but less mechanically efficient MU could result from a deficiency in contraction-excitation coupling. The relationship between this deficiency and the presence of serum antibodies to L-type calcium channels from muscle has to be considered.

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COMPARATIVE STUDY OF FACIAL NERVE NEUROGRAPHY BY TRANSCRANIAL MAGNETIC STIMULATION AND CONVENTIONAL ELECTRIC STIMULATION IN BELL'S PALSY PATIENTS. J Montalt, J Escudero, R Barona and A Campos. *Valencia; Spain.*

Transcranial Magnetic Stimulation (TMS) is a new electrodiagnostic technique that allows the stimulation of deep nervous structures such as the cranial nerves. Conventional electroneurography of the facial nerve is a reliable method with prognostic value in Bll's palsy patients after 4 days from the onset of the palsy. The aim of this paper is to study a group of patients with clinical diagnosis of Bell's palsy by means of both electrophysiological techniques and to compare their results. A group of 20 patients with unilateral Bell's palsy have been included in this study. Electric stimulation was made using a bipolar surface stimulator (Medelec EL213M). Transcranial Magnetic Stimulation was performerd using a Novametrix Magstim 200 magnetic stimulator capable of generating a 2T field. Results: Tolerance was excellent, and none of the patients complained of pain of discomfort. Mean value of the results obtained are shown below:

* latency (ms):	E= 3.01 (0.35;	TMS= 3.78 (0.49
* amplitude (mV):	E= 1.54 (0.58;	TMS= 1.72 (0.60
* duration (ms):	E= 6.36 (0.85;	TMS= 6.94 (0.66

Similar results were obtained by employing both techniques. TMS has several advantages over electrical stimulation, which however not only is painless but allows the exploring of proximal portions of the facial nerve. We believe that TMS can be used as an early prognostic evaluation technique, within the first days of the onset of the palsy.

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SINGLE FIBER ELECTROMYOGRAPHY IN FRONTALIS MUSCLE. K Varli, E Ertem. *Ankara, Turkey*

Variable diseases cause ptosis and ocular motility disorders. Sometimes standard investigation techniques are not adequate for diagnosis. Single fiber electromyography (SFEMG) is the most sensitive method to reveal impairment of transmission at the neuromuscular junction. Therefore it is of in the differential diagnosis of ocular motility disorders. In the present study SFEMG of frontal muscle during voluntary contraction was recorded in 25 patients with ptosis and \ or extraocular motility disorders. Frontal SFEMG findings of patients with adequate follow-up and other laboratory investigations are discussed. SFEMG findings were pathological in 14 of 15 patient with definite myasthenia gravis (MG). Repetitive stimulation recordings of orbicularis oculi muscle were recorded in 10 patients of this group and significant decrement of response was observed only in five. In four of the five patients with a different definite diagnosis other than MG, FEMG findings were normal. SFEMG was normal in 8 patients out of a total of 25. Only one of these 8 patients, had symptomatic MG. We may conclude that, diagnostic sensitivity and specificity of frontal SFEMG is very high in neuromuscular junction pathologies and has priority to repetitive nerve stimulation.

90
ERECTOR SPINAL MUSCLE RESPONSES TO CORTICAL MAGNETIC STIMULATION. B Uludag, A Yagiz, C Ertekin, *Izmir, Turkey*

Erector spinal muscle responses were recorded after the stimulation of the cerebral cortex by using magnetic coil stimulation in 30 normal adult subjects. The level of the recording were Th1, Th6, Th1 2 and L3 spines. Six responses were superposed with voluntary facilitation during in sitting position and/or in easy standing. The conduction velocities from Th1 to Th6, Th6 to Th12 and Th12 to L3 were calculated and found that the conduction velocity along the spinal can was about 50- 60 m/sec. The method was somewhat helpful to localise the restrict spinal cord lesions i.e. cord tumour, transverse myelopathy so on.

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SOMATOSENSORY POTENTIALS (SEP) STUDY IN WHIPLASH INJURY. Z Privorkin, Y Steinvil, E Kott, *Kfar Saba, Israel*

Somatosensory potentials (SEP) were studied in is whiplash injury patients suffering from pains in the upper limbs and paresthesias. Neurological investigation, X-rays and cervical CT were normal. EMG studies: muscle studies and motor nerve conduction velocity (MCV) of the median nerve were normal. SEP studied following simulation of the median nerve revealed: abnormal latencies in N9 in 4/10 patients, abnormal N13 in 1/12 studies, prolonged P22 in 2/6 studied. Abnormal Rt to Lt differences of latencies of potentials evoked at C5 were found in 6/11 and abnormal EP (Erb Point) potential was observed in 5 out of 10 patients. A difference in latencies of P22 was found in 3 out of 6 patients. The findings suggest the presence of a nerve root traction lesion in whiplash injury (WI) SEP may be used as a tool for the assessment of (WI) and follow up.

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ABSENCE OF F- WAVES AS AN EARLY ELECTRODIAGNOSTIIC FINDING IN INFARCTION OF THE CONUS MEDULLARIS. O Combarros, R Sanchez- Pernaute, P Orizaola, C Leno, J Berciano *(Santander, Spain).*

A 69- year- old hypertensive woman had a sudden onset of pain in the buttocks, radiating down both was. Urinary retention and severe motor and sensory impairment in an L4 to S5 distribution followed within one hour. A lumbar myelogram and CSF examination were normal. Axial view of the conus medullaris in T2- weighted MRI showed hyperintense signal involving the anterior and posterior horns of the gray matter. The initial electrophysiological examination 5 days after onset of symptoms was remarkable for an absence of F- waves on stimulating both peroneal nerves at the ankle, despite normal motor conduction velocities, distal motor latencies and M potential amplitudes. By four weeks she had developed severe wasting of calf and tibialis anterior (TA) muscles, especially on the right. Over the next months, serial studies revealed abundant denervation potentials in the right TA and the extensor digitorum brevis (EDB), absent M responses in EDBs from ankle stimulation of the peroneal nerves and very low M- potential amplitude in TAs with peroneal stimulation at the fibular head. At 12 months F- responses were obtainable in TAs and in the

left EDB muscles. A repeated MRI still showed high signal confined to the gray matter of the conus medullaris. As shown in this patient, loss of F- responses can be a useful indicator of acute anterior horn cell involvement in the early stages of spinal cord ischaemia.

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THE VALUE OF ELECTROTHERAPY IN REHABILITATION OF LESIONS OF PROXIMAL NERVE LESIONS. Th Mokrusch, *Erlangen, Germany*

Electrotherapy is widely used in neurological rehabilitation. Particularly for peripheral lesions, however, its value is discussed controversially. - After having proved effective in animal experiments, a special technique, using long duration balanced bidirectional rectangular impulses, was successfully introduced in neurological rehabilitation. 13 patients were investigated, suffering from chronic proximal nerve lesions (traumatic or inflammatory destruction of the cauda equina, n=3; lesions of the brachial plexus or cervical root avulsion, n=10). Paralysis was complete and without reinnervation in all patients. Treatment started 1-21 months after the trauma or the begin of the disease. Therapy was successful in all of the patients. During a subsequent observation period of up to 38 months, the electrically inducible contraction force increased in all muscles (16-400%), to a preliminary maximum of one third that of normal controls. MRI investigations of several muscles showed an increase of muscle volume by 9-29% and 33-84% (thigh).

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INVOLUNTARY MOVEMENTS IN AMPUTATION STAMP. E Kutluaye, B Uludag, D Selcuki, C Ertikin, *Izmir, Turkey*

Although recognized for over a century, the involuntary movements of the stump together with the pain and phantom sensation after the amputation ,have been recently brought to the attention of clinical neurology.The involuntary spasms without pain and phantom sensations are seldom reported. In this paper, a diabetic patient is presented with intermittent muscle spasms similar to smooth "chorea-athetotic" movements in a partially amputated stump of the left leg without pain and phantom sensation. The Tibialis Anterior and Triceps Surae muscles in the stump were recorded simultaneously. They were suppressed only during the continuous electrical stimulation of their muscle nerves above the motor threshold. Based upon our clinical and electrophysiological findings we propose that these involuntary spasms originate by the continuous overactivity of some interneurons situated at the unilateral L5-S1 spinal cord segments. In our case ;acute differentation of the left leg must have been superposed with the sensory-motor polyneuropathy and the altered afferent inputs into the left L5-S1 cord segments may have led to reorganisation of local neuronal circuit and enhancement of the motor output probably mediated by the segmental interneurons situated at the same level.

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APOPTOSIS ELIMINATES INFLAMMATORY T CELLS IN DIFFERENT MODELS OF EXPERIMENTAL AUTOIMMUNE NEURITIS (EAN) IN THE LEWIS RAT. U Zettl, R Gold, GK Harvey, HP Hartung, KV Toyka, *Wurzburg, Germany*

An important issue in understanding the pathogenesis of T-cell mediated neuropathies is the elucidation of how and where T-cells are activated and eventually eliminated. We investigated this issue in Lewes rat EAN induced by immunisation with peripheral myelin (active EAN), adoptive transfer of P2-specific T-cells (AT-EAN), or ovalbumin specific T-cells in rats intraneurally injected with ovalbumin (OVA-EAN). T-cell infiltrates in sciatic nerves were detected by immunocytochemistry. Apoptosis was assessed using morphological criteria and confirmed by molecular labelling techniques. Cell proliferation was evaluated using the bromo-deoxy-uridine labelling method. Clinical disease peaked at day 17 in active EAN, at day 7 in AT-EAN and at day 4 in OVA-EAN. In all models studied, apoptotic T-cells were already found in sciatic nerves at the onset of disease and plateaued thereafter (active EAN 19 % apoptotic T-cells on day 35, AT-EAN 17 % on day 14, OVAEAN 25% on day 7). Intraneural proliferating cells were only rarely detected. Maximal values of proliferating cells were observed in germinal centres of splenic tissue in AT-EAN on day 2 (491 (239 cells/mm2). These data obtained on different models of EAN show that apoptosis is a general elimination mechanism for infiltrating T-cells in the peripheral nervous system. Identification of the molecular have therapeutic implications. Signals inducing apoptosis may have therapeutic implications

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AUTOSOMAL DOMINANT SENSORY ATAXIA? A BENIGN VARIANT OF FRIEDREICH'S ATAXIA ? JHJ Wokke, PL Oey, PF Ippel, GH Jansen, H. Franssen. *Utrecht, The Netherlands*

We present the results of clinical and laboratory examinations in a family of 5 sibs of unrelated parents. The father was in good health at age 65 years, when sensory ataxia occurred. He became bedridden at 69 years. From age 40-52 years, three of his 5 children noticed symptoms or signs of ataxia, which progressed dramatically on eye-closure. There was a gradual progression during a 5-11 years follow-up period, but they remained independent. Eye movements were saccadic of 3 patients. A forth patient was subclinically affected. Normal tests included: brain CT/ MRI, electromyography and motor nerve conduction studies, VEP and BAEP. Sensory responses were absent in 3 and reduced in patient. These patients also had abnormalities of autonomic function tests of 2 or more out of 4 organ systems (vasomotor, baroreceptor, pupillary, sudomotor). Oculography showed fixation instability in 3 patients, who also had abnormal SEP. Sural nerve biopsy of 1 patient showed axonal degeneration and some regeneration. Density of myelinated fibres was 764/mm^2. As involvement of peripheral sensory and autonomic nerves in spinocerebellar degeneration is usually not pronounced, this syndrome seems a novel entity. Differences with Friedreich ataxia are: 1. onset at adult age; 2. benign course; 3. autosomal dominant inheritance.

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FAMILIAL AMYLOID POLYNEUROPATHY RELATED TO THE TRANSTHYRETIN GLY42 MUTATION. K Toyooka, H Fujimura, S Ueno, H Yoshikawa, S Yorifuji, T Yanagihara, *Osaka, Japan*

We describe the first detailed neuropathological findings of the familial amyloid polyneuropathy (FAP) related to the novel variant of transthyretin (TTR) Gly42 mutation (Muscle and nerve, 1992). At autopsies of two affected members, extensive quantitative analyses of the peripheral nerve using light and electron microscopy and teased fiber study were performed. Pronounced amyloid deposition was found in sympathetic ganglia, dorsal root ganglia, and throughout the length of the nerve, with some accentuation at more proximal region. Severe neuronal loss in the ganglia and nerve fiber depletion in the initial portion of the nerve trunk were found, while only a small amount of amyloid deposition with mild fiber loss was seen in the spinal roots. Regenerated sprouting axons were very scanty even at the spinal nerve or the roots. A teased fiber study revealed that fiber condition was predominantly demyelinating, but axonal degeneration was also present even at proximal portions. Electron microscopically, fine amyloid fibrils frequently attached to the axolemmal membrane of the demyelinated axon and some destruction of axon was seen. We conclude that the pathological features in this type of FAP resemble those in type 1 FAP (TTR Met30). However, direct axonal damage due to amyloid fibrils may be more important than in type 1 FAP.

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IMMUNOLABELING OF CELLS AND SECRETORY PRODUCTS OF MACROPHAGES IN DIFFERENT PATTERNS OF LEPROUS NEUROPATHY. C Talamon, C Tzourio, G Said, *Le Kremlin Bicêtre, France*

The clinicopathological pattern of leprous neuropathy strongly depends on the cell mediated immune response to antigens of Mycobacteria leprae. We tried to learn more about the mechanisms of nerve lesion that occur in this context, we performed an immunolabeling of T lymphocytes and macrophages, and of secretory products of activated macrophages, in 9 nerve specimens from patients with different patterns of leprosy including 2 with tuberculoid, 3 with lepromatous leprosy, 2 with a reversal reaction and 2 with erythema nodosum leprae (ENL). Frozen sections were labelled with antibodies to surface molecules CD8, CD4, CD68 and HLA-DR, and to secretory products of activated macrophages TNFa and urokinase. The anti-HLA-DR antibody marked 72% of the cells in the lepromatous and 95% in the tuberculoid form, including Schwann cells, endothelial cells and cells of the infiltrate (11% in controls). The CD4 T cells were 40% in the tuberculoid forms, 34% in the reversal reaction, 11% in the lepromatous forms and 2% in ENL (controls: 0.08%). The CD8+ cells were 25% in the lepromatous forms and 35% in the tuberculoid forms, 10% both in the reversal reaction and in ENL (controls: 0.8%). The macrophages rep-

resented 23% of the cells in the lepromatous forms versus 31% in the tuberculoid forms, 23 % in the reversal forms and 12% in ENL (controls: 7%). The cells labelled for TNFa were 0.2% in lepromatous, 1.8% in tuberculoid form and in reversal reaction, 0.5% in ENL (controls: 0%). The same proportion of cells were found positive for urokinase, the activator of plasminogen. Our findings are in favour of a delayed type hypersensitivity reaction in tuberculoid leprosy and in reversal reaction, with lesions induced by highly activated macrophages.

99
DIFFERENTIAL EXPRESSION OF TRANSFORMING GROWTH BETA (TGF-β) IN IMMUNE NEUROPATHY AND WALLERIAN DEGENERATION. R Kiefer, S Jung, K Toyka, HP Hartung. *(Wurzburg, Germany)*

In an attempt to elucidate mechanisms responsible for terminating the immune response in GBS and EAN, we studied the expression of the immunosuppressive cytokine TGF-β 1. In EAN, TGF-β 1 mRNA levels increased 3 days following injection of T-cells and peaked by day 6 as revealed by quantitative Northern blot analysis. In situ hybridization demonstrated the expression of TGF-β 1 mRNA in mononuclear cells, probably T-cells, within the inflammatory infiltrates at days to 8. A more diffuse pattern was observed at later stages suggesting its expression in macrophages. Following nerve transection, TGF-β was expressed within the proximal and distal nerve stump and along severed axons. However, the levels were lower than in inflammatory infiltrates as observed in EAN. Ongoing studies on human sural nerve biopsies revealed strong expression of TGF-β 1 in cases with GBS and borreliosis. In contrast, in a biopsy with noni-nflammatory axonal degeneration, only a weak signal was observed. Our studies suggest that TGF-β mRNA expression is associated with inflammation and to a lesser degree with Wallerian degeneration of peripheral nerve. TGF-β 1 expression might be associated with recovery from inflammatory lesions .

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NERVE BIOPSY IN THE DIAGNOSIS OF POLYNEUROPATHIES. I Ruolt, C Tranchant, M Mohr, JM Warter, *Strasbourg, France.*

The contribution of nerve biopsy to the diagnosis of polyneuropathies of the adult has here been studied in 100 biopsies carried out in a neurological service. In two-thirds of the patients, the clinical history, the study of antecedents, the clinical examination and complementary tests were sufficient for the identification of the neuropathy. The nerve biopsy confirmed the level of the lesion, as did the electrophysiological examination. The investigation of specific abnormalities suggested by particular signs was always negative, except in one case of amyloid neuropathy. In almost one third of the cases, a diagnosis was not made, and the nerve biopsy provided no diagnostic clarification. Lastly, in a few rare cases, the clinical signs suggested a peripheral neurological condition, but the electrophysiological examination was hardly perturbed. Nerve biopsy then revealed a neuropathy involving mainly unmyelinated fibres, but did not clarify the cause of the condiction. This study shows that the role of nerve biopsy in the diagnostic procedures of polyneuropathies in the adult is of very limited interest in daily practice.

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SENSORY NEUROPATHY IN AIDS: DEMONSTRATION OF VASCULITIS AND HIV ANTIGENS IN PERIPHERAL NERVE. DS Younger, G Rosoklija, AP Hays, *New York, NY; USA*

We studied a patient with human immunodeficiency virus (HIV) infection and primarily sensory neuropathy associated with necrotizing peripheral nerve vasculitis and evidence of HIV infection in peripheral nerve without opportunistic infection. immunoperoxydase and alkaline phosphates stained sections of a sural nerve biopsy showed infiltrating macrophages that expressed p24 and gp41 HIV- related antigens, as well as IL1-alpha, IL1-beta, TNF-alpha- Strongly immunoreactive C3d, C5b-9, and IgM were present in the affected vessel walls The vascular inflammatory cell infiltrate consisted primarily of CD68, CD45, and CD8+ cells. We conclude that sensory neuropathy can arise as an immune response to HIV antigens present in peripheral nerve.

102
LOW AMPLITUDE OF THE MEDIAN NERVE ACTION POTENTIAL IN THE FOREARM SEGMENT IN PATIENTS WITH CARPAL TUNNEL SYNDROME. R Kurita, O Hasegawa, M Matsumto, A Komiyama, Y Nara. *Yokohama, Japan*

In the carpal tunnel syndrome (CTS), it is known that conduction in the median nerve is slowed between the elbow and the wrist and that the amplitude of the action potential is reduced at the thenar muscles. To elucidate the retrograde axonal changes of entrapped median nerves, we examined the median nerve action potentials by means of intraneural neurography. Twenty-four arms of 15 patients with CTS were studied. The median nerve was stimulated supramaximally with a surface electrode at the wrist. The compound action nerve potentials were recorded with a microelectrode inserted into the median nerve trunk at the elbow. By using the conventional conduction technique, distal motor latency was also measured in the median and ulnar nerves. In CTS patients, distal motor latency was prolonged in the median nerve 1.5 times greater than in the ulnar nerve. The amplitude of the median nerve action potentials was significantly reduced in parallel with the prolongation of the distal motor latency ($P<0.01$). The nerve conduction velocity was slowed and the action potential showed temporal dispersion. The retrograde degeneration of the entrapped axons may account for these findings since the amplitude of the nerve potential is known to roughly correlate with the density of large myelinated fibers.

103
POLYNEUROPATHY.IN .GLUE SNIFFERS. S Oueslati, S Belal, I Turki, C Ben Hamida, F Hentati, M Ben Hamida. *Tunis, Tunisia*

We report a clinical, electrophysiological and morphological study in three male glue sniffers (12, 12 and 24 years-old) with sensorimotor polyneuropathy. The clinical manifestations appeared several months after the substance abuse. On clinical examination we found in all 3 case, distal weakness in all four limbs and absent ankle jerks. Steppage gait, distal amyotrophy and hypesthesia were marked in two cases .and mild in the third one. No pyramidal or cerebellar signs were found. CSF was normal. EMG showed a neurogenic pattern with decreased motor and sensory nerve conduction velocities. The distal motor latencies and F waves were prolonged. The sensory nerve action potentials were reduced in amplitude. Nerve biopsy showed loss of large myelinated fibers in all three cases and hypermyelination features in one, without giant axons. These findings are compatible with n-Hexane toxic peripheral polyneuropathy described in industrial workers (Herskowitz et al 1971, Spencer et al 1980) and in glue sniffers (Matsumura et al 1972, Korobkin et al 1975, Altenkirch et al 1977). SEPs, VEPs and BAEPs performed in two patients revealed some abnormalities suggesting central nervous system impairment.

104
MRI AND SPECT INVESTIGATION OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS. H Kwiecinski, L Krolicki, A Domzal-Stryga, *Warsaw, Poland*

About 85% of patients with amyotrophic lateral sclerosis (ALS) may show clinical features of both upper and lower motor neuron degeneration. In our own experience, however, in many ALS cases corticospinal involvement signs are masked by lower motor neuron muscle weakness and wasting. We used MRI and single-photon emission computed tomography (SPECT) methods to determine the frequency of CNS abnormalities in 18 patients with clinically definite ALS. MRI studies (1.5 Tesla) including proton density, T1- and T2-weighted images revealed abnormalities in 5 (28%) patients. The MRI abnormalities consisted of enhanced T2-weighted signals along the pyramidal tract. Focal areas of increased signal intensity extended from the uppermost sections through the corona radiata, posterior limb of the internal capsule into the cerebral peduncles. Two of the 5 patients with MRI abnormalities had classical ALS with Babinski signs and 3 others showed probable upper motor neuron signs. We measured regional cerebral blood flow (rCBF) with HmPAO using SPECT system. Strikingly, only 2 patients in our series had normal SPECT images. Almost 90% (16/18) had abnormal rCBF with reduced flow, mostly in the fronto-parietal regions. We conclude that SPECT and MRI abnormalities in ALS may reflect loss of corticomotoneurons and pyramidal tract degeneration.

105
THE EFFECT OF ACTH (4-9) ANALOGUE ORG 2766 ON NEUROPATHIC PAIN. PLI Dellemijn, P van Deventer, B van Moll, T Drogendijk and ChJ Vecht. *Rotterdam, The Netherlands.*

The ACTH (4-9) analogue Org 2766 has been found to ameliorate chemotherapy-induced neuropathies. Based on individual observations of pain- relief, we investigated whether Org 2766 can improve peripheral neuropathic pain. 21 Patients with a history of cancer without evidence of disease and with a diagnosis of peripheral differentiation pain for at least 12 months, were studied. Post- dissection pain was present in 16 patients, post- rhizotomy pain in two and pain secondary to radiation plexopathy in one patient. Previous analgesics, including amitriptyline, had not provided satisfactory pain relief. Pain- measurement was performed by 11-point numerical rating scale, 6-point categorical pain-relief scale, and by recording of daily analgesic consumption. All patients were allowed to continue their previous analgesic medication. After one month of baseline recordings, pain assessment and analgesic consumption, Org 2766 was administered subcutaneously, 2 mg 3 times per week for 4 months followed by two months follow-up. 19 Patients were available for pain- assessment. Six (32%) patients reported pain- relief of 20% or more with a simultaneous decline of 2 steps or more on a 6-point categorical pain intensity scale and pain-relief scale. Eight (42%) patients consumed significantly less analgesic medication. Gradual progressive pain- relief reached a plateau after 10 weeks during the 16 weeks treatment period. Following discontinuation of Org 2766, the original pain recurred after two weeks. This study shows a potential effect of Org 2766 on peripheral differentiation pain. These results are promising and warrant a phase 111 double- blind study on Org 2766 versus placebo in neuropathic pain.

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HIGH DOSE INTRAVENOUS IMMUNOGLOBULIN (IVIG) TREATMENT IN DYSIMMUNE NEUROPATHIES. Nemni, S Amadio, R Fazio, G Galardin G Comi, *Milan, Italy*

We treated 16 patients (Pts) with polyneuropathy with IVIg: 9 had chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) not responsive to prednisone and/or plasma exchange; 2 had chronic neuropathy (N) with IgM monoclonal gammopathy without anti-MAG activity, and not responsive to chlorambucil; 5 had multifocal motor N. All Pts were treated initially with IVIg 0.4 g/kg, for 5 consecutive days and again after 6 to 10 weeks. Clinical and neurophysiological (NF) evaluation was performed before each IVIg course. After the first IVIg course all Pts except 2 with CIDP had a significant improvement in scores of muscle strength. NF tests demonstrated a substantial increase of the proximal-to-distal ratio of the compound Motor Action Potential amplitude but never a resolution of the conduction block when present. After months of therapy we found a significant improvement in scores of muscle strength in all Pts except 3 CIDP, but no significant improvement of NF data. Serum autoantibody titers did not change. IVIg is an effective treatment in refractory dysimmune N. A large controlled trial is now needed to indicate how IVIg should be used in practice.

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CHRONIC SYMETRIC SYMPTOMATIC POLYNEUROPATHY (CSP) IN THE ELDERLY: PREVALENCE AND RISK FACTORS IN ONE ITALIAN-AREA. ML Delodovici, E Peghi, ML Monticelli, A Sessa, *Milano Italy*

We have selected 5979 individuals aged 55 years and older from Varese (VA), Northern Italy, among the affiliates of a group of General Practitioners (GPs). Patients were interviewed randomly by the GP using a preserved previously validated questionnaire an a check list of the commonest factors and diseases associated to polyneuropathy. Screened subjects were 3080. Individuals with 2 or more affirmative answers to the screening questions (18%) were examined by a neurologist. The diagnosis of CSP was made in presence of bilateral impairment of two or more modalities among strenght, sensation and tendon reflexes. CSP was present in 116 cases (37%), giving an age and sex-adjust prevalence rate of 3.4 (CI 2.8-4). Diabetes was recorded in 253 subjects (8%), with CSP in 48 cases (OR 9.5; CI 6.8-13.3). 158 patients had neoplasms (5%) and CSP was present in ll cases (OR 2; CI 1.0-4.0). Alcoholics were 62 (2%), with CSP in 8 (OR4.0;CI 1.8-8.7). Non alcoholic liver diseases were present in 5 cases (2%) with CSP in 5 cases (O 2.9; CI 1.0-8.5). We can conclude that CSP is a common and clinically mild disease in the elderly, diabetes and alcoholism beeing the commonest risk factors

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CRITICAL ILLNESS POLINEUROPATHY A PROSPECTIVE STUDY. ML Viguera, JM Fernandez, M Palomar, J Gamez, C Cervera, C Navarro, *Barcelona, Spain*

Critical illness polyneuropathy (CIP) is increasingly recognised as a complication of sepsis and multiple system organ failure (MSOF). In order to assess the incidence and morbidity of the CIP we studied prospectively patients of the Intensive Care Unit (ICU) at risk of developing sepsis and/or MSOF. All patients underwent complete neurological examination weekly, and at less two electrophysiological examinations, the first one week after admission, and the second when the full-blown picture of CHIP was already present. Patients with history of neurological disease were excluded. Over a 24 month period 31 patients met inclusion criteria. Twenty one (67,7%) showed clinical and EMG abnormalities. Most of cases showed low amplitude motor and sensory responses, fibrillations and poor voluntary recruitment suggesting neuropathy. However, in a proportion of cases the EMG features were clearly myopathic. Muscle biopsy performed in 7 of these patients showed a wide range of abnormalities, including necrosis, myophagia, perimysial infiltrates, and deposits of lipids and calcium. In conclusion, we found a high incidence of neuromuscular abnormalities in patients with sepsis or MSOF. The clinical, electrophysiological and pathological findings suggest that this entity is more proteiform than previously suspected.

109
ANTIGANGLIOSIDE ANTIBODIES IN SERA AND CSF OF PATIENTS WITH GUILLAIN-BARRE SYNDROME. J Serena , I Duran, AL Fernandez, M Comabella, C Nos, J Rio, A Codina, J Montalban, *Barcelona, Spain.*

The etiology and pathogenesis of Guillain-Barre syndrome (GBS) are unknown, increased titers of antibodies directed against gangliosides are found in the serum and cerebrospinal fluid (CSF) from these patients. Some authors have reported correlation between severity and antiganglioside antibodies (AGA) of patients with GBS. The present study was designed to determine antibodies against GM1, GDla, GDlb, and GTlb in paired CSF and sera from patients with GBS, to characterize the IgG or IgM isotype, and to elucidate their relationship to clinical parameters, including the severity and outcome of patients. Sera from 17 patients and CSF from 12 patients (mean age 45.3 years) who fulfilled the criteria for GBS of the NINCDS, and sera from 19 subjects and CSF from 13 healthy controls were studied by a modification of an enzyme-linked immunoabsorbent assay method (ELISA). According to the criteria proposed by Simone et al. (1992) we found high levels of AGA in serum of 83.3 % and in CSF of 82.3 % of patients with GBS patients. Nevertheless, using other criteria, an important decreased in the number of positive patients (40%) was observed. Conclucion: No correlation between severity and AGA was found in any case.

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FUNCTIONAL CHANGES IN PERIPHERAL NERVES IN HYPER AND HYPOTHYROID RATS. X Navarro, E Verdu, S Darbra, M Buti, *Bellaterra, Spain*

The influence of thyroid hormone status on peripheral nerve and target organ function was investigated in 3 groups of 5 rats each. Hypothyroidism was induced with methimazole (group ht), and hyperthyroidism with T4-hormone (group Ht) from the 9th gestational day to 21 postnatal days. Control group (C) was untreated. Sudomotor, motor and sensory functions were evaluated by silicone imprints, electromyographic and neurographic recordings from the distal hindpaw and tail by 2.5 months of age. The number of sweat glands reactive to pilocarpine averaged 1 15, 244 and 228 in ht, Ht and C groups respectively. Motor nerve conduction velocity (NCV) averaged 33, 32 and 33 m/s and the muscle action potential amplitude 5, 7 and 7 mV in the same experimental groups. Sensory NCV of the sciatic nerve averaged 48, 60 and 55 m/s, and in tail nerves 30, 28 and 32 m/s while the mean nerve action potential amplitude was 8, 12 and 19 μV in ht, Ht and C groups respectively. These results suggest that neonatal hypothyroidism but probably not hyperthyroidism causes axonal peripheral neuropathy in rats, evidenced by decreases in action potential amplitude and sudomotor responses.

111
IS THERE AN AXONAL FORM OF GUILLAIN BARRE SYNDROME : DISCUSSION ABOUT 4 NEW CASES C. Tranchant, M. Mohr, J.M. Warter, *Srasbourg, France*

The term Guillain-Barré syndrome (GBS) has for a long time reserved to acute inflammatory demyelinating neuropathy with albumino-cytological dissociation in cerebrospinal fluid (CSF). However, an acute axonal form of GBS has been described in 1986 by Feasby et al, and subsequently numerous others authors. The separation of these two clinical forms seems justified not only because of pathological differences but also because of differences in therapeutic responses, in prognosis and perhaps in physiopathological mechanisms. We report 4 new cases of patients with an acute axonal neuropathy. These patients had clinical features consistent with GBS although the period of worsening was short, and cranial and respiratory nerves were normal in spite of severe weakness all for limbs. Protein concentrations were moderately elevated in CSF, but electrophysiological and pathological studies demonstrated early axonal degeneration; functional improvement was poor. From these 4 cases, the concept of axonal form of GBS will be discussed.

112
ACUTE DEMYELINATING INFLAMMATORY POLYRADICULONEUROPATHY ASSOCIATED WITH HYPERTHYROIDISM. A Mrabet, M Fredj, R Gouider, S Oueslati, H Tounsi, N Khalfallah and A Haddad. *Tunis; Tunisia.*

Polyneuropathy has been reported in thyroid diseases, but Guillain-Barre syndrome associated with hyperthyroidism has received little attention. We report a case of a 18 year-old lady with hyperthyroidism who was hospitalized in our department for Guillain-Barre syndrome. Myokymic discharges were found with visible undulating movements. EMG studies showed rhythmical spontaneous discharges, in the upper and lower limbs. Nerve conduction studies showed reduction in velocity (more than 30 percent of the normal mean) and delay of the F wave in more than two nerves. Diagnosis of a typical Grave's disease was based on clinical and laboratory findings (TSH, T3, T4) and thyroid isotopic scan. All these abnormalities were improved following a two-month treatment by benzyl thiouracile . The association of demyelinating inflammatory polyradiculaneuropathy (DIP) with hyperthyroidism suggests that DIP, known as an auto-immune disease, could be the results of a greater peripheral nerve sensitivity to the excess of thyroid hormone. This would explain the good response of GBS to the treatment of hyperthyroidism.

113
A CASE OF MULTIPLE SCLEROSIS WITH CHRONIC DEMYELINATING POLYNEUROPATHY. MRI AND PATHOLOGICAL FINDINGS. T Dbaiss, R Ghnassia, E Rouillet, G Said, A Ameri, F Chedru, *Meaux & Paris, France.*

We report a case of multiple sclerosis (MS) associated with a chronic demyelinating neuropathy (CDPN) in which MRI and pathological features were of particular interest . A 33 year old man developed, over five years, a spastic paraplegia, cerebellar signs and bilateral optic neuritis. The course of the disease was relapsing-remitting then progressive. T2 weighted MRI showed multiple high signal areas in the periventricular white matter. A diagnosis of definite MS was made according to POSER's criteria. Cerebrospinal fluid analysis disclosed an elevated total protein concentration (2,09 g/l), with normal IgG pattern, and slightly increased mononuclear cell count (4 /mm^3). Two years after onset, the patient experienced distal numbness of four limbs; examination showed absent deep tendon reflexes in the upper limbs and gloves-stocking hypoesthesia. Lumbar MRI showed marked enlargement of the spinal roots, the cauda equina occupying more than half of the dural sac. There were slow motor conduction velocities (MCV) and prolonged distal latencies (dl). (MCV right peroneal nerve :19 m/s; dl: 14 ms) On nerve biopsy, there was segmental demyelination with concentric Schwann cell proliferation ("onion bulb ") . These clinical and pathological findings suggest the association of central and peripheral demyelinative disorder.

114
PERIPHERAL NERVE LESIONS IN PATIENTS BEFORE AND AFTER CARDIAC TRANSPLANTATION. H Porsche, H Strenge, *Kiel, Germany.*

In order to evaluate mono- and polyneuropathic lesions in patients undergoing cardiac transplantation (HTP) at the Clinic of Cardiovascular Surgery, Univ. of Kiel we investigated 30 patients, 26 male and 4 female, average age 54 (35-65) years, before (mean 2.3 months) and at 1, 3 and 12 months following HTP. Besides the clinical-neurological examination the patients underwent a sensory and motor neurography of the right median, peroneal and sural nerves. Pre-operatively, already 45 % of the patients showed lesions in 2 or 3 nerves by the neurography with clinical signs of a polyneuropathy (PNP) in two third of the cases. Mononeuropathies of the median and peroneal nerves were found in 7 patients. The first month after HTP, more patients (64%) exposed mild to moderate generalised neurogenic lesions of the axonal sensorimotor type, being in parts subclinical (7 cases). The PNP occurred newly or worsened in 12 and ameliorated in 4 patients early after the operation. Mononeuropathies were diagnosed in 13 cases. The frequency of polyneuropathic lesions slowly decreased, so that signs of a PNP were found in 54% and 46% of the patients, the 3. and 12. post-operative month, respectively, but new or worsened lesions were still detected in 4 patients, one year after HTP. In 3 cases a sensory PNP was registered besides the other axonal sensory-motor lesions. The implication of the immunosuppressive medication with Ciclosporin and other risk factors for the pathogenesis of these polyneuropathic lesions will be discussed.

115
PANDYSAUTONOMIA A CLINICOPATHOLOGICAL REPORT OF 5 CASES. SW Li, YP Young. *Beijing, P R China.*

Five cases of pandysautonomia are reported. Pupils, salivary glands, sweat glands, gastrointestinal tract, urinary bladder and heart were mainly impaired in all cases, indicating that the peripheral part of both sympathetic and parasympathetic nervous systems were involved, especially the cholinergic post ganglionic efferent fibers. In addition, two cases showed distal sensory impairment, slight atrophy of small hand muscles and depressed or absent tendon reflexes. Three cases showed elevation of CSF protein without cellular reaction. Sural nerve biopsy was performed in 3 cases; changes included reduction of myelinated fibres and Schwann cell atrophy. One case also showed small vasculitis among neurofascicles. It seems that the disease results from an autoimmune dysfunction, which may be due to a variant type of Guillain- BarrÈ syndrome or a distinct disease. The prognosis of pandysautonomia in the present group was good; four cases have shown some improvement after 1- 4 years follow- up study.

116
NERVE CONDUCTION STUDIES IN INFANTS WITH CHARCOT-MARIE- TOOTH DISEASE TYPE 1A. A Garcia, O Combarros, J Calleja, J Berciano, *Santander Spain.*

The present study was undertaken to determine whether serial nerve conduction studies are a valuable method for identifying symptomatic or asymptomatic carriers of the dominant gene for Charcot- Marie- Tooth (CMT) disease type 1A in the first 5 years of life. We have studied 21 children at risk from 6 unrelated CMT- 1A families. Electrophysiological study included determination of motor conduction velocity (MCV) and corrected distal motor latency (DML) in 2 or more nerves (usually median and posterior tibial nerves). Serial electrophysiological studies (2 or more) were systematically performed, the initial study being done during the first 3 years of life in most cases. Twelve (56%) children were eventually considered to be affected as indicated by clinical, electrophysiological and molecular genetic studies (17p11 .2 duplication). Starting from 2 years of age all 12 patients had abnormal MCV and DML. Six affected children were studied within the first 24 months of life. In 3 of these patients the initial electrophysiological examination demonstrated both MCV and DML abnormalities. In the remaining 3 cases prolonged DML preceded development of MCV slowing. We conclude that electrophysiological examination is a reliable method for detection of CMT- 1A gene carriers in infancy.

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GLIAL FIBRILLARY ACIDIC PROTEIN (GFAP) EXPRESSION IN THE PERIPHERAL NERVOUS SYSTEM DURING EXPERIMENTAL DIABETIC NEUROPATHY. G Conti, P Baron, E Scarpini, R Bianchi, A Conti, S Livraghi. *Milan; Italy.*

Increased levels of P0 and MBP mRNA have been recently demonstrated in experimental diabetes (Conti et al., 1993), suggesting a metabolic disturbance in myelin forming Schwann cells. Non myelin forming Schwann cell express GFAP, while Schwann cells surrounding myelinated axons are GFAP negative. GFAP expression markedly increases in human axonal neuropathies. To investigate whether metabolic modifications of Schwann cells occur during diabetes, we examined expression of GFAP in the sciatic nerve of diabetic rats. Diabetes was induced in adult Sprague-Dawley rats by intraperitoneal injection of STZ (50 mg/Kg body weight). Clinically all rats developed: hyperglycemia, glycosuria, weight loss and elevated food and water intake. GFAP expression was analysed by immunocytochemistry on nerve frozen sections obtained from normal and diabetic rats 15, 35 and 150 days after STZ administration. In normal sciatic nerve, GFAP was slightly expressed, probably by non myelin forming Schwann cells. After STZ administration, GFAP was markedly induced by day 15 and 35, but by day 150 decreased to normal levels. In conclusion, the temporary injection of GFAP at the early stages of experimental diabetes together with increased levels of major myelin protein mRNAs at later stages, suggests a phenotypic plasticity of Schwann cells that can modulate gene expression in response to STZ induced hyperglycemia.

118
MILLER FISHER SYNDROME ANTI-GO1B ANTIBODIES AND CAMPYLOBACTER. JEJUNI INFECTION. JH Rees, NA Gregson, RAC Hughes. *London, UK.*

Miller Fisher syndrome (MFS), a variant of Guillain-Barre syndrome (GBS), defined by the occurrence of ataxia, areflexia and ophthalmoplegia with insignificant limb weakness (1). It is uniquely associated with the presence of anti-GQ1b ganglioside IgG antibodies (2,3). The enteric organism Campylobacter jejuni (Cj) is one of the commonest infections preceding the onset of GBS. However there has been only one case report of an antecedent Cj infection in MFS (4). We are attempting to establish the link between Cj infection and MFS. In a series of 7 MFS patients 3 patients were culture positive for Cj. Symptoms of MFS appeared 1-2 weeks after the initial diarrhoeal illness. All 7 patients' sera had IgG antibodies to GQ1b, with variable cross reactivity with other gangliosides. Furthermore 5 out of the 7 had serum antibodies against Cj. Anti-GQ1b antibodies were strongly absorbed by the Cj isolates from the MFS patients as compared to a control strain. Western blotting of patients serum against two of the patients' isolates and a number of control isolates indicate the presence of antibodies against a wide variety of antigens. No specific antigens were associated with the MFS isolates. The Western blot pattern was not discernibly changed by absorption of the anti-GQ1b antibodies. We are currently investigating the possible crossreactivity of anti-GQ1b antibodies and the lipopolysaccharide (LPS) from the MFS patients' isolates. The LPS from the MFS-Cj isolates (both of which are Penner type o-64) is recognised by MFS serum, but not that from a Cj isolated from a GBS patient with mixed axonal demyelinating disease.

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GUILLAIN-BARRÉ SYNDROME IN CANTABRIA, SPAIN. AN EPIDEMIOLOGOGICAL AND CLINICAL STUDY. J Berciano, MJ Sedano, J Calleja, E Canga, *Santander, Spain.*

Seventy- one patients with Guillain- Barré syndrome (GBS) were retrospectively selected from within a defined area (Cantabria) in northern Spain, from 1975 to 1988. Excluding two non- resident cases, epidemiological analysis was based on 69 cases. The annual incidence rates were stable during the 14- year period of study with an average incidence of 0.95 (age- adjusted, 0.86) cases per 100,000 population. No difference was found for sex, urban or rural residence and there was no significant seasonal clustering. Antecedent events were recorded in 57% of patients, the most frequent being upper respiratory infection and gastro- enteritis. No association between use of gangliosides and the syndrome was found. Eight patients had variant syndromes. Recurrences occurred in 3 cases. Clinical analysis was based on 60 cases. Patients were divided into three groups as a function of their peak weakness. Significant features of the severe group were a requirement for ventilation, presence of bulbar palsy or dysautonomia and a longer duration of the plateau phase. However, it was not possible at an early stage of the clinical course to predict future motor deficit. Outcome was assessed by means of serial examination up to 24 months after the onset of symptoms using a functional scale. At 3, 6 and 24 months 70%, 46% and 12% of patients, respectively, had a poor outcome. Features associated with poor outcome at three months include speed of progression, duration of the plateau phase, age greater than 40 years, severe weakness at the nadir, presence of denervation and a small or absent compound muscle action potential of the median nerve.

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GUILLAIN-BARRE SYNDROME: A SERIES OBSERVED AT RIYADH ARMED FORCES HOSPITAL (JAN 1983-APR 1993). Y Bahou, N Biary, SM Al Deeb, *Riyadh, Saudi Arabia.*

Retrospective study of 47 cases of Guillain- Barré syndrome; 37 males, 10 females; mean age = 27 years (range 6 months-81 years). 60% were preceded by a flu- like illness; 40% occurred in the cold season. 100% had objective limb weakness, 60% limb pains and cranial nerve involvement while only 25% had sensory symptoms. Functional grading (Hughes) showed that 75% were severe (grade 4,5) with a rapid evolution towards the peak (mean = 11 days); 12 required artificial ventilation. 60% had cytoalbuminologic dissociation in the CSF after an average of 25 days from onset. The most common motor electrodiagnostic findings were slow conduction velocities and prolonged distal and F- wave latencies. Sixteen had plasmapheresis after a mean latency of 30 days. It was beneficial in improving the grading at 4 weeks (69% compared to 50% for controls) and is shortening the time for independent locomotion (57,5 days compared to 71 for controls) but plasmapheresis had no benefit on the duration of artificial ventilation (14.5 days compared to 15 for controls) or on the grading at the last follow- up (50% able to walk independently compared to 57% for controls). Outcome was better in children of whom 57% regained independent locomotion. Overall only 55% were able to walk independently after a mean follow-up of 11 months.

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HEREDITARY NEUROPATHY WITH LIABILITY (HNPP) : CONCORDANCE BETWEEN ELECTROPHYSIOLOGICAL ABNORMALITIES AND THE PRESENCE OF A DELETION WITHIN 17 P 11.2. R Gouider, ELE Guern, M Gugenheim, S Tardieu, TM Aisonobe, Y Agid, P Bouche, A Brice, *Paris, France*

The association between hereditary neuropathy with liability to pressure palsies (HNPP) and deletion within 17 p 11.2 has been recently established (Chance et al 1993; Le Guern et al, 1994). The results of the electrophysiological evaluation were compared to the presence or not of a deletion within 17 p 11.2 in 45 individuals: 12 HNPP index cases and 33 consenting at risk relatives . All individuals were tested for the deletion either by allele segregation of RM 11 GT microsatellite and VAW409R3 RFLP or by gene dosage. Thirty one individuals were diagnosed as affected by electrophysiological examination, 23 of which were clinically symptomatic. A deletion within 17 p 11.2 was detected in all patients. At risk individuals with normal electrophysiological examination were heterozygotes in 12 cases and not informative for the tested markers in the remaining 2. our study confirms the complete electrophysiological penetrance of HNPP and the presence of a deletion within 17 p 11.2 in 12 families.

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NEW MUTATION OF THE P0 GENE ASSOCIATED WITH CHARCOT-MARIE TOOTH NEUROPATHY TYPE 1B. B Rautenstrauss, E Nelis, H Grehl, C Van Broeckhoven, RA Pfeiffer. *Erlangen, Germany, Antwerpen, Belgium.*

Charcot-Marie-Tooth neuropathy type 1 (CMT 1; Hereditary Motor and Sensory Neuropathy 1, HMSN1) is a genetically heterogeneous disorder of the peripheral nervous system causing a demyelinating polyneuropathy. The CMT1A locus is located on chromosome 17p11.2 and includes the PMP-22 gene while the CMT 1 B locus is on chromosome 1 q22-q23 including the P0 gene. We have investigated a small pedigree with one case of HMSN and manifestation in early childhood. Nerve conduction velocities in the patient are markedly decreased at the age of 4 years. The parents revealed normal NCV and no clinical symptoms of neuropathy. MspI restricted genomic DNA was hybridized to probes pVAW 409R3a (D17S122), pVAW412R3Hec (D17S125) and pEW401HE (D17S61). No

CMT1A duplication in chromosome 17p11.2 was detected. Also a PCR analysis of duplication-specific CA-repeats RM11 GT and Mfd41 revealed no duplication. Further, SSCP-analysis of the PMP-22 gene revealed no mutation. The SSCP analysis of the P0 gene, however, revealed a band of different mobility in exon 6 of the patient. Thus a de novo alteration of the P0 gene seems to be responsible for the CMT disease in this family. Sequence analysis of the altered P0 exon 6 will show the exact nature of the mutation.

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ANTI-SENSE FLUORESCENCE IN SITU HYBRIDIZATION IN HUMAN AND RAT TISSUE USED FOR DETECTION OF PMP-22 mRNA. T Liehr, H Grehl, E Ganzmann, B Rautenstrauss, *Erlangen, Germany.*

PMP-22 is the candidate gene for the hereditary motor and sensory neuropathy IA, also called CMT (Charcot-Marie-Tooth) IA. The *PMP-22* gene is regularly found to be duplicated or mutated in CMT IA patients. We studied the expression of *PMP-22* on mRNA level at first in sciatic nerves of the rat (rattus norvegicus) and subsequently in sural nerves biopsies of six CMT IA patients and two healthy control persons. The in situ hybridization approach was performed with three *PMP-22* specific antisense and one sense oligonucleotide probe (the later for negative control). The detected fluorescence pattern in all human biopsies analysed up to now is typical for *PMP-22* mRNA in peripheral myelin in rat tissue as well as in patients and in healthy persons. We conclude that *PMP-22* is expressed at high levels in myelinated human peripheral nerves of healthy people as well as in CMT IA patients.

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CLINICAL MORPHOLOGICAL AND MOLECULAR DIAGNOSIS OF HEREDITARY MOTOR-SENSORY MONOPATHY (HMSN). H Grehl, C Gehring, B Rautenstrauss, E Nelis, D Claus, C van Broeckhoven, RA Pfeiffer, B. Neundörfer, *Erlangen, Germany & Antwerpen, Belgium.*

The classification of hereditary motor-sensory neuropathies (HMSN) is based on clinical and morphological criteria. The most frequent autosomal dominant form (HMSN 1 a) was shown to be linked to a duplication of about 1.5 Mbp on chromosome 17p11.2. This region includes the gene of PMP-22, which is a major structural protein of peripheral myelin as are P0 and P2. The duplication has been found in up to 70% of patients with typical HMSN 1, however there are many patients with atypical forms of hereditary neuropathies.We examined a group of 10 patients with the clinical diagnosis of HMSN. In all patients clinical and laboratory examinations had been done before to exclude a symptomatic neuropathy. 2 patients had a family history of neuropathy, mean age of onset was 11 years (1-50 yrs). In only one patient the typical 1 7p11 .2-duplication was found. In two other cases, however, a DNA defect in the P0 gene locus (1q22-q23) was observed. The age of onset in these patients was 2 1/2 years and 20 years. In conclusion up to now there is no consistent correlation of clinical course and genetic findings in HMSN. Thus, in all HMSN patients genetic examinations should be done in different gene loci to confirm diagnosis and to avoid invasive diagnostic.

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PERIPHERAL NERVE INVOLVEMENT IN HIV INFECTION ELECTROPHYSIOLOGICAL AND PATHOLOGICAL STUDY. L Geremia, R Doronzo, G Sacilotto, P Sergi, E Scarpini, GC Pastorino, G Scarlato, *Milan, Italy*

We studied 47 patients with HIV infection, Aids Related Complex or AIDS, 39 without symptoms or signs of peripheral neuropathy and 8 with clinically evident peripheral neuropathy. Latency, amplitude and conduction velocity of median motor and sensory, sensory, common peroneal, sural, lateral and medial plantar nerves were measured, with a standardised method. Mild slowing was found in 13 out of 39 asymptomatic patients (33%), both in sensory and motor conduction, with an amplitude reduction, more marked in lower limbs. In particular, sensory action potentials (SAP) of medial and lateral plantar nerves were absent in 5 patients, with a decrease of amplitude and slowing of conduction velocity of sural nerve. Moreover, the presence of a peripheral neuropathy was confirmed by electrophysiological evaluation in 8 symptomatic patients, and by pathological study in 3 of them. Sural nerve biopsy showed axonal degeneration without inflammation or demyelination. There was a mean reduction of 40 % in myelinated fibre density; the loss principally affected the large fibers. The electrophysiological evaluation suggests that SAPs absence or changes in plantar nerves can be considered a marker of a subclinical neuropathy. The pathological changes in these symptomatic patients consist of axonal degeneration, similar to that seen in other chronic disorders.

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UNCOMMON FEATURES IN HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSY (HNLPP). V Planté-Bordeneuve, A Mantel, G Said, *Bicêtre, Paris, France.*

Charcot-Marie-Tooth disease (CMT1A) and HNLPP are caused by unequal crossing over of the 17p11.2-p12 region. Peripheral myelin protein 22 (PMP22) lies within this segment which is duplicated in CMT1A and deleted in HNLPP. Alteration in PMP22 gene expression is thought to be responsible for these diseases. We describe a family with clinical and morphological features of cmt1a while molecular analysis showed a deletion of the 17p11.2-p12 region consistent with HNLPP. A 37 year-old woman complained of recurrent, asymmetrical episodes of weakness and paresthesiae in the upper limbs of one month duration, since the age of 11. Neurological examination showed bilateral pes cavus, peroneal muscular atrophy and visible hypertrophy of cutaneous nerves. All modalities of sensation were decreased distally and permanent distal weakness was present in legs. Her mother had manifested transient weakness of the right upper limb associated with pupils abnormality. On examination she had pes cavus, mild distal weakness in the limbs, generalised areflexia. Superficial sensory examination was normal and pallesthesia abolished to the knees. Pupils were unequal with light-near dissociation. Electrophysiological data showed diffuse low conduction velocities (20-25 m/sec) and increased distal latencies. Loss of large myelinated fibres, "onion bulbs" were noted on the peroneal nerve biopsy performed in the index case along with widespread segmental demyelination and ´ tomacula ª on teased fibres. Molecular analysis using microsatellite and restriction length polymorphisms found a deletion of the 17p11.2-p12 region in both individuals as described in HNLPP. These cases show that clinical and morphological features might be shared by patients with deletion or duplication of the 17p11.2-p12 region, both abnormalities that alter the control of myelin formation by the PMP22 gene.

Four additional abstracts belong in this section. They are printed on p. S162.

Symposium I
Presidential Symposium

Diseases of the Myelin
Chairman: WI McDonald *(London, UK)*

Presidential address

HOW SHOULD MULTIPLE SCLEROSIS BE TREATED. WI McDonald, *London, UK.*

The increased understanding of the pathogenesis of multiple sclerosis deriving from in vivo and in vitro studies offers unparalleled opportunities for new treatment strategies. Serial magnetic resonance imaging provides a means of assessing rapidly, with fairly small numbers (<100), whether a putative therapy has an effect on the pathological process, but does not provide a surrogate for the assessment of clinical benefit. The latter still requires large scale trials with disability as the primary outcome measure. Agreement is urgently needed on the best way of conducting such trials. In the meantime there is a dilemma which I shall discuss.

INHERITED NEUROPATHIES CAUSED BY DEFECT OF PERIPHERAL MYELIN PROTEIN GENES. F. Baas, *Amsterdam, The Netherlands.*

About a century ago, a hereditary demyelinating peripheral neuropathy was described by Charcot, Marie and Tooth. This disease is currently known as Charcot-Marie-Tooth (CMT) or hereditary motor and sensor neuropathy (HMSN). (Genetic studies identified 3 distinct loci for demyelinating CMT. Two autosomal loci (CMT1A and 1B) and a locus on

the X-chromosome (CMTX). The most frequent form is linked to chromosome 17 (CMT1A), whereas CMT1B is linked to chromosome 1. Recently, the genes mutated in these forms of demyelinating CMT have been identified. In all three cases the genes encode proteins highly expressed in Schwann cells, confirming the initial hypothesis that the primary defect in these forms of CMT is located in the Schwann cell. In most cases of CMT1A, a DNA duplication of a 1.5 Mb region on chromosome 17p was identified. The de novo appearance of the duplication in 9 of 10 isolated cases of CMT1A showed that the duplication was the pathogenic mechanism in CMT1A. The gene for the peripheral myelin protein 22 (pmp22), which is mutated in the Trembler mouse, is located in the duplication and was proposed to be a candidate gene for CMT1A. The identification of mutations of pmp22 in non-duplicated cases of CMT1A confirmed this hypothesis. In hereditary peripheral neuropathy with liability to pressure palsies (HNPP) large deletions encompassing the pmp22 gene are found. The identification of a mutation in pmp22) leading to a premature stop codon in a HNPP patient without the deletion, supports the hypothesis that pmp22 is also the gene for HNPP. Thus, either a mutation or an alteration of the copy number of pmp22 can result in neuropathy. The role of pmp22 is not known yet. The pmp22 gene encodes a 22 kD protein with 4 predicted membrane spanning domains. It is highly expressed in peripheral nerve, and its low expression in fibroblasts, at least 10-times lower than in Schwann cells, is upregulated upon growth arrest. pmp22 could either be involved in maintenance of a quiescent state, or have a structural role in the Schwann cell membrane in myelin formation or, both. In CMT1B, the chromosome-1-linked form, mutations of the myelin protein zero (PO) gene are found. PO, a transmembrane protein and a member of the immunoglobulin superfamily, is highly expressed in peripheral nerve and is considered necessary for compaction of myelin by homophilic interaction. The gene for connexin 32 (Cx32) was identified as being mutated in CMTX. Cx32 is a gap-junction protein, thought to be involved in the transfer of ions and small molecules from cell to cell. In peripheral nerve, Cx32 is present at, nodes of Ranvier and of Schmidt-Lanterman incisures, and could allow transfer of nutrients to the inner layers of myelin. The identification of the genes mutated in hereditary peripheral neuropathy, might lead to a better understanding of the pathogenesis and provide a basis for the development of a rational therapy.

Gordon Holmes Lecture

ADRENOLEUKODYSTROPHY. H Moser, *Baltimore, USA.*

Adrenoleukodystrophy (ALD) is an X-linked recessive disorder that affects mainly the adrenal cortex, the nervous system white matter and the testis. It was first described in 1923 by Siemerling and Creutzfeldt. In 1963 Fanconi postulated an X-linked recessive mode of inheritance on the basis of pedigree analysis. The gene was mapped to Xq28 in 1981, and a putative gene was isolated in 1993 by Moser, Aubourg et al. in Strasbourg and Paris. The principal biochemical finding is the abnormal accumulation of saturated very long chain fatty acids (VLCFA) due to the impaired capacity to degrade these substances, a reaction which normally takes place in the peroxisome. While the biochemical defect has been pinpointed to the deficient capacity to form the Coenzyme A derivative of VLCFA, a reaction which is catalysed by the enzyme lignoceroyl CoA ligase, study of the putative gene demonstrated homology not to the ligase but to a peroxisomal membrane protein (ALDP) which is involved in transport. It is postulated that the basic gene defect interferes with the capacity to transport the ligase to the peroxisome. Moser and Aubourg showed that approximately 7% of ALD patients have large deletions of the ALD gene, and we have confirmed this finding. We have demonstrated, in addition, single base pair mutations in 70% of ALD patients who did not have deletions. The specific mutations vary among families. ALD shows great phenotypic variability, ranging from the severe childhood cerebral form, which often leads to an apparently vegetative state within two years of onset, to S3 adrenomyeloneuropathy (AMN), which manifests in adulthood and is slowly progressive over decades and to forms in which there is adrenal insufficiency with little or no nervous system involvement. These phenotypes often co-occur within the same family. The phenotypic variation cannot be accounted for by the severity of the biochemical defect or the nature of the primary gene defect. Segregation analysis indicates that the action of an autosomal modifier gene is the most likely explanation. While the adrenocortical insufficiency appears to be accounted for by storage of cholesterol esterified with VLCFA, the rapidly progressive demyelinating process is associated with a perivascular inflammatory response which resembles multiple sclerosis. The inflammation appears to represent a cytokine (tumour necrosis factor alpha) or immune-mediated response to the abnormal accumulation of VLCFA. The postulated autosomal modifier gene is thought to act by modulating this inflammatory response. Adrenal hormone replacement corrects the adrenal insufficiency but does not alter neurological progression. Oral administration of glyceryl trioleate and trierucate oils (Lorenzo's Oil) normalises the levels of VILCFA in plasma but does not benefit patients who are already neurologically involved. The oil may help to prevent the onset of neurological disability, although this effect may be due to ascertainment bias and requires further study. Bone marrow transplantation and efforts to modulate the inflammatory response are under investigation. Gene therapy is the long-range goal.

Oral Session 1 - Parkinson's Disease

1
CEREBRAL DOPAMINE METABOLISM AND DOPAMINE D2 RECEPTOR BINDING IN PATIENTS WITH PARKINSON'S DISEASE (PD) AND OTHER MOVEMENT DISORDERS. A Antonini, M Psylla, I Günther, P Vontobell, HF Beer, KL Leenders; *Villigen, Switzerland*

Different degenerative processes of the extrapyramidal motor system may result in similar clinical syndromes. Their differential diagnosis on a clinical basis may be difficult, particularly in early patients. We studied striatal dopamine metabolism and dopamine D2 receptor binding with PET and the tracers [18F]fluorodopa and [11C]raclopride in 7 clinically asymmetric patients with PD and 3 patients with multiple system atrophy (MSA). Data were compared with 10 healthy control subjects. Specific [18]fluorodopa uptake (Ki) and [11C]raclopride binding to dopamine D2 receptors were calculated in putamen and caudate nucleus. PD patients showed reduced Ki values and increased [11C]raclopride binding particularly in putamen. The putamen contralateral to the more affected body side showed in all PD patients the lowest fluorodopa metabolism and in 5 the highest [11C]raclopride binding. The remaining two PD patients did not reveal a [11C]raclopride side to side difference. MSA patients had severely reduced Ki values as well as dopamine D2 receptor binding. In conclusion PD patients show reduced striatal dopamine metabolism and upregulation of the post-synaptic dopamine D2 receptors. The reduction of [11C]raclopride binding in MSA patients suggests an additional impairment of the post-synaptic dopaminergic system.

2
REVIEW OF SIX YEARS TREATMENT WITH APOMORPHINE IN FLUCTUATING PARKINSON'S DISEASE. K Ray Chaudhuri, J Parker, IF Pye, PAH Millac and RJ Abbott. *Leicester; UK.*

Twenty-two nondemented patients with Parkinson's disease (PD, mean age 62 yrs, 6 female) and refractory on-off oscillations have been treated with subcutaneous apomorphine over a mean period of 4 yrs (range 1-6 yrs). Nineteen still continue with treatment. The mean duration of PD is 17 yrs (range 5-26 yrs). Nine patients use a penject system (mean 3 injections/day) for delivery of apomorphine (mean dose 10 mg/day, range 4-15 mg,) while 10 patients continue with apomorphine infusion over 12 hrs (mean dose 42 mg, range 24-60 mg). Mean daily levopoda requirement has fallen by 25% with significant improvement in off periods and overall quality of benefit, rated on a scale of 4 (0=none, 4=excellent) is 2.5 at 4 yrs after being 3.6 at 1 yr. Unusual side effects have included development of contact dermatitis, dose related amenorrhoea and severe weight gain in two patients (10 & 19 kg, refractory to dieting). Two patients with severe neuropsychiatric problems on oral therapy continue to tolerate apomorphine satisfactorily. We conclude subcutaneous apomorphine continues to be an useful therapeutic option after six years in PD patients with refractory oscillations. Penject delivery of the drug is better tolerated and may be particularly indicated in those requiring lower doses of apomorphine.

3
TRACKING TEST PREDICTS LONG TERM L-DOPA RESPONSE IN PARKINSONIAN PATIENTS. M Sutter, C Albani. *Zurich, Switzerland .*

We examined the value of a computer assisted tracking test performed during a Levodopa challenge to predict long term response to L-DOPA medication in patients with Parkinsonism. After a wash-out lasting 12 hours and overnight fasting 41 Parkinsonian patients (mean age 62.2 ± 12.4, Hoehn & Yahr stage 2.5 ± 1.5. mean duration of disease 5,1 ± 5) received 60 mg of domperidone and a formulation of 200 mg L-DOPA and

50 mg Benserazide early in the morning. The antiparkinsonian effects of medication were evaluated at baseline and 0.5, 1,2,3 and 4 hours after medication with the Unified Parkinson's Disease Rating Scale (UPDRS) and with a computerised choice reaction visual tracking test. Average values of reaction times for extension (RTUP) and flexion (RTDW) movements of the thumb were computed as well as movement times (MTUP, MTDW) and tracking error areas. All patients were subsequently treated with standard medication. After three months the long term effects of antiparkinsonian therapy were evaluated :a positive effect of antiparkinsonian medication was found in 21 patients, 20 did not respond to therapy. Receiver operating analysis (ROC) revealed a predictive value with 90% sensitivity and 70% specificity of MTUP for correct long term outcome as compared with a sensitivity of 81% and a specificity of 90% for UPDRS scores. The combined analysis of movement parameters (MTPUP and error area of tracking) improved the specificity of the tracking test (86% sensitivity and 90% specificity).

4
PREVALENCE OF PARKINSON'S DISEASE IN THE ELDERLY. THE ROTTERDAM STUDY. MC de Rijk , MMB Breteler, GA Graveland, FGA van der MechÈ, A Hofman, *Rotterdam, The Netherlands.*

We assessed the prevalence of Parkinson's disease in a general elderly population in the Netherlands. The study forms part of the Rotterdam Study, a population-based door-to-door study and included 7834 people aged 55 years and over, living in a suburb of Rotterdam, the Netherlands. All subjects who had at least one possible cardinal sign for parkinsonism at the neurological screening examination or reported to have Parkinson's disease or were taking antiparkinsonian drugs were invited for further evaluation. In total, 8.0 % of the participants were screenpositive. Based on the people evaluated thusfar (65 % of the screenpositives) our estimate of the prevalence of probable Parkinson's disease in this population is 1.2% (1.0% for men; 1.4 % for women). The prevalence increased with age, prevalences for those aged 55 to 64 years, 65 to 74 years, 75 to 84 years and 85 years and over were 0,3 %, 1.0 %, 2.7 % and 2.2 %, respectively. The corresponding age-specific figures for men were 0.3 %, 1.0 %,2.1 % and 1,5%, and for women 0.3%, 0.9%, 3.0% and 2.4 %. Twenty-two percent of the subjects with probable Parkinson's disease were newly diagnosed through the study protocol.

5
GENE POLYMORPHISM FOR MONO-OXYGENASE IN EARLY ONSET PARKINSON'S DISEASE. A CASE CONTROL STUDY. M Keipes, Ch Hilger, N Diederich, H Metz, F Hentges. *Luxembourg.*

The ecogenetic theory for the pathogenesis of Parkinson's disease (PD) finds renewed interest with the description of different gene mutations coding for cytochrome P-450 monoxygenase. Two heterogeneous groups of PD patients have shown more frequent homozygous mutant alleles CYP2D6B than controls. These findings may contribute to a higher susceptibility to neurotoxins. The theory of defective xenobiotic metabolism is of particular interest in Young Onset PD patients. Twenty-seven Caucasian PD patients (age: 47 ± 8.1 years) with an age at onset of disease of 38.9 ± 8.3 years (range: 23-49) are genotyped by PCR and compared to 47 non parkinsonian caucasian controls. We totally identify 5 homozygous (HOM)(6.75%) and 18 heterozygous (HET)(24.3%) samples for the allele. The distribution is the following: one HOM (3.7%) and 7 HET (25.9%) in the PD versus 4 HOM (8.5%) and 11 HET (23.4%) in the control group. Conclusion: Early Onset PD patients do not show increased incidence of mutated alleles of cytochrome P-450. These results are in concordance with early reports denying substantial disturbance of debrisoquine metabolism in early PD. They are not in line with recent genetic studies of unselected PD patients. This fact may be due to the selection of the group or its small size.

6
IMPROVEMENT OF PARKINSONIAN SYMPTOMS BY SUBTHALAMIC NUCLEUS STIMULATION. P Pollak, AL Benabid, P Limousin, D Hoffmann, A Benazzouz, J Perret, *Grenoble, France*

Selective lesions or high frequency electrical stimulations of the subthalamic nucleus (STN) in MPTP-treated monkeys alleviate parkinsonian symptoms. We present the results obtained in two akineto-rigid parkinsonian patients, suffering from severe on-off effect. In patient 1 the target was chosen according to stereotaxic atlases. In patient-2 the STN was visualised on MRI. Stereotaxic surgery was done under local anaesthesia, on one side in patient-1 and bilaterally in patient-2, in 2 separate sessions. Peroperative 130 Hz stimulations at the target site improved greatly contralateral rigidity and akinesia. A quadripolar DBS Medtronic electrode for chronic stimulation was inserted in the same area. The best frequencies of stimulation were 100 Hz and over. Rigidity and akinesia were improved time-locked to the stimulation in patient-2. Bilateral STN stimulation improved UPDRS motor score and timed tests in the same range as levodopa. Off-phases disappeared in both patients. Levodopa induced abnormal involuntary movements were not modified after surgery. No adverse effect was observed, especially no hemiballism. A long-term experience in more patients is necessary to confirm these very satisfactory results.

7
PET STUDIES ON THE DOPAMINE TRANSPORTER WITH IIC CIT IN THE NORMAL SUBJECTS AND PARKINSONIAN PATIENTS A Laihinen, JO Rinne, H Ruottinen, K Nagren, P Lehikoinen, V Oikonen, U Ruotsalainen, UK Rinne, *Turku, Finland*

The cocaine analogue B-CIT (2B-carbomethoxy-3B-[4-iodophenyl]-tropane) has been labelled with [11C] for positron emission tomography (PET) to study the dopamine reuptake sites. Three normal subjects and nine parkinsonian patients were investigated. Each of them underwent dynamic PET scan (25 time frames over 80 min) with [11C]B-CIT. A dose of 2.77-5.71 mCi of this ligand was administered i.v. and a PET examination with an ECAT 931/08 PET camera was carried out. Ratios between the striatal and cerebellar uptake of this compound were calculated. [11C]B-CIT accumulated significantly less in the putamen of the parkinsonian patients than in the normai subjects. The putamen ce rebellum ratio in the parkinsonian patients was 1.59 (0.14 and in the normal subjects 1.80 ± 0.20 ($p<0.0l$). In the caudate there was no significant difference between the parkinsonian patients and the normal subjects. These results imply that [11C]B-CIT is a useful compound for studying the extent of presynaptic damage in Parkinson disease in vivo.

Oral Session 2 - Neurogenetics

1
A NEW GENE IN THE FRIEDREICH'S ATAXIA REGION ON CHROMOSOME 9q. S Cocozza, A Pizzuti, F Cavalcanti, A Monticelli, L Pianese, E Redolfi, F Paiau, S Di Donato, M Pandolfo. *Naples & Milan, Italy; Valencia, Spain.*

The mutated gene in Friedreich's ataxia (FRDA) has been mapped on chromosome 9ql3-q21.1 within 1 cM from the marker loci D9S15 and D9SS. A few recombination events allowed to localize the FRDA locus proximal to the markers, solving gene order as cen - FRDA - D9S5 - D9S15 - tel. A gene, XII, spanning 80 Kb of genomic DNA proximal to D9S5 has been isolated by Duclos et al., but no mutations have been detected on FRDA chromosomes. We constructed a YAC contig extending 800 Kb from D9S5 toward the centromere and subcloned part of the YACs into cosmids. A polymorphic microsatellite we isolated 190 Kb proximal to D9S5, D9S202, apparently overcame the crossing-overs in all informative recombinant families. A new gene expressed in brain was found between XII and D9S202 using a modification of the "direct selection" method. We detected by single-strand conformation polymorphism (SSCP) analysis a sequence variation within one exon of this gene. This variation appears to be a polymorphism present on normal as well FRDA chromosomes. A family in which recombination had occurred between D9S 15 and FRDA with all other markers being non-informative resulted informative and non-recombinant for this polymorphism. Further analysis of this gene is in progress.

2
EVIDENCE FOR GENETIC HOMOGENEITY OF FRIEDREICH'S ATAXIA WITH RETAINED REFLEXES ON CHROMOSOME 9q. F Palau, S Cocozza, M Pandolfo, E Monros, G De Michele, P Smeyers, J Lopez-ArLandis, J Uilchez, S Di Donato, A Filla. Valencia, *Spain; Naples & Milan, Italy.*

Absence of lower limb tendon reflexes is considered an essential diagnostic criterion for defining classical Friedreich's ataxia (FRDA). However, some patients showing Friedreich' phenotype but retained lower limb tendon reflexes (FARR) have been reported, which makes FRDA diagnosis

more difficult, especially in isolated cases. To address this problem, we have evaluated the hypothesis that FARR patients are allelic forms of the FRDA locus on chromosome 9ql3. Linkage analysis was performed in six families with 11 patients. At least an affected child manifesting FARR phenotype was observed in each family. FRDA-linked marker loci, D9S111, D9S15, D9S110, D9S5, FD1, and D9S202, were analysed. A maxlod of 3.385 at zero of the recombination fraction was obtained, which confirmed linkage to the FRDA locus. We concluded that FARR is a clinical variant of FRDA.

3
PREMONITORY SIGNS AND SYMPTOMS OF SPINAL CEREBELLAR ATROPHY TYPE 1 DETECTED BY ANALYSIS OF THE SCA1 CAG-REPEAT EXPANSION. D Genis; T Matilla; V Volpini; MI Blanchs; A Davalos; A Molins; J Rosell, X Estivill. *Girona, Spain..*

We report the clinical and genetic studies of a large kindred with ADCA1 (M-ADCA1) a family with autosomal dominant cerebellar ataxia type 1 (ADCA1) Clinical data were obtained in 18 members. Mean age of onset was 36.8 years. Duration was 15.2, and age of death was 53.8.years.Onset symptoms and clinical findings were the classical of ADCA1. Anticipation was detected between 7th and 8th generation. A worse course of disease occurred in offspring of affected males. We have analysed the CAG-repeat mutation responsible for the ADCA1 phenotype in a total of 10 clinically affected and 48 unaffected members. The expansion was found in a total of 19 subjects. All affected patients and 10 unaffected ("at risk") members were heterozygous with one allele being between 41 and 59 repeats (ADCA1 mutation) and the other in the range of six to 39 repeats. The size of the repeat increased throughout successive generations, but we observed stabilization (2) and contraction (1). In seven of the "at risk" affected subjects we detected signs and symptoms (intermittent dysarthria, nystagmus, hand tremor...) that correlated with disease, and were not present in the unaffected group. These early premonitory symptoms can herald disease by years and are powerful markers of ADCA1 before the development of clinical picture.

4
FAMILIAL SPASTIC PARAPLEGIA (FSP): A STUDY OF ELEVEN FAMILIES. P De Jonghe, G Smeyers, L Krols, R Mercelis, J Hazan, J Weissenbach, C Van Broeckhoven, JJ Martin, *Antwerpen, Belgium & Paris, France*

We examined eleven families with familial spastic paraplegia (FSP). Nine families belonged to the pure form. In one family some patients had hearing loss. In another family IQ was generally low, possibly due to social-economic circumstances. In all families patients were found with an age at onset before 45 years. Three families showed anticipation with earlier and more severe involvement in younger generations. In one family age at onset varied from 2 to 50 years. Severely affected individuals with early onset age always inherited the disease gene from their father suggesting genomic imprinting. This findings have important implications since several inherited neurological diseases with anticipation are caused by an expansion of a trinucleotide repeat. Measurements of central motor conduction in FSP patients showed different patterns: slowed in upper and lower limbs, only reduced in the legs, and no abnormalities. These patterns were however consistent within individual families probably representing clinical heterogeneity within the FSP syndrome. Nine families were examined with chromosome 14q24 markers but none showed linkage with the reported FSP locus in this region.

5
MOLECULAR GENETIC BASIS OF DentatoRubropallidoluysian atrophy IN EUROPEAN FAMILIES. TAT Warner, L Williams, AS Orb, AE Harding, *London, UK*

Dentatorubropallidoluysian atrophy (DRPLA) is a neurodegenerative disease with distinctive pathology. It is most commonly seen in Japan, and is thought to be very rare in Europe. Most cases exhibit autosomal dominant inheritance although some are sporadic. Age of onset varies from childhood to late adulthood, with various combinations of seizures, dementia, ataxia, myoclonus and other movement disorders. DRPLA can clinically be confused with Huntington's disease (HD). Recent studies have shown that DRPLA is associated with an expanded CAG trinucleotide repeat which maps to chromosome 12, with a correlation between age of onset, severity and repeat size. report 2We families in whom this expanded repeat was present. The first was British and DRPLA was diagnosed at autopsy. The second was of Maltese origin with an autosomal dominant neurodegenerative disorder inwhich no diagnosis had been made. Onset varied from 5-50 years with a variable phenotype of dementia and seizures, ataxia, chorea and myoclonus. The pathological features of DRPLA were not present in 2 patients autopsied. DRPLA in Europeans has the same molecular genetic basis as in Japanese families, and should be considered in cases of obscure multisystem neurodegenerative disorders.

6
THE TRINUCLEOTIDE REPEAT EXPANSION ON CHROMOSOME 6p (SCA1) IN AUTOSOMAL DOMINANT CEREBELLAR ATAXIAS. P Giunti, MG Sweeney, M Spadaro, C Jodice, A Novelletto, P Malaspina, M Frontali, AE Harding, *London UK & Rome, Italy*

Affected members of 73 families with a variety of autosomal dominant late onset cerebella ataxia's (ADCA) were investigated for the trinucleotide (CAG) repeat expansion which is found in pedigrees exhibiting linkage to the SCA1 locus on chromosome 6. Most of the families were too small for linkage analysis. The mutation was only found in ADCA type I, in 16 of 38 such kindred's investigated (42%). It was slightly more common in Italian (58%) than British (50%) families, and was also found in Malaysian, Bangladeshi and Jamaican kindred's. ADCA type I patients with the expansion had a lower incidence of hyporeflexia and facial fasciculation than those without. The trinucleotide expansion was not found in eight families with ADCA and maculopathy or 24 kindred's with a pure type of ADCA, confirming that these syndromes are genetically distinct. It was also not detected in 12 patients with sporadic degenerative ataxias. DNA analysis for the SCA1 mutation is useful diagnostically in single patients or small families, and can be used for presymptomatic testing where appropriate.

Oral Session 3 - Dementia (1)

1
CEREBRAL METABOLISM AND TISSUE LOSS IN ALZHEIMER'S DISEASE. E Salmon., Gregoire, Del Fiore, Comar, G Franck, *Liège, Belgium*

Does the characteristic temporo-parietal and frontal hypometabolism observed in vivo with positron emission tomography (PET) in Alzheimer's disease (AD) result from irreversible tissue loss or from functional deactivation ? Neuropathology in AD shows alteration of brain proteins, degeneration and loss of neurons, and reduction of cytoplasmic RNA content, nuclear and nucleolar volume, which should be detectable by a determination of the local rate of protein synthesis. Using PET in 10 patients with probable AD, we demonstrated that accumulation of (^{11}C) methionine in brain proteins of temporo-parietal cortex was significantly lower (0.78 ± 0.05%, p=0.003, ANOVA) than that in age matched controls (0.84 ± 0.03%). However, (^{11}C) methionine accumulation was not correlated with temporo-parietal hypometabolism, and incorporation of (^{11}C) methionine in frontal cortex was not reduced, although frontal metabolism was significantly decreased (p=0.005, ANOVA). We conclude that tissue loss and degeneration in AD is not sufficient to explain cerebral hypometabolism, which is mainly functional in nature.

2
EXPERIENCE WITH VELNACRINE IN THE TREATMENT OF ALZHEIMER'S DISEASE. PH Scheltens, K. Siegfried, E Dartigues, P De Deyn, R Horn and The European Velnacrine Study Group, *Amsterdam, the Nertherlands*

Velnacrine is a 1,2,3,4-tetrahydro-9-aminoacridine l-ol maleate which was synthesised in the early 80s. Biochemically, it acts as a potent cholinesterase inhibitor. Recently, a large European multicentre Velnacrine study was completed. This study made use of an enrichment procedure, followed by a 4-month double-blind parallel group comparison of Velnacrine (50 mg twice daily) and placebo. 239 patients with a diagnosis probable AD" (NINCDS-ADRDA criteria) and mild to moderately severe degrees of dementia (MMSE scores between 10 and 27) were enrolled by 12 European study sites; 210 patients received the study drugs. After the enrichment procedure, a subgroup of 114 patients (55%) entered the 4-

month double-blind segment. Statistically significant effects were observed in favour of Velnacrine on cognitive subscale of the Alzheimer's Disease Assessment Scale, in various cognitive performance tests, and on carers' rating scales of patients' everyday behaviour. The most frequent safety problem was a significant, asymptomatic, increase of transminases. Side effects were of cholinergic nature (diarrhoea, nausea, vomiting, in <6% of all patients). Rare but clinically important events were mild forms of neutropenia which occured in 3 patients under treatment.

3
A NEW MITOCHONDRIAL DNA MUTATION ASSOCIATED WITH PROGRESSIVE DEMENTIA AND CHOREA. I Nelson, MG Hanna, MG Sweeney, JA Morgan-Hughes, AE Harding, *London, UK*

We report a novel heteroplasmic transfer RNA mutation associated with an unusual mitochondrial encephalopathy phenotype. The patient presented at the age of 40y with progressive dementia and chorea in the absence of clinical myopathy. He was also deaf, ataxic, and had peripheral neuropathy. There were ragged red and cytochrome oxidase negative fibres on muscle biopsy. Muscle mitochondrial enzyme studies showed decreased complex 1 activity. Autopsy macroscopically revealed widespread atrophy affecting cerebral cortex and white matter, basal ganglia in particular the right caudate nucleus, brainstem and cerebellum. Microscopically there was extensive gliosis and neuronal loss throughout but no evidence of microvacuolation. The mutation is in a highly conserved position in tRNA tryptophan and was not found in 100 controls. It had a widespread tissue distribution, being present in high amounts in both clinically affected and unaffected tissues. This report defines an unusual mitochondrial phenotype at a genetic level and highlights the importance of considering mitochondrial disorders in the differential diagnosis of progressive encephalopathy in the absence of clinical myopathy.

4
NEW APPROACHES TO DIAGNOSIS IN HUMAN PRION DISEASES. J Collinge, MS Palmer, T Campbell, S Mahal, K Sidle, C Humphreys, *London, UK*

Molecular genetics has now revealed a wider phenotypic spectrum of the human transmissible spongiform encephalopathies, now better referred to as Prion diseases, which can be subclassified into inherited, sporadic and iatrogenic forms. At least 18 pathogenic mutations are recognised causing the inherited prion diseases, and we have demonstrated significant genetic susceptibility factors in both sporadic and iatrogenic disease. We have now screened over 800 cases of neurodegenerative disease for prion protein gene mutations in the UK, and identified 2 cases with mutation at codon 102, 2 at codon 117, 1 at codon 178, 3 at codon 200. Individuals with insertions of a various numbers of additional octarepeat elements have now also been identified in addition to 6 and 9 repeat insertions already described in the UK.

5
POSITRON EMISSION TOMOGRAPHY STUDIES WITH ACETYLCHOLINESTERASE INHIBITORS PROPOSED FOR THE TREATMENT OF ALZHEIMER'S DISEASE. B Tavitian, S Pappata, A Jobert, AM Crouzel and L DiGiamberardino. *Orsay, France; Barcelona, Spain.*

The aim of our work is to image the neurochemical deficits found in the brains of Alzheimer patients with positron emission tomography (PET). Two candidate PET ligands, both inhibitors of acetylcholinesterase (AChE) proposed in the treatment of Alzheimer patients, have been labelled with C11: [^{11}C]physostigmine ([^{11}C]PHY) and [^{11}C]methyl-tetrahydroaminoacridine ([^{11}C]MTHA). Here we present the data from PET experiments with these new ligands in non-human primates. The distribution of [^{11}C]PHY is superimposable to that of AChE: concentrations are highest in caudate nucleus and putamen, intermediate in the thalamus, and lower in cortex and cerebellum. The half-life of [^{11}C]PHY in the brain is 20-30 min and competition with unlabelled physostigmine reduces its cerebral uptake 15-50 % depending on the regions. These results are in accordance with the pharmacological characteristics of physostigmine, and support the view that [^{11}C]PHY could be useful to image in vivo the active sites of this enzyme. [^{11}C]MTHA 's cerebral distribution is different: its uptake is highest in the frontal and temporo-parietal cortex and in the basal ganglia, intermediate in the occipital cortex and thalamus, and low in the cerebellum and white matter. The elimination of cerebral radioactivity after [^{11}C]MTHA injection is slow, over 4 hours in the cortex, and injection of a pharmacological dose of unlabeled THA reduces by 20-50 % the radioactivity concentrations depending on the region. These results suggest that the distribution of [^{11}C]MTHA is not correlated with that of AChE, rather is representative of the "THA binding sites" whose nature remains to be determined. Work is now in progress to define the value of these two new PET ligands for the exploration of Alzheimer patients.

6
VARIOUS CLINICAL AND PATHOLOGICAL PHENOTYPICAL EXPRESSIONS IN A FAMILY WITH GERSTMANN-STRAUSSLER-SCHNEIDER DISEASE AND MUTATION AT CODON 17. C Tranchant, G Steimetz, M Mohr, JM Warter, *Strasbourg, France.*

Four different forms of GSS have been delineated on the basis of clinical and pathological presentation correlated with localisation of prion protein (PrP) gene mutation (at codon 102, 117, 198 or 217). However, clinical and pathological studies of several patients of one of the two GSS family with mutation at codon 117 demonstrated some heterogeneity in phenotypic expression of the mutation. In this family, age of onset and duration of illness are variable. In the first generation a diagnosis of Alzheimer disease (AD) had been entertained but in the most recent cases pyramidal or pseudobulbar signs are predominant. Pathological studies of the 3 last patients who died at age 21,43 and 73 showed spongiform changes, gliosis and amyloid plaques stained by anti-PrP antibodies. Only in the oldest patient, some senile plaques stained by anti-13 amyloid protein antibodies and above all numerous neurofibrillar tangles (NFT) were found as well. These abnormalities could reflect advanced age but the large number of DNF was unusual even for a diagnosis of Alzheimer's disease. NFT have been reported in others GSS families but seemed specific of mutation at codon 198 or 217. Our findings argue in favour of the phenotypic classification of GSS disease, since various phenotypic expressions of a same mutation can exist in a same family.

7
RAPIDLY PROGRESSIVE GERSTMANN-STRAUSSLER-SCHEINKER SYNDROME (GSS) WITH CODON 102 MUTATION OF THE PRION PROTEIN GENE (PRNP) IN A LARGE ITALIAN KINDRED. P Barbanti, G. Fabbrini, M. Salvatore, MG Buzzi, V Di Piero, R Petraroli, A Sbriccoli, M Pocchiari, G Macchi, GL Lenzi. *Rome, Italy.*

GSS is a rare familial neurodegenerative disorder, characterised by spinocerebellar ataxia and dementia, caused by unusual infectious agents called prions. PRNP codon 102 mutation has been associated with the ataxic form of GSS. We studied an Italian kindred with rapidly progressive GSS with PRNP codon 102 mutation. All affected members with dementia as a prominent sign showed an unusually short illness duration (5-12 months). The proband, a 53 y.o. woman, developed ataxic gait, extrapyramidal-pyramidal signs and rapidly progressing dementia; she died 9 months after symptomatic onset. Clinical diagnosis was confirmed by western-blot detection of PrP_{27-30} from cerebral samples. Neuropathological examination revealed widespread spongiform and spongiotic changes, gliosis, neuronal loss, amyloid plaques deposition and some kuru plaques throughout the cerebral cortex and the cerebellar molecular layer, thus resembling Creutzfeldt-Jakob disease (CJD) aspects. Amyloid plaques were immunostained by PrP antibody. PRNP codon 102 mutation was found in the proband and in 6 out of 52 yet clinically unaffected members. Her cousin and six ancestors presumably died of GSS and carried the same mutation, as inferred from siblings genotype. This study suggests that clinical-neuropathological overlap between codon 102 mutation GSS and CJD may occur.

Oral Session 4 - Dementia (2)

1
STRIATAL DOPAMINE D2 RECEPTORS AND GLUCOSE METABOLISM IN GENE CARRIERS AND PATIENTS WITH HUNTINGTON'S DISEASE (HD). A Antonini, R Spiegel, P Maguire, W Schmid, KL Leenders; *Villigen & Zurich, Switzerland*

HD is characterised by widespread degeneration of striatal neurons. Although the gene mutation responsible for the disease has been recently identified, not much is known about the course of the disease before symptoms become manifest. We studied glucose metabolism and dopamine D2 receptor binding in caudate nucleus and putamen of 5 HD gene carriers, 9 subjects with positive HD familiarity but gene negative and 4 patients with

manifest HD, using PET and the tracers [11C]raclopride and [18F]FDG. Data were compared with 30 healthy subjects. patients with manifest HD showed severe reduction of glucose metabolism and raclopride binding in caudate nucleus and putamen. Four of 5 gene carriers revealed decreased glucose metabolism and raclopride binding in caudate nucleus. one gene carrier as well as all gene-negative subjects had values in the normal range. Glucose metabolism decrease appeared to run in parallel with reduction of raclopride receptor binding. These results suggest parallel and progressive loss of neuronal synapses and dopamine D2 receptors in HD gene carriers and patients. The finding of normal values in one gene carrier indicates that striatal neurons may be functionally normal for many years and cellular impairment may begin only few years before chorea onset.

2
ATHEROSCLEROSIS AND DEMENTIA. MMB Breteler, A Ott,ML Bots, DE Grobbe,A Hofman.A, *Rotterdam, The Netherlands*

We investigated the relation between atherosclerosis and dementia among participants of the Rotterdam Study, a population-based study of nearly 8,000 subjects aged 55 years and over. We screened for cognitive impairment with the MMSE followed by a complete dementia work-up for subjects with a MMSE-score of 25 or less. A myocardial infarction on an electrocardiogram, ultrasonographically assessed presence of atherosclerotic lesions in the internal carotid arteries, and an ankle to arm systolic blood pressure ratio below 0.90 were used as non-invasive indicators for atherosclerotic disease of the coronary, carotid and peripheral arteries, respectively. The odds ratio, adjusted for age, gender and previous stroke, was 1.7 (95%CI 0.9-2.9) for coronary atherosclerosis, 1.7 (95%CI 1.2-2.6) for carotid atherosclerosis, and 1.4 (95%CI 1.1-1.9) for peripheral atherosclerosis. When we excluded subjects with a diagnosis of vascular dementia these odds ratios were 1.7 (95%CI 1.0-2.9), 1.7 (95%CI 1.1-2.4) and 1.4 (95%CI 1.1-1.9); and for subjects with a diagnosis of possible or probable Alzheimer's disease 1.7 (95%CI 0.8-3.7), 1.4 (95%CI 0.8-2.6) and 1.5 (95%CI 1.0-2.2), respectively. This study suggests that atherosclerosis is associated with dementia, independent of a history of stroke, not only among subjects with vascular dementia but also among subjects with Alzheimer's disease.

3
MITOCHONDRIAL DISEASE IN THE INTENSIVE CARE UNIT. RS Howard, S Russell, N Losseff, AE Harding, DH Miller, NP Hirsch., *London, UK*

Mitochondrial disease may present to the Intensive Care Unit (ICU) with a variety of coexisting neurological and general medical disorders. Eight patients were admitted to a neurological ICU between 1970 and 1990 because of respiratory insufficiency, status epilepticus and/or metabolic encephalopathy associated with mitochondrial disease. Respiratory impairment occurred in 7 patients and was associated with nocturnal hypoventilation due to respiratory muscle weakness, aspiration due to bulbar weakness and abnormalities of central control leading to a reduced CO2 drive, irregular respiratory patterns and sleep apnoea. Six patients received continuous respiratory support during the acute illness, 3 were subsequently weaned to domiciliary ventilation and 3 died. Three patients had ischaemic cerebrovascular events with 1 having recurrent episodes. Four patients developed tonic clonic grand mal epilepsy associated with myoclonic fits (2 patients), absences (2) and status epilepticus (2). Encephalopathy was associated with recurrent lactic acidosis (2 patients), cardiac failure (2), hyponatraemia (2), renal abnormalities (3) and complete heart block (1). Although rare, mitochondrial disease should be considered in any patient with unexplained respiratory failure, intractable epilepsy, lactic acidosis or recurrent stroke.

4
APOLIPOPROTEIN E AND ALZHEIMER'S DISEASE. COMPARISON WITH MULTI-INFARCT DEMENTIA, PARKINSON'S DISEASE AND STROKE. F Mahieux, A Moulignier, R Couderc, S Bailleul. *Paris, France*

T (apoE) genotypes, with a high frequency of the e4 allele. It has even been suggested homozygosity 4/4 is a diagnostic element for probable AD in case of atypical symptoms. However, this can only be the case if the disequilibrium is specif c for AD. We thus studied the phenotypes of apoE in 498 healthy young blood donors (general population), 90 AD patients, 13 mixed and vascular dementia (MID), 24 Parkinsonian patients (non demented n=16 and demented, n=8) and 69 stroke patients. The repartition of apoE phenotypes are described in the table. (The table could not be incorporated in the abstract. The Editor). These preliminary results suggest good specificity of homozygosity 4/4 in AD, and a different mechanism for dementia in PD. Moreover, we found a significantly higher apolipoprotein A1 levels in AD patients than in the other groups ($p<0.001$). These findings will be discussed as a new pathophysiological feature of AD.

5
AWARENESS OF MEMORY DEFICITS IN ALZHEIMER'S DISEASE: HETEROGENEITY OF ANOSOGNOSIA. MC Nargeot, J Touchon, MC Picot - *Montpellier, France* -

Awareness of memory loss is frequently reported in Alzheimer's disease. Psychological and neurobiological hypotheses have been proposed to explain this anosognosia . The aim of the study was to assess awareness of memory deficit in Alzheimer's disease and to analyse the neuropsychological process underlying anosognosia. A series of 14 patients with mild dementia (MMS: 21,5 ± 3,6) matched by sex, age, educational level with 14 control subjects, were assessed using a self rating questionnaire (QAM: Van der Linden 1989). The questionnaire was administrated to patients, normal control, and a relative who had to evaluate subjects memory. The score of nosognosia was defined as difference between patient's and relative's evaluation. Neuropsychological tests (MMS, MADRS, Weschler Memory, Rivermead Behavioural Memory Test, Trail Making Test, verbal fluency) and computed tomographic measures of regional cerebral blood flow completed this study. Results: 1) the patients had an important variability of anosognosia (from full awareness of memory loss to full anosognosia). 2) the variable intensity of anosognosia could not be explained by disease duration, severity of dementia, depression, global memory deficit. 3) the score of nosognosia in Alzheimer's disease is correlated with frontal lobe dysfunction and with some processes underlying particular memory components. Conclusion: Frontal lobe involvement and the presence of specific memory impairment may be important determining factor to explain anosognosia of memory deficit. Further analysis of these issues will be useful to a better understanding of normal brain, and cognitive process.

6
SIMULATED DRIVING AND CAR CRASHES IN AGING AND COGNITIVELY IMPAIRED DRIVERS. M Rizzo, G Watson, D McGehee, T Dingus. *Iowa USA*

Faulty driving causes car crashes with enormous human costs. Aging and neurological disease pose special risks because of impaired perception, attention, memory, language and decision making. Yet, surprisingly, there are no reliable criteria for predicting safe or risky driving. We propose that such predictions can enhanced by high-fidelity driving simulations. This is the purpose of our current research on the Iowa Driving Simulator (IDS). The IDS replicates critical elements of driving without the peril of live road-testing. It comprises a real car with functioning gauges and controls, mounted on a B-S2 simulator motion base and housed within a large dome containing an interactive visual display, wind and road noise effects. We tested 110 young and elderly drivers and 3 Alzheimer patients on a scenario covering ISO square miles around an imaginary town in rural, urban (small town), and freeway traffic. Two crash avoidance situations were also tested. Measures of vehicle and operator performance were acquired at 6O Hz. Data reduction included mean velocity, following distance, deviation from the posted speed, deviation of lane placement, numbers of accelerator reversals, steering reversals, center line crosses, shoulder crosses, and obstacles hit. The results showed that most drivers rated the simulation highly realistic. older drivers showed reduced performance along several performance dimensions. The Alzheimer patients performed worst, compatible with diminished automatic and controlled processes of attention. We conclude that high fidelity driving simulations are feasible, useful, and safe. The IDS simulates the complexity and demands of real driving and quantifies driving performance, even under emergency situations that are impossible to test on-the-road. Future applications will allow us to test models of driving in different neurological diseases.

Oral Session 5 - Multiple Sclerosis (1)

1
EUROPEAN MULTICENTER TRIAL ± DEOXYSPERGUALINE (DSG) VERSUS PLACEBO. RESULTS OF THE FIRST INTERIM ANALYSIS: L Kappos, EW Radü, J Haas; CH Hartard, HP Hartung. *Basel, Switzerland; Hannover, Hamburg & Würzburg, Germany*

DSG suppresses the maturation of T-lymphocytes into functional cytotoxic T-cells and of B-cells into antibody secreting cells, and reduces the production of toxic radicals by macrophages. In EAE it has been shown to have both a preventive and therapeutic effect. In September 1992 a controlled clinical trial was started in order to assess the efficacy of the drug in patients with relapsing progressive and secondary chronic progressive MS. To be included patients had to have documented disease activity in the 2 preceding years and at least 1 Gadolinium enhancing lesion in cranial MRI in the screening examination within 2 weeks before inclusion, but no clinical relapse requiring steroid treatment in the last 4 weeks. Patients were randomized to placebo, 2 and 6 mg/kg bw DSG which was given i.v. on 4 consecutive days in 5 cycles every 4 weeks. In the first part of the study (N=104) monthly cranial MRI (plane and enhanced) were performed during the first 6 months, then at 12 and 24 months. Patients in the second part of the study (N=132) were treated and followed with the same protocol except for frequent MRI. The two main efficacy criteria were changes in EDSS at month 24 as compared to baseline and mean number of Gadolinium enhancing lesions in the first 6 months. Additional clinical, evoked potential and immunologic studies were done. Results: The first interim evaluation (with the complete 6 months data of the first of the study) did not show significant differences in the number of Gadolinium enhancing lesions. But one treated group had an improvement in the EDDS score (6 months versus baseline, $p<0.05$). The data for this analysis should be available in early summer 1994.

2
MULTIPLE SCLEROSIS: LONGITUDINAL RELATIONSHIP BETWEEN MRI ACTIVITY AND TNFA LEVELS, IN CSF AND SERUM. S Spuler (née Schönbeck), T Yousry, R Voltz, A Scheller, E Holler, R Hohlfeld. *Munich, Germany*

There is evidence that TNF plays an active part in multiple sclerosis (MS) lesions. However, the practical value of measuring tumor necrosis factor (TNF) in MS patients is controversial. The reasons for this controversy include differences in study design, TNF assays and selection criteria of MS patients. In this study. TNF-α concentrations were measured by ELISA prospectively and longitudinally for one year in serum and CSF of 9 MS patients (14 timepoints, 131 observations). The TNF detected by ELISA correlated well with the TNF concentration as determined by bioassay indicating that only active TNF was measured. Each TNF value was related to the EDSS score and to Gd-DTPA-enhanced MRI obtained on the same day. Results: 1. In relapsing remitting disease bursts of MRI activity were detected during the observation period, even in patients without clinical relapse. 2. MRI activity was associated with an increase of TNF-α concentrations in serum and CSF ($p<0.02$. logistic regression analysis). 3. TNF titers higher than 50 pg/ml in serum or the presence of TNF in CSF were closely associated with MRI activity. 4. After corticosteroid treatment there was a dissociation between the appearance of new active lesions in MRI scans and TNF levels that were suppressed for a prolonged period of time. Conclusion: Disease activity in MS as determined by MRI scans is paralleled by bursts of TNF secretion in untreated patients. Corticosteroid treatment resulted in longlasting reduction of TNF-α levels while the appearance of new lesions on MRI scans was unaffected.

3
T.C.R. «PEPTIDE THERAPY IN PROGRESSIVE MS. AA Vanderbark, H Offner, *Portland, Oregon, USA*

The biased expression of VB5.2 and VB36.1 by T cell clones specific for myelin basic protein (BP) in progressive MS patients led to a preliminary phase I trial using two TCR pep tides for treatment of 11 patients. This study demonstrated that low doses of peptide could be administrated to patients for up to 16 months without significant side effects. In several patients, successful TCR peptide immunization appeared to alter the circulating frequency of BP specific T cells. The extensive parallels between human T cells specific for VB5.2 and VB36.1 peptides and rat T cells specific for VB8.2 peptide that are highly protective against EAE strengthen the rationale for the therapeutic use of TCR pep tides in human autoimmunity. Based on these results and the observation by others that VB5.2 message with a CDR3 motif characteristic of BP reactive T cells occur led significantly more often in the brain of MS patients, a placebo controlled clinical trial has been initiated in a larger group of DR2, Dw2+ progressive MS patients using the VB5.2-39-59 peptide. Supported by NIH grants NS23444, NS23221, Dept. of Veterans Affairs, and XOMA Corp.

4
IN VITRO STUDIES OF OLIGODENTROCYTES DERIVED FROM ADULT HUMAN WHITE MATTER. NJ Scolding, J Sussman, *Das Compston, Cambridge, England*

In sclerosis, oligodendrocytes and the myelin sheaths they and maintain are selectively and often repeatedly damaged, ultimately in permanently demyelinated Recent findings indicate that the adult CNS does, however, an inherent capacity for repair, that oligodendrocyte precursor-like cells are abundant in acute lesions, and that the early stages of are initially apparent. Understanding the developmental biology of oligodendrocytes may not only yield helpful insights into the of repair in acutely demyelinated areas, but also suggest strategies by which remyelination might be promoted or indeed augmented by glial transplantation. Much information is already available concerning the developmental of rodent oligodendrocytes but differences rat and human cells are apparent. Recently, however techniques for culturing human glia have become available. We have studied cells derived from the white matter of adult patients (age 16-40) undergoing a variety of neurosurgical procedures for non-malignant conditions, mostly epilepsy. Oligodendrocytes are readily identifiable and can be in vitro; in addition, novel preliminary evidence has also emerged of the presence in low numbers (approximately 1% of oligodendroglial-lineage cells) of a precursor cell which appears to be the human counterpart of the well-characterised rat bipotential oligodendrocyte progenitor.

5
CONTINUOUS IMMUNOSUPPRESSION IN MULTIPLE SCLEROSIS (MS). OJ Kolar, MR Farlow, PH Rice *Indianapolis, USA*

In 178 definite MS patients who failed to stabilise their objective neurological symptoms following oral and/or eve. treatment with steroids CIT was initiated. Prednisone (7.5 mg - 15 mg per day) and Azathioprine (50-200 mg per day) was replaced by Prednisone and Cyclophosphamide (50 mg on alternating days- 150 mg per day) in MS patients with progressive neurological symptomatology following at least four month treatment with Prednisone and Azathioprine. In 57 MS patients from this series CIT was applied longer than 3 years (media 66 months). The patients were periodically neurologically examined in 1- 4 month intervals. Periodic examination of their phenotypic immunologic profile in peripheral blood was helpful in adjusting the daily dose of immunosuppressive medication. In 27 (47.3%) from the 57 MS patients no persistent worsening in their neurological symptomatology was established. In 17 of them (29.8%) with the median . duration of CIT presently lasting 76 months the neurological symptomatology improved (from 3.8 ±1.7 KEDSS to 3.2 ±1.4 points). In these patients the average age at the onset of CIT was lower (median –34 years) as compared to the remaining MS patients in this series (median –41 years; p – 0.0046).

6
INCREASED PRODUCTION OF LYMPHOTOXIN AND TNFα BY ANTIGEN-SPECIFIC T-CELL LINES FROM HLA-DR2-POSITIVE INDIVIDUALS: IMPLICATIONS FORMULTIPLE SCLEROSIS. F Zipp, F Weber, S Sotgiu, E Holler, EH Weiss, H Wekerle, R Hohlfeld. *Munich, Germany.*

Multiple sclerosis (MS) is associated with HLA-DR2 in North American and North European populations. It is not known whether HLA-DR2 has a direct or indirect effect. We tested the hypothesis that HLA-DR2 is associated with increased production of tumour necrosis factor (TNF)β (lymphotoxin) and TNFα. These cytokines have been implicated in the immunopathogenesis of MS. Furthermore, the TNFα/β genes are polymorphic and located in the HLA region. We established a panel of CD4+ T cell lines from HLA-DR2-positive and DR2-negative normal individuals

and MS patients. The T cell lines were stimulated with relevant antigen and irradiated autologous peripheral blood cells. The supernatants were assayed by ELISA for TNFα/β, and interferon (IFN). The T cell lines from HLA-DR2-positive donors produced significantly more TNFα/β than the T cell lines from HLA-DR2-negative individuals. In contrast, T cells from HLA-DR2-positive and negative donors produced similar amounts of IFN. Cytokine production was not related to antigen specificity or HLA restriction of the T cells. There was no obvious association between TNFα/β production and HLA -associated cytokine alleles. The results indicate that the association of MS with HLA-DR2 may be related to the level of TNFα/β production rather than to gene polymorphisms of TNFα/β.

7
MITOCHONDRIAL DNA ANALYSIS IN MULTIPLE SCLEROSIS. R Chalmers, N Robertson, DAS Compston, AE Harding, *Cambridge & London. UK.*

Two observations favour the hypothesis that mitochondrial genes may play a role in genetic susceptibility to multiple sclerosis (MS). Females with MS are more likely to have affected children than males, and mitochondrial DNA (mtDNA) is maternally transmitted. A high proportion of women with Leber's hereditary optic neuropathy (LHON) and the pathogenic mtDNA mutation at 11778 bp develop a neurological illness indistinguishable from MS. There is evidence that mitochondrial genes play a part in the immune response in rodents, in the form of a mtDNA-encoded, maternally transmitted, murine histocompatibility antigen (maternally transmitted factor: MTF). Variation at amino acid residue 6 in NADH dehydrogenase subunit 1 determines MTF antigenicity. This residue is in a conserved chain of 23 hydrophobic amino acids followed by three charged residues. We have sequenced the corresponding region of mtDNA (~150 bp) in: 20 patients from 7 families showing maternal transmission of MS; 29 patients with affected sibs; 51 index cases from a twin study of MS; 10 patients with MS/LHON; and 31 controls. The human sequence equivalent to the critical murine MTF sequence was remarkably conserved; base substitutions were identified in only one control subject and two MS patients, resulting in three different conservative amino acid changes. These data suggest that polymorphism of the MTA region is not important in MS susceptibility.

Oral Session 6 - Multiple Sclerosis (2)

1
T-LYMPHOCYTES PREFERENTIALLY EXPRESS A NEW γ-INTERFERON-ACTIVATED CA2+ INFLUX DURING CLINICALLY ACTIVE MULTIPLE SCLEROSIS. G Martino, E Clementi, E Brambilla, L Moiola, V Martinelli, B Colombo, A Poggi, M Rovaris, G Comi, LME Grimaldi, *Milan, Italy*

In multiple sclerosis (MS), activated T-lymphocytes are considered essential in mediating the inflammatory processes leading to demyelination. They operate through a network of cytokines among which g-interferon (γ-IFN) plays a key role. Intracellular Ca2+ ([Ca2+]) level varies during lymphocyte activity and therefore can be considered as a cell response marker. For this reason, we studied the [Ca2+] modifications in response to γ -IFN in lymphocytes from 57 steroid-free MS patients and 40 controls. Unexpectedly, we found that γ-IFN activated a hitherto undescribed Ca2+ influx functionally coupled to the γ-IFN receptor. This influx was detectable in T-lymphocytes (mainly CD4+) from 8 of 12 relapsing-remitting MS patients when analysed within the first week after the onset of a new clinical exacerbation. When serially evaluated, the influx faded progressively after the first week and completely disappeared after 6 to 8 weeks. The influx was also found in 14 of 33 patients with stable MS but in only 3 of 25 pathological control patients and in none of the 15 healthy subjects studied. Lymphocytes bearing the γ-IFN activated Ca2+ influx showed intense proliferative responses when stimulated with submitogenic doses of PHA (1 ug/ml) added with γ-IFN (5 U/ml); this response was usually absent in the g -IFN-dependent Ca2+ influx-negative lymphocytes. Our results document the appearance of a γ-IFN-activated Ca2+ influx which seems to regulate the proliferation of antigen stimulated lymphocytes in MS. This finding suggests that at least part of γ-IFN contribution to the pathogenesis of MS is exerted through a Ca2+-dependent regulation of T-lymphocyte activity.

2
MULTIPLE SCLEROSIS IN THE PYRENEES-ATLANTIQUES: PREVALENCE AND ASSOCIATION WITH GENETIC MARKERS ON CHROMOSOME 6. M.P. Roth, P. Descoins, S. Ballivet, J.B. Ruidavets, E. Waubant, L. Nogueira, A. Cambon-Thomsen, M. Clanet- *Toulouse, France*

A population-based case-control study was conducted in the French "departement des Pyrenees-Atlantiques" between 1988 and 1990. The goal was: i) to determine the prevalence of multiple sclerosis (MS) in this region; ii) to evaluate genetic risk factors for the disease. On prevalence day (January 1st, 1988), 217 individuals living in the Pyrenees-Atlantiques (572,073 inhabitants) were found to suffer from MS, giving a prevalence of 37.9 per 100,000 population. The patients were classified according to the criteria of Poser, and 198 had definite or probable MS. Clinical profiles of these patients were similar in most respects to those commonly observed in the MS population (17% had chronic progressive MS, 83% had initially remitting-relapsing MS). Mean age at onset was 31.6 yr. Nine precent had a family history of MS. Molecular HLA typing was performed for alleles at DRB1, DQA1, DQB1 and DPB1 loci. Patients and controls were also characterized for a NcoI and three micro satellites in the region of the TNF genes. The HLA haplotype DRB1*1501-DQA1*0102-DQB1*0602 was three times more frequent in the disease group, but there was no association of any of the TNF polymorphisms with MS, independent of that already described for the HLA class II region. This, with the lack of association of DP alleles with MS, effectively marks the boundaries of the MS associated haplotype.

3
INHIBITION OF T LYMPHOCYTE MIGRATION THROUGH SUBENDOTHELIAL BASEMENT MEMBRANE BY INHIBITING TWO COLLAGENASES SECRETED BY THESE LYMPHOCYTES. E Waubant, D Leppert, S Hauser, *Toulouse, France; Basel, Switzerland; San Francisco, CA, USA*

In CNS inflammation, T lymphocytes infiltrate brain parenchyma. Concerning therapies interfering with T-cell migration into CNS, much attention has focused on the interaction of T- cells to endothelium mediated by different families of adhesion molecules (selections, integrins). By contrast, little is known of the mechanism by which T-cells penetrate the subendothelial basement membrane (BM) to enter the CNS. Here we show that: 1) T-cells produce mRNA and protein for 72kD and 92kD collagenases. These enzymes selectively degrade type IV collagen, a major component of the extracellular matrix of BM. In the CNS, this collagen is present only in , the subendothelial BM; 2) T-cell expression of the two collagenase genes are differentially regulated. The 92kD isoform is constitutively present, whereas cytokines trigger the 72kD isoform; 3) The 92kD collagenase product is specifically down regulated by beta interferon; 4) T-cell migration across an extracellular matrix in vitro is specifically inhibited by; 1 oligopeptide inhibitors of collagenase, indicating a key role for these enzymes in T-cell penetration across BM. These data suggest that specific inhibition of these T-cell proteases may reduce T-cell homing to the CNS. Down regulation of T-cell collagenase expression by beta interferon may contribute to the clinical benefit observed in MS.

4
OPTIC NEURITIS: CORRELATION OF VEP, PERIMETRY AND MRI FINDING. A Lugaresi, A Tartaro, P D'aurelio, L LO Befalo, A Thomas, G Malatesta, D Gambi - *Chieti, Italy.*

Aim of the study was to compare the sensitivity of MRI, pattern reversal VEP and computerised perimetry (CP) in diagnosis and follow-up of ON. We studied 28 patients, 14 within 1 month from onset of ON, bilateral in 4, and 14 3 mo.s to 10 yrs after ON, bilateral in 5. MRI was performed using the double-echo short tau inversion recovery technique (DESTIR; ET= 20, 80 ms, RT= 2500 ms, IT= 150 ms) before and after gadolinium-DTPA administration. All patients with acute ON had positive CP and VEP on the affected side. Lesions of the symptomatic nerve were shown by the short echo sequence in 12/18 and by the long echo sequence in 16/18 nerves; in acute cases lesions were also present in 1/10 and 3/10 asymptomatic nerves by short and long echo sequences respectively. Perimetry was normal in 3/14 cases with history of ON; VEP and MRI were positive in 2 and negative in 1 case. In particular 11/19 and 14/19 affected nerves had lesions by short and long echo sequences respectively. No additional lesions were shown after gadolinium-DTPA administration. In conclusion

perimetry and VEP show a very high sensitivity in demonstrating acute ON. VEP can show abnormalities in a few cases of past involvement of the optic nerve without residual visual field defects. The DESTIR technique increases significantly the sensitivity of MRI in identifying the lesional site in ON.

5
THE 1939-1945 POST WAR MULTIPLE SCLEROSIS EPIDEMIC IN ICELAND; A REQUIEM. JEG Benedikz, H Magnusson, CM Poser, G Guomundsson. *Reykjavik, Iceland & Boston, USA.*

Many clusters suggesting epidemics of MS have been reported but non have withstood closer analysis unscathed. One such has been ascribed to Iceland but despite frequent rebuttals is still quoted. The data is from a total population survey of MS in Iceland 1 Jan. 1900 to 31. Dec. 1989, pre 1958 retrospective, since then prospective. The putative aetiological agent, about 50.000 allied troops, were stationed in Iceland 1940- 1945, the vast majority in three well defined areas. The total population at this time was 126.000. All patients have been examined by one or more neurologists. The diagnostic criteria of Poser et.al. have been applied in all instances. For disability we have used Kurtzke's revised scale. Total number of patients: 323, women 205, men 118. Alive 31. Dec. 1989: Total 252, women 163, men 89. Results and Conclusions: 1) The average annual incidence is between 2.5 - 4.5 per 100.000 from 1930. There are three apparent peaks which are clearly the result of improved case detection due to an influx of resident neurologists and to the first MS survey in Iceland. 2) The increase of MS patients in Iceland was well under way before the arrival of allied troops. 3) There was a consistent and significant excess of MS patients in non-occupied areas at all times, whether calculated according to domicile at onset or at the age of acquisition (14 years as proposed by Dean and Kurtzke).

6
ABNORMAL NEURONAL MITOCHONDRIA: A CAUSE OF REDUCTION IN N-ACETYL CONTAINING COMPOUNDS (NA) IN DEMYELINATING DISEASE. RE Brenner, TE Bates, SEC Davies, PMG Munro, SCR Williams, JB Clark, DN Landon, WI McDonald, *London, UK*

A frequent finding in proton magnetic resonance spectroscopy (MRS) in neurological disease is a reduction in the peak assigned to N-acetyl containing compounds (NA). The fact that neuronal loss is a frequent pathological accompaniment, has led to the suggestion that this is the cause of reduction in signal intensity. N-acetylaspartate (NAA) is a major constituent of the NA peak. It is synthesised within mitochondria and has been shown to be localised to neurons. We have found evidence of structural mitochondrial abnormalities in the cerebral neurones of 6 guinea pigs with chronic EAE, which at MRS, we observed a reduction in NA. Mitochondria were then isolated from 5 guinea pigs with acute EAE. a model characterised by inflammation without neuronal loss or demyelination, and the NAA synthesis rate determined biochemically. It was found to be significantly lower (37.36 ± 8.79) nmo/min/mg protein) than values obtained from 10 control animals (63.49 ± 23.63 nmo/min/mg protein, p<0 05). These findings suggest that aside from neuronal loss, a disturbance of mitochondrial function may also cause a reduction in NA. A similar mechanism may contribute to the reduction in NA reported active MS plaques particularly when it is reversible.

Oral Session 7 - Cerebrovascular Disorders (1)

1
MAGNETIC RESONANCE ANGIOGRAPHY OF SPONTANEOUS VERTEBRAL ARTERY DISSECTION. J RÜther, A Schwartz, W Rautenberg, M Hennerici. *Heidelberg, Germany*

Spontaneous vertebral artery dissections are rare causes of cerebrovascular disease which are often difficult to diagnose even by conventional arteriography. While Doppler ultrasound and magnetic resonance imaging (MRI) failed to deliver reliable criteria for vertebral artery dissection, the diagnostic value of magnetic resonance angiography (MRA) is undetermined. In order to establish the reliability of a combined non-invasive approach, 11 patients were prospectively examined for vertebral artery dissections by means of colour-coded duplex studies, MRI and 3-D time-of-flight MRA prior to conventional angiography. From 11 patients with suspected vertebral artery dissections on Doppler examination, angiography confirmed the diagnosis in 7 patients, but found a vertebral artery occlusion in 3 patients and a vertebral artery stenosis in one patient. The combination of MRI and MRA findings correctly established the diagnosis of dissection in 3 patients, of vertebral artery occlusion in 3 patients, and of vertebral artery stenosis in one case. Vertebral artery dissections was misinterpreted as vertebral artery occlusion in 4 patients. Conclusions: The non-invasive diagnosis of vertebral artery dissections cannot reliably be made by MRI, MRA, and Doppler ultrasound. Although Doppler ultrasound serves as a valuable screening method, the diagnosis of vertebral artery dissections can only be established in the presence of a typical intramural vessel wall hematoma in T1-weighted MRI combined with MRA findings of irregular artery stenosis or occlusion.

2
NEUROPROTECTION WITH NBQX AND THROMBOLYSIS WITH RT-PA IN RAT EMBOLIC STROKE. K Overgaard, T Sereghy, H Pedersen, G Boysen. *Copenhagen Denmark*

The effects of delayed thrombolysis with alteplase and neuroprotection with an excitatory amino acid receptor antagonist and their combination were tested in an embolic stroke model. In 61 rats the carotid artery territory was embolized with arterial-like fibrin-rich clots. Hemispheric cerebral blood flow before and after embolization was measured by intraarterial 133Xenon injection method. The animals were assigned to one of the following treatments; 1) vehicle treated controls (n = 15), 2) Dizocilpine 1 mg/kg i.v. 5 minutes after embolization (n = 16), 3) Alteplase 2O mg/kg as i.v. continuous infusion starting 2 hours after embolization (n = 16), and 4) both agents (n = 14). Carotid angiography displayed the rate of occlusion of the cerebral arterial tree immediately after and 3 hours after embolization, and clinical neurological score was assessed after the rats recovered from anesthesia and before the rats were killed. Brains were fixed after two days. Both alteplase and dizocilpine reduced the total infarct volume. Dizocilpine reduced the incidence of cortical infarctions by 48 %. Only the combined treatment reduced significantly deep brain infarctions. The combined treatment also improved the clinical score by 83 % compared with controls, by 75 % compared with the group treated by dizocilpine alone and by 50 % compared with the group treated by alteplase alone. Sixty seven percent of thrombolyzed animals recanalized completely compared to 39% of those given no thrombolytics. The clinical outcome correlated with infarct size. Conclusions: 1) We found comparable efficacy of delayed thrombolysis and excitatory amino acid receptor antagonism in this model, and 2) suggest that combination of these two therapeutic approaches may yield additional benefit in treatment of thromboembolic stroke.

3
PREVENTION OF REPERFUSION INJURY AFTER GLOBAL CEREBRAL ISCHEMIA BY A CALCIUM BLOCKER. E Diez-Tejedor, F Carceller, M Gutierrez, R Lopez-Pajares, JM Roda. *Madrid, Spain.*

Reperfusion injury is a pathophysiolological entity distinct from the primary ischemic damage. This study aims to analyse whether calcium blockers reduce cerebral damage after transient global cerebral ischemia, using our previously described experimental model. Animals in Group (n=13) served as normal controls. Rats in Groups 2 (n=7) and 3 (n=7) were subjected to global cerebral ischemia and either isotonic saline (Group 2) or nimodipine solution (Group 3; 40 μg/kg) was intraarterially injected through the external carotid artery during ischemia and reperfusion and distributed to the circle of Willis. Somatosensory evoked potentials were evaluated and the peak onset of P1 wave was 8.13 ± 1.5 msec, 18.63 ± 3.1 msec and 13.17 ± 2 msec for Groups 1, 2 and 3 respectively. P1 latency was significantly higher in Group 2 than in Groups 1 and 3 (p<0.01). Histopathological findings showed that the volume of injury in the hippocampus and striatum in Group 3 was more limited than in Group 2. It is concluded that the intraarterial injection of nimodipine lessens brain damage caused by transient global cerebral ischemia in rats.

4
NIMODIPINE IN THE MANAGEMENT OF STROKE. B Chandra. *Surubaya, Indonesia.*

The effects of nimodipine administration intravenously and orally were compared of a double blind study, in 143 patients with stroke, who were admitted to the hospital within 6 hours after the onset of symptoms. In both the infarct group and the hemorrhagic stroke group, there was a significant improvement as evaluated by the Mathew scale and Barthel index, especially in the nimodipine infusion group. For the nimodipine oral group, the results were less evident. The data suggest that nimodipine should be given as an infusion a early after stroke as possible.

5
NUTRITIONAL STATUS AND CLINICAL OUTCOME IN ACUTE CEREBRAL INFARCTION. A Davalos, W Ricart, F Gonzalez-Huix, A Molina, D Genis. *Girona, Spain*

Malnutrition has received little attention in acute stroke although represents a risk for decreased immunity and nosocomial infections. To determine the relationship between nutritional status, stress response and neurologic outcome in acute stroke, nutritional (triceps skin fold, mid-arm muscle circumference (MAMC) and serum albumin) and immunological parameters (skin delayed reaction and lymphocytes) were measured on admission and weekly during hospitalisation in 83 patients with cerebral infarction of less than 24 hours. Stress response (serum and free urinary cortisol) was evaluated on days 1, 2, 4 and 7. Protein-energy malnutrition was observed in 12% of patients at inclusion and in 21% after the first week, with a significant decrease in fat and visceral protein compartments (P<0.05). Malnourished patients showed impairment of cellular immunity (1402+498 vs 2048 ± 577 lymphocytes, P<0,001), increased stress reaction (serum cortisol 30.8 ± 13.9 vs 20.2 ± 7.9 ug/dl, p=0.021) and higher frequency of infections and bedsores (64% vs 20%; P=0.004) in comparison with the non malnourished group. MAMC (Odds ratio(OR)=3.15, 95% confidence interval(CI)=1.012.1) and serum albumin (OR=7.1, 95% CI=1.8-28.3) had predictive value of poor outcome (death or Canadian scale score 5 on the 30th day of follow-up) independently of the stress response and immunological parameters. Our findings demonstrate that protein-energy malnutrition is a risk factor of poor outcome in acute ischemic stroke.

6
ULTRASOUND EMBOLI DETECTION IN PATIENTS WITH CAROTID AND CARDIAC DISEASE. T Rundek, V Demarin. *Zagreb Croatia*

Carotid and cardiac disease are frequently source of cerebral emboli that cause ischemic stroke. Transcranial Doppler (TCD) has been recently used for detection of emboli showing transient and randomly occurred spectral signatures of air or particulate emboli with amplitude>l0 dB above the background Doppler signal. In order to count cerebral emboli, 15 patients with previous stroke were analyzed. Simultaneous TCD monitoring of the MCA during 30 minutes was performed by Multi-Dop X (DWL). Eight patients had carotid artery disease (4 stenosis<50%, 3 stenosis 50-75%, and 1 occlusion), and 7 patients had cardiac disease (3 atrial fibrillation, 1 mitral and 1 aortal stenosis, and 1 with prosthetic valve). In patient with prosthetic heart valve the number of embolus signals were 11.25 signals/min. In patients with aortal and mitral stenosis there were 9.25 ± 3signals/min, and with atrial fibrillation 7.35 ± 2 signals/min. In patients with carotid stenosis<50% there were 0.75 ± 0.08 signals/min, in patients with stenosis of 50-75% 3.15 ± 0.55/min, and with occlusion 6.75/min (p<0.01). Emboli signals were frequent in patients with cardiac disease, especially with prosthetic heart valve (p<0.0001). Recording of cerebral emboli is a new method for detection of subclinical embolisation with potential value for stroke prediction, prognosis and prevention.

7
A POSITRON EMISSION TOMOGRAPHY STUDY OF CAVERNOUS ANGIOMAS AND ARTERIOVENOUS MALFORMATIONS OF THE BRAIN. J De Reuck, G De la Meilleure, P Boon, D Decoq, K Strijckmans, P Goethals, I Lemahieu. *Ghent, Belgium.*

The cerebral haemodynamic and metabolic changes due to cavernous angiomas in 3 patients and to arteriovenous malformations in 4 patients were compared by positron emission tomography, using the steady state technique with ^{15}O. In the brains with a cavernous angioma no important changes in blood flow were observed. Only a decreased oxygen consumption was present in the cortex supplied by the arterial branches of the angioma, most probably related to neuronal deafferentation. In the 4 cases of arteriovenous malformation cerebral blood flow was significantly increased in the territory of the feeding vessels of the angioma. In 2 huge ones the oxygen extraction rate was increased in vascular areas remote from the supply territory of the angioma and in the contralateral hemisphere, indicating chronic ischaemia. The present study confirms that chronic vascular steal phenomena can occur in large arteriovenous malformations, while cavernous angiomas do not induce important haemodynamic changes.

Oral Session 8 - Cerebrovascular Disorders (2)

1
CADASIL: CLINICAL AND GENETIC ANALYSIS OF 6 UNRELATED FRENCH FAMILIES, ESTABLISHING DIAGNOSTIC CRITERIA FOR THIS AUTOSOMAL DOMINANT CEREBRAL ARTERIOPATHY. E.Tournier-Lasserve, A Nibbio, H Chabriat, K Vahedi, A Joutel; T Nagy, M Verin, JL Mas, J Julien, X Ducrocq, M Baudrimont, MT Iba-Zizen, EA.Cabanis and MG Bousser. *Lyon, Caen, Paris, Rennes, Bordeaux & Nancy; France.*

Since 1977, we and others have reported several families affected with a new mendelian syndrome causing stroke, and designated under various names including "hereditary multi-infarct dementia". We recently described a large pedigree which allowed the precise definition of the clinical, neuro-imaging, pathological and genetic characteristics of this condition. The genetic linkage analysis assigned the disease locus to chromosome 19. The acronym CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) was suggested to name is condition. Six additional unrelated French families including 143 members have been collected. Affected members presented one or several of the following symptoms and signs: 1) ischemic sensory and/or motor deficits and dysarthria; 2) attacks mimicking migraine with aura; 3) mood and behaviour disturbances; 4) progressive subcortical dementia. Magnetic resonance imaging of the brain showed small deep infarcts on T1W1 and extensive areas of increased signal in the hemispheric white matter on T2W1. No or few vascular risk factors were observed and the pattern of transmission was autosomal dominant. Linkage analysis with chromosome 19 markers demonstrated genetic homogeneity between all these families. These data establish the value of the combined clinical and MRI criteria used to diagnose families affected by this recently identified disorder, which prevalence is most likely underestimated. Gene identification is ongoing.

2
NEW PHENOTYPE OF CADASIL WITH MIGRAINE AS PROMINENT CLINICAL FEATURES. M Verin, Y Rolland, F Landgraf, B Bompais. H Chabriat, E Tournier-Lasserve, MH Lemaitre, G Edan. *Rennes, Paris, France*

We conducted a retrospective and prospective survey of a large family presenting the symptoms of the familial arteriopathy /CADASIL/ recently described and mapped to chromosome 19ql2. Forty three members aged above 20 years over 4 generations were studied clinically (31 living and 12 deceased), genetically and radiologically with MRI (n = 26). We found 20 (over 43) clinically and 12 (over 26) radiologically symptomatic members, only one of whom was asymptomatic. Genetic studies mapped this condition to the locus of CADASIL (lod score > 3). The typical clinical and radiological history followed 3 successive stages: I) between 20 and 35 years with frequent migraine-like episodes and well-delineated lesions of the white matter; II) between 35 and 50 years with stroke-like episodes, bipolar-like psychotic disorders, multiple well-delineated lesions of the basal ganglia and coalescent lesions of the white matter; and III) after 50 years with subcortical dementia, pseudobulbar palsy and diffuse leukoencephalopathy. The relation between this condition and familial hemiplegic migraine, recently mapped in the same locus of the chromosome 19, is confirmed.

3
TOMOGRAPHIC CEREBRAL BLOOD FLOW DURING CAROTID SURGERY. S Vorstrup, L Knudsen, K Skovgaard Olsen, C Videbaek, T Schroeder. *Copenhagen, Denmark.*

We attempted to depict changes in regional cerebral blood flow (CBF) during carotid cross clamping using ^{99m}Tc-hexamethylpropylene amine oxine (HMPAO) and to evaluate if preoperative CBF studies and transcranial doppler (TCD) measurement including a potent vasodilatory stress-test (acetazolamide, Diamox^{R}) could predict these changes. Fifteen symptomatic patients with 50-95% stenosis of the internal carotid artery were included. During carotid endarterectomy HMPAO was injected intravenously 5 minutes after carotid cross clamping. Tomographic recording of CBF was done a few hours later. A marked CBF decrease in ipsilateral middle cerebral artery (MCA) territory was induced by carotid cross clamping, correlating significantly with the stump pressure (r=n.78; p=0.00003). Peroperatively, 9 patients showed 5 different flow patterns with a pronounced flow reduction in the territories supplied by: 1) ipsilateral MCA, 2) ipsilateral anterior cerebral artery (ACA) and MCA, 3) ipsilateral ACA, MCA, and posterior cerebral artery, 4) both ACA and ipsilateral MCA, 5) ACA and MCA bilaterally. No neurologic complications were seen. The preoperative CBF and TCD studies did not predict the peroperative CBF findings. Conclusion: The marked effect of carotid cross clamping upon regional flow distribution in 9 of the 15 patients was interpreted to reflect the limited flow capacity of the constituents of the circle of Willis, thus depicting the anomalous segments of the circle. Our results question the predictive significance of the preoperative CBF and TCD studies.

4
HERNIATION AFTER ISCHAEMIC STROKE - A RETROSPECTIVE STUDY. HB van der Worp, LJ Kappelle, J van Gijn, *Utrecht, The Netherlands*

Tentorial herniation caused by unilateral swelling of the brain is an important cause of death in the first week after ischaemic stroke. The factors leading to massive swelling and herniation are incompletely known. The size of the infarct, absence of cerebral atrophy and early reperfusion are considered to play a role. To find predictors of herniation we retrospectively studied the records and CT scans of 18 women and 14 men, aged 23 to 92 years (mean 65 years, SD 18) who died of herniation after a brain infarct between 1984 and 1993. The interval between infarction and death was 1 to 8 days (mean 4 days, SD 2). All patients had a large cortical MCA territory infarct. Nine patients were fully alert or probably alert (patients with dysphasia) on admission (day 0 or 1), 23 had decreased level of consciousness. Blood pressure, body temperature and biochemical and haematological indices on days 0 - 3 did not predict herniation. Ac least 10 patients had atrial fibrillation. We conclude that patients from all age groups with large infarcts in the MCA territory are at risk of death from herniation, notwithstanding a normal level of consciousness in the acute stage. In this retrospective study no other predictive factors were detected.

5
VISUALIZATION OF DAMAGED BRAIN TISSUE AFTER ISCHEMIC STROKE WITH ^{55}Co POSITRON EMISSION TOMOGRAPHY. HML Jansen, J Pruim, AMJ Paans, ATM Willemsen, JM Hew, AM. vd Vliet, R Haaxma, W Vaalburg, JM Minderhoud J Korf, *Groningen, the Netherlands*

In animal experiments the radionuclide 55-cobalt (Co) has been shown to accumulate in degenerating cerebral tissue in a similar way as does calcium (Ca). Elevation of intracellular Ca is linked with the process of neuronal cell decay. Co-uptake is correlated with Ca-accumulation through divalent cation-permeable kainate-activated receptor-operated channels in the neuronal membrane. Since there is no Ca-isotope with suitable radiation characteristics for PET, we suggest Co as a neuronal Ca-marker to visualise endangered brain tissue with PET. We included 10 patients with an ischemic cerebrovascular accident (CVA) in our Co-PET study, performed 20h-25h after iv-administration of 1-2 mCi Co. All patients underwent CT and/or MRI both with and without contrast-enhancement. Patients had to present all of the following features: being over 50 years of age, neurologic symptomatology in agreement with an acute cortical ischemic stroke, clear consciousness and admission between 24h-72h after onset of the accident. Regional specific Co-accumulation irrespective of blood brain barrier integrity (as affirmed by CT or MRI) could be demonstrated in the (clinically appropiate) affected cerebral region, thus suggesting neuronal decay in the early phase of infarction. In conclusion we think Co-PET may become a tool in estimating brain pathology quantitively not only in CVA,but also in other degenerative diseases.

6
NEUROPROTECTION BY EXCITATORY AMINO ACID ANTAGONIST AUGMENTS. THE BEFIT OF THROMBOLYSIS IN EMBOLIC STROKE IN RATS. K Overgaard, T Sereghy, G Boysen, *Copenhagen, Denmark.*

The efficacy of delayed thrombolysis with recombinant tissue plasminogen activator was tested in combination with the ischemic protecting drug NBQX in an embolic stroke model. In 113 rats the carotid territory was embolized with a fibrin-rich clot formed in polyethylene tube. Hemispheric cerebral blood flow (CBF) was measured by intraarterial ^{133}Xenon injection method before and after embolization. Two hours after embolization 67 animals were treated with tissue plasminogen activator 20 mg/kg, 46 control animals with saline. NBQX was given to 53 animals, of which 41 animals also received thrombolytic therapy and 12 were saline controls. Carotid angiography displayed the rate of occlusion of the cerebral arterial supply before and after treatment. Brains were fixed after two days, evaluated neuropathologically, and infarct volume was measured. Embolization caused a 60 - 78 % reduction of median CBF. The comparison of post-treatment angiography of thrombolytic treated animals to controls showed significant ($p < 0,01$) reperfusion in thrombolytic treated animals, while NBQX alone did not enhance reperfusion. Thrombolytic therapy significantly reduced the total infarct volume from 19.5 % to 4.5 % of embolized hemisphere volume ($p = 0.006$). NBQX alone reduced total infarct volume from 19.5% to 6.5% and cortical infarct volume from 7.9 % to 0.3 % ($p = 0.03$). In thrombolytic treated animals NBQX reduced total infarct volume from 4.5 % to 2.1 %. The more than 50% reduction of total infarction volume caused by NBQX was not statistically significant due to the variation of infarct size in this model. Small hemorrhagic lesions in infarcts were observed in thrombolytic treated animals. The clinical outcome correlated well with infarct volume. Delayed thrombolytic therapy induced recanalization and significantly reduced infarct volume after embolic stroke. The ischemic protecting drug NBQX significantly reduced cortical infarctions.

Oral Session 9 - Peripheral Neuropathy (1)

1
A PROSPECTIVE CASE CONTROL STUDY TO INVESTIGATE THE RELATIONSHIP BETWEEN CAMPYLOBACTER JEJUNI AND GUILLAIN-BARRÉ SYNDROME. JH Rees, SE Soudain, NA Gregson, RAC Hughes. *London, UK.*

Campylobacter jejuni (Cj) has been implicated as the most common pathogen associated with Guillain-Barre syndrome (GBS). Most previous series have been retrospective and have relied on serological methods to determine the incidence of previous Cj enteritis. We therefore looked prospectively at the frequency of Cj infection in a group of GBS patients and controls by analysing both stool and serum samples. We collected clinical and electrophysiological data and tested the patients' sera for the presence of ganglioside antibodies. To date we have found 67 GBS patients and 122 hospital and community controls. 6 patients and 1 asymptomatic control had Cj detected in their stools ($P<0.05$). One stool positive patient had no measurable antibody response. A further 21 patients and 14 controls (out of 54 tested) had serological evidence of recent Cj infection (NS). Positive antiganglioside antibodies were found in 5 out of 5 stool positive patients and 9 out of 17 seropositive patients tested. 3 of the 6 stool positive patients had severe disease with evidence of axonal degeneration (AD) and 2 had Miller Fisher syndrome (MFS). 6 of the 21 seropositive patients had AD and 1 had MFS. In comparison only 2 of the 40 Cj negative cases had AD and only 1 had MFS. Ganglioside GM1 and GQ1b antibodies were found in all those with AD and MFS respectively. These results suggest that Cj is a very common infection preceding GBS and that it is associated with rare variants of GBS, namely AD and MFS, in a significant proportion of patients.

2
THE ASSOCIATION OF CAMPYLOBACTER JEJUNI WITH DIFFERENT FORMS OF THE GUILLAIN-BARRE SYNDROME. TW Ho, B Mishu, CY Li, I Nachainkin, CY Gao, DR Cornblath; JW Griffin, AK Asbury, MJ Blaser, GM McKhann. *Baltimore; USA.*

Based on electrophysiology and pathological studies, GBS has become synonymous with Acute Inflammatory Demyelinating Polyneuropathy (AIDP). Summer epidemics of acute flaccid paralysis clinically similar to GBS have been occurring in Northern China. The electrophysiology and pathological studies showed that most of the patients had noninflammatory motor axonal degeneration. We have termed them Acute Motor Axonal Neuropathy (AMAN). Between 1991 and 1992, we prospectively characterised 129 patients by electrodiagnostic criteria. For the 38 patients presented in 1992, we included serologic assay for antibodies to C. jejuni and glycolipids. The AMAN form was present in 65% of patients and the AIDP for in 24%. Seventy six % of patients had serological evidence of recent C. jejuni infection as compared to 16% of Village controls (p=0.001). Eighty six % of AMAN patients and 58% of AIDP patients were seropositive. Antibodies to glycolipid showed significant raise in anti-GM1 IgG titer in the both AMAN and AIDP compared to village controls (42% vs. 6%, p<0.01). However, no statistically significant difference in the titer levels or presence of antibodies were found between the disease pattern or C. jejuni titer. Preliminary data with C. Jejuni cultures and typing will also be shown. Conclusion: C. jejuni may play an important role in clinically diagnosed GBS in Northern China, especially the AMAN form.

3
CLINICO-PATHOLOGICAL FEATURES OF GUILLAIN BARRE SYNDROME IN CHINA AND ELSEWHERE. AK Asbury *(Philadelphia, USA),* CY Li , T Ho, C Macko, P Xue, EM Stadlan *(Bethesda, USA),* M Ramos-Alvarez *(Mexico City, Mexico),* L Valenciano *(Madrid, Spain),* CY Gao, DR Cornblath, GM McKhann, JW Griffin *(Baltimore, USA; Shijiazhuang, PRC)*

Guillain-Barre Syndrome (GBS), as clinically recognised, is encountered throughout the year in northern China; however, a preponderance of cases occur as a summer epidemic, mainly in children and young adults. Eighty-six percent of epidemic cases have increased titers to Campylobacter jejuni versus 10-20% in controls. Most of the epidemic cases have only motor findings by clinical and electrophysiological criteria, and the pathological findings at autopsy in such cases are wallerian-like degeneration in ventral roots and nerves, variable in severity, but without inflammation and with striking chromatolysis of anterior horn cells. Similar pathological features are seen in fatal cases of acute flaccid paralysis meeting clinical criteria for GBS occurring in children in Mexico and South America and from an epidemic outbreak in Spain in 1966-67. We believe all of these cases represent the acute motor axonal subtype of GBS.

4
CLINICAL AND LABORATORY CHARACTERISTICS OF A SUBGROUP OF THE GUILLAIN-BARRÉ SYNDROME: THE PURE MOTOR TYPE. LH Visser, FGA van der Meché, PA van Dam, J Meulstee, PIM Schmitz, B Jacobs, PG Oomes, RP Kleyweg, and the Dutch Guillain-Barré study group, *Rotterdam, The Netherlands*

We analysed 26 patients out of a group of 147 patients with Guillain-BarrÈ syndrome (GBS), who presented at entry and during a follow-up period of 6 months with only motor symptoms (pure motor GBS) at clinical examination. Clinical and laboratory parameters of these 26 patients were compared with the other 121 Guillain-Barre patients. The pure motor patients had significantly more often: an antecedent episode of diarrhea (46% as compared with 13%, P < 0.001), a rapid onset of weakness (3,9 days versus 6,1 days, P = 0.007), an earlier reaching of the nadir (6,3 days versus 9,1 days, P< 0.001) and less often involvement of the cranial nerves (19% versus 58%, P < 0.001). Often serological evidence of a Campylobacter jejuni infection was found in the pure motor patients (46%, p=0.08) as well as the presence of anti GM1 antibodies (48%, p=0.06). The association of C. jejuni infection and anti-GM1 antibodies in this group is however weak. Electromyographic data at nadir showed little or no demyelination and in half of the patients abundant denervation. Furthermore in the pure motor group we found a predominant weakness of the distal muscles at onset of weakness (70%), little or no autonomic dysfunction and a much better response to immunoglobulins as compared with plasmaexchange.

5
ANTI-GO1b IgC ANTIBODIES CAN SPECIFICALLY BIND TO CAMPYLOBACTER JEJUNI STRAINS FROM MILLER FISHERS PATIENTS BC Jacobs, HP Endtz, PA van Doorn, FGA van der Mech., *Rotterdam, The Netherlands*

C. jejuni strains were isolated from the stools of three patients with the Miller Fisher syndrome (MFS) and serotyped as PEN 23, PEN 4,50 and PEN "nontypable". IgG antibodies (Abs) against the ganglioside GQ1b could be demonstrated in the serum of all three patients using an ELISA. Abs against GM1, GM3, GD1a, GD1b, GT1b, LM1, AGM1 and globoside were not found. The anti-GQ1b IgG Ab titers were significantly reduced after preincubation of the serum samples of the MFS patients with the *C.jejuni* PEN 23 and PEN "nontypable". The Ab titer was not influenced by preincubation with the third MFS *C.jejuni* strain PEN 4,50 or by non-MFS related control *C.jejuni* strains PEN 22, PEN 23 and PEN 41. Furthermore, the two anti-GQ1b IgG binding *C.jejuni* strains did not bind anti-GM1 IgG Abs from the serum of a Guillain-Barre patient. These results indicate that anti-GQ1b Abs can specifically bind to an epitope on the surface of some *C.jejuni* strains isolated from MFS patients. It is therefore possible that Abs primarily formed against MFS associated *C.jejuni* strains may, trough cross-reaction with GQ1b in cranial nerves, contribute to the pathogenesis of MFS.

6
THE FREQUENCY OF MUTANT T-CELLS IN PATIENTS WITH INFLAMMATORY NEUROPATHY. LH Van den Berg, JHJ Wokke, I Mollee, T Logtenberg, *Utrecht, The Netherlands*

As elevated serum Interleukin-2 concentrations and T-cell infiltrates have been found in patients with inflammatory neuropathies, T-cells may be involved in the pathogenesis. It is possible to measure frequencies of activated, mutant, T-cells (FMC) in vivo by comparing the growth of T-cells in the presence and in the absence of the purine analogue 6-thioguanine. FMC were measured in 17 patients with the Guillain-Barre Syndrome (GBS), 8 patients with chronic inflammatory demyelinating polyneuropathy (CIDP) and in 12 normal controls. Mean FMC in GBS was 19.1×10^{-6} (SD 9.1), in CIDP 15.1×10^{-6} (SD 9.1) and in controls 6.8×10^{-6} (SD 4.7). In both disease groups FMC were significantly higher (Mann-Whitney U test: in GBS $p < 0.001$ and in CIDP $p<0.05$). No correlation was found between the severity of the neuropathy and degree of FMC. In 6 patients FMC were also measured during recovery. FMC had returned to normal values. These results suggest that T-cells are activated in inflammatory neuropathies.

7
EPIDEMIC NEUROPATHY IN CUBA. PK Thomas, G Plant, PJ Baxter, R Santiago Luis. *London & Cambridge, UK; Havana, Cuba*

Cases of subacute bilateral optic neuropathy on a background of weight loss began to appear in Western Cuba in 1991. Examination showed symmetric central or caecocentral scotomata, optic disc pallor and loss of fibres in the maculopapillary bundle. Such cases then came to be associated with painful burning and tingling paraesthesiae in the feet, mild leg weakness and occasionally urinary precipitancy and deafness. Examination revealed, in addition to bilateral optic neuropathy, distal sensory loss in the limbs, brisk knee jerks, absent ankle jerks and flexor plantar responses. Angular stomatitis was occasionally present. A predominantly sensory axonopathy was demonstrated by nerve conduction studies and confirmed by sural nerve biopsy. The disorder extended to other areas of Cuba and by mid-1993 over 50.000 cases had been notified. In the later cases in the epidemic, sensory symptoms predominated. After B vitamins had been administered to the whole population of the island, the epidemic subsided. The features of this epidemic suggest that it has affinities to Strachan's syndrome, originally described in Jamaica in the last century and on various occasions since and assumed to be on the basis of a nutritional deficiency.

Oral Session 10 - Peripheral Neuropathy (2)

1
ASSESSMENT OF DELAYED POTENTIALS OF LARGE MYELINATED FIBERS WITH INTRANEURAL NEUROGRAPHY IN HUMAN PERIPHERAL NERVES. O Hasegawa, A Komiyama, R Kurita, M Matsumoto. *Yokohama, Japan.*

We applied the intraneural neurographic technique to examine the 'positive' abnormal signal conductions ('jumping' phenomenon and cross-talk) in demyelinated nerves, focusing on delayed action potentials of large myelinated fibres. This study included 45 patients with polyneuropathy and 28 controls. A tungsten microelectrode was inserted into the median nerve at the elbow. With a stimulus delivered at the wrist, compound nerve action potentials were recorded. These potentials were made up mainly of large triphasic waves followed by some small delayed potentials. Irrespective of the presence or absence of overt neuropathy, delayed potentials in 55 of 73 subjects disappeared as the electrical stimulus was increased. In 13 subjects, however, potentials of the same configuration appeared with a shorter latency, suggesting the 'jumping' phenomenon. Using 8 potentials in 7 subjects, the effect of moving the stimulation site on the latency of the delayed potentials was determined. Paradoxically the latency of delayed potentials in 2 subjects were increased as the stimulation site was brought closer to the recording microelectrode. These potentials were considered to transmit distally and spread by cross-talk. No persistent complications were encountered in any subjects. Our study constitutes the first and direct visualisation of 'positive' abnormal signal transduction of a single unit potential in human injured nerves by means of sensitive intraneural neurography.

2
POLYNEUROPATHY ASSOCIATED WITH MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS). A PROSPECTIVE STUDY OF THE PROGNOSTIC VALUE OF CLINICAL AND LABORATORY ABNORMALITIES. N-C- Notermans MD, J-H-J- Wokke MD, H-M- Lokhorst MD, H. Franssen MD, Y. van der Graaf MD, F.G.I. Jennekens MD, *Utrecht, The Netherlands*

The natural course of polyneuropathy associated with monoclonal gammopathy of undetermined significance (MGUS) is not well known. Therefore we prospectively studied 32 untreated patients for a period of 5 years. Fifteen patients had an IgM M-protein, 15 an IgG and two an IgA. There was a male predominance, the mean age at onset was at the end of the 6th decade, and sensory signs were more pronounced than motor deficits. By quantifying the neuropathy (motor and sensory sum scores, vibration threshold perception, tapping tests, quantified Romberg test, electrophysiological measures) we found a significant difference between the natural histories of polyneuropathy associated with IgM-MGUS and IgA/IgA-MGUS. The polyneuropathy in IgM-MGUS is more progressive, with significantly more weakness and sensory signs, indicating that the neuropathies associated with IgM-MGUS and IgG/A-MGUS may be two different entities. A rapid progression of the neuropathy occured in five patients. We found no predictive factors for this severe fast and severe. Of these five patients three (2 IgM, 1 IgG) developed a non-Hodgkin-lymphoma, and two patients (IgG) could have CIDP. Because of the progressive course we advocate treatment of the gammopathy for all patients.

3
SENSORY FUNCTION STUDY IN 15 CASES OF MULTIFOCAL MOTOR NEUROPATHY. J Pouget, JP Azulay, F Bille-Turg, P Valentin, GG Farnarier, JF Pellissier, G Serratrice. *Marseille; France.*

We investigated sensory function in 15 patients affected by multifocal motor neuropathy (MMN). All had electrophysiological evidence of multifocal motor conduction block, 13 had elevated serum titers of anti-GM1 antibody. Sensory investigations included clinical examination, sensory nerve conduction velocity studies, quantitative evaluation of vibratory and thermal thresholds and somatosensory evoked potentials (SEP). We particularly studied SEP elicited by stimulations of nerves affected by motor conduction blocks. Sural nerve biopsy was performed in three patients. Sensory abnormalities on both clinical and physiological testing were much more frequent than expected. Considering these results, it appears that the splitting of MMN in two groups (one with pure motor involvement and another with sensory impairment as described by Lewis and others in 1982) is not justified. Furthermore, the relations between MMN and CIDP have to be reconsidered.

4
IN VITRO MEASUREMENTS OF AXONAL MEMBRANE CURRENTS OF HEALTHY AND DISEASED HUMAN SURAL NERVE BY COMPOUND ACTION POTENTIALS, ELECTROTONUS AND PATCH CLAMP REGISTRATIONS. S Quasthoff, U Schneider, P Grafe, *Munich, Germany*

The present study is based on 46 sural nerve biopsy which were done for histological studies to support the clinical diagnosis. We applied neurophysiological methods (compound action potential, electrotonus and patch clamp measurements) to sural nerve fascicles obtained from various neuropathies. The aims of this study were (a) to compare functional and morphological parameters and (b) to gain access to the possible involvement of abnormal ion channels in the pathophysiology of neuropathies and (c) to do pharmacological experiments. This methods allowed a clear separation of Aβ, Aδ and C fibres action potentials and current recordings of Na+ and K+ channels from Aβ and Aδ fibres. Electrotonus and patch clamp current recordings of sodium and potassium currents from axons of the nerve biopsies were made in order to find alterations in the channel behaviour in a variety of neuropathies and to investigate the effect of acidosis on axonal ion currents. Low pH was a powerful blocker of voltage gated K+ channel which could be used as a model of some pathophysiological aspects in some neuropathies. However, normal sodium and potassium channels were found even in the absence of Aβ and Aδ compound action potentials.

5
SEVERITY OF CISPLATIN NEUROPATHY IN RELATION IN DIFFERENT DOSING SCHEDULES. PHE Hilkens, JWB Moll, MEL van der Burg, AST Planting, WLJ van Putten, Ch J Vecht, MJ van den Bent, *Rotterdam, The Netherlands*

Sensory neuropathy is a dose-dependent side-effect of cisplatin chemotherapy in patients with cancer. The influence of dosage interval is unknown. We studied prospectively whether the severity of neuropathy is dependent on the dosing schedule of cisplatin. 66 patients (mean age 55) with advanced solid tumours were treated with a weekly regimen of 6 cycles of different doses (70-85 mg/m^2) in I day (group 1), 23 patients (mean age 57) with ovarian cancer with a 3-weekly regimen of 6 cycles of 75 mg/m^2 in I day (group 2) and 23 patients (mean age 28) with testicular cancer in a schedule of 20 mg/m^2 for 5 days every 3 weeks in 4 cycles (group 3). In some patients more cycles were given. The vibration perception threshold (VPT; Vibrameter III, Somedic) was used as the measure of outcome. The mean cumulative dose for the weekly regimen (group 1) was 435 mg/m^2 (range 280-630 mg/m^2). The average VPT was 1.01 (SD 1.40) pre-treatment and increased to a maximum of 2.90 (SD 3.96) 3 months after treatment. The maximal VPT post-treatment correlated strongly with the cumulative dose of cisplatin (p=0.0001). The mean cumulative dose was 489 mg/m^2 (range 375-675 mg/m^2) in group 2 and 474 mg/m^2 (range 400-900 mg/m^2) in group 3. The average pre-treatment VPT in group 2 and 3 was lower, 0.65 (SD 0.48) and 0.31 (SD 0.17) respectively, reflecting younger age and/or better clinical condition. The maximal post-treatment VPT was 5.81 (SD 5.40) in group 2 and 4.87 (SD 8.25) in group 3. Following correction for cumulative dose of cisplatin and pre-treatment VPT, the maximal post-treatment VPT did not show differences between the three groups. As we did not find differences in neuropathy between 3 different dosing schedules dosage interval is not a factor of importance for the severity of cisplatin neuropathy.

6
THE COURSE OF DIABETIC NEUROPATHY - A FOLLOW-UP. F Birklein, A Spitzer, E Lang, D Claus, B Neundorfer. *Erlangen, Germany.*

24 patients with signs of peripheral diabetic neuropathy (13 males 11 females, mean age 50 ± 14 years, 11 with IDDM, 13 with NIDDM) were observed over a period of 24 months. The mean duration of diabetes was 14,7 ± 1,16 years. The patients were examined at the beginning and, thereafter, every 6 months according to the same protocol. Nerve conduction velocities were assessed in the peroneal and tibial nerves, the motor nerve

action potentials of these nerves were recorded, cold and warm perception thresholds were measured at the dorsum of the foot (Marstock - method) and the vibratory threshold was measured at the malleolus internus. A significant deterioration of the amplitudes of the motor nerve action potentials of the peroneal as well as the tibial nerves was observed ($P<0.02$ and $P<0.01$ respectively, MANOVA) whereas the motor nerve conduction velocities of these nerves remained unaltered. The quantitative sensory testing provided no significant change, too (MANOVA). The conclusions drawn from this investigation are: 1) Ongoing axonopathy is more pronounced than demyelination in this late course of diabetic neuropathy 2) The variability of the quantitative sensory testing is too high to yield significant changes within two years in this investigation.

Oral Session 11 - Disorders of the Autonomic Nervous System

1

TRANSCRANIAL DOPPLER AND BLOOD PRESSURE MONITORING IN SYNCOPE. RR Diehl, D.Linden, D Lücke, P Berlit, *Essen, Germany*

The mechanisms of syncope often remain unclear when only conventional diagnostic tools (blood pressure monitoring, autonomic testing) are used. We developed a combined transcranial Doppler (TCD) and blood pressure monitoring system to study simultaneously cerebrovascular and circulatory regulation. Continuous monitoring of cerebral blood flow velocity (CBFV) from both middle cerebral arteries by TCD and of arterial blood pressure (ABP) and heart rate (HR) by Finapres was carried out under the following conditions: supine position, head-up tilt, six per minute breathing and Valsalva. Valsalva ratio, blood pressure and CBFV drop to head-up tilting, spectral density of low-frequency oscillations in HR, ABP and CBFV) were calculated from these data to describe sympathetic and vagal function and cerebrovascular regulation. We studied 62 patients with a history of syncope and a reference sample of 30 healthy subjects. Results: Twenty-four patients (39%) showed evidence for autonomic dysfunction with normal autoregulation. In three patients (5%) dysautoregulation occurred in the absence of dysautonomia. Nine patients (15%) with a large increase in sympathetic gain but otherwise normal autonomic parameters showed a strong reduction in CBFV during head-up tilt. One of these patients developed syncope during testing. The combination of cerebrovascular and circulatory parameters improves the assessment of syncope. In one fifth of our patients pathological results were found only in CBFV parameters. A drop in CBFV by sympathetic hyperactivity seems to be a possible condition for syncope.

2

ABNORMAL BLOOD PRESSURE RESPONSE TO EXERCISE IN FAMILIAL AMYLOID POLYNEUROPATHY TYPE 1, WITH AUTONOMIC IMPAIRMENT; COMPARISON WITH PURE AUTONOMIC FAILURE. GDP Smith, CJ Mathias. *London, UK.*

We describe the cardiovascular responses to supine exercise in 6 subjects with familial amyloid polyneuropathy (FAP) Type 1, compared to 10 age matched normal subjects (controls) and 10 with pure autonomic failure (PAF). Autonomic testing in FAP indicated sympathetic and parasympathetic impairment. Blood pressure (BP) was recorded before, during and after 9 minutes of incremental supine bicycle exercise. During exercise, BP increased in controls ($116 \pm 2/69 \pm 3$ to $153 \pm 3/92 \pm 4$ mmHg, each $p<0.001$), fell in PAF ($146 \pm 4/88 \pm 3$ to $124 \pm 4/70 \pm -3$, each $p<0.005$), and was unchanged in FAP ($114 \pm 5/74 \pm 5$ to $117 \pm 8/65 \pm 3$). Postural hypotension did not occur in controls, but was greater post exercise in both PAF and FAP. Resting heart rate was highest in FAP (controls 70 ± 3, PAF 69 ± 3, FAP 86 ± 3, beats/min, $p<0.01$). At the end of exercise it had risen most in controls (controls 121 ± 5, PAF 88 ± 2 FAP 102 ± 2, beats/min, $p < 0.01$). In FAP, exercise did not raise BP as in controls, nor lower it as in PAF; postural hypotension, however, increased post exercise, as in PAF. The heart rate response to exercise was less in both PAF and FAP. The contribution of autonomic impairment and cardiovascular amyloid deposition to the abnormal responses will be discussed.

3

MECHANISMS OF NEUROGENIC FLARE IN HUMAN SKIN. J Serra, M Campero, JL Ochoa, *Portland USA.*

Mechanisms of neurogenic flare were investigated in normal human skin. Cutaneous flare was induced in the forearm of 20 volunteers by intradermal injection of capsaicin (100 ug) or histamine (0.2 ug), noxious mechanical (forceps), heat (1 cm^2 Peltier thermode, 50°C for 30 seconds) or electrical stimulation. Flare was monitored with infrared telethermography. Effects of strips of intracutaneous anaesthesia and local block of nerve trunks supplying the tested area were investigated. Striking images of "thermographic" flare revealed rapid onset of multifocal increase in temperature due to dilatation of discrete cutaneous arterioles. The neurovascular response was stereotyped regardless of the nature of the triggering stimulus. Distance between injury site and a focus of vasodilatation may be as log as 12 cm. Mean maximal area covered by the multifocal "thermographic" flare (capsaicin) was 94.33 cm^2. Flare did not expand beyond an intracutaneous anaesthetic strip, and local anaesthetic block of the corresponding nerve trunk did not impair its development. We conclude that, there exists a specific neurovascular system responsible for neurogenic flare in human skin, that this "nocifensor" neural system interconnects broad areas of skin, and it probably operates through axon reflexes in a special subset of afferent fibers.

4

OCTREOTIDE PREVENTS ALCOHOL INDUCED POSTURAL SYMPTOMS IN PRIMARY AUTONOMIC FAILURE. K Ray Chaudhuri, D Pavitt, CJ Mathias. *London; UK.*

Alcohol induced postural symptoms are common in primary autonomic failure (AF). We report on the effects of Octreotide (Sandostatin, Sandoz), a peptide release inhibitor, on the systemic and mesenteric circulation, and postural symptoms in six patients with AF after an overnight fast. After 30 min supine rest, blood pressure, heart rate (BP, HR, Sentron), superior mesenteric artery blood flow (SMABF), pulsed Doppler ultrasound, Acuson 128) and blood alcohol levels were measured. Following alcohol (0.5g/kg, 40% vodka in sugar free orange juice) ingestion, patients were kept supine for 45 min (measurements every 15 min) and then tilted head-up 45° for 10 min. The study was repeated 30 min after subcutaneous injection of Octreotide (1ml, 50mcg/ml) on a separate day. After alcohol, supine BP (mmHg) fell (125 ± 6 to 96 ± 9) falling further when tilted (to 58 ± 8) (each $P < 0.05$). All felt faint and were intolerant to 10 min tilt. After Octreotide and alcohol, BP fell during tilt only (124 ± 6 to 80 ± 5). None were symptomatic and all withstood 10 min tilt. SMABF rose after alcohol but not after Octreotide prevents mesenteric vasodilation and alcohol induced postural symptoms in AF and may be clinically useful to counteract post-alcohol prandial symptoms.

5

THE EFFECT OF THE SOMATOSTATIN ANALOGUE OCTREOTIDE ON 24 HOUR AMBULATORY BLOOD PRESSURE AND SUPINE EXERCISE INDUCED HYPOTENSION IN PRIMARY AUTONOMIC FAILURE. G D P Smith, M Alam, C J Mathias. *London, UK.*

In primary autonomic failure octreotide reduces post prandial arid postural hypotension and increases walking time. We, therefore, studied its effects on exercise induced hypotension. In 18 subjects with autonomic failure 24 hour ambulatory blood pressure (BP) recordings (SpaceLab 90207) were analysed, with and without octreotide 0.1 µg/kg sc bd, to compare mean BP by day and night and after a 3 minute walk. In 10 subjects BP was compared, after an overnight fast, before, during and after supine exercise. After octreotide; BP was higher by day ($118 \pm 3/74 \pm 2$ off, $127 \pm 4/78 \pm 2$ mmHg on, each $p=0.01$) and after walking ($97 \pm 6/63 \pm 4$, $112 \pm 7/69 \pm 5$, $p<0.05$ and NS), but was lower at night ($142 \pm 2/84 \pm 1$, $133 \pm 2/80 \pm 1$, each $p<0.05$). During exercise testing BP, on octreotide, was higher supine ($152 \pm 11/88 \pm 5$, $167 \pm 6/96 \pm 3$, each $p < 0.05$), fell to similar level during exercise ($124 \pm 9/68 \pm 4$,$128 \pm 8/70 \pm 3$), but recovered more quickly post-exercise ($126 \pm 11/83 \pm 5$, $151 \pm 7/88 \pm 3$, $p<0.05$ and NS). BP was higher on standing pre (pre $82 \pm 5/47 \pm 4$, $117 \pm 11/66 \pm 6$, each $p < 0.005$) and post exercise ($71 \pm 5/44 \pm 4$ and $86 \pm 9/53 \pm 5$ mmHg, NS) with fewer postural symptoms on octreotide. In autonomic failure octreotide did not reduce supine exercise induced hypotension, but improved post-exercise BP recovery and reduced postural hypotension. Octreotide also improved the 24 hour blood pressure profile and reduced walking induced hypotension.

6
NEUROVASCULAR REFLEXES IN DIABETIC NEUROPATHY. A NEW METHOD. A Spitzer, E Lang, F Birklein, D Claus, HO Handwerker B Neundorfer, *Erlangen, Germany*

Painful stimulation of a hand induces a reflex vasoconstriction resulting in a decreased blood flow and therefore decreased skin temperature in the skin of the stimulated hand. The interdigital web between the 2nd and 3rd fingers was pinched for periods of 2 min duration by a clamp to induce tonic pain perception. By thermographic recording the skin temperature of the middle finger was measured before and after the stimulus. In 20 control subjects the temperature after stimulation was reduced by 0.86°C compared with the baseline temperature. In diabetic patients without neuropathy (0.68°C, n= 14) and with neuropathy, but normal heart rate variation (0.47°C, n=22) the degree of cooling was not significantly reduced (p=0.43 and 0.11). In 18 patients with cardiac autonomic involvement of the heart temperature reduction was significantly smaller than in the control group (0.26°C, p<0,001). Within the diabetic group cooling of the middle finger after pinching correlated with reduced nerve conduction velocity (NCV), warm thresholds at the foot, and heart rate variability. However, there was no significant correlation with ulnar motor or sensory NCV or with subjective pain rating. Our findings suggest that reduced reflex vasoconstriction in diabetics is caused mainly by dysfunction of efferent vasoconstrictive fibres.

7
DISSOCIATION BETWEEN AUTONOMIC SYMPTOMS AND SIGNS IN FAMILIAL AMYLOID POLYNEUROPATHY - THE NEED FOR CARDIOVASCULAR AUTONOMIC ASSESSMENT. CJ Mathias, K Bleasdale-Barr, G Smith, NMF Murray, P Hawkins, M Pepys, PK Thomas. *London, UK.*

Liver transplantation has been successfully used in familial amyloid polyneuropathy (FAP). Cardiovascular autonomic abnormalities, however, can result in peri-operative morbidity and mortality. We describe 8 FAP, with few, if any, symptoms of postural hypotension. on testing all had postural hypotension (from 126 ± 8/77 ± 5 to 98 ± 13/60 ± 8mmHg on 45 head-up tilt) with impaired pressor responses, a blocked Valsalva manoeuvre, a relatively fixed heart rate and impaired sinus arrhythmia. Food lowered blood pressure whilst supine and worsened postural hypotension. After supine exercise blood pressure was unchanged, but postural hypotension was increased. Plasma noradrenaline levels were below normal (213 ± 62 pg/ml) and rose minimally with head-up tilt (233 ± 64). The neurophysiological findings indicated a small fibre neuropathy in 2, with a mild to moderate generalised axonal neuropathy in the rest. In conclusion, despite few symptoms, all FAP had definite postural hypotension, and abnormal responses to food and exercise challenge. The findings indicated both sympathetic vasoconstrictor and parasympathetic cardiac involvement. Amyloid deposition in blood vessels and heart may have contributed. Cardiovascular autonomic function, therefore, is important in initial assessment, in monitoring progression and in determining the efficacy of intervention in FAP. As will be discussed, awareness of the deficits maybe of critical importance in preventing peri-operative cardiovascular/autonomic complications.

Oral Session 12 - General Neurology (1)

1
FATAL MITOCHONDRIAL ENCEPHALOPATHY CAUSED BY FUMARASE DEFICIENCY: A MOLECULAR-GENETIC STUDY. C Gellera, S DiDonato, F Taroni. *Milan, Italy*

Fumarase deficiency is a rare autosomal recessive disorder resulting in organic aciduria and severe neurological impairment. Mammalian cells contain two fumarase isoenzymes, one mitochondrial and one cytosolic. In rat, the two proteins are encoded by the same gene and are synthesised by alternative initiation of translation at two in-phase AUG codons. one single fumarase gene locus has been identified on human chromosome 1. We present a study on a 7-month-old child who died of a progressive encephalopathy characterised by generalised seizures, hypotonia, psychomotor deterioration, microcephaly, and fumaric aciduria (Gellera et al., Neurology 40:495-9, 1990). Postmortem examination revealed diffuse cerebral atrophy and islets of cell heterotopia in the parietal and occipital areas as well as in the cerebellum. The activities of both fumarase isoenzymes were severely affected, supporting the hypothesis of one fumarase gene also in humans. Molecular analysis of the patient's fumarase cDNA amplified by RT-PCR showed the presence of two mutations affecting the amino acid composition of both isoforms, a missense mutation resulting in the nonconservative amino acid substitution at codon 190 (Arg190Cys) and an amino acid inframe insertion at codon 434 (Lys434ins). Genomic DNA analysis demonstrated that the patient was heterozygous for both mutations, having inherited the arg-to-cys substitution from the father and the inframe insertion from the mother. Finally, the effects of the mutations on enzyme function were investigated by expressing both normal and mutated fumarase cDNAs in a fumarase-deficient S. cerevisiae strain.

2
ABNORMAL BRAIN AND MUSCLE MITOCHONDRIAL FUNCTION IN FAMILIAL HEMIPLEGIC MIGRAINE. A Uncini, A Di Muzio, S Servidei, G Silvestri, R Lodi, S Iotti, D Gambi, B Barbiroli, *Chieti, Roma & Bologna, Italy*

Familial hemiplegic migraine (FHM) is a rare autosomal dominant disorder of unknown pathogenesis characterized by migraine and transitory hemiplegic attacks. We describe a kindred with FHM in which: 1) blood lactate was increased after effort; 2) muscle biopsy showed rare ragged red fibers (1 of 2 cases); 3) brain 31 phosphorus magnetic resonance spectroscopy (31P-MRS) showed a significantly reduced phosphocreatine content accompained by high ADP, high V/Vmax for ATP biosynthesis and a low phosphorylation potential; 4) muscle 31 p MRS showed a reduced rate of phosphocreatine recovery after excercise; 5) the study of muscle mitochondrial DNA did not reveal deletions or the point mutations at nt-3243 and nt-3271 in trasferRNALeu(UUR) characteristic of mitochondrial myopathy, encephalopathy. lactic acidosis and stroke like episodes (MELAS). The defective energy metabolism of brain and muscle found in this family suggests primary generalized abnormality of mitochondrial function in FHM. Conditions which increase metabolic demand of brain cells such as trauma, febrile episodes or stress may trigger the transient neurological deficits of FHM.

3
SUBACUTE BILATERAL SIMULTANEOUS OPTIC NEUROPATHY OF UNCERTAIN CAUSE IN ADULTS. SP Morrissey, FX Borruat, DH Miller, AE Harding, D Francis, I Mosely, *London, UK*

The aetiology of clinically isolated subacute bilateral simultaneous optic neuropathy (BSON), in adult life is often uncertain. We now report a follow up study of 24 (12 females and 12 males) patients with a past history of BSON. At follow up (range 1 month to 17 years, mean: 5,5 years) Magnetic Resonance Imaging (MRI) of the brain and optic nerves, a full neurological and opthalmological examination were performed, and a blood sample was taken for mitochondrial DNA analysis and HLA typing. Results: 5 patients (21%) developed MS on clinical ground (in all cases supported by MRI). 4 patients (17%) were diagnosed as LHON (11778 mutation (3); 14484 mutation (1)). 15 patients remained clinically isolated. Of this group, multiple white matter MRI lesions were seen in only 3 (20%), the HLA-DR2 antigen was present in 3 (20%) and CSF oligoclonal bands only in 1/7 who had an LP. Conclusion: With the assistance of MRI and mitochondrial DNA-analysis, a diagnosis was made in almost 40%. The low frequency of risk factors for MS (on MRI, HLA and CSF) in the remaining 60% suggests that the overall risk of MS following BSON is relatively low.

4
OPTIC NERVE SONOGRAPHY FINDINGS IN ACUTE INTRACRANIAL PRESSURE: ENLARGEMENT OF PERINEURAL SHEATH. HC. Hansen, K Helmke, K Kunze , *Hamburg-Eppendorf, Germany*

Intracranial hypertension, an important determinant of prognosis in severe traumatic or vascular cerebral disease, is usually difficult to assess clinically and its monitoring largely depends on epidural pressure transducers. Though reliable, papilloedema usually appears too late in the course of an expanding intracranial mass lesion or brain oedema. The underlying trans-

mission of the subarachnoid pressure to the anterior optic nerve expands the optic nerve sheaths (ONS), and can be visualised by MRI and optic nerve sonography (Guthoff et al 1990). In 16 patients with severe cerebrovascular or traumatic brain damage (lethal outcome 8, neurological deficits 7, complete recovery we performed transorbital sonography to look for ONS diameters and papilledema in both eyes. Precision of measurement was within acceptable limits (mean error 0.3 to 0.5 mm). Control data (age-matched) never exceeded 4,3 mm while the patients averaged at 5.5 mm (range 4,2 to 6.9 mm). Papilledema, if present, was always preceded by ONS-enlargement. Our data suggest that ONS-sonography can be of additional diagnostic value in the evaluation of critically ill neurological or comatose patients, esp. when enlarged diameters are found (>5mm) bilaterally.

5
EVOLUTION OF STRIATAL METABOLIC AND BIOCHEMICAL DYSFUNCTION IN Striato-nigral degeneration (SND). E Salmon, Sadzot, Maquet, Lemaire, Plenevaux, Damhaut, G Franck. *Liège, Belgium.*

We followed a patient with clinical likelihood of striatonigral degeneration using PET. A progressive extrapyramidal syndrome started at age 49 with a left hand cogwheel rigidity and tremor and the symptoms evolved to an asymmetrical, predominantly left rigidity, global hyperreflexia, axial rigidity with a flexed posture of the trunk and pseudo bulbar palsy with dysphagia, dysarthria and emotional lability. High dosage of L-dopa had only moderate efficacy. Glucose metabolism expressed as a fraction of the mean control value (right/left).

	(PET1)	(PET2)	(PET3)
Caudate	0.8/0.9	0.7/0.8	0.6/0.7
Anterior Putamen	0.7/0.9	0.5/0.8	0.5/0.7
Posterior Putamen	0.7/0.8	0.5/0.7	0.5/0.6

Twenty months after the first clinical signs, (PET1) showed that the metabolism was predominantly decreased in the entire right putamen, but it was also reduced in the right caudate and in the left posterior putamen. At that time, D2 receptors were decreased in the posterior part of the right putamen. Two years later (PET2), there was a major hypometabolism in the entire right putamen, and the metabolism gradually decreased in all other striatal structures until the next year (PET3). Labelling of D2 receptors was markedly reduced in the right putamen and in the left posterior putamen. It was also midly reduced in the right caudate. A low (18F)dopa uptake persisted only in both caudate. We conclude (1) that PET maps in vivo biochemical dysfunctions of neurons known to be lesioned in SND and (2) that the decrease of metabolism may occur before the reduction of D2 receptors.

6
INHIBITION OF TUMOR NECROSIS FACTOR (TNF) BY THALIDOMIDE ABOLISHES AN EARLY PHASE OF THERMAL HYPERALGESIA IN NEUROPATHIC RATS. C Sommer, RR Myers, *Aachen, Germany & San Diego, California, USA*

An experimental neuropathy in the rat, the chronic constriction injury (CCI) (1), produces hyperalgesia and allodynia in one hindlimb. We previously described the importance of Wallerian degeneration for the development of hyperalgesia (2, 3). In order to analyse single elements of Wallerian degeneration, we selectively blocked TNF by thalidomide. Groups of 10 rats with CCI were tested for thermal hyperalgesia before surgery, and at regular intervals thereafter. 5 rats of each group received thalidomide, 10 mg daily, 5 rats received vehicle only. All animals developed thermal hyperalgesia by day 3. Between days 5 and 9, thermal hyperalgesia in thalidomide treated animals was diminished. On days 7 and 9, the hyperalgesia score of the thalidomide group was no different from values before surgery. On day 11, hyperalgesia was present again in both thalidomide and control groups, with a parallel time course toward recovery at 42 days. We conclude that TNF has a role for the development of hyperalgesia in CCI between days 5 and 9 after surgery. Later, other factors, like ectopic activity from nerve sprouts, may provide additional mechanisms of hyperalgesia. The early hyperalgesia on day 3, which was present in both the treated and the control group, is also likely to be due to a TNF-independent mechanism.

Oral Session 13 - Disorders of the Neuromuscular Junction

1
PROTEIN A IMMUNOADSORPTION IN SEVERE MYASTHENIA GRAVIS. E Berta , P Confalonieri, M Zuffi, R Mantegazza, F Cornelio, C Antozzi. *Milan, Italy*

Myasthenia Gravis (MG) is an autoimmune disorder mediated by antibodies against the acetylcholine receptors (AntiAChRAb). Few patients respond poorly to immunosuppression and may benefit from prolonged apheresis. Since AntiAChRAb are mostly IgG, MG represents an indication for immunoadsorption with protein A (PAI) which selectively binds with high affinity immunoglobulins, particularly IgG. Four immunosuppression-resistant MG patients were treated, of which three were affected with bulbar and one with severe generalised MG. All but one had a positive pre-treatment AntiAChRAb dosage. Patients were submitted to cycles consisting of two/three PAI sessions on alternate days. Plasma, separated by centrifugation, was passed in series through two columns containing protein-A covalently bound to sepharose (Immmunosorba, Excorim). A total of 61 sessions have keen performed. The mean clinical follow-up seven months. The volume of plasma processed at each session was 4288 ± 787 ml. Reductions of immunoglobulins were as follows: IgG 70 ± 11%, IgM 45 ± 14%, IgA 19 ± 13%, AntiAChRAb 84 ± 18%. A significant improvement was observed: one patient was symptom free during three months from the last session, whereas in two the effect was significant but limited in time. No side effects occurred. our data suggest that PAI, associated to immunosuppression, is an apheretic approach for severe treatment-resistant myasthenic patients.

2
LAMBERT-EATON MYASTHENIC SYNDROME (LEMS) IN LYMPHOPROLIFERATIVE DISORDERS (LPD). Z. Argov, Y. Shapira, I. Wirguin. *Jerusalem, Israel*

LEMS is a presynaptic neuromuscular junction disorder that manifests with weakness, fatiguability, areflexia and dysautonomia. Marked increment of the compound muscle action potential (CMAP) upon tetanic nerve stimulation is the cardinal diagnostic electrophysiological feature. The disorder is typically associated with small cell lung carcinoma, but appears also without malignancy. We report 3 LEMS patients who had a LPD. 1. A 43-years-old male with active Castleman's disease had weakness, areflexia and dry eyes and mouth since the onset of his LPD 3 years earlier. Small CMAP increased after 20 Hz nerve stimulation by 618-890% (normal<125%). Antibodies to calcium channels were absent. His condition progressed to respiratory failure. 3-4 diaminopyridine (100 mg/day) improved his functional condition in association with a decrease in the increment to 155-250%. 2. A 7 year old boy with Burkitt's lymphoma and lymphocytic leukemia developed ptosis, ophthalmoplegia and legs weakness during acute relapse. This unusual rapid LEMS onset was confirmed by CMAP increment of 350% at 20 Hz stimulation.3. A 60 year old woman with non-Hodgkin lymphoma had progressive muscle weakness and areflexia for 3 months. She had increments of 190-300%. Clinical data from these 3 patients and 5 additional ones found by literature survey suggest that LPD is another, hitherto unrecognised, type of malignancy to be specifically associated with LEMS. The increased tendency for autoimmune disorders in LPD may be an etiologic factor. Any LPD patient with weakness should have tetanic nerve stimulation as part of his work-up.

3
ACUTE EFFECTS OF ANTIBODIES AGAINST THE NICOTINIC ACETYLCHOLINE RECEPTOR (nAChR). J Beuuer, KV Toyka, C Franke, *Munich, Germany*

The aim of the study was to investigate direct effects of antibodies against the nAChR which may cause the rapid changes of muscle weakness in patients with myasthenia gravis (MG). nAChRs of mouse myotubes were investigated with the patch clamp technique in the cell-attached and the outside-out mode. We tested a monoclonal antibody (WF6) specific to the binding site for acetylcholine (ACh) and a pool of IgG Fab-fragments of MG patients. We found that the nAChR is activated by low concentrations of WF6 or Fab-fragments (10^{-7} to 10^{-12} M). If the antibodies or the Fab fragments were applied together with ACh with a fast application system,

a block of the nAChR was observed after incubation of several minutes. The block was partially reversed after 30 min washout, the response to ACh was about 50% of the control. Our results show that a reversible block of the nAChR is caused by antibodies and Fab fragments of MG patients. This may explain the relatively rapid improvement of MG patients after plasmapheresis. A second more general result of our study is that we found a rapid interaction between the immune and the nervous systems.

4
A SERUM FACTOR CAUSING NEUROMUSCULAR BLOCK IN MILLER FISHER SYNDROME. M Roberts, H Willison, A Vincent, J Newsom-Davis. *Oxford & Glasgow, UK*

Serum IgG anti-GQ1 b ganglioside antibodies are frequently detected in the Miller Fisher (MFS) variant of Guillain-Barre syndrome (GBS), and in GBS when ophthalmoplegia is present (Chiba et al. Neurology, 1993). Recently we reported that 3 MFS sera (anti-GQ1 b positive) blocked neurotransmitter release from motor nerve terminals in the mouse phrenic nerve-diaphragm preparation within 4 hours of application in vitro. This was preceded by an initial eightfold increase and subsequent decline in miniature endplate potential (mepp) frequency. Control sera and convalescent anti-GQ1 b negative serum had no effect. We now show in a further MFS case using the same nerve-muscle preparation that the activity is in the lg. fraction (ammonium sulphate precipitate). Mepp frequency increased from 0.5/sec to 6/sec after 2 hours incubation in plasma or lg., declined to zero at 3.5 hours, when neuromuscular transmission ceased altogether. The response to direct muscle stimulation was preserved. The results suggest that the MFS serum factor causing neuromuscular block in our experiments is in the antibody fraction, and is likely to be anti-GQ1 b ganglioside antibody. This factor may contribute to clinical paralysis in MFS by an action at the neuromuscular junction.

5
TOWARDS IDENTIFICATION OF THE GENE FOR SPINAL MUSCULAR ATROPHY. KE Morrison, R Damels, M Francis, L Campbell, KE Davies. *Oxford, UK*

Childhood onset proximal spinal muscular atrophy (SMA) is a neuromuscular disorder characterised by selective loss of alpha motor neuron cell bodies. The 3 forms of the disease, distinguished on the basis of severity of disability, show autosomal recessive inheritance and in 1990 were mapped by genetic linkage analysis to chromosome 5q 11.2-13.3. We have extended these initial studies by developing several new microsatellite markers from yeast artificial chromosomes (YACs) and cosmids which map within the region, and genotyping 75 SMA pedigrees. Analysis of key recombinants has narrowed the candidate SMA region to an interval of 300kb. No evidence of linkage disequilibrium of any allele with SMA, nor of genetic heterogeneity, has been obtained. A protocol for prenatal prediction of the disorder has been established. The entire candidate region has been cloned in a series of overlapping YAC and cosmid clones. Genes are now being isolated from fetal brain and spinal cord cDNA libraries by screening with groups of cosmids in a coincident sequence cloning approach. To date 20 cDNAs which map within the region have been characterised, 12 of which show portions of high homology to the β-glucuronidase gene. No mutations in any of these cDNAs have as yet been detected in SMA patients.

6
IMMUNADSORPTION IN MYASTHENIA GRAVIS. W Kohler, C Bucka, G Hertel. *Berlin, Germany*

Immunadsorption (IAD) has been reported to be a successful therapeutic procedure for the treatment of severely compromised myasthenic patients. 15 patients with severe generalised myasthenic deterioration (group IIb,III or IV according to Osserman's classification) were treated in 21 IAD series in a 2 year period. Results: 11/15 patients improved clinically after each treatment series at least to slight generalised myasthenic symptoms (Osserman IIa), 4/15 patients remitted completely. 1 patient relapsed after 13 months and gained complete remission after a second IAD series. 1 patient relapsed after 17 months and was treated again successfully. 1 patient relapsed twice after 10 and 9 weeks respectively and remained clinically improved for more than 12 month after the 3rd IAD series. 1 patient needs repeatedly IAD's in changing intervals from weeks to months, always responding from severe life-threatening symptoms to only mild myasthenic signs. Finally in 7/15 patients clinical improvement was stable for more than 12 months and in 6/15 patients for more than 6 months up to today. All patients improved after treatment with IAD. The clinical effect in most patients is outlasting if IAD is combined with a very slowly decreasing corticosteroid treatment and chronic immunosuppression (azathioprin 50 to 150 mg/d). IAD is a new and very well tolerated, highly effective method in the treatment of severe Myasthenia gravis.

7
LONG-TERM TREATMENT OF IDIOPATHIC LAMBERT-EATON MYASTHENIC SYNDROME. P Kanovsky, *Brno, Czech Republic*

Two patients with idiopathic Lambert-Eaton myasthenic syndrome (LEMS) were followed, one for 16 and the other for 6 months. A combination therapy including four drugs was administrated: the acethylcholine-estherase inhibitors, pyridostigmine and ambenonium, and immunosuppresive agents, prednisone and azathioprine. The starting high doses of prednisone were slowly decreased to obtain the best effect with the lowest possible dose. Serum levels of potassium, sodium, calcium, magnesium, blood cell count, liver enzymes, circulating immunocomplexes and renal functions were monitored. Very good clinical improvement with only slight side effects was observed in both patients. Marked decrease of the increment in the EMG after repetitive stimulation in the 30 Hz frequency was observed eight weeks after onset of the combination therapy. This combination of drugs is a successful and safe option in the therapy of idiopathic Lambert-Eaton myasthenic syndrome.

Oral Session 14 - Neuro-imaging

1
FUNCTIONAL MAGNETIC RESONANCE IMAGING OF COGNITIVE TASKS AT 1.5 T. D Auer, H Ackermann, U Klose, Th Naegele, S Bien, K Voigt, *Tubingen, Germany*

The blood oxygenation level dependent contrast of fast T2* weighted susceptibility images allows to study non-invasively the regional brain activation. The aim of the present study was an evaluation by various language tasks in healthy volunteers and in patients with focal lesions such as AVMs in respective areas. The examinations were performed at 1.5 T using a T2* weighted multislice or 3D FLASH-sequence (TE=60ms; 3-8mm). The stimulus and control conditions were alternated 5-10 times. The tasks consisted of automatic and spontaneous speech, verb generation, word association and comprehension. 14 volunteers and four patients, 2 with transient ischemic aphasia and 2 left-sided AVMs of Broca's and Wemicke's area were included. The best signal yield was associated with spontaneous speech within the left inferior frontal gyrus Internal automatic speech leads to a lower activation with the most consistent area being the right post.sup. temporal gyrus. The association task gave better results than verb generation in thesubjects tested. The two patients with AVMs in the left inferior frontal and left superior temporal area did not show any marked displacement of Broca's and Wernicke's area, respectively. In conclusion, different regional cortical activation during internal and normal speech can be studied at 1.5T and the possibility to localize speech areas preoperatively could be shown.

2
IMAGINATION OF MOVEMENTS AFTER STROKE. GR Fink, KM Stephan, RJS Wise , N Mullatti, L Hewer, RSJ Frackowiak, *London, Bristol, UK & Düsseldorf, Köln, Germany*

Studying normals we demonstrated that imagining movements involves a whole network of cortical areas participating in motor processing. Pursuing this work, we have so far studied two patients with ischaemic infarcts within the left MCA territory who have impaired right hand movements. We wished to see, whether impaired motor performance is paralleled by impaired imagination. We used Positron Emission Tomography to image neuronal activation using H215O to measure relative cerebral blood flow (CBF) distribution. The patients per-formed three different tasks with their paretic hand: joy-stick movements, imagining joy-stick movements, and a resting (control) task. CBF during the three tasks was compared using sta-

tistical parametric mapping ($p<0.05$) and MRI. In the patient with good clinical recovery imagining movements activated most of the areas activated during the performance of movements. However, in the patient with poor recovery neuronal activation during imagining movements differed and did not include parietal and perisylvian areas which are important secondary motor areas. We conclude, that imagining movements activates the same or very similar pathways as the actual performance of movements. Imagination of movements in paretic patients might conceivably help rehabilitation by activating the same functional networks.

3
FUNCTIONAL MRI OF THE HUMAN MOTOR CORTEX AT 1,5T : FIRST RESULTS OF 10 PATIENTS RECOVERED FROM STROKE. JH Faiss, CS Weiller, M Rijnites, M Jueptner, T Bauermann, M Krams, HC Diener. *Essen, Germany.*

Functional activation of the brain can be visualised by conventional MRI. Initial studies used echo planar imaging or very high magnetic fields, which are available in only a few centres. Against this background, we used conventional MRI operating in a routine clinical environment to map regions of the brain that are activated with a motor task and compared the results with PET-data. 10 healthy volunteers as well as 10 patients recovered from stroke were studied. Anatomical and functional images were obtained by a conventional MRI-system working at 1.5T with a standard head coil. The activated images were obtained using a FLASH-sequence with long echo (60ms), a slice-thickness of 10 mm, coarse matrices of 128 x 64 or 128 x 128 in tilted axial and oblique planes through the primary motor cortex. Data were collected in 30 - 45 s blocks of 6 control images followed by 6 images during motor activation. This procedure was repeated 5 - 10 times for both hemispheres. Activation was visualised by subtracting sets of control images from those acquired during activation. The motor task consisted of repetitive finger-to-thumb opposition movements. In all studies with healthy volunteers the maximal signal increase during motor activation was about 6 % compared to 18 % increase in rCBF obtained by PET. The activated regions were consistent with the hand area of the primary cortex which would be expected to be activated by this task. Interestingly also in all patients recovered from stroke a signal increase during motor activation of the lesioned hemisphere was seen, located predominantly rostral related to the hand area. In 5 patients a co-activation of the ipsilateral hemisphere appeared. Present data suggest that functional mapping of the human brain using conventional MRI is possible and that in patients recovered from stroke a signal increase during motor activation could be demonstrated.

4
CORRELATION OF QUANTITATIVE MRI ABNORMALITIES AND DISABILITY IN MS. MAA van Walderveen, F Barkhof, OR Hommes, CH Polman, J Valk, *Amsterdam & Nijmegen, the Netherlands*

MRI is frequently used as an outcome measure in phase II trials in MS, assuming that MRI activity predicts clinical disability. We studied the relation between increase in MRI lesion load and clinical disability. MS patients (n=48) were examined twice clinically (EDSS) and with MRI (mean interval 24 months, range 10-42 months). MRI (spin-echo sequences) included T2-weighted images in all and T1-weighted images in 18 patients, which were computer quantitated with a seed-growing technique. Increase in EDSS correlated with increase in T2-weighted lesion load ($r=0.53$, $P<0.0001$), while the subgroup with T1-weighted images showed a significant correlation of increase in EDSS and area of decreased signal intensity ($r=0.89$, $P<0.0001$). The short duration of follow-up period might explain the weakness of the relation between increase in disability and T2 lesion load (25 % variance explained). More probably T2-weighted images also detect areas of oedema and mild demyelination, which are still functionally intact, whereas areas of decreased signal intensity on T1-weighted images represent only severe demyelination, marked gliosis and axonal loss, having little residual function, hence the strong correlation with increase in EDSS (80% variance explained).

5
VALIDATION OF A CT SCAN MEASUREMENT MODEL IN THE DIAGNOSIS OF DEMENTIA OF THE ALZHEIMER TYPE (DAT). JP Willmer, DA Guzman, *Ottawa, Canada*

A previously defined diagnostic model for DAT, based on measurements of CT scans was prospectively tested by applying it to 200 consecutive patients (mean age = 69 years) referred to a memory disorder clinic. The CT scans were measured by one author (JPW), while the patients were classified clinically using NINCDS-ADRDA criteria by the other (DAG). Both remained blinded to the other's diagnosis. Of patients clinically diagnosed as DAT, the diagnosis based on the model agreed in 84% of cases, while it agreed in 66% of those diagnosed as not having DAT. If the data are analyzed by age group (< 65 years and > 65 years), the older patients have a much greater chance of being misdiagnosed as having DAT by the model (91% agreement for DAT, 44% agreement for non DAT) and the younger patients have a greater chance of being misdiagnosed as being non DAT (43% agreement for DAT, 88% agreement for normal). This is not related to age, as the measurements were found in the original model not to correlate with the age of the patient. This was tested in the new data set, and for the three measurements used, no correlation with age was found (r^2 values range from 0.212 to 0.285). These findings may suggest that for older patients, the structural changes (atrophy) may precede the cognitive ones and that for this group, the CT measurements may be a good marker. To confirm this the group misclassified as DAT will have to be followed prospectively to see if they will develop DAT. In the younger group, which may progress more rapidly, the cognitive changes may precede the structural ones, and this model may not be all that useful.

6
MOTOR IMAGERY AND PERFORMANCE OF HAND-MOVEMENTS. KM Stephan, GR Fink, RE Passingham, D Silbersweig, A Ceballos-Baumann, CD Frith, R Frackowiak. *London, UK; Koln & Dusseldorf, Germany*

Using a neuropsychological approach, Kohl and Roencker demonstrated in 1989, that motor imagery and motor performance share some but not all aspects of motor function. We were interested, which cortical areas participate both in imagining movements and performance and whether activation of some areas was unique to one form of motor behaviour. Six right handed healthy volunteers were investigated with Positron Emission Tomography (PET) using radiolabeled water. They performed three different tasks: (1) joystick movements, (2) imagining of joystick movements and (3, as a control state) preparing to move. Movement was controlled for by visual inspection and surface EMG. Relative degrees of activation during the three tasks were compared by statistical parametric mapping analysis. Both motor imagery and performance of movements involve premotor and parietal areas which are known to act as 'secondary motor areas'. During performance of movements additional activation of primary sensorimotor areas, anterior cingulate and superior parietal area (Brodmann area 5) were observed. Thus imagining movements is a complex 'motor-related' task, which involves premotor and parietal areas, known to be concerned with sensory-motor and visuo-motor integration, before and during movement.

POSTER SESSION 2

1
HIGHER PREVALENCE OF ATRIAL SEPTAL ANEURYSMS IN PATIENTS WITH ISCHEMIC STROKE UNKNOWN CAUSE. CH Lucas, L Goullard, MJ Marchau, O Godefroy, PH Rondepierre, E Chamas, F Mounier-Vehier, D Leys. *Lille, France.*

Atrioseptal aneurysms (ASA) are frequent on transesophageal echocardiography performed in stroke patients. Whether they are potential sources of cerebral emboli remains unclear. The aim of the study was to investigate whether ASA have a different prevalence between patients with ischemic stroke of unknown cause and those with a determined cause. Amongst 154 consecutive ischemic stroke patients, we compared demographic data, cerebrovascular risk factors and presumed causes of stroke, between those who had an ASA and the remainder. Sixteen patients had an ASA. They were younger ($P=0.001$), less likely to have hypertension (95%CI.OR: 0.03-0.68) or patent cardiac sources of emboli (95% CI.OR: 0.04-0.77), and more likely to have a patent foramen ovale (PFO) (99% CI.OR: 5.17-173.97) or ischemic strokes of unknown cause (99% CI.OR: 1.04-18.08). Patients with ASA unassociated with PFO were also more likely to have ischemic strokes of unknown cause (95% CI.OR: 1.20-5.74). Patients with ASA did not differ for other demographic data or cerebrovascular risk factors. This finding leads to the hypothesis that ASA is a potential source of emboli independently of the presence of PFO.

2
PHENTOLAMINE SYMPATHETIC BLOCK IN PAINFUL POLYNEUROPATHIES FURTHER QUESTIONING OF THE CONCEPT OF "SYMPATHETICALLY MAINTAINED PAIN". J Renato, MSC Verdugo. M Campero, L Jose. DSc Ochoa, *Santiago Chile & Portland, Oregon, USA.*

Patients with painful polyneuropathies share many descriptive features with patients classically diagnosed with "Causalgia/Reflex Sympathetic Dystrophy" (RSD). In RSD patients the pathophysiological diagnosis of sympathetically maintained pain (SMP) is frequently made. SMP has been summarized as "all pain syndromes relieved by sympathetic blockade". To test for SMP, 14 patients with painful polyneuropathies, referred to the Neuromuscular Unit, Good Samaritan Hospital, were given placebo controlled phentolamine sympathetic blocks. Six received i.v. infusion of saline for 30 minutes, followed by phentolamine (35 mg). In 8 patients the saline phase was followed by a) double blind infusion of phentolamine or phenylephrine (500 ug.), b) a second saline phase and then c) the other active drug. Magnitudes of spontaneous pain and mechanical hyperalgesias were assessed on a 0-10 pain scale every 5 minutes. Sensory and sympathetic effects were monitored clinically and through quantitative thermotesting and thermography. Five patients volunteered significant diminution of pain (50%), all in response to placebo. Neither phentolamine nor phenylephrine contributed drug specific pain relief even though all patients expressed signs of pathophysiological mechanisms reputed as causative of SMP. The results endorse previous studies demonstrating non-existence of SMP among RSD patients, thus further questioning the concept of SMP.

3
STROKE DUE TO ABUSE OF COCAINE. F Vivancos, E Diez Tejedor, N Martinez, J Roda, A Frank, P Barreiro. *Madrid, Spain.*

Cocaine is an alkaloid, whose basic structure is ecgonine. At present, cocaine is considered as cause of stroke, specially in young people. Recently we have studied a series of 9 patients with stroke (5 ischemic and 4 hemorrhagic) related to cocaine abuse either sporadic or chronic representing 0.5% of total strokes admitted in our department. These patients were young (20-48 years), and 8 were males. The most frequent administration route was nasal in ischemic, and intravenous in hemorrhagic cases. Most patients also were habitual abusers of other drugs, and they might have had several risk factors. The latency between cocaine intake and stroke was frequently very short. Angiography showed a basilar artery and a posterior cerebral artery thrombosis in two ischemic were and a cerebral vasospasm in two hemorrhagic cases. These complications are uncommon, but their consequences are very important because of the severity of signs and permanent deficits affecting young people. To conclude we encourage the search for these substances in the first hours following stroke in all young patients, specially in absence of risk factors.

4
INCREASED OXYGEN EXTRACTION FRACTION ASSOCIATED WITH LEUKOARAIOSIS. Y Satoh, K Nagata, T Maeda, Y Hirata. *Akita, Japan.*

This study was designed to elucidate the pathophysiology underlying leukoaraiosis (LA) from the view point of cerebral circulation and metabolism. Thirty-nine patients (mean age 62.0 years) with chronic cerebral infarction were included. According to the grade of LA on x-ray CT, they were divided into 2 groups: group A, 18 patients with mild or no LA; group B, 21 patients with moderate or severe LA. Using positron emission tomography, cerebral blood flow (CBF), cerebral oxygen metabolism ($CMRO^2$), oxygen extraction fraction (OEF) and cerebral blood volume were measured quantitatively during the resting state. Seven aged-matched healthy people served as control. CBF in both groups was significantly reduced as compared with the controls, but group B showed a more extensive reduction than group A. On the other hand, CMRO2 reduction was more localised than CBF. OEF was significantly higher in group B as compared with the controls, but there were no area of increased OEF in group A. The results suggest that latent cerebral ischemia, the so-called misery perfusion syndrome, may underlie LA.

5
ETIOLOGY OF ISCHEMIC STROKES IN YOUNGER PATIENTS. B Yalçinerner, C Ozkara, F Ozer, S Ozer, L Hanoglu. *Istanbul, Turkey.*

The etiologic factors accounting for stroke in the later decades of life may not be applicable in younger patients. In order to examine these factors patients with ischemic stroke aged between 15-45 were observed according to a standard protocol of investigations. The study group consisted of 40 (9 females, 31 males) inpatients admitted to the Neurology Division of Bakirköy State Hospital for Neurological and Mental Diseases in 1990-1991. All patients had cranial computerised tomography, echocardiography, biochemical and haematological studies and some of them had Magnetic Resonance Imaging, carotid Doppler ultrasonography and cerebral angiography. The possible risk factors such as abortus, migraine, previous stroke, oral contraceptives (OC), alcohol and smoking were taken into account and etiologic factors were classified as premature atherosclerosis, cardiac abnormalities, extracranial vascular pathologies, others and unidentifiable causes. 16 patients had lesions involving the carotid. 5 had vertebrobasilar and 18 had both carotid and vertebrobasilar systems . In 7 patients cardiac pathologies, in 16 premature atherosclerosis were diagnosed. 3 patients had vasculitis, 5 had extracranial vascular pathologies and 10 had unidentified reasons. We did not find migraine, trauma, OC, as risk factors (OC) is not widely used in Turkey). Atherosclerosis and cardiogenic factors seem to be most important features in the etiology.

6
HYPERINSULINISM AS A PATHOGENETIC FACTOR IN CEREBRAL MICROANGIOPATHY. P Zunker, JL-Pozo, C Oberwittler, A Schick, H-Ch. Buschmann, E Bernd Ringelstein, *Münster, Germany*

A high insulin level is a well known risk factor for atherosclerosis. Microvascular endothelium is more susceptible to metabolic and mitogenic effects of insulin than large vessel endothelium. Additionally, high insulin levels impair spontaneous fibrinolysis by elevating plasminogen-activator-inhibitor levels. In this study we wanted to test the hypothesis that serum insulin and C-peptide levels are elevated in patients with cerebrovascular events due to microangiopathy as compared to cerebral macroangiopathy. Four subgroups of patients established by CT, MRI as well as extracranial and transcranial Doppler sonography findings were investigated. (1) patients with lacunes (N=18), (2) patients with subcortical arteriosclerotic encephalopathy (SAE, N = 19), (3) patients with strokes due to large vessel disease (N=33) and (4) normal controls (N=16). Fasting blood glucose, insulin and C-peptide levels were determined in all patients. The highest insulin levels were measured in the lacunar group (28,7 ± 10,7 mU/l), and the SAE group (20.7 ± 7,8 mU/l), i.e. those with small vessel disease. By contrast, insulin levels in patients with large vessel disease from the macroangiopathy (14,1 ± 5 mU/l) and from the control group (16,1 ± 4,9 mU/l) were rather similar. The same held true of the C-peptide levels and, to a minor extent, the blood glucose values. We conclude that an elevated insulin level plays a causative role in the pathogenesis of cerebral small vessel disease but much less, if at all, in occlusive disease of large cerebral arteries. Whether this adverse effect of elevated insulin levels is confined to atherosclerotic lesions of the vessel wall arteries or whether changes in hemorheology are also operative as well remains to be established.

7
CEREBRAL INFLAMMATORY ANGIOPATHY ASSOCIATED WITH COCAINE ABUSE. HISTOLOGICAL STUDY. E Diez-Tejedor, N Martinez, A Frank, M Gutierrez, M Lara, P Barreiro. *Madrid; Spain.*

Pathogenic mechanisms of vascular complications associated with cocaine abuse are still elusive. Recently, three cases of cerebral vasculitic have been described in cocaine addicts. We present our experience in a similar patient. A 21-year old male, intranasal cocaine user, showed time- and space disorientation, slowness in speech, movements and thinking, severe dressing and constructive apraxia, and a right hemiparesis with hemisensory loss. Later postural tremor and dystonia appeared. Haematological, biochemical, immunological examination, copper metabolism, lead, B12 vitamin, folic acid, and serological studies against the most frequent infectious agents in serum and CSF samples were normal or negative. The immunocytochemical CSF study showed a mild lymphocyte pleocytosis (63 cells/ml), intrathecal IgG synthesis, and 4 oligoclonal bands. EEG showed an important generalised cerebral dysfunction. TC and MRI showed global cortical atrophy. The cerebral angiography demonstrated an absence of vascularization in the territories of the precentral and left central artery group. A corticomenigeal cerebral biopsy demonstrated a transmural and

perivascular lymphocyte infiltration. Treatment with prednisone improved the symptoms and signs. These findings seem to confirm the existence of an inflammatory cerebral angiopathy associated with cocaine abuse. However, more clinical and experimental data are necessary to define with more accuracy the pathophysiology of this pathology.

8
EARLY DERANGEMENT OF VASOMOTOR TONE IN STROKE PATIENTS. GP Anzola, M Magoni, G Dalla Volta. *Brescia, Italy*

Early vasomotor abnormalities on the side of paralysis in stroke patients might be detected by telethermography (TT) and could predict the future development of reflex sympathethic dystrophy. We performed TT in 20 consecutive stroke patients admitted for ischaemic stroke within 5- 15 days (mean=7) of the ictus. Thermal differences(> 1°C) were detected between sides in either upper or lower limbs or both. Patients were thus subdivided in two classes: 1) Normally symmetrical vasomotor tone (i.e. negative TT); there were 8 patients 5 with right and 3 with left brain damage. None of them showed evidence of sensory disturbances. The mean motor deficit (on a 4- points scale) was 2.9. The lesion site was in centrum semiovale in 5 in; the temporo- occipital junction in 2 retrorolandic in 1 case. 2) Unilaterallly deranged vasomotor tone (i.e. cutaneous thermal asymmetry greater than 1%C).Twelve patients (4 with right, 8 with left brain damage) showed a relative hypothermia on the paretic side. Six of them had objective disturbance of cutaneous sensation. Mean motor score was 3. The lesions were clustered in two sites: the posterior parietal lobe (4 cases) and basal ganglia (8 cases). Many stroke patients show early disturbance of vasomotor regulation on the paretic side unrelated to the degree of motor impairment and or to the presence of sensory disturbances. The cerebral lesions associated with the contralateral vasomotor disturbances seem to be distinctively clustered in the posterior parietal cortex and in the basal ganglia. Whether these early signs of vasomotor derangement are predictive of subsequent reflex sympathetic distrophy will be determined in a ongoing prospective study.

9
THE PREVALENCE AND SOME RISK FACTORS OF' CAROTID ARTERY STENOSIS (CAS) IN THE NATIVE POPULATIONS OF CHUKOTKA AND NOVOSIBIRSK. A Tarasov, V Feigin, *Novosibirsk, Russia*

Studies of CAS prevalence in different populations are very important for understending of the mechanisms of atherosclerosis and cerebrovascular diseases development. In 1991- 1992 we examined 192 women and 170 men (25- 64 years of age, chukchi and eskimo) in Chukotka, and 128 women and ll6 men in Novosibirsk (25- 64 years of age, Russian) using Doppler ultrasonography. Prevalence of CAS among native population of Chukotka has been proved lower than among population of Novosibirsk (14,6% and 15,5% respectively). It also turned out that the prevalence of CAS among men of Novosibirsk has been 19,00 % and among women - 10.9 %. This ratio is inverse in the native people of Chukotka- Men with CAS were - 11,7%, but women - 17,4%. CAS was most wide spread among chukchi population, than among eskimo (76,9% and 23,1% respectively). Some differences in significance level of the stenosis risk factor have been founded in both populations. One of the most important GAS risk factor among the Chukotka population was smoking. Relative risk (RR) for men was 1.6, for women RR - 1.3. Novosibirsk men- smokers had 1.5 RR. Novosibirsk women with CAS didn't smoke. High prevalence of smoking has been found among Chukotka population, especially in women, among Novosibirsk. population - 57% and 3% respectively. There were more important risk factors among Novosibirsk population, including high levels of total cholesterol and triglycerides of blood serum.

10
STROKE REGISTRY IN THE SAGUENAY REGION, CANADA. MG Beaudry, S Carrier, Chicoutimi, *Quebec, Canada*

We present our results from a community-based stroke registry in the Saguenay region, Quebec, Canada, for the first 18 months of data collection (Oct 91 -Apr 93). We actively sought referral from all physicians in a well defined geographical district (population=172,790 in 1991). We used data from private office, hospital charts or separation form in case of rapid death. Most cases were seen by collaborators to the study (neurologist or internist) as well as by a research nurse. Akin to other European stroke registries, we observed a high rate of CT scanning (87%, 2/3 within 3 days), a high hospitalization rate (95%) and average hospital stay of 40.3 days. We collected 315 cases of incident stroke. During that period, 65 cases with recurrent strokes, 100 TIAs and 12 non-stroke cases were seen. Crude incidence rate for first-ever stroke was 122/100,000. Rates were almost similar between men 128/100,00) and women (116/100,000). Age-specific rates for patients 75 years old and over were 1497/100,000 for men and 1300/100,000 in women. Our region has had higher stroke mortality rate than the rest of Canada which itself ranks amongst the lowest in the world. Stroke incidence in our region is comparable to many European countries having established similar registries.

11
STROKE IN PATIENTS WITH KNOWN HEART DISEASE: PREDICTORS OF CARDIAC VERSUS NON CARDIAC ETIOLOGY. IL Henriques, J Bogoussslavsky, G van Melle. *Lausanne, Switzerland*

Stroke patients with known heart disease do not always have a cardioembolic cause for their stroke. We tested the hypothesis that associated factors could predict a cardiac vs. a non cardiac cause for stroke. From 209'7 patients with first ischemic stroke prospectively included over 10 years in the Lausanne Stroke Registry(LSR), 734 had known heart disease (history of myocardial infarct (MI), angina, arrhythmia(ARR), left ventricular hypertrophy(LVH) or valvulopathy). We considered cardioembolism(CE), large artery disease(LAD), lacunar(LI) and other causes(OC) as defined in the LSR. We used logistic regression and stepwise selection of variables. Only 367 patients had a cardioembolic cause for their stroke which was strongly associated with previous ARR (Odds Ratio: 17.6; 95% Confidence Interval: 11.2-27.8). Non ARK patients with previous MI(115) had 32% of non cardiac causes, and no predictor was found. In patients without history of MI or ARR only 20% of strokes were cardioembolic, independently of previous history of angina, LVH or isolated valvulopathy. In conclusion half of the patients with heart disease had a non-cardiac cause of stroke. In patients with previous ARR or MI, cardioembolism was the most likely cause of stroke. For the other patients history of hypertension, smoking and TIA indicated a potential non-cardiac cause. The distribution of causes was then similar to what was found in non-cardiac patients.

12
FAMILIAL INTRACRANIAL ANEURYSMS IN THE SAGUENAY-LAC SAINT-JEAN REGION (QUEBEC, CANADA): INCIDENCE RATES OF RUPTURED ANEURYSMS. J Mathieu, L Perusse, P Allard, C Prevost, L Cantin, JM Bouchard, M De Braekeleer, *Chicoutimi Canada*

The Saguenay-Lac Saint-Jean (SLSJ) region is a geographically isolated area (population 286,155) located in the Northeastern part of the Province of Quebec (Canada). Using a population- based register, the genealogical reconstruction of 463 individuals with intracranial aneurysm showed familial aggregation (the presence of aneurysm in two or more first- to third-degree relatives) in 149 (32.2%) of them; this proportion is much higher than reported elsewhere. As part of an ongoing project to assess a genetic predisposition to intracranial aneurysms in the SLSJ population, the objective of the present study was to determine whether increased age- specific ruptured cerebral aneurysms were observed in this population. All cases of ruptured aneurysms which were hospitalized during the 1973 to 1992 period were collected. Age adjusted rates were obtained by applying age- specific rates to the world population. We identified 413 cases of ruptured aneurysms. The age adjusted incidence rate is 7.2/100,000/year (6.2 for men, 8.1 for women), which is quite similar to incidence rates found in other studies. Although the mean age at time of rupture is younger (46.6 years(13.8) than usually reported, the age- specific incidence rates are identical to other studies. The results of this study do not support the hypothesis of a genetic predisposition to intracranial aneurysms in the SLSJ population. In this region, very large kinships are common; therefore, the high familial occurrence may be mostly explained by accidental aggregation.

13
EVENT RELATED AUDITORY EVOKED POTENTIALS AND EPILEPSY. C Agbo, JP Neau, AM Tantot, M Dary-Auriol, P Ingrand, R Gil. *Poitiers, France*

Clinical or neuropsychological evaluation of cognitive deficit in epilepsy may be subject to misinterpretation. The present study utilised a class of long latency auditory event- related potentials known as P300 as an objective electrophysiological index of cognitive function in 85 patients with epilepsy. In addition, these patients were subjected to a set of neuropsy-

chological tests. Epileptic patients had significantly longer latencies of N200 and P300 than normal controls. However, increased latencies of the so-called exogenous potentials N100 and P200 were also observed in epileptic patients. A significant correlation was found between P300 latency and Trail Making (A and B) tests. P300 latency correlated also significantly with the duration of illness and the number of drugs used. Smaller increased in N200 and P300 latencies were observed in patients treated by carbamazepine and sodium valproate; the most prolonged latencies were observed with phenobarbitone and phenytoin. P300 latency was longer in patients with partial seizures and in patients with polytherapy. Evoked potentials related with cognition might in the future constitute a fruitful method of evaluating early cognitive dysfunction in patients with epilepsy with regard to frequency and evolution.

14
METHOD FOR MEASURING THE INFORMATION. VALUE OF CLINICAL DATA IN PATIENTS WITH EPILEPSY. D Baltadjiev, D Zekin, K Sabey; *Sofia, Bulgaria.*

In the study is presented a new method for measuring the information value of clinical data in patients with epilepsy, developed by the authors. It is based on the Theory of chances and estimate descriptive value of data. This means to what extent a given parameter is able to describe a given diagnosis. Performance of the method is done as an information coefficient (I), calculated by multiplying a posteriory probability ($P(S_i/D_j)$) by the number of diagnoses (n) minus one: $I=[n.P(S_i/D_j)-1].L$ (L=100). To assess the reliability of the method it was compared with other similar methods - Melnikov's, Bihovski's. The study was done using a diagnostical database of 120 cases. Forty-four cases with generalised seizures, twenty-two - with partial seizures, eight - with complex partial seizures, six - with partial seizures secondary becoming generalised and forty healthy volunteers. 117 parameters with 256 possible combinations were examined. Seventy-four findings of high diagnostic usefulness were classified in seven groups: family history - 9 parameters, medical history - 7, etiologic factors - 5, clinical picture of the seizures - 17, provoking seizures factors - 9, EEG data - 15, sleep disorders - 14. These results were used for the development of a decision support system. The method determines more accurately the information value of clinical data and give the results in convenient scale, close to the physicians' view of relative quantity.

15
RETROSPECTIVE ANALYSIS OF A SERIES OF IDIOSYNCRATIC REACTIONS TO MEPHENYTOIN. CP Gennaula, BA Pope, *Pittsburgh, PA, USA*

A six year retrospective analysis of idiosyncratic reactions to mephenytoin was undertaken with an emphasis on symptomatology and time course of recovery. Efficacy of mephenytoin therapy is long established, but use is limited by reported idiosyncratic reactions. Nirvanol, the principle metabolite and active agent of mephenytoin has a long half- life of 96 hours. A retrospective analysis of the computerized medical records at the University of Pittsburgh Medical Center over a six year period (1/87 through 1/93) was completed in search of all idiosyncratic reactions to mephenytoin requiring inpatient care. Three cases were found during the above time period. Symptomatology included: fever and maculopapular rash (3), diffuse lymphadenopathy and pharyngeal erythema (1), abdominal (1), and scattered arthritis with subcutaneous nodules of the lip and distal thighs confirmed as erythema nodosum by biopsy (1) . The time to symptom resolution after the discontinuation of mephenytoin averaged 13 days (range 8- 23 days). These cases illustrate a variety of idiosyncratic reactions to mephenytoin, along with the more common fever and rash. No previous cases of biopsy proven erythema nodosum related to mephenytoin were found in the literature. The prolonged course of illness in these patients is likely related to the long drug half life, but poses significant diagnostic uncertainty in patients remaining ill several weeks after discontinuation of medication.

16
DACRYSTIC EPILEPSIA: WHERE ARE THE CAUSAL LESIONS? D Caparros-Lefebvre, I Girard- Buttaz, JP Pruvo, H Petit, *Lille, France*

Dacrystic epilepsy is a very uncommon form of focal epilepsy, associated with involuntary crying. The nature and location of the underlying lesions are unknown. A 33 year old man, with an encephalopathy of unknown etiology, had an history of epilepsy for 30 years. Different types of seizures were seen, including grand mal, and frontal attacks. Epilepsy was associated with mental retardation and behavioural disorders. At the age of 33, he was admitted for repetitive general convulsions. Epilepticus status lasted for 2 weeks and improved with vigabatrin and clonazepam. General seizures, frontal motor convulsions with arm and trunk antepulsion, and dacrystic attacks were seen. The latter seemed to be like normal crying because they were accompanied by lacrimation, contorted and mournful facies, and sobbing sounds. EEG patterns included theta and delta activity with rhythmic slow wave epileptic activity, predominating in the right posterior and temporal areas. CT scan was normal. MRI showed right cerebral atrophy, prevailing in the infero- postero temporal region, with right temporal horn enlargement. This is the Seventh case report of dacrysis epilepsy and the First with MRI study. This case report suggested that the occipito- temporal gyrus and para- hippocampic gyrus of the non-dominant hemisphere may be involved in dacrystic epilepsy, which agrees with previous report.

17
CARBAMAZEPINE-RELATED TOXICITY FOLLOWING INTRODUCTION OF VIGABATRINE AS AN ADD-ON THERAPY IN REFRACTARY PARTIAL EPILEPSY. D Hipola, M Martin, S Giménez-Roldan, *Madrid, Spain.*

Nine (30%) out of 30 patients suffering from either partial (n=27) or secondary generalized seizures (n=3) refractory to treatment, developed unwanted side-effects following vigabatrine (GVG) (2,000-3,000 mg/d) introduction (dizziness, somnolence, blurred vision, diplopia). Drug-related toxicity resolved in 6 patients following a slight reduction in carbamazepine (CBZ) dosage and in another one following reduction of both CBZ and GVG, mean serum CBZ drug levels dropping from 7.9 ug/ml to 7.2 ug/ml, without increasing seizure frequency. A 34,2% reduction in seizure frequency from the overall group occured by 6 months following GVG introduction. An average of 26,4 months follow-up was completed in 16 patients, benefit being maintained in 13. However, attempt to gradually reduce concomitant medication resulted in an increase in seizure frequency in 6 out of 9 patients .We believe that GVG may potentiate the development of CBZ-related toxicity without significant changes in CBZ serum levels. Interesting enough, long-term benefit from GVG introduction in refractory seizures seems to depend on the maintainance of associated comedication

18
USEFULNESS OF CRANIAL MRI IN LONG TERM REFRACTORY PARTIAL SEIZURES. V Ivanez, E Diez-Tejedor, P Barreiro. *Madrid; Spain.*

MRI is more useful in the diagnosis of refractory partial seizures (RPS) than CT, regardless to the duration of the disease. This study compared, the usefulness of MRI in managing long term RPS patients with normal CT scan. Twenty nine patients (13 men, 16 women) with a mean age 39.7 ± 15.2 years who had had RPS for over 10 years 'mean 24.1 ± 11.2) with normal or non-specific CT scans were studied with MRI. Seizures foci were temporal in 20, frontal in 7 and occipital in 2 cases. Seven patients (24%) showed abnormalities on MRI; T2 weighted hyperintensity in the hippocampus or other sites (4 cases) possibly abnormal neuronal migration (2 cases), or an expansive lesion (one case). These lesions correlated semiologically and/or electroencephalographically with the seizures. The presence of these MRI lesions correlated neither with patients age at onset, now the duration of the disease. In long term RPS, MRI is diagnostically more sensitive than CT, therefore we fell it is the neuroradiological procedure of choice. Although MRI is primarily used in long term RPS when surgery is planed to heat epilepsy, it can also reveal structural lesions that may require surgery for their own sake.

19
MIDDLE-LATENCY RESPONSE AND SLOW CORTICAL POTENTIAL IN PATIENTS WITH GENERALIZED EPILEPSY. G Japaridze. *Tiblisi; Republic of Georgia.*

Middle-latency responses (MLRs) and slow cortical potentials (SCPs) were registered in 15 patients with generalized epilepsy untreated previously with anticonvulsants. Monaural clicks served as the accoustic stimuli in recordings of MLRs while SCPs were evoked by 1 kHz tone bursts.

The intensity of the stimuli was held at 70 dB nHL. Repetition rate of cliks was 10/1s and that of tone bursts was 1/2s. The active, reference and ground electrodes were attached to the vettex, contralateral and ipsilateral earlobes, respectively. Amplitudes and peaklatencies of averaged weveforms were estimated abd evaluated statistically. The obtained data were compared with those in healthy individuals. MLS NaPa and PaNb amplitudes showed a trend toward higher values in epileptic patients vs control group, although the difference appeared statistically not significant. MLR Na, Pa and Nb peak-latencies were longer in patients, the difference being significant with regard to Nb peak-latency only. SCP P1N1 anf N1P2 amplitudes were significantly greater in patients while N1 and P2 peak-latencies were longer. Considering the MLR and SCP generation mechanisms, it is suggested that pathological alterations in epilepsy involve both modally specific as well as non-specific auditory structures.

20
ANALYSIS OF EPIDEMIOLOGICAL DATA ON EPILEPSY IN SPAIN. JL Carrasco, I Picomell, JL Herranz, JA Macias, M Nieto, M Noya, L Oller. *Santander, Valladolid, Sevilla, Coruna & Barcelona, Spain.*

An epidemiological study was conducted in Spain in patients with epileptic disease. The number of patients recruited was 4,432 presented by 202 specialists. Interim results provide the following data: Mean age of patients was 25.9 + 18.13 years (33% were under 14 years), of which 44.5% were women and 55.5% men. Fifteen percent of all patients studied were significant or moderate alcohol drinkers and just under 1% were drug users. Patients with a regular job represented 55.3%, while 26.6% were unemployed. Children attended school normally in 44.2% cases; 15.2% showed poor academic achievement, while the rest comprised a group needing psychotherapeutic support, special teaching or non-schooling. A familial background of first grade epilepsy was seen in 6% cases; 10.8% exhibited grade 2 epilepsy of maternal lineage, and 8,5% cases had paternal lineage. In 89.3% cases antiepileptic medication was being taken with adverse effects being observed in 28% of all treated patients, the most common symptom observed being drowsiness followed by gingival hyperplasia. With regard to the type of epilepsy, the most frequently reported cases were site-related syndromes (51.4%) followed by epilepsy and extensive syndromes (43.9%). As for the quality of life scores, 30.6% considered they were ill and 31.3% that their condition had an influence on their lives.

21
ACTIVATION OF EPILEPTOGENIC ACTIVITY AFTER SLEEP DEPRIVATION. G Kiteva-Trencevska. *Skopje; Macedonia.*

The aim of the paper is to show the activation of epileptogenic activity after sleep deprivation /SD/ of 24 hours, in patients with epileptic seizures, when conventional and quantitative EEGs are normal. EEG after SD was performed, during wakefulness and non REM sleep in 21 patients with epileptic seizures. Epileptic seizures were classified as: complex partial seizures, partial seizures secondary generalized and generalized tonic-clonic seizures. The control group of 6 persons underwent the same protocol. EEG abnormalities during wakefulness after SD were: focal spikes and sharp waves in 5 patients; bilateral frontal spikes and sharp waves in 2 patients; focal theta activity in 2 patients; generalized intermittent theta activity in 1 patient. There were no abnormalities during wakefulness in 11 patients. EEG abnormalities during non REM sleep were: focal spikes and sharp waves in 11 patients. There were no abnormalities during non REM sleep in 10 patients. In 5 patients there was no activation of epileptogenic activity during wakefulness and non REM sleep after SD. There were no EEG abnormalities in the controls. EEG after SD during wakefulness and non REM sleep is an important diagnostic tool in patients manifesting epileptic seizures.

22
THE INTERACTIONS OF PHENOBARBITAL AND PHENYTOIN WITH CARBAMAZEPINE AND CONCENTRATIONS, CONCENTRATION RATIOS AND LEVEL/DOSE RATIOS IN EPILEPTIC CHILDREN. MR Delgado, H Liu. *Dallas, Texas, USA*

The effect of phenytoin (PHT) or phenobarbital (PB) co- medication on the concentrations, concentration ratios and level/dose ratios of carbamazepine (CBZ) and its metabolites was investigated Compared with patients on CBZ monotherapy, serum CBZ level/dose ratios in patients with CBZ polytherapy were decreased, while carbamazepine- 10, 11- epoxide (CBZ- E) and trans- 10, 11- dihydroxy- 10, 11- dihydro- CBZ (CBZ- H) concentrations were increased The concentration ratios of CBZ- H/CBZ and CBZ- E/CBZ were also higher in patients taking CBZ+PHT (n=17) or CBZ+PB (n=13) than patients on CBZ alone (n=57) There were no significant differences in CBZ- H/CBZ- E concentration ratios, the free fractions of CBZ and its metabolites, and CBZ- E or CBZ- H level/dose ratios among the three groups of patients. Additionally, positive correlations between CBZ- H/CBZ or CBZ- E/CBZ concentration ratios with serum PHT concentration were observed, but not with serum PB concentration The results suggest that PHT has a potent induction effect on CBZ epoxidase, while PB is a moderate inducer More frequent serum concentration monitoring may be needed when co- medication of PHT or PB with CBZ is required, or in the process of tapering and discontinuing the co- medications.

23
PREVALENCE OF EPILEPSY IN ADULTS IN NORTHEASTERN MADRID A Luengo, J Parra, J Colas, MJ Fernandez, R Manzanares. *Madrid, Spain.*

We made a survey to determine the prevalence of Epilepsy in adults in a closed sanitary area in the Northeast of Madrid, with a total population of 119,236 inhabitants, completely controlled by the Public Health System. Four villages (Coslada, San Fernando de Henares, Mejorada del Campo and Velilla de San Antonio) formed the area, with 7S,231, 27,088, 13,862 and 3,057 inhabitants respectively. The survey was carried out during two years. Prevalence day was established on July, 1993. First-phase was carried out by SS Primary Care physicians and during 100 consecutive weeks, 130,250 patients were screened according to WHO protocol (1982). 589 patients passed to the second phase, performed by senior neurologists with EEG, CT and MRI when necessary. Sensitivity obtained for consciousness disorder was 98,5 % . Specificity was studied in the second-phase in 183 healthy people and was 92,7%. TLAE criteria were used. Primary Generalized Epilepsy was present in 25 men and 31 women; symptomatic Generalized in 3 men and 3 women; Partial Epilepsy in 62 men and 61 women had, 23 men and 24 women had no precise diagnosis. Generalized/Partial Ratio was 0,5. Sex/ratio was O,94. Prevalence of epilepsy was 1,77 in men and 1,87 in women. Age adjusted prevalence ratios are also provided.

24
pH AND AMINO ACIDS IN SERUM, CSF AND ARTIFICIAL FLUIDS. ME Kornhuber, B Conrad, *Munich, Germany*

Amino acids (AAs) are important neurochemical parameters because of their roles as neurotransmitters, neurotoxins and key molecules in metabolism. 21 AAs were studied in an artificial fluid (A), in blood serum samples (B) and in CSF (C) under different pH conditions, storage duration, storage temperatures and deproteinization conditions. Close to neutral pH no significant AA changes were noted after storage for up to 1 year (A and B). Furthermore, at neutral pH no significant AA changes were observed after up to 3 freeze-thaw cycles (A and B). Under acid and alkaline conditions most of the measured amino acids were entirely stable. Glutamine and Asparagine were most susceptible to hydrolysis to glutamate and aspartate, respectively, under alkaline conditions more than under acid conditions (A, B, C). These changes were dependent on the pH-level as well as on the duration and temperature of storage. The mode of deproteinization was of no considerable influence on AA concentrations, if samples were stored at neutral pH. These results have implications for any study on AAs.

25
IMMUNOGENETIC ASPECTS OF EPILEPSY.V Malashkhia, G Orkodashili, *Tbilisi, Georgia*

Twenty-six patients with idiopathic and 28 patients with symptomatic generalised epilepsy were studied. Microversion of the method of mixed allogenic lymphocyte culture (ALMR) of mother (responder) an child (stimulator) was applied (in Cook's plotting boards according to Dupont B. et al.,1980). Spontaneous cultures of responder cells served for control.

ALMR value were expressed as delta counts per minute (cpm). Cpm of T-cells (responder) cultured with mitomicine C treated T-cells (stimulators) minus cpm or T-cells cultured alone (control). Results: Cultivation of child's T-Lymphocytes (responders) with those of the mother blocked by mitomicine C (stimulators) in idiopathic epilepsy patients was equal 18980±6750 ($p< 0.01$ as compared to control group), in symptomatic epilepsy patients 7092±1430 and did not differ from the control group ($p> 0.05$). High rate of stimulated lymphocytes in idiopathic epilepsy patients shows the incompatibility of lymphocytes of child and mother ACC. To HLA-D antibodies. The analysis of certain cases proved that the grater is the genetic difference between the lymphocyte antigens of the child an mother, the higher is the stimulation effect of lymphocytes. Mixed lymphocyte reaction in culture allowed delicate differential study of HLA-D antigen's complex of the child and mother an revealed the presence of immune disturbances in idiopathic epilepsy patients.

26
EPILEPSY IN THE EDERLY: PREVALENCE, ETIOLOGY AND PROGNOSIS. M Martinez, I Bonaventura, G Porta, I Martinez, A Fernandez and M Aguilar. *Terrassa, Barcelona; Spain.*

Epidemiological studies showed an increase in frequency of epilepsy after age 60 years. However both etiology and prognosis of late onset epilepsy remain undefined in more than 50% cases. Ninety patients, seen in the Neurological service of the Hospital Mutua de Terrassa for unprovoked seizures with onset after 60 years were retrospectively studied. They represent 15% of all patients with unprovoked seizures during the last three years. All patients had a CT scan. A vascular cause was by far the most frequent (57%). This included multiple subcortical lacunar infarctions (19%) and sequelae of hematoma (7%). Six patients with ischemic cortical lesions had no previous recognisable stroke. Five of these had lesions in the parietal lobe. Cryptogenic seizures accounted for 27%, followed by posttraumatic epilepsy (4 patients) and non-vascular dementing illnesses (4 cases). Tumor was poorly represented (3 cases). Primary generalized epilepsy was diagnosed in only one patient. Prognosis was very good (83% seizure free at follow-up > to 6 months). Toxicity was however unusually (11% of the patients had to change or stop medication because of side effects). We conclude that vascular diseases are the main etiological factor in epilepsy occurring after age 60. Prognosis of late-onset epilepsy is good, although toxicity of antiepileptic drugs is a significant problem for management.

27
PHOTOSENSITIVE EPILEPSY: AN UNUSUAL CASE WITH SELF INDUCED SEIZURES. P Masnou, A Drouet, *Le Kremlin-Bicêtre, France*

We report on a 22 year old woman who presented with photosensitive primary generalised epilepsy associated with self induced absence seizures. The epilepsy started at the age of seven. The trig erring stimulus consisted in an alternative movement of the right hand in front of here eyes, in artificial or sun light. These attacks provoked a sensation of pleasure and were sometimes self induced during sexual behaviour. By contrast, the patient never experienced seizures induced by TV, video games or stroboscopic lights. She presented a tonic clonic seizure only once a the age of 15, provoked by sleep deprivation. Psychiatric examination found an immature personality. IQ was 90. This self induction behaviour was interpreted as the equivalent of masturbation. A conflictual mother-daughter relationship was obvious from the projective tests. EEG recordings showed photosensitivity mainly during low frequencies intermittent light stimulation. In one occasion, only, EEG recorded absence seizure during ILS (5hz). The patient was given valproic acid during a few months which stopped the self induced seizures. Subsequently, she refused to continue any antiepileptic therapy.

28
ANTI-PLATELET ANTIBODY IN A PATIENT TREATED WITH SODIUM VALPROATE. M Dreyfus, P Masnou. J Cartron, MC Morel-Kopp, G Tchernia, C Kaplan. *Le Kremlin Bicêtre, France*

The treatment of a frontal astrocytoma in a 37 year old woman included surgery and irradiation, followed by a long term therapy with sodium valproate 1,500 mg/day. Four years later, the patient underwent a surgical repair of a local baldness. In spite of preoperative platelet count of $160x10^9/l$, without any coagulation abnormalities, an hemorrhage developed, requiring the transfusion of 2 red blood cell units. An extensive hematologic study showed a platelet count ranging between 115 and $200x10^9/l$; Prothrombin time, activated partial thromboplastin time were normal, as well as factors V, VII, X, II, XIII, Fibrinogen, a2-antiplasmin, Willebrand factor, and bleeding time. Unexpectedly, platelet aggregation to collagen and arachidonic acid were markedly decreased, suggesting a platelet release defect. An anti-platelet antibody directed against GPIa IIa, and an IgG anti-erythrocyte antibody (which specificity was not detected) were evidenced, without any other biological sign of auto-immunity. Valproic acid was stopped and replaced by Carbamazepine. Platelet function had returned to normal 3 weeks later, whereas anti-platelet and anti-erythrocyte antibodies were no longer detectable. In conclusion, the anti- GPIa IIa antibody which might have impaired platelet function and induced a bleeding episode was associated with a sodium valproate treatment. This drug has already been incriminated for the occurrence of auto-immune thrombocytopenia. However, further studies are needed in order to ascertain a causal relationship betwen treatment with sodium valproate and occurrence of anti GPIa IIa and anti-erythrocyte antibodies.

29
MONOTHERAPY OR POLYTHERAPY FOR EPILEPSY REVISITED A QUANTITATIVE ASSESSMENT. MW Lammers, YA Hekster, A Keyser, H Meinardi,WO Renier, *Nijmegen, The Netherlands.*

Since the 80's several authors have advocated the use of monotherapy in the treatment of epilepsy. However little evidence was provided. In this prospective study we compared the prevalence and severity of side effects in patients treated with monotherapy and with polytherapy with similar exposition to medication, expressed in PDD/DDD ratio's, using clinimetric indexes. We also assessed the prevalence and severity of side effects of AED in all our patients on polytherapy. We applied a neurotoxicity score and a systemic toxicity score, which score the severity of side effects. The data of 292 patients, 161 on monotherapy and 131 on polytherapy with similarPDD/DDD ratio's, were reanalysed. In the indexgroup (monotherapy) the maximum PDD/DDD ratio was 2.0. No difference was seen in either the prevalence or the severity of side effects between both groups, with the exception of sedation and cognitive impairment.These two side effects ocrurred more frequently in the group of patients on polytherapy, although the severity did not differ from that of patients on monotherapy. The patients on polytherapy with a PDD/DDD ratio >2.0 (n=134) was compared separatelywith the group on polytherapywith a PDD/DDD ratio of <=2.0 There was little increase of either prevalence or severib of side effects as a function of dosage. We conclude that observational studies are unsuited to provide an answer to this question, due to uncontrollable factors, like duration of disease, and therapy bias.

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DIPOLE MODELING IN PATIENTS WITH REFRACTORY PARTIAL SEIZURES AND AN UNDERLYING INTRACRANIAL STRUCTURAL LESION. PAJM Boon, M D'Have, *Gent, Belgium.*

In 15 patients with a mean age of 34 years and a mean duration of refractory partial seizures of 17 years 1.5 T MR demonstrated intracranial structural lesions (spaceoccupying:n=9; atrophic: n=6) and video-EEG monitoring showed complex partial seizures. Four patients underwent additional intracranial EEG monitoring that demonstrated hippocampal seizure onset in all. Spatiotemporal dipole mapping of interictal epileptic discharges revealed 2 distinct dipole types. Patients with lesions in the medial (and lateral) temporal lobe uniformly presented a stable, combined dipole that consisted of a radial and a tangential component with a high degree of elevation relative to the axial plane. Patients with extra temporal lesions had a dipole which was less stable and had a predominant radial component. Dipole modelling of epochs of early octal discharges revealed a striking correspondence with the interictal findings in individual patients. Interictal spike voltage topography and corresponding dipole mapping provided additional and reliable information that was relevant in surgical candidates for refractory partial epilepsy, e.g. by demonstrating in some patients that the medial temporal structures were not primarily involved. Octal dipole modelling revealed concordant results with interictal data. It shows promising but needs further confirmation and validation in a larger patient population with intracranial EEG recordings.

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SUBACUTE SCLEROSING PANENCEPHALITIS, PROGRESSIVE MYOCLONUS EPILEPSY AND LAFORA BODIES: differential diagnosis in a particular case. P Boon, G de la Meilleure, B Kint, J de Reuck, *Gent, Belgium.*

A 17-year-old Pakistani boy, presented with myoclonic seizures and progressive cognitive impairment. Video-EEG monitoring demonstrated frequent myoclonic jerks involving all extremities and the head and showed simultaneously destructured and attenuated background activity and periodic bisynchronous discharges of irritate delta activity. MRI of the brain showed a limited area of sub cortical gliosis in the right occipital lobe. 1502-PET scan of the brain showed widespread and small cortical areas of decreased oxygen metabolism. The tentative diagnosis of progressive myoclonus epilepsy was made and treatment with sodium valproate was initiated but proved to be unsuccessful. CSF analysis showed an elevated protein content and a mild pleocytosis. Serum and CSF IgG and IgM against measles were markedly elevated. The initial diagnosis was questioned and the possibility of subacute sclerosing pan encephalitis (SSPE) was considered. Treatment with isoprinosine, interferon and clonazepam was started. Skin biopsy revealed Lafora bodies, while results of muscle biopsy were irrelevant. After a 4-year follow up the patient is alive with a cognitive deficit and rare myoclonic seizures. This fully documented case demonstrates the diagnostic pitfalls in differentiating progressive myoclonus epilepsy from SSPE.

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COMPUTERISED PERIMETRY AND VISUAL EVOKED POTENTIALS IN ACUTE MULTIPLE SCLEROSIS: EVALUATION OF THERAPY. P Cruz, A Cadilha, R Almeida, M Goncalves, M Pimenta, *Lisbon, Portugal*

Computerised perimetry (CP) and visual evoked potentials (VEP) are sensitive methods to detect clinical and subclinical neuro- ophthalmologic abnormalities in multiple sclerosis (MS) patients. Fifteen patients with probable or definite MS – remission- relapsing form – in acute phase were selected. We studied the campimetric normalities with Octopus programs 31 and Delta, and the evoked responses (pattern reversal) before and after corticotherapy. VEP was more often abnormal than CP. Our results confirmed the sensitiveness of these methods in detecting and quantifying the benefit of this therapy, in patients with clinical or subclinical neuro- ophthalmologic abnormalities.

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NO CORTICAL ATROPHY IN REFRACTORY EPILEPSY. LMP Ramos, TW Polder, CA Broere, L Polman. *Utrecht, Nijmegen, The Netherlands*

Refractory epilepsy is defined as failure of optimal treatment to provide adequate control of generalized fits. The risk of generalized fits is in the damage to the CNS due to the repeated periods of hypoxia. Prolonged oligaemic hypoxia may result in almost total destruction of the cerebral cortex (Hume et al 1984) . The aim ofthe present study is to compare the neocortex volume in vivo in controls and in patients with refractory idiopathic epilepsy. MRI scans of 10 patients (4 males, 6 females) and 16 controls (6 males, 10 females) without neurological deficit were used. Mean age was 29,9 years (SD 11,1) in epilepsy patients and 37 years (SD 16,6) in controls). Axial MRI scans (Gyroscan, 1.5 Tesla) were obtained (slice thickness 8 mm, interslice gap 1.6mm). A spin-echo sequence (TR/TE = 2,000/50) was used for a high contrast between neocortex and white matter. Cavalieri's principle provides an unbiased volume estimator ((Gundersen, 1986). The coefficient of error ranged from 0.017 to 0.041 in the individual measurements.

Neocortex volume (cm^3)	Controls	Patients	Wilcoxon
Male	753.7 (SD 101.1)	723.8 (SD 75.6)	n.s
Female	728.5 (SD 61.19)	741.6 (SD 50.9)	n.s
All	745.7 (SD 75)	734 (SD 62.6)	n.s

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TOPOGRAPHY OF EEG BACKGROUND ACTIVITY FOR THE CLINICAL CLASSIFICATION OF EPILEPTIC PATIENTS A PROSPECTIVE PILOT TRIAL. I Rother, M Rother, *Jena &, Wiesbaden, Germany*

The EEG topography of spectral parameters is said to be more sensitive to focal and generalised changes of the EEG topography than visual analysis (vEEG). Although not conclusive, assymmetries of the EEG background activity may help to locate the epileptogenic focus (Nuwer 1988, Panet-Raymond & Gotman 1990). We tested prospectively whether this quantitative EEG method (qEEG) provides additional information on the clinical classification of epileptic patients. 21 patients (8 partial epilepsy, 7 partial epilepsy with secondary generalisation, 6 primarily generalised epilepsy) subsequently admitted to a neurological ward were compared to 35 controls using different recording modes (spontaneous, vigilance controlled) and references (A1+A2, Fpz). Statistics included (1) individual differences to a control population (z-statistic), (2) nonparametric tests for group differences, (3) determination of the best parameter set from qEEG, vEEG and clinical data (variable selection procedure of the multiple regression analysis).. qEEG was not superior to vEEG and clinical data despite statistically significant differences to healthy controls for both the single patients and the various clinical groups. The best qEEG parameter was the theta frequency band of the Fpz-referenced EEG. Simple clinical data show best results of multiple regression (The table could not be inserted in the abstract, The Editor). Overall, a combination of qEEG, vEEG and clinical data was selected to optimally distinguish between various groups of epileptics.

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LOCALIZATION OF INTERICTAL FOCUS IN FRONTAL LOBE EPILEPSY USING PET. G Schlaug, S Arnold, H Holthausen, G Wunderlich, A Ebner, H Luders, ow Witte, RJ Seitz. *Dusseldorf & Bielefeld, Germany*

Resective surgery in patients with medically intractable frontal lobe epilepsy (FLE) is dependent on a precise localization of the epileptic focus. We investigated the sensitivity of interictal FDG-PET for focus localization in relation to non-invasive EEG recordings and magnetic resonance imaging (MRI). Regional cerebral glucose metabolism (rCMRGLc) was measured with [^{18}F]-fluoro-2-D-deoxyglucose during resting wakefulness. The rCMRGlc was determined quantitatively in anatomically oriented regions of interest (Rols) as well as qualitatively by two investigators in a blinded manner. In 12 out of 14 patients in which surface EEG and video-monitoring already lateralized the epileptic focus, qualitative FDG-PET analysis revealed a focal hypometabolism corresponding to the presumed focus. In two of those patients FDG-PET was nonlocalizing. In 8 patients with nonlateralizing epileptic activity using surface EEG, qualitative FDG-PET analysis revealed a regional hypometabolism in 5 patients. only 7 of 22 patients showed a lateralizing structural abnormality on MRI corresponding to a focal hypometabolism in FDGPET. Quantitative analysis of homologue Rols increased sensitivity of FDG-PET up to 90%. It is concluded that interictal FDG-PET has a high sensitivity in localizing focal metabolic abnormality as a marker for the epileptic region, providing a guidance for invasive EEG-investigations.

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CALCIUM ANTAGONISTS IN THE TREATMENT OF DRUG RESISTANT EPILEPSY. LL Serra, B Gallicchio, FP Serra, F Rotondi, *Naples, Italy*

Bearing in mind the beneficial effects on many CNS pathological conditions exerted by Calcium antagonists (CA), especially in epileptic disorders, we have assessed the clinical relevance of CA as "add on" care of intractable epilepsy in ten patients (6 males and 4 females) aged 22-47 years with drug-resistant partial complex epileptic seizures (DREPI) after ineffective treatment of average 13.7 years, free from general degenerative or dysmetabolic CNS diseases, submitted to an open trial with two CA in a prospective study lasting 48 months. Patients received firstly for six months a daily 10 mg flunarizine (F) administration and after a six month withdrawal (W) were treated for other six months with 30 mg nimodipine (N) daily administration. After another W patients received a second six month daily 30 mg N administration and after another W a second F administration. The seizure free state (SFS), the EEG photosensitivity range (PSR) and the psychic symptoms were considered prior, during and after each CA administration and W. SFS increased of 43.23% after F treatment with a slight reduction to 41.86% vs. basal values after withdrawal. SFS increased of 33.8% after N treatment with return to 11.3% vs. baseline-values after withdrawal. The PSR was reduced in 4 patients after F treatment, lasting for six months after W in 3 patients. PSR was reduced in 5 patients after N treatment, lasting for six months in 3 patients. A slight reduction in concomitant mood disorders have been observed after second F administration. The above results could be probably accounted for the different effect on depolarisation/calcium influx played by the two tried CA.

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CONVULSIVE SYNCOPE AND BRAINSTEM LESION. U Wieshmann, A Bock, H Meierkord. *Berlin; Germany.*

Convulsive syncope is frequently encountered in medical practice and its phenomenology may resemble focal epileptic seizures. In this report we describe a patient with convulsive syncope without changes in heart rate and blood pressure during the episodes. The non-epileptic nature of the convulsions was identified by video-EEG telemetry. Magnetic resonance imaging (MRI) and angiography revealed displacement of medullary structures. To explain both the loss of consciousness and the convulsions we propose a central mechanism. In our patient coughing may have caused a dysfunction of the ascending reticular formation by (i) compressing the brain-stem, or (ii) by temporary occlusion of brain-stem vessels, or (iii) by succussion of a CSF pressure wave into posterior fossa.

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CHARACTERISTICS OF INTER-ICTAL STAGE OF EPILEPSY. D Zekin, K Sabev; *Sofia, Bulgaria.*

Eighty patients with clinically verified diagnosis of epilepsy and forty healthy controls were studied in both stationary and ambulatory conditions. The study included the filling of a computerized questionnaire that included.117 items and the conduction of EEG screening consisting of activational tests (prolonged hyperventilation and photostimulation). The attention was focused toward early clinical features and the peculiarities of symptoms in the inter-ictal stage of the disease. Following mathematical and computer data processing the clinical signs were arranged according to an informative coefficient. High diagnostic values were found for the parameters related to family history -9, medical history - 7, etiologic factors - 5, clinical picture of the seizures - 17, provoking seizures factors - 9, EEG data - 15, sleep disorders - 14. Diagnostic significance of the results supports the use of the detached parameters in the early diagnosis of epilepsy.

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TRAUMATIC RADICULOPATHIES; SEGMENTAL EVOKED. POTENTIALS AND MRI WITH AND WITHOUT CONTRAST V Di Carlo, *Tampa, Florida, USA*

It is generally assumed that moderate spinal trauma can often produce intervertebral disc protrusions and these, in turn, can be the cause of most of the frequently encountered pain and disability. However, our experience supports the possibility that nerve roots, particularly dorsal root ganglia, may also suffer direct lesions in traumatic events, such as motor vehicle accidents, and these lesions may contribute significantly to the clinical picture and explain some of the electrophysiological changes. In studying a series of 100 cases of radiculopathy in which clinical signs, somatosensory and segmental evoked potentials, as well as MRI results were compared, we reached the conclusion that clinical signs and electrophysiological tests were positive in most MRI-positive (disc protrusions) cases, but were positive also in a sizeable percentage of MRI-negative cases. However, the MRI-negative cases may not necessarily remain so, if contrast is used. We are presently using Gadolinium contrast to visualise by MRI traumatised dorsal root ganglia in our cases.

40
TOPOGRAPHIC CORRELATION BETWEEN ELECTROPHYSIOLOGY AND SPECT DATA IN ALZHEIMER'S DISEASE. B Gueguen, Ch Derouesné, D Ancri, MC Bourdel, S Guillou, *Paris, France*

Probable demented patients of the Alzheimer type (according to NINCDS-ADRDA criteria) were studied with computerised EEG (Q-EEG) 16 channels-linked earlobe reference and P300 in an auditive odd ball paradigm. Data were compared with SPECT features with iodoamphetamine (123 IMP). The typical feature of Alzheimer SPECT change in EEG parameters and preserved P300 latency. Frontal hypometabolism is correlated with normal Q-EEG and delayed P300 latency. These results suggest that different type of Alzheimer's disease could explain some of the variations of electrophysiological disturbances in Alzheimer's disease. This could have important implications in the selection of patients for epidemiological or therapeutical studies.

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THE TIMING OF TRANSLATION: AN ARGUMENT FOR A SPECIALIZED, LANGUAGEINDEPENDENT CORTICAL NETWORK. R Aliaga, MA Chornet, A Rodrigo, A Pascual-Leone Pascual, M.D. Catala, A Pascual-Leone, *Valencia Spain*

The neural organisation of the ability to translate between two languages in bilingual subjects is uncertain. Isolated impairment of translation abilities despite relatively preserved linguistic abilities in both languages can occur after injury. We have studied the time required for reading and translating two languages in 9 native Catalan speakers and 4 native English speakers living in a primarily Spanish speaking environment. A list of randomly ordered words was presented on a computer screen. Reaction time was measured between word presentation and subject's verbal response. Each subject completed 4 tasks: read aloud a list of words in Catalan or English (task 1) and one in Spanish (task 2), and translate the same lists from Catalan or English to Spanish (task 3) or vice-versa (task 4). The reaction time difference between tasks I and 3 and between tasks 2 and 4 indicates the time required for translation discounting the reading and speaking times. This time difference was approximately 350 to 450 ms in all subjects. No time difference was noted regardless of language and the direction of translation. This constancy in translation time requirements supports the notion of an language-independent, function-specific network. Topographic mapping of EEG activity during these tasks also support this hypothesis.

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OBJECTIVE CRITERIA FOR LANGUAGE DOMINANCE BY INTRACAROTID AMOBARBITAL PROCEDURE. SR Benbadis, DS Dinner, GJ Chelune, HO Lüders, MR Piedmonte.*Cleveland, Ohio, USA*

In order to propose a standardised method for reporting language lateralization by intracarotid amobarbital procedure (IAP) we retrospectively reviewed 165 IAPs, and classified language lateralization as left, right or bilateral by 3 different methods, all based on the duration of speech arrest following each injection: Absolute duration, side to side difference, and a "laterality index" defined as [L-R/L+R]. Cutpoints were determined by 90th percentile values in a pure subgroup of clearly left hemisphere dominant right-handed subjects. Of the 165 patients, 142 (86%) were classified the same (left, right or bilateral) regardless of the method used. There were 23 (14%) "equivocal" cases who changed categories depending on the criteria used. These cases will be presented in detail, and the 3 methods evaluated. We conclude that there is no gold standard to verify the accuracy of the interpretation of IAP. The laterality index provides an objective, quantitative and graded method to measure speech laterality, analogous to certain handedness questionnaires. This index will be helpful to standardize and compare IAP results from different series.

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EFFECT OF MENTAL EXCERCISE ON THE MOTOR CONSEQUENCES OF TRANSIENT IMMOBILIZATION OF A HAND. T Blanco, MP Lopez, B Romero, A Deltoro, A Pascual. Leone Pascual, MD Catala, A Pascual-Leone, *Valencia, Spain*

We studied the effects of mental finger movements on the motor consequences of complete immobilisation of hand and fingers in a cast for 5 days. Six volunteers were randomly assigned to a control group who simply wore the cast, or to a test group who mentally performed a series of finger exercises at least 2 hours/day. Before placement of the cast and after its removal, we measured maximal voluntary force for grip, thumb-index and thumb-pinkie opposition, serial choice reaction time with individual digits, and Grooved Pegboard performance with the involved hand. Before and after the cast, we also mapped with transcranial magnetic stimulation the cortical motor outputs to abductor policies brevis, first dorsal interosseuos and adductor digit minim muscles bilaterally. All control subjects showed poorer performance in all tasks for 4 hrs. after removal of the cast and a reduction in size of the cortical output maps to the muscles in the castled hand. Mental finger exercises prevented these effects in all test subjects. Mental motor exercises may help speed up functional recovery after prolonged immobilisation of a limb by preventing the modulation of the cortical outputs to immobilised muscles.

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ONEIRIC EPISODES OCCURRING IN SEVERE GUILLAIN-BARRÉ SYNDROME. F Bolgert, MO Josse, P Tassan, E Touze, D Laplane, *Paris, France.*

Confusional states have been reported in Guillain-Barré syndrome(GBS). Among 100 consecutive patients, with a GBS of varying severity, we have encountered oneiric episodes (OE), especially in patients with quadriplegia. Clinical information was available in 88 patients; others were excluded for lack of data or psychiatric history. Forty-one patients reported dream-like episodes, that were long-lasting for 13 of them. The duration and richness of the episodes varied greatly from one patient to the other, and shared common features: good recollection, always different from a "normal" dream; its content, marked by many visual, somatic or spatial hallucinations, elementary or complex. Confusional states, usually mild, were found in only 13 patients. The possible role of stress, sensory de-afferentation, sleep deprivation, treatments, metabolic disorders and disturbances of autonomic functions will be presented. Sensory de-afferentation seems to influence the content of the hallucination; the therapy and metabolic disorders play a minor role, if any. Disturbance of autonomic functions seem be linked to OE : OE are recalled only by patients with autonomic dysfunction, and appear soon after them; their intensity appears correlated to them. Only two patients with myasthenia gravis under mechanical ventilation with sepsis experienced OE. Conclusions: Onciric episodes during severe GBS seems frequent and linked with disturbance of autonomic functions.

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POLYSOMNOGRAPHIC RECORDING IN GUILLAIN-BARRE SYNDROME. F Bolgert, F Godenberg, MO Josse, P Tassan, D Laplane, *Paris, France*

Forty-one of 88 patients with Guillain-Barré syndrome (GBS) recalled dream-like hallucinations (DLH); all had severe GBS with autonomic dysfunction. Polysomnographic (PSMG) recordings were done in ICU in 11 such patients, to identify abnormalities. Twenty-two recordings with a Medilog 9,000 (Oxford Instruments), with 4 EEG, 2 EOG, 2 mental and submental EMG during 48 hours, at time of maximum of paralysis. RESULTS : Seven GBS patients and a control (myasthenia gravis) without DLH had a normal sleep: normal nocturnal sleep cycles, normal amounts of different stages and REM sleep occurring cyclically. Only two patients had a night sleep fragmentation. Three among these six patients had a few short naps during the day. The four patients with DLH were awaken during the DLH periods. At that time, patients exhibited a certain degree of sleep deprivation: total sleep time (TST) and slow wave sleep (SWS) were decreased. REM sleep was normal (EEG, REMs and normal EMG abolition),but REM sleep amount was diminished. The sleep fragmentation was high with periods of sleep scattered within the 24 hours. CONCLUSIONS : PSMG of severe GBS patients with DLH show a sleep deprivation with a decrease of TST, SWS and REM sleep, but REM sleep criteria are normal. Seven GBS patients without DLH, in ICU, had a normal sleep.

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PRIMACY AND RECENCY MEMORY EFFECTS IN ALZHEIMER'S DISEASE. E Brizioli, M Del Gobbo, G Pelliccioni and O Scarpino, *Ancona, Italy.*

Verbal memory impairment represent a typical feature of Dementia of the Alzheimer's type (DAT) which the nature of has been assumed to represent an unitary disorder expressed as a progressive deterioration in the extent of memory abilities. We studied 15 DAT (8 males, 7 females, mean age 67,4) and 15 MID (9 males, 6 females, mean age 70,2), clinically diagnosed on the bases of the DSM III, NINCDS-ADRDA criteria for DAT, and ADDTC for MID, having a score of 16–22 on the MMSE. subjects were tested in an immediate free recall task, using the serial-position function as the dependent measure. We administered a whole neuropsychological battery, including specific tests for memory and attention. The performances of the two groups significantly differed in the serial-position function, particularly for primacy effects. Both groups showed a modification of the serial-position function with a progression toward a unimodal curve, but the group of DAT patients showed a more marked deficit of primacy effects, respect to the MID group. Our data suggest that changes in the serial position function express a specific deficit in learning memory mechanism in DAT patients: neural structures and neurochemical systems that could influence

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SPECT FAS WORD GENERATION TEST AS A DIAGNOSTIC TOOL IN PSEUDODEMENTIA-DEPRESSION: A CASE REPORT. H Durak, G Damlacik, Z Tunca, H Fidaner, Y Yurekli, B Yemez, A Kaygisiz, *Izmir, Turkey*

Pseudodementia-depression is difficult to distinguishable from dementia, but can be successfully treated with antidepressants. There is no specific marker or laboratory test to differentiate these two clinical entities. We observed 62-year-old woman with a clinical history negative for affective disorders, who developed anhedonia, insomnia, weight loss and suicidal ideations 8 months after an aortic valve replacement operation. This picture was accompanied by severe impairment of memory and orientation, resistant to trazodone and fluoxetine. Brain perfusion SPECT was performed with 740 MBg 99m Tc HMPAO. Cortical hypoperfusion and perfusion defects in the left inferior frontal and posterior temporal regions were observed. Modified FAS word-generation test was performed and significantly increased frontal activity was found. This finding was considered as a clue for pseudodementia-depression and the patient was treated with the combination of amitryptilline and lithium carbonate. Full recovery was noted in 5 months. SPECT was repeated at the time of clinical recovery and found to be normal. In conclusion, our patient may be a further example for the value of FAS word-generation test in the diagnosis and follow-up of pseudodementia-depression cases.

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PROCEDURAL SEMANTIC MEMORY IN APHASIA. EA Anllo, R Gil, E Esperet, JP Neau. *Poitiers, France*

Amnesic patients present an explicit memory disturbance but nevertheless can still perform normally such memory tests as skill learning or verbal priming which involve procedural or implicit memory. However the anatomical organisation of the implicit memory system remains poorly known. The present study was undertaken in order to explore procedural learning of semantic categorisation, employing a serial reaction time paradigm in normal subjects and aphasic patients. Aphasic patients responded more slowly and with more errors than controls but all nonetheless manifested a decreasing reaction time. There was no difference between fluent and nonfluent aphasia which both appeared to preserve the procedural semantic categorisation capacity. The categorisation of living words was more difficult than that of nonliving words but implicit learning with living categories was more pronounced than with nonliving categories. Furthermore this study points in the same direction as previous assessments of verbal priming in aphasia and suggests that left cerebral hemisphere lesions causing aphasia do not play a significant role in procedural semantic memory.

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COGNITIVE FUNCTIONS TO HIPPOCAMPAL SCLEROSIS. AR Giovagnoli, M Casazza, R Spreafico, G Avanzini. *Milano, Italy*

Thirty-nine epileptic patients with left (n=23) or right (n=16) hippocampal sclerosis (HS), detected on the basis of MRI, and 33 healthy controls matched to the patients for age and schooling entered this study. EEG epileptic discharges involved both temporal lobes in 12 right and 9 left HS patients. All subjects were tested for abstract reasoning, attention, auditory comprehension, visual perception, constructive praxia, word fluency, shifting attitude, verbal and visual memory. In comparison with controls, patients groups showed an impairment of frontal lobe functions and visual memory. Right HS patients also had an impairment of visual perception, while left HS patients had deficits of auditory comprehension, and constructive praxia. Left HS patients relative to right HS patients showed a deficit of verbal memory. Whereas memory deficits may be accounted for by HS per se, extra-temporal cognitive deficits might be mediated by the widespread effect of longstanding seizures and epileptic discharges on adjacent and distant brain areas. Furthermore the data suggest that, whereas verbal memory is strictly lateralized function, visual memory probably involves a dual encoding, i.e. visual and verbal, which are represented in right and left temporal hippocampus, respectively.

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INTERFERENCE EFFECT ON VERBAL RETENTION IN TEMPORAL LOBE EPILEPTIC PATIENTS. AR Giovagnoli, S Mascheroni, M Casazza, G Avanzini. *Milan, Italy.*

Sixty-four patients with hippocampal sclerosis (HS, n=37) or cryptogenetic temporal epilepsy (CE, n=27) and 22 healthy controls entered this

study. All subjects underwent the Wisconsin Card Sorting test (WCST), Story Recall (SR), and Brown-Peterson task (BP) which measures verbal retention after various intervals (5,10,15,30,and 60 seconds) filled by a distracting activity. Recalls at the BP declined as a function of distraction interval in every group. Compared to right HS patients and controls, left HS patients showed a significant impairment at the BP, SR, and WCST. Left CE patients were found impaired at the BP were compared to controls. No other comparison showed significant differences, but left CE performed rather worse than right CE patients at memory tests. In left HS patients the BP scores showed a significant correlation with the SR scores, but not with the WCST scores. No between test correlations were found in the other groups. The data show that the BP task may be useful in discriminating the left side of temporal lobe epilepsy. An increased susceptibility to interference effect can contribute to the memory impairment in temporal epileptic patients due to the hippocampal damage per se, in agreement with the hypothesis that the hippocampus inhibit interference. Nevertheless, the effect of a concomitant frontal love involvement on recall's strategy may not be excluded.

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TRANSIENT GLOBAL AMNESIA AND CEREBRAL INFARCT: TWO CASES REPORT. I Vecchio, C Tornali, A Antonuzzo, AA Grasso, R Bella, G Pennisi, R Raffaele. *Catania, Italy.*

Transient global amnesia (T.G.A.) is a syndrome described in association with various diseases including head trauma and brain tumours. Rare instances of acute transient memory dysfunction associated with focal cerebrovascular accidents or with other focal lesions have been reported. The exact mechanisms of T.G.A. remain uncertain, but the most valuable pathogenetic hypotheses are the epileptogenic, the migrainous and the ischaemic one. We report two cases with transient global amnesia (without other neurological signs and resolution within 24 h with a residual amnesia of the acute episode) in whom computed tomography (CT) showed an hypodense area in left thalamus, ten days after the transient memory dysfunction. Our cases suggest that transient global amnesia represent a benign form of transient ischaemic cerebral disease in some cases. The aim of our study is to contribute further data to the solution of this problem.

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EFFICACY OF PIRACETAM IN THE REHABILITATION OF STROKE PATIENTS. J Broeckx, F Schildermans, W Hospers, W Deberdt. *Braine-l'Alleud, Belgium & Enschede, The Netherlands)*

This multi-centre, double-blind, randomised study compared treatment with piracetam against placebo in recovering from acute ischaemic or haemorrhagic infarction in the area supplied by the carotid artery.21 patients (13 %) were excluded from the efficacy analysis leaving the results from 137 patients in the analysis. Baseline testing took place between the 5th and 10th week post stroke. Patients were then randomly assigned to receive piracetam 4,8g/d or placebo for 12 weeks. Testing was performed during the 5th and 12th week of treatment. Some patients returned for follow-up testing 12 weeks after treatment termination to evaluate maintenance of performance. The primary efficacy variables included standardised tests of activities of daily living, aphasia and perception. Every patient received appropriate rehabilitation treatment and, if aphasic, speech therapy. The groups at baseline showed remarkable comparability. Treatment showed no substantial difference between the groups on motor and functional tasks (Barthel and Kuriansky). However, significant differences were observed in the evolution of aphasia and selected perceptual tasks in favour of the piracetam group. Aphasia improved about twice as much under piracetam treatment as under placebo. There were no remarkable side effects or significant differences in aspects such as hospitalisation, or blood pressure.

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REVERSAL OF ISCHEMIA-INDUCED DEFICITS IN SHORT-TERM MEMORY AND LOCOMOTOR BEHAVIOURS IN THE GERBIL FOLLOWING TREATMENT WITH PIRACETAM. JM Carney, M Aksenova, MS Chen. *Lexington, KY, USA*

Stroke produces a number of neurological and cognitive changes that may not recover. We have previously demonstrated that ischemia/reperfusion injury (IRI) of the brain following bilateral carotid occlusion in the gerbil results in increases in both locomotor activity and the number of radial arm maze errors 14 days after IRI that are a function of the duration of ischemia [2 and 5 min ischemia produce no change in either parameter; 10 min ischemia increases activity from control of 1085 counts/hr to 2469 counts/hr and errors from 4 to 18]. Pretreatment with piracetam (300 mg/kg) 1 hr before testing on day 14 significantly reduced the number of radial maze errors (7 + 1.7), compared to control (18 + 2.3). Locomotor activity was similar to nonischemic controls (control: 1085 cts/hr vs piracetam IRI: 749 cts/hr) and both were significantly different from the saline treated IRI gerbils (2469 cts/hr). Thus, a single dose of piracetam produces an acute improvement in short-term temporal/spatial memory following IRI-induced neurodegeneration.

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NEUROPSYCHOLOGICAL FINDINGS IN RIGHT HEMISPHERE DAMAGED PATIENTS. M Juncadella, N Busquets, I De la Fuente, A Rodriguez F Rubio, R Soler. *Barcelona, Spain.*

Neuropsychological literature refers that injuries in certain areas of the right hemisphere can cause alterations in perception, attention to spatial coordinates, construction and visual memory (De Renzi, 1982). Elaboration of electric intracranial stimulation maps of epileptic patients (Mateer, 1983; Fried & cols., 1992) and research on cerebral metabolism (Kushner & cols.,1988) contributed data on the right hemisphere superiority for visuo-spatial functions. This study intends to evaluate (visuo-spatial, attentionals, behavioural) deficits in patients who suffered a right hemisphere stroke. A total of 16 patients (11 males and 5 females), mean age 60 years, with unilateral right hemisphere stroke. Assessment was carried out in chronic state. The neuropsychological battery consisted of the following tests: Barcelona Test subtests, Line Bisection, Judgement of Line orientation, WAIS puzzle subtest, WISC Labyrinth subtest and Rey Complex Design. Results: Alterations were found in visuo-constructive and visuographic tests as well as in behavioural variables. The ANOVA shows significative differences in test performance between anterior cortical and posterior cortical injured patients: the latter being more affected. Patients with cortical injury obtain better results in attention, visuo-constructive an visuo-graphic functions and execution time, than individuals with subcortical injury. We conclude that both cortical and subcortical right-hemisphere structures are implicated in these functions, the posterior part of this hemisphere being specially relevant.

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ALTERATION OF COGNITIVE SKILLS IN FOCAL LESIONS OF THE CEREBELLUM. C Khati, B Pillon, B Deweer, C Malapani, N Malichard, B Dubois, G Rancurel, *Paris, France*

Six patients with focal lesions restricted to the cerebellum, of vascular ischemic (n=4) or surgical (n=2) origin were analysed. No extracerebellar lesion was demonstrated on MRI. All of them completed a neurologic examination and an extensive psychological testing including evaluation of : global efficiency ; explicit memory and implicit learning (mirror reading, serial reaction time task, rotor pursuit); executive functions: verbal fluency, Wisconsin, frontal behaviour, graphic series (frontal score), Delis test; simple visual reaction time and time estimation ability for visual and auditory paradigm; assessment of mood and comportmental disorders. Preliminary results showed: 1) normal global efficiency 2) mild executive dysfunction without frontal behaviours; 3) decreased performance in explicit memory tests that seems to correlate with the dysexecutive syndrome; 4) perturbation of both motor and non-motor procedural learning; 5) time estimation impairment; 6) absence of significant affective or behavioural disturbance. In conclusion, the results showed that lesions of the cerebellum do not induce profound cognitive or memory dysfunction but rather specific impairments mainly for executive functions and cognitive skills. These features are reminiscent of the cognitive syndrome associated with lesions of basal ganglia.

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CT-BUT NOT MRI IDENTIFIED PERIVENTRICULAR WHITE-MATTER LESIONS PREDICT SUBSEQUENT CEREBROVASCULAR DISEASE IN PROBABLE ALZHEIMER'S DISEASE. DL Lopez, JT Becker , G Jungreia, D Rezek , C Estol, ST DeKosky, F Boller, *Pittsburgh, PA, USA & Paris, France.*

We evaluated the clinical consequences of periventricular white-matter lesions PWMLs) on CT scan and MRI scans in probable Alzheimer's disease (AD). PWMLs seen on are associated with subsequent cerebrovascular disease (CVD) in AD patients and in non-demented individuals. However, there are no data directly comparing the ability of CT and MRI to predict development of CVD. We longitudinally evaluated the clinical

characteristics of 27 probable AD patients who had both CT and MRI within a short time frame (mean 20.5 ± 13.0 days). All patients were followed for a period of 36 months and occurrence of transient ischemic attacks (TIAs) and strokes was monitored. PWMLs were observed on CT in 12 AD patients (44%), and in 21 (78%) with MRI. Six tients developed TIA's and strokes during the 36 month follow-up. CT (4/6, 70%) and MRI (6/6, 100%) were sensitive to predict the development of strokes and TIAs based on the presence of PWMLs at baseline examination. However, predictions of vascular events by MRI resulted in twice the false positive error rate of CI (15 vs. 6). Although MRI may be the method of choice to study PWMLs, CT-scan is equally sensitive but more specific detecting abnormalities which predicts subsequent cerebrovascular events.

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SPEECH REPRESENTATION AND HANDEDNESS IN NORMALS: A POSITRON EMISSION TOMOGRAPHY STUDY. M Krams, C Weiller, M Rijntjes, SP Mueller, HC Diener, *Essen, Germany*

We tried to learn more on the patterns of speech representation in left (LH) as compared to right handed (RH normal subjects. From amobarbital studies, dichotic listening tests and clinical observations of aphasic patients there is evidence that a subgroup of LH may show a more bilateral cerebral organisation of language than most RH. Methods: Six LH and six RH (age 23-50) underwent measurement of regional cerebral blood flow (rCBF) during an intrinsic verb generation task, using a c1502 inhalation technique. Images were stereotactically normalised into Talairach-space. Significant rCBF changes during verb generation were localized using SPM. Results: * The strongest activation in both groups was found in the left inferior frontal gyrus (areas 45,44). LH also showed some right hemispheric activation in area 45.* Both LH and RH showed strong bilateral, but more marked left hemispheric activation in the superior and medial temporal gyrus (areas 22, 21). Bitemporal activation was stronger in LH. Conclusions: LH and RH show a common pattern of speech representation: prominent left hemispheric activation of areas 44,45 and bilateral activation of areas 22 and 21. Right hemispheric activation in area 45 however was found in LH only and may indicate a more bilateral language organisation in this group.

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SPATIAL MEMORY AND SPATIAL ORIENTATION AFTER UNILATERAL TEMPORAL LOBECTOMY AND NEOCORTICECTOMY. EA Maguire, ET Burke, H Staunton, J Phillips, *Dublin, Ireland.*

The role of the temporal neocortex and mesial temporal lobe structures in humans in the formation and storage of internal spatial representations of an everyday real-life environment, was examined. 20 patients who had undergone unilateral temporal lobectomy or neocorticectomy (11 left, 9 right) for intractable epilepsy and 10 matched controls were exposed to video presentations of routes through a novel urban area. Learning and memory for this area were assessed across several parameters: Both patient groups required significantly more exposures to the video before a criterion level of learning was reached, than control subjects. Analysis of recognition memory error types during this learning showed the-left temporal group made significantly more omission errors, while the right temporal group made significantly more inclusion errors. Right temporal subjects were also significantly impaired on tests of landmark selection from among foils, relative to controls and the left temporal group, and also on tests of proximity and distance judgements. Both patient groups were impaired on tests of route planning and execution, and in their sketch map representations of the stimulus area. Further analyses are presented exploring the influence of extent of tissue removal on spatial representation, and lateralization of such functions in humans.

59
THE RELIABILITY OF REACTION TIME MEASUREMENT IS GOOD IN BRAIN DAMAGED PATIENTS. O Godefroy, D Leys, M Rousseaux. *Lille, France.*

Chronometric analysis is often used in neuropsychological studies because of its higher sensitivity. But the higher variability of patients reaction times (RT) usually leads to an increase in the number of measurements in order to improve the accuracy of RT estimates. This implies that the reliability of RT measurement is good, a point which has never been evaluated in patients to our knowledge. The first study assessed the reliability of simple RT measurement in 11 brain damaged patients. Patients were evaluated using 3 simple detection RT tests repeated in 3 different sessions. The second study used one binary choice RT test repeated over 4 sessions in 14 brain damaged patients. The evaluation of reliability was performed using the Kendall coefficient of concordance W. The first study showed a good (W=0.796, 0.723 and 0.8) and significant (P:0.01) reliability of simple RT measurement. The second study showed a good (W=0.685) and significant (P:0.0001) reliability of choice RT measurement. This good reliability of RT measurements shows that test repetition could be used with confidence in neuropsychological studies and suggests that 1 or 2 measurements only might be necessary when the variable of interest is the patient global rapidity.

60
THE NATURE OF BEHAVIOURAL DISORDERS IN KLUVER-BUCY SYNDROME. OL Lopez, JT Becker, ST DeKosky. *Pittsburgh, USA*

We examined the clinical features of a 69 year-old patient who developed a Kluver-Bucy syndrome (KBS) (e.g., hyperorality, bulimia, hypersexuality, placidity) after 2 cerebral ischemic episodes. The MRI of the brain failed to reveal structural damage that could explain the patient's KBS. However, a SPECT scan demonstrated hypoperfusion of the left anterior temporal lobe, and of the right frontal-anterior cortex. He performed abnormally on tasks that require attention, response inhibition, and the ability to shift central sets. He showed deficits verbal and non-verbal memory as well as in olfactory discrimination. Productive language was minimally affected and auditory comprehension was preserved. He did not exhibit visual agnosia or prosopagnosia. These findings have important implications for understanding the behaviour of KBS patients where not only attentional deficits but also significant frontal lobe dysfunction, which regulate the affective experience and the interaction with the environment, are involved.

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POSTERIOR FOCAL ATROPHY SYNDROME WITH DOMINANT VISUOSPATIAL MANIFESTATIONS. J Pena, I Bertran, P Santacruz, R Lopez, A Catafau, F Lomena, R Blesa. *Barcelona, Spain.*

We tried to characterisation progressive focal atrophic syndrome with predominant impairment of visuospatial areas. Visual impairment as the predominant manifestation of slowly progressive dementia is rare. We have studied three patients with progressive Balint-"plus" syndrome. Three women (61,59,58 years) explored with standard laboratory tests, dementia scales, cartography/EEG, P300. Neuropsychological evaluation: "Barcelona-Test" Battery, Rey Figure, Trail Making Test, WAIS, Boston Naming Test. Neuroimaging CTscan, Magnetic resonance imaging and SPECT. Common initial complaints: difficulties for performing activities of daily living due to visual and memory disturbances. Cognitive determination: perceptual paragnosic failures, alexia. agraphia, constructional apraxia and memory impairment. Evolution: Global worsening, especially visual alterations with Balint's syndrome and dyschromatopsia, and reduction of abstract capacities. Formal language was preserved. EEG: diffuse slowing. P300: delayed and diminished amplitude. PEV: normal or delayed and diminished. MRI: Widespread atrophy, mainly in posterior areas. SPECT: Occipitoparietal hypoperfusion. Conclusion: Progressive focal posterior atrophy pattern with prevailing visuospatial signs show distinctive clinical features within the spectrum of primary progressive cortical atrophies.

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EEG IN DEMENTIA OF ALZHEIMER'S TYPE. R Raffaele, I Vecchio, C Tornali, L Rampello, R Bella, A Nicoletti, G Pennisi. *Catania, Italy.*

Several studies have reported slight EEG alterations in normal aged individuals: slowing of the alpha rhythm and focal theta activity in the left temporal region. The electrical activity of the brain is preserved in healthy aging if the presence of disorders adversely affecting brain functions and use of drugs are excluded. In our study (50 patients) in the early stage of Alzheimer's disease (A.D.) even 50% of the patients may have a normal EEG, while in the moderate and severe stage of A.D. over 80% of patients show slowing parallels the cognitive decline: early EEG slowing showed a decline in praxic, visual and memory functions and in language. The A.D. patients had slower average frequency of the dominant occipital rhythm and showed accentuation of theta and delta than normal elderly controls. The severity of cognitive impairment as assessed by neuropsychological tests correlated with the peak occipital frequency. In conclusion EEG can define some soubgroups of patients predicting the clinical course of dementia.

63
MAY MEMORY DISORDERS RESULTING FROM ANTERIOR COMMUNICATING ARTERY ANEURYSMS (ACAA) RUPTURE BE CALLED "KORSAKOFF" OR "AMNESIC" SYNDROME? M Rousseaux, M Cabaret. F Lesoin, *Lille, France*

The aim of this study was to evaluate cognitive deficits after rupture of ACAA. Main inclusion criteria were: - ACAA rupture at less 3 weeks before - selective frontal medio-basal lesions on MRI - age < 70 years. 22 patients were included and 1) evaluated at the secondary (22) and at the late (16) stages 2) with WAIS-R, verbal automatisms of Beauregard, estimating "premorbid" IQ, Stroop test, WCST, orientation, spans, Wechsler Memory Test, Batterie 144 (verbal, spatial memory) 3) in comparison with 22 controls (alpha risk:p=0.05). Results. At the secondary stage, the mean IQ (96) was < "premorbid" IQ (114) (p<0.001), without difference between verbal and performance IQ. IQ drop was constant (22/22). MQ (104) was > IQ (p=0.09) and < "premorbid" IQ (p<0.01). MQ was > IQ in 15/22 cases and < in 7, 2 showing a difference > 15; but in both cases, IQ drop (>25) was observed. Deficits of attention, temporal orientation and executive functions were observed (p<0.0 1). Short-term and long-term memory (Batterie 144) were impaired (p<0.01), without any difference between verbal and visuospatial subtests. At the late stage, mean IQ increased of 9 points, remaining inferior to "premorbid" IQ, Batterie 144 of 6 points. orientation and digit spans were normal, WCST nearly normal. Discussion. 1) At the secondary stage, the general cognitive drop was most often more severe than memory impairment. 2) At the late stage, general cognitive performances remain low, without dissociation with memory impairment. 3) Neuropsychological disorders differed from "Korsakoff" and "amnesic" syndromes (Weiskrantz, 1985; Mayes, 1988).

64
SELECTIVE DEFICIT OF VERBAL RECALL AFTER LIMITED EXTERNAL THALAMIC LESION. M Rousseaux, M Cabaret, M Steinling, *Lille, France.*

Verbal amnesia may be associated to left unilateral thalamic lesion. This phenomenon has been described in the learning of new information with recall and recognition procedures. The aim of this study is the description of a case of selective verbal recall deficit and of its consequences on verbal learning, priming and retrograde memory. Case report. A 57-year-old patient of high intellectual level presented selective infarction of the anterior part of the superoexternal thalamus on CT scan and MRI, with rCBF drop (SPECT) in the frontal and temporal cortices. This resulted in mild aphasia and impairment of lexico-semantic memory and verbal learning. Three years later, selective deficit of verbal recall was demonstrated. This affected the learning new information (Batterie 144, 15 words of Rey, figure of Rey, Buschke paradigm, A-B A-C learning), but also the recollection of verbal information associated to famous events (19461986) or general knowledge (historical). Verbal recognition was always normal, as well as visuo-spatial learning. Verbal priming was deficient. Language, attention, executive functions, motor learning were normal. Discussion. 1) Selective deficit of verbal recall can be demonstrated in limited lesions of the antero-superoexternal thalamus. 2) This phenomenon may be due to selective or predominant deficit of retrieval processes of verbal information, encoding processes being preserved. In cognitive models, verbal retrieval must be distinguished from verbal recognition processes and from visuo-spatial retrieval. 3) We suggest that 3 amnesia subtypes would be associated to limited unilateral thalamic lesions (anterior, inferointernal, external).

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SPATIAL DISORDERS IN NORMAL AGING, UNILATERAL BRAIN DAMAGES AND DEMENTIA. I Tournev. *Sofia; Bulgaria.*

The interest in spatial abilities representing the nuclens of the nouverbal human intellect is constantly rising: also rises the interest in studying different spatial disorders. The spatial abilities includes spatial explorations, spatial perception, spatial orientation, spatial cognition, and constructional abilities. Studies of spatial disorders in normal aging patients with unilateral cerebral damages and different dementias, are presented. We found decline with age in the spatial abilities of the helthy elderly subjects. We suggest that visuospatial right-hemispheric functions deteriorate with age more than verbal left-hemispheric functions. It was established a significant hemispheric asymmetry of the spatial disorders in patients with unilateral brain damages. In Alzheimer's disease, patients typically show spatial disorders even in mild, early cases. The deficits tend to be more severe than those associated with unilateral brain lesions, reflecting the diffuse nature of the cerebral pathology. Spatial deficits in different kinds of vascular dementias are discussed.

66
THE RELEVANCE OF EVENT RELATED POTENTIALS (ERP, P 30C) AND NEUROPSYCHOLOGICAL TESTS FOR THE OUTCOME EVALUATION AFTER SUBARACHNOID HEMORRAG AND ANEURYSM SURGERY. K Maier- Hauff, M Schroeder, A Wolf. *Berlin, Germany*

Subarachnoid hemorrhage from ruptured aneurysms often results not only in neurological deficits but also in important cognitive impairment in spite of a favourable spontaneous and operative outcome. The study examines the neuropsychological test results as well as the ERP (P300), with special emphasis placed on the pre- , intra- and postoperative risk factors. P 300 is used as an indicator of cognitive deficiencies. ERP were evoked by using an auditory two- tone discrimination paradigm. The latency and amplitude of the P300 were evaluated comparing the results with a normal population. The neuropsychological battery included reaction time, attention span, stimulus selection, speed of cognitive performance and comprehension as well as verbal and non- verbal short- time memory. The test procedures were conducted upon discharge as well as 6- 8 month later. Significant differences were observed with regard to alertness, reaction time and latency of the P300- component of the ERP. A correlation exists between reaction time and P300 latency, the latter of which seem to be an indicator for intellectual impairment.

67
VALIDATION OF A CT SCAN MEASUREMENT MODEL IN THE DIAGNOSIS OF DEMENTIA OF THE ALZHEIMER TYPE (DAT). JP Willmer, DA Guzman, *Ottawa, Canada*

A previously defined diagnostic model for DAT, based on measurements of CT scans was prospectively tested by applying it to 200 consecutive patients (mean age = 69 years) referred to a memory disorder clinic. The CT scans were measured by one author (JPW), while the patients were classified clinically using NINCDS-ADRDA criteria by the other (DAG). Both remained blinded to the other's diagnosis. Of patients clinically diagnosed as DAT, the diagnosis based on the model agreed in 84% of cases, while it agreed in 66% of those diagnosed as not having DAT. If the data are analysed by age group (< 65 years and > 65 years), the older patients have a much greater chance of being misdiagnosed as having DAT by the model (91% agreement for DAT, 44% agreement for non DAT) and the younger patients have a greater chance of being misdiagnosed as being non DAT (43% agreement for DAT, 88% agreement for normal). This is not related to age, as the measurements were found in the original model not to correlate with the age of the patient. This was tested in the new data set, and for the three measurements used, no correlation with age was found (r^2 values range from 0.212 to 0.285). These findings may suggest that for older patients, the structural changes (atrophy) may precede the cognitive ones and that for this group, the CT measurements may be a good marker. To confirm this the group misclassified as DAT will have to be followed prospectively to see if they will develop DAT. In the younger group, which may progress more rapidly, the cognitive changes may precede the structural ones, and this model may not be all that useful.

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ACOUSTICAL FOLLOWING-UP STUDY OF A PURE DYSARTHRIA. JP Cochin, I Noel, P Augustin, P Auzou, D Hannequin, *Rouen, France.*

The aims of this study were, to determine the disturbed acoustical parameters of a pure dysarthria, to correlate these parameters with clinical characteristics and, to assess their evolution. The patient was an 83 years old woman who suddenly presented a severe dysarthria. Speech was slow and labored7 with dysrhythmia and high pitch level. Articulator impairment mainly affected the stop consonants. CT scanning was normal and MRI showed bilateral white matter lacunes. Method ree acoustic parameters were recorded 4 times from 1 to 6 weeks of evolution (w1, w2, w3, w6): Voice Onset Time (V.O.T.) of stop consonants (/pa/, /ta/, /ka/); mean fundamental frequency (F0) and spectrograms (formats) of sustained vowels (N, /a/, /o/).Results At w1, the VOT duration's were similar for /p/, /t/ and /1-/. At w2, the normal hierarchical progression of the VOT duations, respectively from /pl, to //t/ and /k/, was reorganised, according to the improvement of the stop consonants production. The mean F0 of /a/ and /o/ decreased from over 160 Hz (w1,w2) down to 130 Hz (w3, w6). The ini-

tial high values corresponded to the clinical high pitch level of voice. A normal frequency band (Forman) of the sustained vowels was lacking from wlto w3. This Forman reappeared at w6 corresponding to the improvement of the voice timbre. In conclusion, three parameters correlated with voice disturbances are identified and their evolution demonstrates that improvement concerns: first the VOT duration (timing organisation), then the mean F0 (laryngeal functions), and finally the timbre (supra-laryngeal functions).

69
USE OF INTRAOPERATIVE EEG MONITORING TO EVALUATE THE SIGNIFICANCE OF INTRACRANIAL VASCULAR FINDINGS ON MAGNETIC RESONANCE ANGIOGRAPHY.V Maria, Lopez-Bresnahan, DM Danielle Antin-Ozerkis, B A, *Boston, USA*

To determine whether preoperative magnetic resonance angiographic (MRA) findings, like preoperative angiographic findings, correlate with cerebral ischemia. at cross-elamp during carotid endartereetomy (CEA) we used 16-channel EEG monitoring as an indicator of ischemia in 67 patients undergoing CEA following preoperative MRA. Sixteen patients had ischemic changes. The cause of inadequate collateral flow was visualised in 6/16, including 2 of 8 imaged with 3D time-of-flight (TOF), 2 of 6 imaged with 3D phase contrast (PC), and 2 of 2 imaged with both 3D TOF and 2D PC. Fifty-one patients had no isehemia. Collateral flow through the ACom, was seen in 5 of 18 that had 3D PC imaging and 4 of 5 that had 3D TOF with 2D PC imaging. A symmetrieal eirele of Wills was seen in 22/28 patients imaged with 3D TOF alone, 3 had an absent ACom, Al or PCom on the side of eross-clamp, and 3 on the opposite side. Only 7 intracranial stenoses were identified, 6/7 in the group without ischemia. Intracranial stenoses are seen infrequently with MRA and do not correlate with ischemia. TOF imaging visualises the circle of Wills segments but actual collateral flow can be seen with addition of directional PC imaging.

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TRANSCRANIAL COLOR-CODED DUPLEX ULTRASONOGRAPHY IN PATIENTS WITH CEREBROVASCULAR DISEASE. E Bartels, SO Rodiek, KA Flugel, *Munich, Germany*

Transcranial duplex colour flow imaging (TCI) is a new diagnostic method which allows visual display of blood flow in basal cerebral arteries by means of colour coding the flow velocity information. However, the clinical value of TCI is not yet fully investigated. Fifty eight patients, aged 2180 years, with cerebrovascular disease (stenosis of the middle cerebral artery (MCA) 9 patients, aneurysm 18 patients, arteriovenous malformation - 31 patients) were investigated, using the ACUSON 128 XP 10 colour Doppler imaging system equipped with a 2 MHz sector transducer. In 51 Patients (88%) the sonoqraphic diagnosis corresponded with angioqraphic findings. The stenosis of the MCA was identified in all cases. In 28 patients (90%) the arteriovenous malformation localised in basal or temporal regions of the brain could be visualised. The detection of an aneurysm (in 78%) depended on its size and localisation. TCI is a valuable method for the non-invasive diagnosis in patients with cerebrovascular disease.

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MAGNETIC RESONANCE IMAGING FEATURES IN SJÖGREN-LARSSON, SYNDROME. DM Campos, J Salas-Puig, JM Fernandez, J Sanhez Del Rio, JA Vidal, CH Lahoz. *Oviedo;Spain.*

Sjögren-Larsson syndrome (SLS), is an autosomal recessive disorder defined by: ichtyosis, mental retardation and spastic diplegia or tetraplegia. A deficiency of fatty alcohol NAD+ oxidoreductase involved in myelin formation may be the primary defect. SLS seems to be a demyelinating rather than a demyelinating disease, which affects the central nervous system. We report on the characteristics of Magnetic Resonance Imaging (MRI) in three SLS patients (1M, 2F) aged 20, 31 and 35. Two of them were siblings. Ichtyosis and mental retardation were present since the first months of life. Developmental milestones were delayed, but the children improve with age, and, functional deficits became stationary or slower progressive. MRI T2-weighted showed diffuse hyperintense patchy lesions in cerebral white matter which suggested myelin disease. The distribution of lesions was periventricular and in both semiovale centers. The cortex was also affected and type of could be responsible of the disorder of voluntary movement. Brain stem, corpus callosum and basal ganglia were normal. Conclusions: We present the first MRI study in SLS. The deficiency of fatty alcohol NDA+ oxidoreductase probable caused a dysmyelinating disease. T-2 weighted in MRI showed glistening patchy lesions on the white matter. These lesions, sometimes confluent had a periventricular and semioval center localization. We think that these findings can explain spasticity in SLS.

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HALLERVORDEN-SPATZ SYNDROME: AN ASSESSMENT OF CLINICAL, RADIOLOGICAL AND NEUROPATHOLOGICAL FINDINGS IN TWO FAMILIES. M Eraksoy, O Barlas, M Barlas, C Bayindir, H Ozcan. *Istanbul; Turkey.*

We presented four siblings with Hallervorden-Spatz Syndrome (HSS) who belong to two families and discussed their clinical, and pathological findings. The patients, 3 males, one female, were seen between 1991 and 1993 in our unit, at ages of 8,10,12 and 13 years. The children showed a delayed developmental course. Neurologic evaluation revealed progressive intellectual deterioration, early and prominent dystonia, speech difficulty, impairment of postural reflexes, rigidity, retinal degeneration and pyramidal findings. CT scans showed bilateral high density lesions in the globus pallidus. MRI appearance was similar to previously reported cases. Radiological findings were seen only older siblings. Stereotactic biopsy was done in one patients. Biopsy specimen revealed iron deposition in the globus pallidus and there were axonal spheroids in the same area. We conclude that it may be possible to diagnose HSS while the patient is alive through clinical and radiological findings

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DIFFERENT PATTERNS OF INNER CEREBRAL TRAUMA DETECTED BY MR- IMAGING. G Birbamer, F Gerstenbrand ,S Felber, G Luz, F Aichner. *Innsbruck, Austria.*

The different distribution of lesions after severe closed head injury detected by MR- Imaging are evaluated with special regard to the direction of traumatizing forces. The study included 170 patients (127 male, 43 female), with a mean age of 25,1 (5- 69 range years). Inclusion criteria were suspicion of inner cerebral trauma on CT and sufficient information concerning the direction of traumatizing forces. Clinically acute midbrain syndrome was present in all patients. The MR examination was performed in the acute stage afar the trauma in 27 patients, in the subacute stage of prolonged midbrain syndrome in 30 patients, in the stage of apallic syndrome in 57 patients and in the post- apallic stage in 56 patients. All patients underwent a CT examination at the time of admission. MlR- studies were performed on a 1.5 Tesla unit, using a circular polarized head coil (FOV=25cm). The imaging protocol consisted of sagittal Tl, axial and coronar T2/PD weighted images. Additionally a 3D- FLASH sequence was used in 90 cases. In 70 patients the examination was performed under general anaesthesia. The MR- examination proved superior to CT in the evaluation of inner cerebral trauma in all stages of traumatic brain disease. The different distribution of lesions allowed a new neuroradiological classification into an upper inner cerebral trauma and a lower inner cerebral trauma.

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EVALUATION OF THE VENTRICULAR SYSTEM BY TRANSCRANIAL COLOUR CODED SONOGRAPHY IN ADULTS- A COMPARATIVE STUDY BETWEEN ULTRASOUND AND COMPUTED TOMOGRAPHY. G Seidel, M Kaps, A Hutzelmann, T Gerriets. *Giessen, Germany*

Background: Transcranial colour coded sonography (TCCS) enables the visualization of the intracerebral structures and the angle corrected blood flow velocity in the basal cerebral arteries in adults. We evaluated the size of the third and the lateral ventricle in axial planes and compared these values with computed tomography (CT)images. In a second step we performed a follow up investigation by transcranial duplex in order to evaluate the intra-observer reproducibility. Patients and method: 44 examinations on 32 patients (61.3 + 13,3 Y; 20 male; 12 female) were done using a TCCS system in connection with a 2,5 MHz transducer and a CT scan in axial planes. 12 patients underwent follow up to study the reproducibility. Results: The correlation of the diameter of the third ventricle (r= 0,78; P<0,0001; N=31) and the lateral ventricle (r=0,7; P<0,0001; N=58) between CT scan and TCCS was high. The intra-observer reproducibility in 12 patients evaluating the lateral ventricle accounted to r=0,93; P<0,0001 (N=22). Exemplary cases are demonstrated. Conclusion: In conclusion TCCS proved as a useful tool to evaluate non invasively the ventricular system in adults. These findings provide clinically useful data in patients

with acute disturbance of cerebral spinal fluid circulation and ventricular enlargement.

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AUTOMATICAL FITTING OF ANATOMICAL MASKS TO BRAIN MRI TOMOGRAMS. F Kruggel, *Munich, Germany*

For a deeper analysis of structure-function relationships in the brain, an exact topographic description of a brain lesion is required. This description can be achieved by fitting anatomical maps to slices of MRI tomograms. Because neocortical structures exhibit a high interpersonal variability, simply fitting a model map by an affine transformation only yields a modest adoption. To improve the adoption a non-linear mapping scheme using deformable templates was proposed, where a user has to specify certain corresponding "landmarks" in both mask and brain slice. This procedure is time-consuming and expert-dependent. Following an experts way of analysis we tried to find landmarks automatically by segmentation procedures. Suitable structures for segmentation e the ventricles and the primary sulci, which are relatively invariant and well developed. By processing MRI slices using a sequence of edge-filtering, Voronoi segmentation and graph analysis of the segmentation tree we were able to find the positions of the primary sulci and the tips of the ventricle automatical1y. These landmarks can be used as fix points in the deformable template matching scheme described above. We extended this approach to a 3D-tracing of sulci so that neighbouring gyri (f.ex. sensory and motor cortex) can be depicted automatically in 3D MRI reconstructions. Currently we investigate the validity of these procedures in pathological cases.

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TRANSCRANIAL COLOUR ULTRASOUND FINDINGS IN PATIENTS WITH EXTRACRANIAL CAROTID CONCLUSIVE DISEASE. PJ Martin, ME Gaunt, RJ Abbot, AR Naylor, *Leicester, UK*

In patients with cerebrovascular disease, most attention focuses on the extracranial vasculature. Transcranial colour coded sonography (TCCS) now enables non-invasive colour imaging and haemodynamic assessment of the intracranial vessels. We describe intracranial findings in 71 patients (46 male; median age 69 years) with extracranial carotid disease, graded by colour duplex. On the more severely diseased side, 5 patients had moderate disease (30-70%), 44 had severe disease (70-99%) and 19 patients had occlusions. Contralaterally, the disease was mild in 24 patients, moderate in 24, and severe in 23. Overall, middle cerebral artery (MCA) blood flow velocity and pulsatility index (PI) were reduced ipsilateral to the most diseased carotid (medians; peak systolic 73 cm/s versus 96 cm/s, $P<0.0001$; mean 48 cm/s versus 60 cm/s, $P<0.001$; PI 0.89 versus 1.04, $P<0.0001$). Four patients (6 vessels) had tandem MCA main stem stenosis (medians; peak systolic 218 cm/s; mean 133 cm/s). In 24 patients interhemispheric collateral flow to the more severely diseased side via the anterior communicating artery was identified, all patients had ipsilateral carotid stenosis of at least 80%. The majority of the cerebral circulation can now be imaged using an ultrasound based approach. Knowledge of intracranial stenotic disease or collateral flow may have implications where carotid endarterectomy is contemplated.

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DURAL SINUS IN ROUTI,NE,SPIN,ECHO,SEQUENCES : NORMAL ASPLCT AND.VARIANTS. E Meary, A Dilouya, JF Meder, J De Recondo, R Lebtahi, *Paris France*

Axial T2 and Sagittal and/or Coronal spin echo weighted sequences is the basic MRI protocol for brain study. In these retrospective study,absence of signal (flow void) allowed a good visualization of the sinus and assessed their patency but artifactually I so to high signal are frequent.These artifacts will be describe and their causes discuss. The diagnosis of lateral sinus hypoplasia (15 cases) is easy on sagittal MRI with demonstrates a franck asymmetry of the transverse portion of the sinus. Only large occipital sinus are detectable (5 cases) and are frequently associated with widening of the posterior cistern. Absence of the constant flow void of the straigth sinus is always pathological (agenesy or thrombosis). Knowledge of the normal aspect and signal of the dural sinus, their anatomical and/or signal variants is necessary to avoid miss interpretation (thrombophlebitis) and eventually for preoperative procedure (posterior fossa: occipital sinus).

78
BLOOD FLOW VELOCITY AND VOLUME FLOW DETERMINATION IN BRAIN ARTERIOVENOUS MALFORMATIONS BY DYNAMIC MAGNETIC RESONANCE IMAGING AND ANGIOGRAPHY, AND TRANSCRANIAL COLOUR-CODED DUPLEX SONOGRAPHY. KW Neff, S Meairs, M Hennerici, A Schwartz. *Mannheim, Germany.*

Arteriovenous malformations (AVMs) of the brain are congenital lesions that lead to abnormal hemodynamics of vascular structure, which have been studied by various methods. But little is known about the in vivo measurement of the shunt-volume. We will present the work-up of cerebral AVMs in an example of a patient with a left-sided, temporo-medial AVM, which was filled from the left internal carotid artery, via anterior choroidal artery, and from the basilar artery, via left posterior cerebral artery. Venous drainage filled sinus rectus via the enlarged basal vein and vein of Gallien. In addition to routine evaluation with digital subtraction angiography (DSA), transcranial ultrasonography, and magnetic resonance imaging I (MRI) and angiography (MRA), the hemodynamics of AVMs can be investigated by dynamic MR bolus tracking and phase-contrast cine MR imaging. Both techniques allow the determination of blood flow velocity and volume flow in vessels supplying and draining the AVM. The correlation with transcranial colour-coded duplex sonography leads to a third independent evaluation of the AVM. The results for blood flow velocity measurements obtained with magnetic resonance and ultrasound are highly correlated. In the presented example , the non-invasive determination of blood flow velocity and especially the volume flow in both internal carotid arteries, in basilar artery and in the AVM draining vein presented information about the shunt-volume. Transcranial colour-coded duplex sonography was able to detect the feeder of the AVM via the anterior choroidal artery, corresponding to DSA and high resolution MRA findings.

79
LEUKOARAIOSIS IN CEREBROVASCULAR DISEASE INVESTIGATED BY TRANSCRANIAL DOPPLER. S Viola, E Matta, L Aquilone, D Gambi, *Chieti, Italy*

Periventricular white matter lucencies on computed tomography (CT) in absence of hydrocephalus or well-defined white matter diseases such as multiple sclerosis and leukodystrophies has been called leukoaraiosis (Hachinski 1987). Leukoaraiosis is often associated with lacunar infarcts of the basal ganglia. We studied 34 patients with a history of cerebrovascular disease who had lacunar infarctions and leukoaraiosis demonstred by CT. Twelve patients had 3-12 lacunar infarctions (first group), 12 had leukoaraiosis (second group) and 10 both lesions (third group). All patients were studied by Trancranial Doppler (TCD-3D EME, 2 Mhz probe). We recorded the following doppler parameters: interhemispheric asymmetry index (IA), mean flow velocity (mv) and pulsatility index (PI). TCD-3D showed a significant increase of PI ($p<0.002$) over the large intracerebral arteries in all patients compared to controls. We found no significant difference of PI between the first and second group by ANOVA analysis. The increase of PI, indicating an increase of peripheral resistances, suggests that at the base of leukoaraiosis is a stenosis or occlusion of penetrating branches of the large cerebral arteries and that lacunar infarctions and leukoaraiosis belong the same disease spectrum.

80
TUBERCULOUS MENINGOENCEPHALITIS DUE TO MYCOBACTERIUM AVIUM INFECTION. IR Rise, *Oslo, Norway*

Tuberculous meningoencephalitis is fatal if not treated. The incidence of tuberculosis is slightly increasing in Norway and the incidence of CNS tuberculosis is one per million and usually caused by Mycobacterium tuberculosis. We describe a patient with CNS tuberculosis due to atypical mycobacterial infection. The patient was a 44-year-old diabetic woman who was admitted to our department with a 2-month history of generalized headache and a productive cough. Two weeks prior to admission she had experienced an episode of double vision. The last year she had been nanny for a 5-year-old girl who had suffered from a neck abscess caused by Mycobacterium avium. On admission the patient was fully awake. She did not have focal neurological signs nor evidence of meningeal irritation. Cerebral CT scan showed subdural effusions and small ventricles. MRI taken the day of admission showed enhancement of the meninges. The spinal fluid had an increased protein level, a very slight increase in cell count, but

normal glucose. Examination of the spinal fluid for mycobacterias was negative. Expectorate culture was positive for M.avium 3 months later. Tuberculous meningoencephalitis was suspected and treatment started immediately. Both the meningeal enhancement and the cerebral edema disappeared. This report shows the difficulties which may be experienced in diagnosing tuberculous meningoencephalitis and that M.Avium may be the agent. Cerebral MRI is, however, an important tool in the management of the patients both with regard to diagnosis and follow-up after the initiation of treatment.

81
NECROTIZING MYOPATHY WITH PIPESTEM CAPILLARIES: AN UNUSUAL FORM OF DERMATOMYOSITIS ? FJ Authier, H Kondo, RT Ghnassia, JD Degos, RK Gherardi. *Creteil. France*

Three types of idiopathic inflammatory myopathy are described in adults: dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM). Whereas DM is primarily a vascular disease with deposits of membrane attack complex (C5b-9 fraction of complement) in vessels, PM and IBM constitute primary muscle diseases mediated by immune cellular MHC-I restricted CD8 cytotoxicity. Recently, Emslie-Smith and Engel (Neurology 1991; 41: 936-9) described an additional type of idiopathic inflammatory myopathy they called "Necroziting myopathy with pipestem capillaries, micro vascular deposition of the complement membrane attack complex (MAC) and minimal cellular infiltration", in three patients presenting with a painful myopathy without skin changes. Follow-up duration ranged from 6 to 14 months. We describe a patient with a 7-year history of most unusual exercise-dependant painful myopathy with rhabdomyolysis, who had muscle biopsy findings similar to those described by Emslie-Smith and Engel. Skin examination revealed mild cutaneous signs of DM that had been missed previously. We believe that this case represents a rare presentation of dermatomyositis with prominent muscle involvement.

82
RESTORATION OF DYSTROPHIN MRNA READING FRAME IN A PATIENT WITH BECKER-DUCHENNE DYSTROPHY (BMD) WITH OUT-OF-FRAME DELETION. Bardoni A., Ciafaloni E., Comi G. P., Bresolin N., Robotti M., Moggio M., Rigoletto C., Roses A., Scarlato G. *Milan. Italy; Durham NC. USA*

Exceptions to the correlation between phenotype and type of mutation (disrupted dystrophin Dys mRNA reading frame in Duchenne and altered but functional Dys reading frame in Becker muscular dystrophy) are present in about 8% of cases. We describe a 33 year old male who presented with proximal lower limb weakness at age 7 and was still able to walk at age 31. Dys immunohistochemistry with NH2, rod domain and COOH monoclonal antibodies showed discontinuous subsarcolemmal staining. Western blot analysis demonstrated an apparently 400 kD protein with relative amount of 22% (rod domain ab). Multiplex PCR showed an out-of-frame deletion of exons 48-52, with exon 53 consistently present. Dys mRNA analysis by RT—PCR with primers 47F and 55RC did detect neither the normal band, nor the band expected on the basis of deleted exons. Two abnormal bands were demonstrated: one corresponding to an in-frame splicing of exons 47-54 and a second band corresponding to the same deleted sequence with an insert of 73 bp of unknown significance containing a stop codon at position +22. Frame-restoration at the mRNA level appears to be one possible mechanism in BMD patients with out-of-frame deletions.

83
THE CEREBELLAR CONTRIBUTION TO HIGHER FUNCTION IN DUCHENNE MUSCULAR DYSTROPHY (DMD). E Castelli, A Turconi, N Bresolin, D Perani, G Comi, G Felisari. *Milano, Italy.*

Cognitive function and dystrophin gene mutations were investigated in 50 DMD patients. Neuropsychological assessment in our sample confirmed a higher degree of impairment in verbal versus non-verbal performances and a deficit of semantic memory. DMD patients shared the same spectrum of neuropsychological defects, regardless of whether they were mentally retarded (M.R.) or not. me of these DMD patients and one case with Werdnig Hoffman disease were submitted to Magnetic Resonance Imaging (MRI and Fluoro-deoxyglucose Positron Emission Tomography) studies. MRI was normal in all cases. PET demonstrated a metabolic reduction of both the cerebellar hemispheres and of associative areas in all patients, except in the case with WH disease. Based on the observation that dystrophin is present in cerebellar Purkinje cells, a subtle defect in motor coordination may or procedural learning has been proposed, compounded by a profound and progressive weakness, may account for MR in DMD patients. Recent clinical and research reports suggest that the cerebellum may contribute to the modulation of higher order behaviour. The significant cerebellar hypometabolism in our DMD patients with neuropsychological impairment, gives further support to the possible role of the cerebellum in some aspects of cognition.

84
HMG-COA REDUCTASE INHIBITORS (STATINS) AND MITOCHONDRIAL FUNCTION: EFFECTS ON SERUM UBIQUINONE AND BLOOD LACTATE/PYRUVATE RATIO. P Chariot, G de Pinieux, A Astier, B Jacotot, R Gherardi. *Creteil, France*

We tried to evaluate the effect of HMG-CoA reductase inhibitors (statins) on ubiquinone (Coenzyme QIO) serum level and on mitochondrial function assessed by blood lactate/pyruvate ratio. Statins inhibit mevalonate synthesis that might result in a decrease of ubiquinone, a central compound of the mitochondrial respiratory chain. These cholesterol-lowering agents can induce a toxic myopathy possibly related to mitochondrial dysfunction (Chariot et al., Am J Med 1993; 94: l09). Eighty-three hypercholesterolemic patients (43 treated by statins, 23 treated by fibrates, and 17 untreated patients) and 30 healthy controls were included. Ubiquinone serum level and blood lactate/pyruvate ratio were evaluated in all subjects. Ubiquinone serum levels were lower in statin-treated patients (0.72 μg/mL ± 0.04) than in patients treated by fibrates (0.9O μLg/mL ± 0.09; p = 0.03) or in untreated hypercholesterolemic patients (0.97 μg/mL ±0.09; p = 0.01). High lactate/pyruvate ratios were found in 16 of 4O statin-treated patients, in 5 of 2O fibrate-treated patients, in 2 of 17 untreated patients, and none of healthy controls. Conclusions. Statin therapy can induce a mitochondrial dysfunction associated with a decrease of ubiquinone.

85
RECOVERY OF MDX EDL MUSCLE FOLLOWING DENERVATION DEVASCULARIZATION. V Fischer-Gagnepain, JP Louboutin. *Nantes, France*

X-linked myopathy (mdx) shows features of Duchenne muscular dystrophy (DMD), including dystrophin deficiency. The aims of the present study were to characterize the long term follow up of mdx EDL muscle after denervation and devascularization (DD) and to determinate whether the age at which DD was performed played a role in the plasticity of mdx muscle recovery. DD was performed on EDL muscles from mdx and C57BL/10 strains aged 3 weeks 1/2 and 6 weeks. EDL muscles were isolated 2, 4, 8 weeks after surgical intervention for histologic and histoenzymologic analysis. Two weeks after DD performed at 3 weeks 1/2, mdx EDL showed 8O% of normal fibers and 2O% of fibers with central nucleation. Unoperated mdx EDL muscles at the same age exhibited 52% of fibers with central nucleation and 45% of normal fibers. Cross sectional area (CSA) distribution of operated EDL muscles was shifted toward smaller CSA compared with unoperated muscles, both in mdx and normal strains. When DD was performed at 6 weeks, the percentage of fibers with central nucleation measured 2, 6 or 8 weeks after DD approached 80% in every cases and did not differ between 1) operated and unoperated mdx EDL muscles, and 2) operated control EDL muscles. These results suggest that: 1) the potential to recover from injury is preserved in mdx EDL muscle, 2) the regeneration in mdx muscle after injury does not prevent the appearance of dystrophic changes, 3) neural regulation is involved in the onset of mdx dystrophy.

86
DISTAL MYOPATHY OF MIYOSHI. F Crespo, A Codina, *Barcelone, Spain.*

Early adult onset distal type II (Miyoshi variant) is rare in Europe and has not been reported in Spain. We present 4 patients belonging to 2 families. All 4 patients (2 brothers, a brother and sister, aged 19 to 27) underwent clinical and electromyographic examination, MRI studies and muscle

biopsy. The onset was between ages 16 and 19. Three patients showed severe distal leg weakness with marked atrophy of gastrocnemius muscles. ENG was normal. EMG showed diffuse myopathic changes, particularly severe in gastrocnemius muscles with abundant spontaneous activity (fibrillation and positive waves). Serum CK was increased by 16-46 times the normal values. The forth patient, a male aged 19, has only mild leg weakness. However, CK is consistently elevated and EMG is clearly myopathic. He refused muscle biopsy. MRI revealed severe atrophy and fatty substitution in tibialis anterior and gastrocnemius muscles. No cardiac abnormalities were found. Muscle biopsy was very similar in all three patients with necrosis and myophagia, increased fibre size variability and splittinq. Conclusions: The three patients fit very well in the type II early adult onset of the distal myopathy (Miyoshi myopathy), characterised by early onset with predominant gastrocnemius involvement, sporadic or autosomal recessive inheritance and a dystrophic pattern in the muscle biopsy.

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CYTOKINES IN HIV-ASSOCIATED MUSCLE DISORDERS: IL-1α IS PRODUCED BY AZT FIBERS AND BINDS TO MITOCHONDRIA; RK Gherardi, A Florea-Strat, G Fromont, J-C Sabourin, *Creteil, France*

We evaluated the expression of cytokines in muscle of HIV-infected patients with muscle disorders because cytokines play a central role in HIV infection, and mediate inflammation and tissue destruction which are prominent manifestations of AIDS. Histochemistry for IL-1α, IL-lβ, TNFα, and IL-6 was performed on frozen muscle biopsy specimens from HIV-infected patients with muscular disorders (polymyositis: 5; HIV-wasting syndrome: 5; zidovudine myopathy: 10) and from seronegative individuals (normal muscle: 2; mitochondrial cytopathies:l0). mRNA in situ hybridization (RISH) for IL-lβ and immunoelectron microscopy (IEM) for ILla were also performed on muscle tissue showing zidovudine myopathy. Positive reactivities were observed in vessels (IL-l) and inflammatory cells (IL-1 and TNFα) of HIV-infected patients. In zidovudine myopathy, a majority of AZT-fibers (i.e. ragged-red fibers with marked myofibrillar changes) showed mild to marked expression of IL-lα and IL-lβ. IL-1 expression in the other mitochondrial myopathies was much weaker. RISH showed that IL-1 was produced by muscle fibers and IEM showed that IL-1 accumulated in mitochondria of AZT-fibers. Conclusion: Prominent myofibrillar breakdown of AZT-fibers might result from IL-1-induced proteolysis.

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MALIGNANT HYPERTHERMIA AND NEUROMUSCULAR DISEASES. E-F Gonano, I Moroni, A Prelle, N Bresolin, G Scarlato, *Milan, Italy*

Malignant Hyperthermia (MH) is a rare clinical syndrome characterised by hypermetabolism and triggered by specific anaesthetics agents. The mechanism of this abnormal reaction to uncontrolled influx in the skeletal muscles resulting in a variable clinical syndrome. A causative genetic defect for this condition has not been identified in humans, though in some susceptible families a mutation inherited as autosomal dominant trait of the gene for the ryanodine receptor, a large protein which comprises the calcium channel in the sarcoplasmic reticulum, has been proposed as being possibly responsible for MH. Scattered case reports and investigation of individuals with known myopathy and other muscle related problems, such as acute rhabdomyolysis or idiopathic persistently elevated creatine kinase, suggest a possible association of MH with a variety of neuromuscular diseases and stress syndromes. In order to investigate the relationship between neuromuscular diseases and MH susceptibility, the caffeine and halothane contracture test (European Malignant Hyperthermia Group Protocol) were performed on 20 patients who underwent muscle biopsy because of clinically suspected neuromuscular disease. Two test results were classified as MH susceptible 6 as MH equivocal and 12 MH negative. The large number- of equivocal results is thought to indicate a lack of specificity of the individual component of this test in patients with clinical or histological evidence of neuromuscular disease. The increased "in vitro" sensitivity to the drugs tested may nevertheless provide some explanation for some in vivo "MH-like reactions; reported frequently in these patients. These reactions, however, are likely to be based on pathophysiological factors different from those responsible for a true MH.

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EPIDERMAL GROWTH FACTOR (EGF), B FIBROBLAST GROWTH FACTOR (BFGF) IN TWO ANIMAL MODELS OF DUCHENNE MUSCULAR DYSTROPHY. S Iannaccone, A.Quattrini, F deRino, M Sessa, V Golzi, S Smirne, R Nemni. *Milan, Italy.*

The dystrophin-deficient mdx mouse, presents muscle fiber necrosis, active muscle regeneration, absent fibrosis and normal lifespan. The autosomic-inherited dy mouse presents progressive muscle fiber necrosis, ineffective muscle regeneration, marked fibrosis and reduced lifespan. In Duchenne Muscular Dystrophy dystrophin deficiency is accepted as being responsible for the necrotic muscle stage, but the cause of the inefficient regeneration and fibro-fatty replacement is unknown. The pathology of the mdx mouse supports the hypothesis that fibrosis is not necessarily secondary to dystrophin-dependent muscle fiber degeneration, but different regeneration abilities in response to muscle necrosis could be involved. We investigated, by morphological and immunocytochemical studies, the presence of muscular and connective growth factors at different stages of mdx and dy muscle pathologies. Our results showed: 1) EGF, EGF receptor and Transforming Growth Factor b1are present on endomysial connective associated with active fibro sis proliferation in all dy mice 2) bFGF is present on 50 % of degenerating and regenerating muscle fibers of both animal models but disappeared in mdx when regenerating processes have ceased. Our results suggest that growth factors could play a role in the phenotyping of dystrophic pathologies through the stunulation of regenerative physiological or pathophysiological response to dystrophic injuries.

90
SPONTANEOUS MUTATION IN HUNTINGTON'S DISEASE. JC Turpin, G Lucotte, *Paris, France*

Huntington's disease is an hereditary disease with autosomal dominant transmission which usually occurs in adults. It is usually characterised by association of choreiform movement with signs which often appear more invalidating to family: emotional disorder and dementia. Among 95 French families study, patient has a spontaneous mutation of gene I T 15 from chromosome 4 p caused by expansion of triplets repeats (40 copies of trinucleotide CAG. The mechanism by which the triplet- repeats expand is unknown. In the normal population the lenght of the triple repeat stable inherited. In such patients perhaps a permutation renders the DNA sequence unstable and causes disease (such in the fragile X syndrome). Expansion of triplet repeats constitutes a new form of dynamic mutation.

91
PREDNISONE PROTECTS MUSCLE TISSUE AGAINST EXERCISE-INDUCED MUSCLE DAMAGE. SCJM Jacobs, PWA Willems, PR Bar, AL Bootsma, JHJ Wokke. *Utrecht, The Netherlands*

Prednisone may improve strength in Duchenne muscular dystrophy. This probably does not result from immunosuppressive action on cellular infiltrates in muscle. In dystrophinopathy muscle fibres are prone to injury by the mechanical stress generated by muscle contraction. Therefore we investigated if prednisone protects against exercise-induced muscle damage in an experimental model. Six-week-old rats orally received placebo, or 1, 2.5, 5, 25 or 50 mg prednisone/kg body weight/day for 1 week (5-7 animals per dosage). At day 6, rats were forced to run for 2 h on a level treadmill at a speed of 19 m/min. Creatine kinase (CK) activity was measured before and directly after exercise. Muscle fiber damage was quantified in longitudinal sections of the soleus muscle by means of light microscopy and a semi-automatic image analysis system. CK-activity rose in all groups with about 100% . Muscle fiber damage in the placebo group was 4.0 ± 1.0 % (mean ± SEM) and 1.4 ± 0.5 % in the 5 mg group ($P<0.05$, student' s t-test) . In the other groups no significant protection against damage was observed. We conclude that prednisone may prevent exercise-induced muscle damage in a dose-related manner, but not proportional to the dose. We found no evidence for an immunological mechanism to explain this effect. Other explanations e.g. a direct interaction with the membrane require further study.

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MULTIPLEX SSCP: A USEFUL METHOD FOR MUTATIONS DETECTION IN THE DUCHENNE MUSCULAR DYSTROPHY GENE. A Lasa, M Calaf, M Baiget, B Gallano. *Barcelona. Spain.*

The dystrophin gene is the largest known human gene: it encodes for a 427 kDa protein that is deficiency or abnormal in the DMD/BMD phenotype.

In about 60% of DMD/BMD cases a deletion in the dystrophin gene can be identified by Southern blot analysis or PCR amplification. In the remaining cases where no such gross DNA rearrangements can be detected, point mutations or small structural alterations in the dystrophin gene are presumed to be responsible for the disease. The identification of these point mutations represents a formidable challenge because of the large size and structural organization of the dystrophin gene. Screening of point mutations was performed by multiplex PCR amplification of DNA segments followed by the single strand conformation polymorphism (SSCP) technique. The SSCP analysis is a simple and fast method, although alterations in several gel conditions can affect the SSCP assay. The method allows the simultaneous examination of multiple regions in different samples. Up to date, we have analysed 78 samples for nine different exons, 8 of them present mobility shifts of exons 8,12,43 or 51 and polymorphism were detected in 17 and 45

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REGENERATING MUSCLE FIBRES ARE FORMED IN ADIPOSE CONNECTIVE TISSUE IMPLANTED IN MUSCLE OF DYSTROPHIC MDX MICE. V Fichter-Gagnepain, JP Louboutin. *Nantes, France.*

The transplantation of normal myoblasts to patients suffering Duchenne muscular dystrophy (DMD) is a potentially promising therapeutic concept. However, the replacement of a large part of the muscle mass by connective and adipose tissue in DMD is an important problem that may limit the applications of myoblasts transfer. The mdx mouse myopathy and DMD share some genetic, biochemical (lack of dystrophin) and histopathological features. However, necrosis of muscle fibres in mdx mice is followed by a spontaneous revert of clinical, morphological and physiological characteristics and the adult mdx phenotype is benign compared with DMD. Moreover, the mdx mouse muscles do not show significant fibrosis, except in the diaphragm muscle. Therefore, we have inserted mature fatty connective tissue in the center portion of the Tibialis Anterior (TA) muscle of adult mdx mice, according to the procedure described by Satoh et al. (Transplantation Proceedings 6:3017-3019, 1992). At 7 days after the implantation, numerous myoblasts and myotubes began to invade the implanted fatty connective tissue. At 14 days after implantation, clusters of small regenerating fibres were present in the implanted tissue. At 28 days after the implantation, small and large regenerating muscle fibres occupied the space between muscle stumps in which connective tissue had been implanted. The present study demonstrates that myoblasts from mdx mouse have the potentiality to form myotubes and new muscle fibres across fatty connective tissue without basal lamina. The applications for myoblast transfer are discussed.

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"IN VITRO" EFFECTS OF AZT ON MITOCHONDRIAL DNA. F Mazzucchelli, N Bresolin, MG D'Angelo, M Velicogna, L Bet, GP Comi, A Bordoni, G Scarlato, *Milan, Italy*

Zidovudine-related changes include an inflammatory myopathy with abundant ragged-red fibres (RRF) and proliferation of enlarged mitochondria. Dideoxynucleoside triphoshates, including zidovudine, can serve as substrates for DNA polymerase gamma, which is responsible for the replication of mitochondrial DNA (mtDNA). Acquired mitochondrial myopathy develops in close relation to the duration of treatment with zidovudine (AZT), but very little is known about the effect of this drug on the Central Nervous System . Three zidovudine -treated AIDS patients presented histological features of ragged-red fibers (RRF) and severely reduced amounts of mitochondrial DNA (mtDNA) in muscle biopsy specimens measured by means of Southern blotting. For testing AZT effect "in vitro" human muscle clonal cell were obtained from biopsies of normal subjects of different ages (5-40-70 years). Cultured muscle cells exposed to Zidovudine(5-250 uM /L) showed a remarkable decreases in cell proliferation, more evident in older patients. We also measured mtDNA/nDNA ratios in these clonal cells exposed to AZT and found a marked decrease in mtDNA content above all in young subjects as compared with controls. An inexplicable increase of mtDNA was detectable in AZT treated clonal cells of older subjects. Morover this drug effectively penetrates the blood-brain barrier, which penetration results in antiviral concentration within the CSF. The effects of AZT treatment on cell metabolism in neuronal and glial cell cultured will be presented.

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SCREENING FOR NEW MUTATIONS OF RYANODINE RECEPTOR GENE IN CENTRAL CORE DISEASE AND MALIGNANT HYPERTHERMIA. I Moroni, EF Gonano, GP Comi, A Bordoni, P Bazzi, N Bresolin, G Scarlato. *Milan, Italy*

Biochemical and genetic studies on human and porcine Malignant Hyperthermia (MH) strongly suggest that the primary defect in MH susceptible patients lies in the skeletal muscle calcium release channel, also termed ryanodine receptor (RYR). The gene coding for this protein (RYR1) has been mapped to the q12-13.2 region of chromosome 19, and codes for a protein that forms an elaborate tetrameric structure that acts both as calcium release channel and "foot" structure bridging the gap between the sarcoplasmic reticulum and the t-tubule in skeletal muscle. A point mutation has been described in about 5% of human MH families investigated (Arg to Cys 614) and a second point mutation was reported in a single pedigree (Gly 248 Arg). The Central core disease (CCD) gene maps to the q12-13.1 region of chromosome 19. The clinical and genetic strong association of the two conditions suggests that the CCD may be another phenotypic manifestation of mutations within RYR1. Recently point mutations in RYR1 have been described in restricted number of CCD pedigree and unrelated MHS patients. A mutation in RYR1 that produce both hypersensitive gating and diminished excitation-contraction coupling could cause both MH and CCD phenotypes in an individual. In the present study we have undertaken a mutation analysis of RYR1 cDNA in MH susceptible patients, including MHS pedigrees, Central Core diseases, and unrelated MH patients. Results of in vitro contracture test, histological investigations and genetic analysis will be reported.

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HIGH BLOOD LEVELS OF CREATINE-KINASE (CK) ASSOCIATED WITH CYLINDRICAL SPIRALS IN MUSCLE SPECIMEN. S Rapuzzi, A Prelle, M Moggio, G Comi, G Fagiolari, P Ciscato, A Messina, A Battistel, P Bazzi, G Scarlato, *Milan, Italy*

We studied a muscle biopsy specimen of a 30 year old man who had high CK blood levels. Light microscopy showed subsarcolemmal and intermyofibrillar granular inclusions They appeared bright red with Gomori's trichrome, bluish with HE, lightly reactive with PAS. positive with NADH and SDH, negative with COX and ATPase. EM showed clusters of cylindrical spirals (CS). Many clusters can occur in a single fiber. They consist of concentric lamellae with a rounded central area containing glycogen granules. On longitudinal sections CS are parallel to the axis fiber. CS were first described in 1979 by Carpenter et al. and they have been reported only in 10 cases since then. These cases presented with a wide variety of clinical Phenotypes. CS origin has not been determined although it is postulated they result from a degeneration of sarcoplasmic reticulum. Antibodies against several cytoskeletal proteins did not react with these structures. Finally no reaction was found with antibodies against different COX subunits and mt-DNA analysis did not show deletions.

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EMG STUDIES OF PATIENTS WITH MYOTONIC DISORDERS. B Ryniewicz, H Kwiecinski, *Warsaw, Poland*

Although molecular biology provides now very precise diagnosis of some myotonic patients, the clinical features of patients with different mutations are similar. our studies were undertaken in order to further characterise the phenotypes of several patients with genetically defined diagnosis. The analysis by now included 9 patients examined by means of standard EMG, exercise test and muscle cooling. In patients with paramyotonia congenita (n=3), the most striking abnormality was marked decline of the evoked CMAP after exercise with muscle cooling. In patients with hyperkalemic periodic paralysis (n=3), spontaneous electrical activity was found in limb muscles; slight decrement of the CMAP amplitude was observed after exercise in cooled muscle. In 2 patients with the generalised recessive myotonia, needle electrode examination revealed widespread intense myotonic discharges. After short exercise tests a moderate and early decrement of the CMAP amplitude was observed. Muscle cooling had no significant effect. In one patient with myotonic dystrophy widespread electrical myotonia was present and slight myopathic changes were found in proximal muscles. Transient mild decrement of the CMAP was observed after short exercise, without effect of muscle cooling. Further clinical and electrophysiological studies are required in families with myotonic disorders to correlate specific clinical features with distinct mutations.

98
EXERTIONAL MYALGIA RELIEVED BY VERAPAMIL IN MYOPATHY WITH RIMMED VACUOLES AND MITOCHONDRIOPATHY. I Sangla, J Pouget, JF Pellissier, C Desnuelle, V Paquis, PJ Cozzone, D Bendahan, G Serratrice - *Marseille, France*

We report a case of a 30-year-old man presenting an exercice intolerance for 2 years. There was no family history. CK were mildy increased and electromyography study revealed diffuse myogenic signs. Muscle metabolism as studied by bicycle ergometer exercice test and 31p NMR spectroscopy indicated oxydative pathway abnormalities. Muscle biopsy showed rimmed vacuoles without inflammatory infiltrates. Biochemical analysis indicated a deficiency of complex Ill activity (38% of the control mean) and there was a mitochondrial DNA polymorphism on muscular analysis (PVU2). Co Q treatment performed during 14 months remained clinically ineffective and NMR study revealed only a partial improvement of pH recovery. Then, verapamil treatment followed during 5 months dramatically improved exertional myalgia. There was a parallel improvement of muscle metabolism, as seen on NMR study: resting PCr/Pi ratio, PCr/Pi and PCr recovery kinetics increased significantly, while pH recovery still remains delayed. Verapamil was interrupted for 2 months, and myalgias quickly reappeared. After renewal of verapamil treatment exertional myalgia again disappeared. Muscle pain seems to be due to mitochondrial dysfunction but the effect of calcium blocking agents is not clearly understood.

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THE METABOLIZATION OF ANDROGENIC/ANABOLIC STEROIDS IN MUSCLE BIOPSIES FROM PATIENTS WITH NEUROMUSCULAR DISEASES. HJ Sturenburg, G Kohncke, K Kunze, *Hamburg-Eppendorf, Germany*

The activation and deactivation of steroid hormones in the target tissue through enzymatic transformation represents an important regulating mechanism in the effect of steroid hormones. We investigated the metabolism of testosterone and dihydrotestosterone in muscle biopsies taken from patients with neuromuscular diseases (n=30) and from operative tissue in vitro (n=4). We found no relevant metabolism of testosterone to estradiol, androstendion or dihydrotestosterone.The metabolism of dihydrotestosterone to 5-alphaandrostane-3-alpha,beta-17-beta-diol could be determined. Healthy tissue: Vmax= 6,64 (± 1,26)* 10 -12 Mol/mg Protein*min.(SEM), Km: 16,75 (± 3,93) Mikromolol (SEM) Neuropathies: Vmax= 7,44 (± 1,5)* 10-12Mol/mg Prot*min., Km: 13,31 (± 3,37) micromol (SEM). Myopathies: Vmax = 8,79 (± 1,86)* 10-12 Mol/mg Prot*min.(SEM), Km: 1 5,39 (± 2,77) micromol/l. There were no significant differences between groups of patients or between men and woman patients. The age distribution was as follows: Healthy tissues: 51,3 ± 6,77 years (SEM), Neuropathies: 58,6 ± 5,1, Myopathies: 52,2 ± 6,41. There was a significant negative correlation between Vmax and age distribution ($p<0.05$, Spearman rank correlation coefficient and F-test). Therefore, the metabolism of the active androgen dihydrotestosterone (DHT) to inactive metabolites decreases with age. This corresponds to a reduction in the deactivation of the androgenic/anabolic steroid DHT.Vmax of the oxidative metabolic pathway of 3-alpha,beta-hydroxysteroid-dehydrogenase from 5-alpha-androstane-3alpha-l 7-beta-diol to DHT - thus the building of more active anabolic/androgenic steroids - was significantly less. The Km constants were identical. Vmax: 1,71 (± 0,5)* 10-12 Mol/mg Prot.*min. (SEM), Km: 15,31(± 2,0) micromol/l.

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CLINICAL FEATURES AND NEUROPSYCHOLOGICAL FUNCTIONS IN DUCHENNE MUSCULAR DYSTROPHY CARRIERS AND THEIR AFFECTED SONS. A Turconi, E Castellli, N Bresolin, G Comi, G Felisari, M Moggio. *Milano, Italy.*

Non progressive mental retardation (MR) is present in about a third of Duchenne Muscular Dystrophy (DMD) patients. Dystrophin is localised in post-synaptic regions of mammalian central nervous system. The objective of this study is to correlate clinical features and global neuropsychological performance in DMD obligate carriers and their affected sons, to evaluate specific brain involvement, manifested by mental impairment, as a symptom of carrier status and help elucidate the etiology of MR in DMD. Fifteen women were diagnosed as obligate carriers. Clinical, laboratory, EMG, ECG and neuropsychological assessment were carried out in DMD carriers and DMD patients. Immunohistochemistry and Western blot analysis were performed on muscle samples on DMD patients and DMD carriers. DMD carriers IQ and DMD patients IQ were lower than controls, with specific neuropsychological defects. A statistically significant correlation was found for these items and for impaired mental performance between a carrier and her affected boy. DMD carriers and DMD patients present commons clinical features and neuropsychological defects with a direct correlation between mother and affected boy.

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MUSCLE FIBRE CONDUCTION VELOCITY CHANGES IN MC ARDLE'S DISEASE. W Linssen, D Stegeman, R Binkhorst, S Notermans, *Nijmegen & Amsterdam, The Netherlands.*

The functional role of local muscle electrophysiology in the complexity of local muscle fatigue still is uncertain. Often intramuscular lactic acid accumulation is considered a major indirect cause of fatigue. As far as observable in EMG parameters, this influence of lactic acid is likely to be mediated by a sarcolemmal excitability deterioration. The sarcolemmal excitability can be estimated by measuring the mean muscle fibre conduction velocity (MFCV). In patients with myophosphorylase deficiency (McArdle's disease) the muscles are unable to produce lactic acid. We studied the important role of the absence of lactic acid accumulation on the sarcolemmal function by means of the MFCV changes in these patients and showed that the normal MFCV decline during fatigue was completely prevented during ischemic voluntary submaximal exercise In contrast however, an almost normal MFCV decline is found in McArdle's disease beyond the moment where the force level can be maintained (failure point) and during supramaximal electrically elicited contractions at different stimulation frequencies. These results are not explained by one leading mechanism. At a sarcolemmal level, lactic acid appears to be not the only mediator of voluntarily induced local fatigue. The results with electrically elicited contractions suggest deviating voluntary motor unit recruitment mechanisms in McArdle's disease patients.

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CORRELATION OF CLINICAL SYMPTOMS WITH THE SIZE OF THE UNSTABLE DNA SEQUENCE IN MYOTONIC DYSTROPHY. A Jaspert, R Fahsold, H Grehl, D Claus, B Neundörfer, *Erlangen Germany*

An unstable DNA sequence in the myotonic dystrophy (DM) gene on chromosome 19, stemming from a multiplication of a base triplet (CTG)n, has been identified as the molecular basis of the disease. We investigated the correlation between the size of this triplet repeat and different clinical symptoms. Detailed clinical and electrophysiological examinations as well as psychological and laboratory tests were performed in 14 DM patients. DNA was prepared from whole blood by standard procedures and investigated by Southern block hybridization and polymerase chain reaction. Amplifications of 220 to 1500 base triplets (0.66 - 4.5 kb) were found in the patient group. Triplet size correlated significantly with muscular disability and inversely with age of onset of the disease. Mental and gonadal dysfunction could be observed with a greater frequency in patients with larger repeat sizes. Other clinical manifestations such as cataract, myotonia, gastro-intestinal and cardiac symptoms as well as morphological alterations in the muscle biopsy were not correlated with triplet size. The clinical variability at a given triplet size might be explained by somatic mosaicism with different amplification rates in various tissues by different expression of the DM gene in individual patients.

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INFLUENCE OF THE SEX OF THE TRANSMITTING GRANDPARENT IN CONGENLTAL MYOTONLC DYSTROPHY. A Lopez de Munain, A Cobo, L Martorell, JJ Poza, D Navarrete Palau, JI Emparanza, M Baiget, *San Sebastaian, Spain.*

We tried to analyse the influence of the sex of the carrier grand parent in congenital cases of Myotonic Dystrophy (CMD). We have studied the expansion size of the DM gene in CMD patients, their mothers and maternal grandparents. The relative intergenerational increase defined as:

$$\frac{\text{Expansion of the individual} - \text{Expansion of the progenitor}}{\text{Expansion of the progenitor}}$$

has been calculated. In all the 76 cases of CMD, the mother was the transmitting parent. The sex of the carrier grandparent was known in 49 cases (40 grandfathers and 9 grandmothers, Chi2, $p < 0.001$). The mean relative intergenerational increase in the 32 grandparent-mother pairs was 5.66 ± 4.10 (6.04 ± 4.24 for the grandfathers and 4 ± 3,07 for the grandmothers), significantly greater than the mean relative intergenerational increase in

the 56 mother-DMC pairs which was 2.75 ± 3.36 (t Student, p<0.001). The mean expansion of the grandfathers (103 CTG repeats) was not significantly different from that seen in the grandmothers group (154 CTG repeats) (t Student, p=0.08). Conclusions. We confirm the exclusive maternal transmission of the CMD as well as the clear predominance of transmitting males in the previous generation. This could be duc to the fact that the degree of intergenerational increase is greater when the premutated allele is paternally transmitted probably reflecting different stabilities during male and female gametogenesis. Hence, the daughters of these males would have an increased probability of having a CMD child.

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MYALGIA AND EXERCISE INTOLERANCE AS AN EXPRESSION OF DYSTROPHYNOPATHY. R Sanchez-Roy, JJ Vilchez, F Palau, M Hernandez, J Garcia Tena, C. Perla. *Valencia, Spain.*

The introduction of immunocytochemical and molecular techniques have permitted the identification of dystrophynopathies other than Duchenne's and Becker's phenotypes. We present a series of 7 cases of a syndrome combining myalgia and intolerance to exercise which showed abnormalities in the immunocytochemical staining sting of dystrophin. Seven cases, 5 males and two females aged 9-27 years presented myalgia during exercise as the main complaint. They also showed muscle hypertrophy, intolerance to exercise (easy fatigue) and increased basal serum Creatine-kinase (1000-5000 U/L) specially after exercise. Three of them presented recurrent episodes of pigmenturia. The common histologic picture consisted of variable myopathic changes with presence of scattered foci of necrosis. Immunocytochemistry using the 3 monoclonal NCL-DYS antibodies and avidine-peroxidase showed either the absence of immunoreactivity of mid rod domain of dystrophin or weak and patchy immunostaining of other domains. Molecular studies of the dystrophin gene with cDNA are currently being carried out.This series confirms that dystrophynopathy is a frequent cause of myalgia, myoglobinuria and intolerance to exercise that until recently were tought to be typical of metabolic myopathies. It appears not only in males but also in female carriers of the mutation.

105
BLINK REFLEX AND MULTIMODAL EVOKED POTENTIALS IN MITOCHONDRIAL MYOPATHY. M Koutroumanidis, P Papathanasopoulos, A Papadimitriou, TH Papapetropoulos. *Athens, Greece*

The mitochondrial myopathies (M.M.) comprise a group of disorders with considerable clinical heterogeneity. Limb weakness, progressive external ophthalmoplegia (P.E.O.) and symptoms and signs arising from the C.N.S. may predominate in various combinations in the clinical picture. However, in apparently monosystemic forms (i.e. pure myopathies with or without P.E.O.) other organs may be subclinically affected. In an attempt to detect C.N.S. involvement, we studied 11 patients with histologically, biochemically, and genetically confirmed M.M. with visual, somatosensory and brainstem auditory evoked potentials (E.Ps.) and blink reflex (B.R.). Two of the patients suffer from MERRF syndrome while all the others are affected by P.E.O. with a varying degree of craniosomatic spreading. Among them, there are 5 patients demonstrating the clinical features of K.S.S. and 3 cases of familiar P.E.O. In all but 2 of the patients at least one modality was abnormal. Furthermore, evidence of central sensory pathways impairment was detected in 5 patients, 2 of whom lacked clinical symptoms and signs suggesting C.N.S. involvement. The most prominent abnormality in B.R. confirmed in three cases is a bilateral delay of R2 component evoked by both-sided stimulation. This finding probably reflects diminished excitability or loss of the interneurons in the pons or lateral medulla. In conclusion, B.R. and E.Ps. are useful methods to detect C.N.S. involvement in patients affected by M.M.

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MULTIPLE DELETIONS OF mt DNA IN AUTOSOMAL DOMINANT INHERITANCE AND SPORADIC CASES OF MITOCHONDRIAL ENCEPHALOMYOPATHY. A Papadimitriou, R Divari, G M Hadjigeorgiou, G Comi, I Anastasopoulos, and N Bresolin. *Athens, Milano*

Multiple deletions of mitochondrial DNA (mt DNA) have been found not only in patients with autosomal dominant inheritance pattern but also in sporadic cases. We present 3 families with 15 affected members (in 3 generations) and one sporadic case with mitochondrial encephalomyopathy where multiple deletions of muscle mt DNA were found. The patients of the first family present chronic progressive external ophthalmoplegia (CPEO) and slight polyneuropathy while the other two families only CPEO. The patient of the sporadic case had extrapyramidal signs, polyneuropathy and mitochondrial myopathy. Morphological studies of muscle biopsies revealed ragged red fibers. Biochemical muscle analysis showed heterogeneity in the activity of mitochondrial enzymes while Southern blot and PCR analysis revealed multiple deletions of the mt DNA with the same pattern, in all examined muscle specimens. Conclusion : Multiple mt DNA deletions are similar in both autosomal and sporadic cases of mitochondrial encephalomyopathies. So one can suggest that the mutation of the nuclear DNA which may be the cause of ,the multiple mt DNA deletion should be the result of a genetic error or the influence of an exogenous factor.

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MUSCLE MULTIPLE mt-DNA DELETIONS: CLINICAL VARIABILITY OF MITOCHONDRIAL. V Sansone, G Rotondo, A Prelle, G Meola, S DiDonato, *Milan, Italy.*

Multiple symmetrical lipomatosis (MLS) is associated with a variety of central and peripheral (particularly peripheral neuropathy) and other organ abnormalities (PEO, hyperuricemia, hypacousia, seizures, optic atrophy, etc.) .Mitochondrial dysfunction is now recognised as the essential biochemical defect in this clinically heterogeneous syndrome. We report on a case with unusual clinical and genetic features of mitochondrial dysfunction associated with MLS: a 59 year old woman with only moderately high CK level (300-400 U/L),exercise-intolerance and multiple lipomas. Serum lactate (at rest and after exercise) was above normal values, EMG showed myogenic suffering and muscle biopsy studies revealed a partial COX deficiency in the muscle biopsy. Muscle mtDNA was analysed by Southern Blot. The region between oligonucleotide-forward /7440 7460 and 7460 and reverse-complementary 16133-16153 was amplified by PCR. Southern Blot analysis, along with a 16.5 Kb band corresponding to wild-type mtDNA, revealed multiple deletions in the patient's mtDNA, confirmed by PCR analysis. The combination of multiple mtDNA deletions and multiple lipomatosis strengthens the hypothesis of pathogenic link between mitochondrial disorders and certain forms of lipomatosis; the absence of significant central, peripheral and multi system involvement other than high CK levels and exercise-intolerance emphasises remarkable phenotypic variability of mitochondrial disorders.

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UTROPHIN EXPRESSION DURING HUMAN FETAL DEVELOPMENT, A Prelle, C Rigoletto P Ciscato, M Moggio, S Messina, G Comi, G Scarlato, *Milan, Italy*

Utrophin is a protein encoded on chromosome 6 highly homologous to the cysteine-rich domain and most of the C-terminal domain of dystrophin. In normal adult skeletal muscle utrophin is expressed at neuromuscular and myotendinous junctions and in vessels. In DMD utrophin is expressed at sarcolemma, to for dystrophin absence. We have expression during human foetal development. We carried out immunohistochemical analyses on muscle from normal human foetuses at different stages of gestation using an antibody directed against a specific COOH-terminal sequence of the protein. Serial sections with antibodies against dystrophin and with alpha-bungarotoxin FITC-BTX have been performed. At week 11 of gestation utrophin is diffusely expressed in the cytoplasm From week 12 to 22, we observed a persistent presence of the protein in the cytoplasm, with a progressive decrease of the intensity of the reaction. A strong reaction in foetal nerve is present at week 18 and 22. No correlation with utrophin expression and the progressive dystrophin membrane localization has been found.

109
CLINICAL ASPECTS OF CONGENITAL MUSCULAR DYSTROPHY. E Szwabowska-Orzeszko, S Jozwiak, R Michalowicz, W Szaplyko, *Warsaw, Poland*

The term "congenital muscular dystrophy" (CMD) has been widely used for a group of infants with weakness, usually associated with hypotonia from birth, and a muscle biopsy showing striking pathological changes similar to a muscular dystrophy. Despite of some clinical modifications

CMD is regarded as a distinct genetic entity, with an autosomal recessive pattern of inheritance. We observed 4 children with CMD. In all of them the condition was present from birth with marked hypotonia and associated weakness affecting the limb, trunk and facial muscles. In one child contractors of various muscles were present at birth, in others developed later. Intellectual development remained normal. Electromyography a myopathic pattern. PK was moderately elevated in all children. Muscle biopsies showed a dystrophic process and a remarkable replacement of muscle by adipose tissue. Brain US or CT scan was normal in all except for one child with perinatal asphyxia. The condition remained relatively static and children could pass some motor milestones, although at a very delayed time.

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SLEEP EEG FEATURES IN ALZHEIMER'S DISEASE. MA Petrella, G Della Marca, G Masullo and GF Mennuni. *Rome; Italy.*

Three consecutive all night polygraphic recordings were carried out in 12 moderately affected demented patients (all females, mean aged: 60.08 ± 7.6). The clinical diagnosis of dementia was made according to the clinical, neuropsychological and neuroradiological criteria outlined by the NINCDS/ADRDA work group; all the patients were classified into "probable" Alzheimer's disease. Night 1, which was considered adaptation to sleep laboratory, was excluded from statistical evaluation. The paper write-outs were second according to standard criteria; for Slow Waves Sleep, we followed the criteria recommended by Williams et al. and Webb and Dreblow. For each patient we calculated the average for each sleep parameter of nights 2 and 3; then we pooled the mean value of each patient and we calculated the overall mean ± standard deviation for all the group. Finally we compared data of our group of patients with those of a control group, matched for age and sex, obtained from normative data. Statistical analysis showed a significant increase, in patient group, of the following parameters: sleep latency, number of stage shifts, stage 1, stage 3 and wakefulness percentages. On the other hand, total sleep time, sleep efficiency index, stage 2 percentage and the average REM period length were significantly decreased. Our results document a sleep disruption in Alzheimer's disease, in partial agreement with those previously reported; it is confirmed the presence of lightened and fragmented sleep. Unlike prior studies, we observed an increase of stage 3 percentage.

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POSITIVE EFFECTS OF MEDICATION ON EVENT- RELATED EEG POTENTIALS IN DEMENTIA. D Kompf, E Wascher., R Verleger., *Lübeck, Germany*

Event- related EEG potentials (ERPs) of Alzheimer patients differ from healthy controls by several features. Above all, the N2 and P3 components are delayed though not necessarily in mild dementia. It is not known whether these differences are reduced by psychotropic medication, and there are still very few studies on vascular dementia. Therefore, in the present study the effects of medication (Nimotop, a calcium antagonist) on the dementing process were evaluated in Alzheimer's disease and in vascular dementia, with psychometric tests and ERPs serving as dependent measures. So far, 13 patients have been studied psychometrically and with ERPs before and after 3 months of treatment. ERPs were measured in auditory and visual oddball tasks. After treatment, P3s reached their peak earlier in both groups of patients, and auditory N2s became larger in vascular patients. Both findings indicate normalization of ERP parameters. Unexpectedly, the vascular patients 'ERPs contained large frontal negative slow waves. In conclusion, ERPs became less deviant after treatment. The patients' relatives who reported that the patients had become more active, but psychometric results did not change. ERPs might thus be a more sensitive index of cognitive change.

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ALZHEIMER PATHOLOGY IN A PATIENT WITH MELAS H Fujimura, M Kaido, F Soga, H Yoshikawa, H Toyooka, S Yorifuji, T Yanagihara. *Osaka, Japan*

A 53-yr-old Japanese female from a family where a typical point mutation in mitochondrial DNA (tRNAL leu(UUR), nt3243) had been maternally inherited (J Pediatr, 1992), suffered a myopathy and psychotic syndrome without any clinical evidence of stroke-like symptom during the last 10 years, and died from an accident. At autopsy 30 hours postmortem, a part of the brain was snap frozen for biochemical and histochemical studies, and other parts were processed for routine examination and electron microscopy. In the brain, there was no vascular lesion including strongly SDH stain positive vessels or ischemic lesions. Instead, primitive/diffuse senile plaques were found throughout the brain, predominantly in the frontal and temporal lobes, while Alzheimer's (Az) neurofibrillary tangles were found only in the parahippocampal gyrus. These plaques were positive for anti-B protein and negative for anti-APP or tau protein. All the mutations in codon 331 of ND2, and codon 693, 713 and 717 of APP, known to be responsible for some cases of familial Az were negative. Furthermore, coincidental Down's syndrome was ruled out by analysis of the chromosomes. This study suggested that correlation might exist between mitochondrial DNA abnormality and Alzheimer pathology.

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APOLIPOPROTEIN E GENE IN ALZHEIMER'S DISEASE. C Bayon, J Rubio, *Segovia, Spain*

Allele 4 of the apolipoprotein E gene (Apoε4) has recently been found to be associated with late-onset familial and sporadic Alzheimer's disease (AD). To confirm this in our population, we performed a case-control study in 50 patients with sporadic AD, and 66 controls. cases were defined as those fulfilling NINCDS-ADRDA criteria for probable AD, and controls as those with no evidence of neurological or cardiovascular disease. Apoε genotypes were determines by polymerase amplification of the region of interest of apoε, followed with Cfo restriction enzyme, and electrophoresis en 20 % acrylamide mini-gels stained with ethidium bromide. Allele frequencies were ε3 0.76, ε2=0.06, ε3=0.58,ε2=0.0 ε4=0.42 in AD. Thus, there were an access of the Apoε4 allele in AD patients, as compared with controls ($p<0.001$). These findings are consistent with previous studies another different populations, and confirm that: 1) Apoε4 is a significant risk factor for sporadic AD; and 2) The frequency distribution of Apoε alleles in our community in similar to that reported in other European and American populations.

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NEUROLOGICAL FEATURES OF VASCULAR DEMENTIA. S Carlomagno, V parlato, A Santoro, A Lavarone, F Boller, V Bonavita, Institute of Neurological Sciences, II University of *Naples*

In order to study the correlations between Vascular Dementia (VaD) and neuroimaging findings we clinical charts of 136 patients consecutively admitted at the Institute of Neurological Science of Naples from 1989 to 1992 suffering from multi-infarct cerebrovascular diseases(MICVD). Patients were classified as having (n.64) or not (n.72) dementia according to DSM III-R criteria. CT scan and NMR were evaluated by a neuroradiologist blind of the clinical information's, and classified as showing cortical, subcortical or cortico-subcortical atrophia, multiple ischemic lesions (mainly involving the left or the right hemisphere), leukoaraiosis. All the considered neuroradiological parameters failed to discriminate the two groups of patients, but the occurrence of subcortical atrophy (51.0% in VaD patients VS 35.7% in CVD non demented patients, $p<O5$). Such findings led us to conclude for a particular involvement of subcortical structures in determining onset of dementia in CVD patients.

115
VISUO-SPATIAL NEGLECT IN ALZHEIMER'S DISEASE. R Pentore, A Venneri, *Bolzano & Modena, Italy*

Neglect in Alzheimer's disease (AD) has received little attention despite reports of impairment with other types of complex visual processing. The lack of previous report about neglect in AD is surprising given the findings of right parietal hypometabolism in AD. In this report we describe two patients with presenile moderate AD patients (GC, MP) who manifested a severe unilateral spatial neglect in the late stage of the disease. At an early stage both patients showed poor abstract thinking, memory disorders, and mild visuo-spatial apraxia; MP also showed severe dysgraphia. About

three years after onset, both patients manifested light symptoms of neglect, initially on the neuropsychological evaluation, but progressively interfering with everyday life: both patients presented severe hemispatial exploration disorders; furthermore GC showed motor neglect. The scarcity of few studies about neglect in AD could explain by be the lower incidence of the disorder, but a more simple explanation may be that the sensory-perceptual testing is an ineffective method of detecting visuo-spatial neglect in AD patients .

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MEMORY IMPAIRMENT IN ALZHEIMER'S DISEASE AND FRONTAL LOBE DEMENTIA. F Pasquier, F Lebert, L Grymonprez, C Lefebvre, H Petit, M Van der Linden, *Lille, France & Liège, Belgium*

The hippocampus and post-rolandic association areas remain intact in dementia of frontal lobe type (DFT) but not in dementia of Alzheimer type (DAT). The aim of this study was to compare memory impairment in DFT and DAT. Patients with DAT (n=9) (NINCDS-ADRDA), DFT (n=9) (primary degenerative dementia, absence of spatial disorientation, normal EEG, and SPECT diagnosis) and 9 controls performed a perceptual identification task. Implicit memory at different encoding levels was measured by facilitation of fragmented figure identification by previous figure presentation (priming), explicit memory by figure recognition and recall of training session presentation mode (whole/fragmented). Priming was evident in all groups ($F(2,1)=61.5$, $p<0.0001$), in controls more than in patients ($F(2,2)=5.98$, $p<0.05$), and in fragmented more than whole figures ($F(2,2)=4.16$, $p<0.02$) in DFT and controls but not in DAT. No relation between priming and explicit memory was found. Site of degeneration and difference in encoding level account for differing memory impairment in DAT and DFT.

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CLINICAL AND NEUROPHYSIOLOGICAL EVALUATION OF 3 DOSES OF S12024-2 (COGNITIVE ENHANCER) IN MILD ALZHEIMER'S DISEASE. C Derouesné, B Renault, B Gueguen, M Van der Linden, L Lacomblez, P Homeyer, L Ouss, E Neuman, M Malbezin, S Barrandon, D Guez. *Paris France*

Cognitive enhancing properties of S 12024, which appears to facilitate noradrenergic and asopressin activity, have been shown in marmoset and rats. The objective was to obtain early evidence that S12024 has potential central pharmacological activity and cognition enhancing properties in out-patients with mild to moderate dementia from Alzheimer's disease. The trial was a placebo controlled study in a latin square design, with 3 doses of S12024 (50, 100 and 200 mg once daily). during 4 periods of 7 days, each separated by 2 week wash-out period. The evaluation criteria included Mini mental score (MMS), Clinical global impression of daily activities, and the Van Der Linden battery (VDL) with assessments of simple and choice reaction time, sustained vigilance (Stroop test), memory scanning and delayed recognition of words, visuo-spatial empan and Brown Peterson test. Testing was performed prior to the first intake and 1.5 h after at DI, and after the last intake at D7 of each treatment period. Quantitive-EEG during a closed eyes test session and event related potential (ERP) during a selective auditory attention task were also performed at D7. Twelve patients (mean age: 64 years old (10, mean MMS: 23 ± 3) completed the study. No treatment effect was observed, neither for MMS, VDL battery and daily activities. On CIBIC a non-treatment effect was shown in favor of active treatment (100>200>50>placebo). On qEEG, significant change was observed at the 200 mg dose versus placebo ($p<0.05$) for the parameters of b1 and d1 signals in favor of a non-specific stimulation of vigilance. On ERP, a significant difference ($p<0.05$) was shown between placebo and S12024 whatever the dose on the amplitude of the "processing negativity" signal. In conclusion, S12024 has shown preliminary evidence of central pharmacodynamic activity on cognitive processes (vigilance or attention) in patients with early AD.

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THE HEREDITARY FORM OF FRONTAL LOBE DEMENTIA; A CLINICAL AND PATHOLOGICAL STUDY. M Stevens, JC van Swieten, CL Franke, *Rotterdam, The Netherlands*

Frontal lobe dementia (FLD), including the most known type Pick's disease, is a predominantly presenile dementia. It is characterised clinically by early onset of behavioural changes and pathologically by fronto-temporal cerebral atrophy. A positive family history is frequently found in patients with FLD, and an autosomal dominant form of Pick's disease has been described. We present here the clinical picture, SPECT, MRI and pathological findings in several members of a large family with FLD. This 5-generation family with 27 affected members (13 females, 14 males) showed autosomal dominant inheritance (50 % of the offspring affected). The mean age of onset was 52 year (43-64 yr), with a mean duration of illness of 6 years (2-6 yrs). The clinical manifestations consist of early disinhibition, echolalia, perseveration, later aphasia and mutism. SPECT in one patient showed hypoperfusion in frontal lobes, and MRI in 2 patients showed atrophy of frontal lobes and of caudate nucleus. Severe neuronal loss, moderate spongiosis and gliosis were found in the frontal cortex of 6 autopsied members. The main goals of a new large genetic-epidemiological study in progress are to determine the incidence of FLD in a 3 million population, the percentage of patients with a positive family history, and to add families to the above-mentioned family to perform linkage analysis.

119
CAG REPEAT EXPANSION IN HUNTINGTON'S DISEASE IN 25 SPANISH FAMILIES A Sanchez, S Castellvirel, M Mila, J Rosell, D Jimenez, F Pallesta and X Estivill. *Barcelona, Spain*

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterised by involuntary movements, and cognitive and affective changes. HD has a prevalence of 1 in 10.000 individuals in most populations of European origin. The IT15 gene is responsible for HD as it contains, a highly polymorphic, unstable (CAG)n repeated sequence that is abnormally expanded in HD chromosomes. The IT15 (CAG)n stretch was analysed in 70 members (35 affected individuals, 25 asymptomatic "at risk" for HD, and 10 unaffected members) of the 25 HD families. Expansion of the CAG repeat sequence was found in 28 affected members and 18 individuals "at risk", with a repeat length of 44 to 85 repeat units. The range of the polymorphic CAG repeat in normal chromosomes was between 11 and 26 repeat units. In the families with several affected members we have found increases of the repeat length in the last generation. Inverse correlation was found between the age of onset and the length of the CAG repeat, the analysis also showed parental male bias. Presymptomatic analysis of HD has been considerably enhanced with the CAG mutation study.

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HUNTINGTON'S DISEASE. A MULTIDISCIPLINARY STUDY. PJ Garcia Ruiz, A Barrio, T Barroso, J Benitez, J Garcia de Yebenes. *Madrid, Spain.*

The study was undertaken (1) to assess associations between functional decline and cognitive-motor aspects in Huntington's disease (HD); (2) to study whether genetic data influence clinical features (3) to study whether verbal memory tests in HD differ from controls and Parkinson's disease (PD). We studied 40 patients with clinically definite HD (according to Folstein) with respect as motor and cognitive aspects (including alternating rapid movements evaluated by an accelerometer; Mini Mental State Exam; Rey figure and Hooper Test). Patients were rated according to Shoulson. We obtained genetic analysis (according to MacDonald) in 28 individuals (24 patients and 4 asymptomatic carriers). The California Verbal Learning Test (CVLT) was evaluated in 24 individuals (9 HD; 10 PD and 5 controls). Trinucleotide repeat lengths correlated with age at onset ($r=0.85$; $P<0,001$).(3) CVLT performance was impaired with respect to normal controls but similar with respect to PD. It is concluded that (1) Functional decline in HD is associated with akinesia>coqnitive disturbances; (2) repeats length influences age at onset; (3) verbal learning is impaired in HD; surprisingly the learning pattern is similar with respect PD.

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INCIDENCE OF DEMENTIA AND PROBABLE ALZHEIMER'S DISEASE IN A GENERAL ELDERLY POPULATION: THE PAMPLONA STUDY. JM Manubens, JM Martinez-Lage, R Larumbe, J Muruzabal, F Lacruz, Pedro Quesada, J Gallego, *Pamplona, Spain.*

Background: incidence studies of dementia and cognitive decline in elderly population gave rarely been attempted in Spain preventing the com-

parison with other epidemiological studies of dementing diseases in, Europe. Since 1989 we are carrying out the Pamplona longitudinal Study on ageing, prevalence and incidence of dementia in a representative sample older than 70, stratified by five-year interval of age and sex randomly collect from the census. Methods: in 1989 we administered the CAMPEX instrument to1367 subject constituting the cohort using a door-to-door approach. This study meant a preliminary work. The incidence rates of dementia were estimated by using two subsequent prevalence surveys. In the first one (1991), each sampled subject underwent the CAMDEX examination as screening. Those who were screened positive (CAMCOG<74) have undergone an extensive neurological diagnostic workup to identify dementia cases and to classify them as Alzheimer's disease or other dementias according to the DSM-III-R and NINCDS- ADRDA criteria. Survivor subjects of the original cohort identified as non-cases were re-assessed 2 years later by using the same procedure, instruments and criteria to estimate incident cases (second prevalence survey). Age-specific incidence figures were calculated from identified incident new cases. Results: Twenty nine incident cases of dementia were recognised. Fifteen of them fulfilled AD criteria. The age-specific rates for dementia and AD were respectively: 10.8 and 4.3 for 75-79 years old population; 23.1 and 9.2 for 80-89 years old ones; 27.5 and 15.8 for those of 90-95 years old. Conclusion: Although not part of the EURODEM group of incidence studies, our findings are comparable to these studies and can contribute to our understanding of the disease processes involved in senile dementia. Study supported by FIS 91/0140

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PREVALENCE OF DEMENTING DISORDERS IN VESCOVATO, NORTH ITALY. L Ferini-Strambi, A Marcone, P Garancini, B Tedesi, S Smirne, *Milan, Italy*

Some recent studies on prevalence of dementia used the door-to-door approach. In Appignano, a small town in Central Italy, it was recently found in the subjects over 59 years a prevalence ratio (PR) of dementia of 6.2 (Neurology, 1990). Aim of our study was to investigate the PR of dementia in a small town of North Italy, Vescovato, Cremona Province, using a similar 2-phase design. Total Vescovato population over 59 years was 856: 669 subjects were screened, while 187 refused to participate or could not be traced. During phase I we administered the Hodkinson abbreviated mental test (AMT) to discriminate between subjects with or without possible cognitive impairment. All the subjects with AMT score <= 7 (n= 120) had to undergo further clinical and laboratory examinations in order to ascertain the diagnosis of dementia (phase II): a standardised diagnostic protocol was followed in 102 subjects. We found 51 patients affected by dementia yielding a PR of 9.6%. The PR standardised on Appignano population was 9.3%. We found that the prevalence ratio of dementia increased steeply with age (60-69 yrs: 2.5%; 70-79 yrs: 12.9%; > 80 yrs: 25.4%). The PR of Alzheimer's disease was higher than PR of multi-infarct dementia (5.3% and 2.9%, respectively).

123
MEMORY DISORDERS UNIT: NECESSITY FOR A PLURIDISCIPLINARY APPROACH. F Pasquier, F Lebert, B Jacob, H Petit, *Lille, France.*

A memory disorders unit (MDU) was created in 1991 in the Lille University Hospital Department of Neurology involving neurologists, psychogeriatrician, neuropsychologists, speech therapist and nurses. Patients come by themselves, referred by a general practitioner (GP) or a specialist to the clinic where are performed a neurological, neuropsychological and psychogeriatric assessment. After consultation, further examinations or tests may be programmed in the day-care unit (neuropsychological tests, language assessment, EEG, CT scan, MRI, SPECT). Diagnosis and course of actions are discussed at the staff meeting. Over 3 years, MDU activity increased from 121 to 245 new patients/year (174 to 471 visits). The diagnoses distribution remained identical: dementia of Alzheimer type 30%, dementia of frontal lobe type and focal atrophy 9%, subcortical dementia 11%, vascular 6%, "age-associated memory impairment" 4%, psychiatric disorders (mainly anxiety) 27%, other 13%. Mean Mini-Mental Scale score at the first visit increased from 12.5 to 19. Mean age remained 65 years. Fifty-two percent of the patients are followed in the MDU, 10% by other specialists, 11% by GP, 7% have been institutionalized, 5% are dead and 15% lost. Pluridisciplinary approach for memory disorders is necessary for diagnosis, therapy, follow-up and research purposes.

124
REVERSIBLE COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS. L Rozewicz, D Langdon, C Davie, M Ron, A Thompson, *London, UK.*

Cognitive impairment is common in Multiple Sclerosis. Around 40% of patients in community-based studies show evidence of cognitive dysfunction on psychometric testing. Deterioration in cognition at the time of relapse has been observed but improvement in cognitive function has proved more difficult to document. We present a 21 one year old woman with a one year history of relapsing remitting multiple sclerosis, who was admitted to hospital following a severe relapse which rendered her quadriplegic. Psychometric assessment was carried out on admission and on recovery of neurological function, eight weeks later (Kurtzke's expanded disability status scale improved from 9 to 6.5). There were striking changes in arithmetic, naming and frontal lobe tasks. The Graded Arithmetic Test score showed improvement from a bright normal to a superior level (13/20, 20/20 respectively). Although initially unable to attempt the Token Test of aural comprehension she managed a flawless performance (15/15) after eight weeks. Performance on a word generation task, which is a measure of frontal lobe function, improved from 3 to 12 words in 60 seconds. The patient had T2 weighted and Gd- DTPA enhanced MRI and Magnetic Resonance Spectroscopy. These showed a reduction in lesion size, lesion enhancement and changes in brain chemistry which parallel the improvement in cognitive performance.

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READING EPILEPSY AND LANGUAGE COMPREHENSION - A CASE REPORT. MJ Koepp, ML Hansen, B Guldin, RM Pressler, S Ried, *Berlin, Germany*

We investigated the precipating mechanism in a 34 year old woman with reading epilepsy. Seizures were triggered by reading and language related activities such as writing and hearing. Comprehension was not a necessary provoking factor. Reading German nonsense words, a Yiddish text and even reading Japanese Kana produced EEG activity indicating that decoding was not essential. Saccadic and pursuit eye movements alone did not provoke any discharges. Magnetic resonance imaging was normal, while an interictal HMPAO-SPECT study of cerebral blood flow showed, by visual inspection, a decreased tracer uptake in the left temporo-parietal region. Our case supports the theory, that grapheme to phoneme transformation seems to be one critical stimulus in reading epilepsy.

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TONIC SPASMS IN CERVICAL MYELOPATHY. A CASE REPORT. ME Kornhuber, C Scholz & B Conrad, *Munich, Germany*

A 70 year old male patient presented with several times daily occurring attacks, which had started two years previously. A few seconds after an onset of paresthesias in his right face, neck, arm and back a tonic spasm of the right arm followed with slight anteversion, the elbow bent to about 150 ° and the fingers slightly bent (video tape). The spasm disappeared after 30 to 60 seconds followed by fading of the sensory symptoms. During attacks the patient was completely conscious and orientated and the EEG was normal. Attacks could not be provoked by movements of head, neck or arm. On clinical investigation mild signs of cervical myelopathy were present (brisk; ankle reflexes contrasting with prominent hypopallesthesia). Magnetic resonance tomography revealed an old pseudarthrotic fracture of the dens axis with impression of the upper cervical myelon. The patient reported a neck trauma 10 years earlier after which he had been tetraparetic with sphincter disturbance. The symptoms improved over 3 months after which he was free of symptoms and engaged in sporty activities. The attacks were interpreted as sort of spinal seizures due to the long-lasting myelopathy. On carbamazepine the patient became completely free of attacks.

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TEMPORAL POLE ATROPHY SYNDROME WITH DOMINANT LANGUAGE REDUCTION AND PERSONALITY CHANGES. R Blesa, R Lopez; P Santacruz, N Vila, A Catafau, F Lomena, I Bertran, J Pena. *Barcelona, Spain.*

We tried to characterize progressive focal predominantly temporal atrophy. Presenile onset, initial behavioural and expressive speech alterations with lobar fronto-temporal atrophy support the clinical diagnosis of Pick s

disease. However, studies of patients with isolated focal temporal atrophy, early word-finding difficulties and personality changes are scanty. We studied 4 patients, mean age: 68 years (61-76); mean duration: 7 years, explored with: standard laboratory tests, dementia scales, EEG, neuropsychological evaluation ("BarcelonaTest" Battery, WAIS, Boston Naming Test), neuroimaging (CTscan, MRI and SPECT).Results: First stage: Anomia with semantic paraphasia, mild recent memory impairment, depression or euphoria. Second Stage: Low verbal fluency, comprehension and repetition with palilalia and circumlocutions, temporal-spatial disorientation and personality breakdowns: hyperactivity, obsessions, lack of insight, social withdrawal and hyperorality. Late stages: KluverBucy syndrome, utilisation behaviour, preservations, frontal signs and incontinence. EEG: normal. CTscan-MRI: anterior temporal lobe atrophy. SPECT: temporal and frontal hypoperfusion. Conclusion: Progressive language impairment and personality changes with focal temporal atrophy show distinctive clinical features within the spectrum of primary progressive cortical atrophies and support the probable clinical diagnosis of Pick's disease.

128
PLASMA AMINDACID IN IDIOPATHIC GENERALIZED EPILEPSY. F Monaco, M Gianelli, MP Schiavalla, P Naldi, R Cantello, R Torta, L Verze, R Mutani, *Sassari, Torino,*

22 plasma amino acids were determined by means of ion-exchange chromatography in 16 previously untreated patients with generalised idiopathic epilepsy and in some of their first-degree relatives (26 subjects), and the results were compared with those obtained from a group of 50 healthy controls. The patients were subsequently treated with valproic acid for one month and then reexamined. In the epileptic subjects, statistical analysis showed significant alterations in the plasma levels of a group of aminoacids, concluding the four associated with neurotransmission (aspartate, glutamate, glycine and taurine) ; aspartate, glutamate and glycine levels were also altered en the first-degree relatives. Valproic acid did not affect amino acid levels. if further confirmed, these alterations might be considered possible neurochemical markers of epilepsy.

129
ANALYSIS OF NINE CASES WITH PARTIAL ACHROMATOPSIA. H Knott,. A Ferbert, A Schulze-Bonhage, W Aust, *Kassel, Germany*

The occurrence of acquired defects in colour perception (achromatopsia) is rare and is seen after lesions of the inferior part of the occipital lobe. Most lesions in that region involve the primary visual cortex or the optic radiations, with a hemianopic field defect, in which the patient reports a blind field, not a colour-deprived one. We prospectively collected nine cases with occipital lobe infarction with disturbance of colour vision in parts of the visual field without corresponding defects for other visual modalities. All patients had vascular lesions verified by CT or MRI scans. One patient with bilateral infarcts was initially blind. He made a good recovery, but a nearly complete disturbance of colour perception remained. Two patients showed no localised scotoma but a hemiachromatopsia. The other six patients had an upper quadranospia, and an achromatopsia in the lower quadrant. The lesions of these six patients were located beyond the calcarine sulcus and extended to the fusiform gyrus. Usually the patients do not complain of colour perception deficits. We suppose that a colour perception deficit is associated in a large proportion of inferior occipital lobe infarcts. Tests for colour perception are appropriate, particularly in the lower quadrant in patients with upper quandranopsia.

130
RELATIONSHIP BETWEEN HEMOGLOBIN CONCENTRATION AND ISCHAEMIC STROKE. R Di Mascio, R Marchioli, F Vitullo, A Di Pasquale, L Sciulli, V Kramer, G Tognoni. *Santa Maria Imbaro (Chieti) Italy*

The hypothesis that high levels of normal hemoglobin could be associated with an increased risk of cerebral infarction. We examined this relationship using data from a hospital-based case-control study conducted in Abruzzo, southern Italy, between April 1990 and March 1992. The analyses were performed on 143 patients with diagnosis of first ischaemic stroke confirmed by CT scan (age 30-69 years) and 143 matched controls by sex and age with acute diseases not related to known or potential bleeding conditions. Hemoglobin, measured at admission, was higher in patients with stroke (mean: 14.2 g/L, SD: 1.6 g/L) than in controls (mean: 13.7 g/L, SD: 1.6 g/L) ($p < 0.05$). Compared with subjects with hemoglobin levels less than 13 g/L (reference category), the relative risks (RR) of ischaemic stroke, after adjustment for sex and age, were 1.8 (95% CI: 0.8-3.9) for the 13-13.9 g/L quartile, 2.2 (95% CI: 1.1-4.6) for the 14-14.9 g/L quartile, and 3 (95% CI: 1.4-6.3) for the 15+ g/L quartile. Estimates adjusted by sex, age and cigarette smoking were 1.6, 2.3, and 2.8 respectively. After allowance for sex, age, cigarette smoking, hypertension, diabetes, cholesterol levels and other covariates, the estimated RR were 1.9 (95% CI: 0.8-4.9), 2.8 (95% CI: 1.2-6.5), and 3.2 (95% CI: 1.4-7.4) for the related categories (x^2 for linear trend: 7.27, $p < 0.01$). No statistically significant effect modification was observed by strata of sex, age, hypertension, smoking and other variables. Further investigations are needed to ascertain whether hemoglobin has a causal role in cerebral infarction.

131
PROGRESSIVE PARIETAL FOCAL ATROPHIC SYNDROME WITH APRAXIA, VISUOSPATIAL ALTERATIONS, "ALIEN LIMB" PHENOMENON AND PARKINSONISM. P Santacruz, R Lopez, MJ Marti, I Charques, A Catafau, F Lomeila, J Peila, I Bertran, R Blesa. *Barcelona, Spain.*

Cortico-Basal Degeneration (CBD), progressive supranuclear palsy and Parkinson's disease share some clinical manifestations, making difficult an accurate diagnosis during patient life. We studied seven patients with clinical and neuroimaging pattern of progressive parietal syndrome and parkinsonism, mean age: 65 years (59-71), duration: 5 years (1-8). The patients were investigated by neuropsychological examination: (Barcelona-Test Battery, WAIS, Boston Naming Test). They were also tested clinically for CBD (Gibb, 1989) and alien hand syndrome (Doody, 1992) magnetic resonance imaging (MRI) and SPECT. Results: Parietal symptomatology (7/7): Gertsmann's syndrome, constructional-ideotionalideomotor apraxia, dysgraphia, amophorsynthesis and tactile agnosia. Mild anomia (7/7). Verbal/visual memory impairment (7/7). Motor dysfunction (7/7): "Alien limb", akinetic-rigid syndrome, spontaneous and reflex myoclonus and postural tremor. Paraphasic and dysarthric speech (3/7). Vertical gaze impairment (5/7). Balint's syndrome (2/7). Colour agnosia (1/7). MRI: Mild-moderate atrophy, predominantly affecting parietal regions (7/7). SPECT: Fronto-parietaltemporal hypoperfusion (7/7). Conclusion: Progressive parietal syndrome and parkinsonism with regional anatomic and functional cerebral abnormalities revealed by MRI and SPECT, in the heterogeneous clinical spectrum of asymmetric cortical degeneration, suggest probable CBD.

28 June 1994

POSTER SESSION 3

1
SUCCESSFUL TREATMENT OF SEVERE NEUROPATHIES IN DIABETIC PATIENTS. DA Krendel, DA Costiga; *Atlanta, Georgia, USA*

We treated ten patients with diabetes and disabling progressive peripheral neuropathy with anti-inflammatory/anti-immune therapy. All 10 improved soon after beginning treatment. In seven, the clinical presentation included involvement of thighs and/or thoracic radiculopathy consistent with diabetic amyotrophy mononeuropathy multiplex. There was autonomic dysfunction in three. Nerve conduction studies showed prominent demyelination in five. Biopsies showed onion bulbs in four, and inflammation involving small vessels in four. Treatment consisted of IV gamma globulin (5), cyclophosphamide (3), plasma exchange (2), corticosteroid (8), and azathioprine (2). These were usually given in combination or sequentially. We feel that anti-immune/anti-inflammatory treatment is warranted in selected diabetic patients with progressive disabling polyneuropathy. Diabetic amyotrophy and mononeuropathy multiplex may have more than one cause, but our findings suggest that the pathogenesis is commonly inflammatory.

2
LONG-TERM NEUROTOXICITY AFTER TESTICULAR CANCER CHEMOTHERAPY. S Koeppen, WM Korn, S Brugge, D Schmitz, ME Scheulen, *Essen, Germany.*

Peripheral neuropathy has been the dose-limiting toxicity of cisplatin-based chemotherapeutic regimens. In a retrospective analysis 27 patients (mean age: 41 years; range: 29 to 58 years) were studied after a mean time interval of 13 years (range: 11 to 15 years) following curative treatment of disseminated non-seminomatous testicular cancer. All patients had received a sequential combination chemotherapy consisting of vinblastine/bleomycin, adriamycin/cisplatin and ifosfamide/etoposide. Eleven patients reported on persistent symptoms related to the peripheral nervous system at the time of follow-up. Frequent subjective complaints were paresthesias in feet and hands, unsteadiness of gait and muscle cramps in the lower extremities. Careful neurological examination revealed neuropathic signs in 23 patients. The presenting clinical signs are mainly sensory disturbances due to large fibre dysfunction and decreased tendon reflexes restricted to the lower extremities. Vibration perception threshold was shown to be significantly elevated in 11 patients. Our results suggest that the severity of sensorimotor neuropathy after discontinuation of chemotherapy is related to the cumulative dose of both cisplatin and additionally administered neurotoxic anticancer agents.

3
ULTRASTRUCTURAL ASPECTS OF SCHWANN CELL-AXON RELATIONSHIPS IN THE TREMBLER MOUSE RHM King, AM Robertson, PK Thomas, *London, UK*

Trembler mice possess a point mutation on chromosome 11 producing a substitution in a transmembrane section of peripheral myelin protein 22 (PMP-22) (Suter et al, 1992) and impairing the myelin forming ability of the Schwann cell. Remak fibres are probably normal (Perkins et al, 1982). Localization of cell adhesion molecules at nodes of Ranvier is abnormal (Rieger et al, 1986). We have found that Schwann cells frequently failed to form normal nodal processes but often possessed a smooth or rounded profile at the node. Many Schwann cells exhibited very limited contact points with axons,. often with considerable lengths of bare axon just surrounded by multiple layers of basal lamina and cell debris. Internodes were sometimes very short and uncompacted myelin lamellae were occasionally seen. It was difficult to identify the dense undercoating of the axolemma normally found in the nodal region. These morphological changes suggest that the abnormality. PMP-22 affects, directly or indirectly, the ability of the Schwann cell both to adhere to the axon and to interact with cytoskeletal components to form nodal processes. Abnormalities in the distribution of axolemmal channel proteins and cell adhesion molecules would be expected to result from the abnormal Schwann cell/axon relationships.

4
VASCULITIC NEUROPATHY PRESENTING WITH CONDUCTION BLOCKS. A Kerkhofs, P Vermersch, O Dereeper, C Daems Monpeun, M Parent, D Deplanque, H Petit, *Lille, France.*

Conduction blocks are unusual electrophysiological findings in vasculitic neuropathy. We report here the case of a man who developed subacute clinical signs of neuropathy associated with polyarthralgia and purpuric skin lesions. Physical examination revealed involvement of both upper and lower extremities. Biological tests showed a very important inflammatory syndrome. Electrodiagnosis confirmed axonal degeneration and showed bilateral conduction blocks in both the ulnar and median nerves, and in the left peroneal too. Skin biopsy demonstrated the presence of a necrotizing angiopathy. Neuromuscular histologic examination provided evidence of neuropathy associated with typical lesions of polyarteritis nodosa. This report suggests that a demyelinating compound may be observed in vasculitic neuropathy.

5
RESPONSE OF HUMAN CUTANEOUS C-POLYMODAL NOCICEPTORS ELICITED BY LOW TEMPERATURES STIMULATION. M Campero, J Serra, JL Ochoa, *Portland, Oregon, USA*

Cold pain results from concurrent activation of cold-specific and nociceptor afferents by low temperature stimulation (LTS). The response of human polymodal nociceptors (PN) to LTS has not been tested systematically. Here we describe receptor properties of human PN, emphasizing their response to LTS. Microneurographic recordings were obtained from the superficial radial and peroneal nerves of normal volunteers. Receptive fields of PN were delineated and mapped using quantified mechanical stimuli (MS). Thermal stimuli were delivered through a 1 cm≤ thermode (10°C/s). Conduction velocity (CV) was calculated for all 11 units. All units responded to noxious mechanical and thermal stimuli, with slow adaptation rates. Mean CV was 0.85 m/s (0.53-1.6). Mean threshold for MS was 2.96 g. (0.53-5.4). Mean firing rate (MFR) during suprathreshold MS was 14.5 imp/sec. Ten of the 11 units also responded to high temperature stimuli (HTS). Mean threshold for HTS was 40.5°C (38-45°C) with MFR of 3.9 imp/sec (2-9). All 11 units responded consistently with low firing rates (mean 1.4 imp/sec, range 0.85-3) to LTS below 5°C. Monotonic increase in firing rates during LTS was seen in 2 units. We conclude that human cutaneous PN exhibit a consistent response, to LTS; their MFR is lower for LTS than MS and HTS, and activity in these cutaneous PNs may contribute to signal cold pain.

6
VASCULITIC NEUROPATHY: CLINICAL AND ELECTROPHYSIOLOGICAL RETROSPECTIVE STUDY ON THIRTY-EIGHT PATIENTS. J.A.Martinez-Matos, J.Montero,M.Olivé, R.Rene, A Vidaller, *Barcelona. Spain*

Neuropathy was found in 38 patients with systemic vasculitis (24 Polyarteritis nodosa, 7 Rheumatoid arthritis with vasculitis, 2 hypersensitivity vasculitis, 2 Cryoglobulinemia, 2 Sjögren, 1 Wegener). Male/female ratio was 2:1.8 and mean age was 58.1. Fourteen cases had nerve involvement as the initial clinical symptom and systemic manifestations appeared with an average delay of 6 months. In 24 cases neuropathy appeared 6 weeks to 17 years average 44.5 months) after the initial systemic symptoms. From 453 nerves investigated electroneurographically (ENG), 206 were abnormal, more frequently in the legs. Axonal neuropathy was present in all cases, being asymmetrical in 34. No signs of demyelination were found. The most frequently abnormal nerves were the sural (78.8%), tibial (76.5%), superficial peroneal (69.4%), peroneal (58.4%), median (33.9%), ulnar (27.1%), sural ENG is a good guide for the biopsy : 22 out of 25 founded abnormal showed pathologic changes (only one from6 ENG normal Sural nerves). The patients were followed up from 4 to 180 months after vasculitic diagnosis. Neuropathy has a good prognosis in terms of functional neurologic recovery.

7
CHARCOT-MARIE-TOOTH DISEASE WITH X-LINKED DOMINANT INHERITANCE : CLINICAL ELECTROPHYSIOLOGICAL AND GENETIC STUDIES IN A FRENCH FAMILY. M Gugenheim, R Gouider, E Le Guern, A Brice, Y Agid, P Bouche. *Paris, France.*

Charcot-Marie-Tooth disease (CMT) is an heterogeneous group of disorders including a most common form with an autosomal dominant inheri-

tance and a rare variant with X-linked dominant inheritance. Neurological and electrophysiological examination was performed in 29 at risk individuals from a family with no male to male transmission. The 38 individuals (29 at risk and 9 non at risk) were genotyped for 3 microsatellite markers localised in the Xq13-Xq21 region: AR (Androgen Receptor), mfd 66 (DXS453) and DXYS1. Seven males and 11 females were affected: 43 % of males and 82 % of females were asymptomatic. Males had earlier age at onset and were severely affected, whereas females had mild or subclinical disability. Nerve conduction velocities were significantly decreased in males and normal or mildly decreased in females but electromyographic examination was always abnormal. Close linkage to DXS453 (mfd 66) was found (Z max: 4.8 at 6 = 0.00). All affected individuals showed the same allele for mfd 66. This study underlines that neuropathy is more severe in males and mainly of axonal type in X-linked CMT disease; the gene is closely linked to DXS453.

8
STEROID-RESPONSIVE AXONAL MULTIPLEX NEUROPATHY IN A PATIENT WITH CENTROBLASTIC GASTRIC LYMPHOMA AND IGG PARAPROTEINEMIA. W Grisold, U Ziflo, M Drlicek, H Budka, K Jellinger, CH Zielinski, *Vienna, Austria*

Polyneuropathies in lymphoma patients may be caused by chemotherapy, direct nerve infiltration and paraneoplastic causes. Retrospective surveys on the incidence of peripheral neuropathy range from 0.1-2%. Clinically mostly sensorimotor types, rarely pure sensory neuropathies and some subacute motor neuropathy have been reported. A 51 year old woman noted burning paresthesias at the medial aspects of the thigh followed by tingling paresthesias in fingers and pal mar aspect of the hands. Additionally painful muscle cramps occurred. Slight Iy asymmetrically sensory symptoms became confined to a median distribution. Sensations of numbness were also reported on her feet. Difficulties in walking developed 2 weeks later. Clinically a patchy sensory distribution and also radicular distribution (intercostal nerves) was found. Proximally accentuated weakness was noted in lower extremities. Tendon reflexes were preserved. The focally affected nerves, Particularity the median nerves gave no evidence for entrapment neuropathy. Sural nerve biopsy revealed axonal neuropathy. No signs of Iymphomatous infiltration or immunoglobulin deposition was detected. A regimen of oral corticosteroids was given and a continuous improvement over several month without recurrence was noted. This mononeuritis multiplex type in association with axonal neuropathy presents a novel observation of paraneoplastic polyneuropathy in Iymphoma. Although the nerve biopsy was negative for immunoglobulin deposition or neoplastic infiltration a paraneoplastic vasculitis type causing focal lesion cannot be excluded.

9
LUMBAR SPINAL COMPRESSIVE SYNDROME IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY. L Ginsberg, RHM King, J Workman, AD Platts, PK Thomas, *London, UK*

A patient with biopsy-proven chronic inflammatory demyelinating polyneuropathy (CIDP) developed cauda equina symptoms due to swelling of the nerve roots in the lumbar spinal canal. Magnetic resonance imaging (MRI) of the lumbar spine revealed markedly thickened nerve roots from the level of the conus medullaris, filling the caudal thecal sac. Immunosuppressant therapy produced partial clinical and radiological resolution. This case shows that spinal compressive syndromes may occur in acquired hypertrophic neuropathies as well as in hereditary motor and sensory neuropathy and expands the spectrum of the clinical presentation of CIDP.

10
CYTOKINES IN HIV ASSOCIATED PERIPHERAL NERVE DISORDERS: DIFFERENT PATTERNS OF EXPRESSION IN THE VARIOUS TYPES OF NEUROPATHIES. RK Gherardi, A Florea-Strat, F Poron, J-C Sabourin, *Creteil, France*

We tried to evaluate expression of cytokines in the nerve of HIV-infected patients. Cytokines play a central role in HIV infection, mediate inflammation and tissue destruction, and may be involved in nerve regeneration. Histochemistry for IL-1a, IL-lb, TNFa, and IL-6 was performed on frozen biopsy specimens from HIV-infected patients with chronic inflammatory demyelinating neuropathies (CIDP: 5), mononeuritis multiplex (MM: 5), and distal sensory polyneuropathy (DSPN: 5), and from seronegative individuals (normal nerve: l; CIDP: 3; diabetic DSPN: 3). Positivities were observed in Schwann cells (SC), axons of myelinated fibers (Ax), unmyelinated fibers (UF), perineurium, vessels and mononuclear inflammatory cells (Mo). Vessels expressed IL-lb in all diseased nerves. HIV-associated DSPN was mainly characterized by IL-1b positivities in UF (5/5), and HIV-associated CIDP by IL-lb positivities in Mo (5/5), Ax (4/5) and SC (3/5). Heterogeneous results were found in patients with MM. Diabetic neuropathies showed virtually no cytokine expression, and seronegative CIDPs showed strong expression of IL-1b in all structures. Conclusion: The pattern of cytokine expression (mainly IL-lb) in the nerve of HIV-infected individuals is likely related to the type of the neuropathy.

11
ANTIBODIES TO VIMENTIN ARE FREQUENTLY ASSOCIATED WITH PERIPHERAL EUROPATHY IN ELDERLY. R Fazio, R Nemni, M Franceschi, I Lorenzetti, L Rinaldi, N Canal. *Milan, Italy*

Recently antibodies to vimentin have been noted in the sera of animals affected by experimental autoimmune grey matter disease , in which both upper and lower motorneurons are involved. These antibodies have also been found in patients affected by some neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and peripheral neuropathy (PN). We studied 240 old people, randomly selected, aged 65 to 85 years and clinically evaluated for the presence of neurological diseases such as AD, PD, and PN. Sera of these subjects were evaluated for autoantibodies to vimentin and to neurofilament proteins by dot blot technique at serum dilution of 1:1000. 36 adult subjects (30-45 year old) were used as controls. The presence of anti-neurofilament antibodies was not significantly different between elderly and adult sera.: 8 (3.3%) sera of elderly but none of adult people showed a positive reaction to vimentin. 3/8 (37%) of these subjects had PN, while only 9% of all elderly had PN. No correlation was found with the other neurodegenerative diseases. Our preliminary data suggest that autoantibodies to vimentin, but not to neurofilament proteins are more commonly present in elderly people, and may be associated with PN in this population.

12
T-CELL RECEPTOR Vα -ELEMENT USAGE IN LEWIS RAT EXPERIMENTAL AUTOIMMUNE NEURITIS. FX Weilbach, A Sennlaub, S Jung, R Gold, KV Toyka, HP Hartung and G Giegerich. *Wurzburg, Germany*

Experimental autoimmune neuritis (EAN), a model for the human Guillain-Barre syndrome, is induced in Lewis rats by immunisation with a peptide consisting of amino acids 53-78 of the peripheral nerve myelin protein P2. Recently it has been proposed that neuritogenic Lewis rat T cells use the TCR elements Vα2 and Vβ8, similar to encephalitogenic T cells in experimental autoimmune encephalomyelitis (EAE). Therefore we investigated TCR Va element usage of 14 P2-reactive Lewis rat T-cell lines by V-element-specific PCR using a panel of primers for the known rat TCR Va-elements. Only 2 of the 14 P2-specific T cell lines expressed the TCR Va2 element, in contrast to MBP-specific T cells in Lewis rat EAE. Several other TCR Va elements were expressed in a nonbiased manner by the neuritogenic T cell lines. The use of a complete panel of primers and testing a sufficient number of specific T cell lines seems indispensable for reaching definite conclusions about restricted TCR gene usage in autoimmune diseases.

13
LONG-TERM FOLLOW-UP AND THERAPY IN NEUROPATHY ASSOCIATED WITH ANTI-MAG IgM MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE. E Ellie, A Vital, AJ Steck, C Vital & J Julien, *Bordeaux, France & Basel, Switzerland.*

Among 33 patients suffering from a neuropathy associated with anti-MAG IgM MGUS, clinical, electrophysiological and biological data relating to outcome (> 1 year) and therapy were available in 30 cases. Mean duration of follow-up was 46 months (range 15-160) and in 9 patients it exceeded 5 years. The neuropathy was classified as slowly progressive [disability score (DS) < 4, 5 years after the onset in 22 cases and as rapidly progressive (DS (4) in 8 cases. Six patients died during follow-up. In 2 cases death was directly related to the neuropathy and another patient developed an intracerebral B-cell lymphoma. Four cases needed no treatment. Prednisone, alone or in combination with cytotoxic drugs, was giver 16 cases with a slight, mostly subjective improvement in 7. Six patients underwent repeated plasmapheresis 6 to 40 exchanges). Five did not improve. One case had an objective and sustained response during four , but later worsened. Intravenous immune globulin (IVIG), 0.4 g/kg/day during 5 days) was administered to 16 patients (1 to 5 administrations with a 1 to 6 months interval). Subjective improvement was

in 8 and objective in 5. The effects were mostly apparent in the disability and ataxia scales. Side-effect toxic hepatitis (2), cytopenia (3) and septicaemia (1) with immunosuppressive drugs, and reversible cardiac failure during plasmapheresis (1). IVIG was well tolerated. When improvement was noted, repeated tests and serum IgM levels did not parallel the clinical scales. Although promising in some cases, IVIG needs to be evaluated on a long-term basis.

14
L-CARNITINE AND ACETYL-L-CARNITINE IN HUMAN NERVES FROM NORMAL AND DIABETIC SUBJECTS. P Doneda, S Pizzul, E Scarpini, P Chiodi, MT Ramacci, S Livraghi, Scarlato G. *-Milan, & Pomezia, Italy*

A lack of neurotrophic factors has been suggested as possible causal mechanism of diabetic neuropathy. A neurotrophic action has been postulated also for acetyl-L-carnitine, as capable of the NGF binding activity in the CNS and the response of PC12 cells to NGF. In this study we measured the concentration of L-carnitine and acetyl-L-carnitine in peripheral nerves from 11 patients with diabetic neuropathy 13 patients with ischemic non neuropathy and in 12 normal controls. L-carnitine and acetyl-L-carnitine were present in all nerves analysed, although results of biochemical assay demonstrated a reduced amount of L-carnitine and acetyl-L-carnitine in nerves from patients affected by diabetic and ischemic non-diabetic neuropathy. These L-carnitine and acetyl-L-carnitine found in the three groups were not statistically significant. Long chain acyl-carnitine concentration was quite similar in all groups of patients. short chain acyl-carnitine levels were negligible. The concentration of acetyl-L-carnitine found in human nerve is higher than that observed in plasma. suggesting the importance of this substance in nerve regeneration as a either direct and indirect mediated by neurotrophins such as NGF) function.

15
CHRONIC SENSORY NEUROPATHY AND CHRONIC VIRAL HEPATITIS TYPE C. D Maimone, P Annunziata, C Salvadori, GC Guazzi. *Siena, Italy.*

Chronic sensory neuropathy (CSN) may be idiopathic or secondary to neoplastic diseases, Sjogren syndrome, or drug intoxication. A 72-year-old man developed unsteadiness on walking and numbness at four limb extremities with prickling and tingling paresthesias, two years after an acute hepatitis. Symptoms progressively worsened over the last three years up to an apparent stabilization. Objective signs included ataxic gait, absence of jerk reflexes, loss of kinesthetic and vibratory senses, and mild reduction of tactile and thermal senses. Neurophysiological studies demonstrated a selective involvement of sensory fibers with inexcitability of sensory action potentials. Sural nerve biopsy showed extensive loss of large myelinated fibers due to severe axonal neuropathy. CSF findings included elevation of IgG index and the presence of a few oligoclonal bands. No anti-dorsal root ganglion antibodies could be detected by immunohistochemistry, but high serum titers of anti-GM1 IgM and IgG were demonstrated at ELISA. Screenings for neoplasms, collagen diseases, or drug intoxication were all negative. Elevated SGPT, SGOT, serum IgM levels and high titers of anti-hepatitis virus C (HVC) serum IgG, pointed to a chronic hepatitis secondary to HVC. The relatively low incidence of idiopathic CSN suggests that the association with HVC persistent infection may be more than fortuitous. Further studies are warranted to clarify whether HCV may cause damage to peripheral nerves.

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FAMILIAL MITOCHONDRIAL MYOPATHY REVEALED BY NEUROPATHY. D.Caparros-Lefebvre, MC Arne-Bes, MB Delisle, N Fabre, JF Hurtevent, A Bes, H Petit. *Lille, France*

Peripheral neuropathy is a common feature of mitochondrial myopathy, but it is usually subclinical. Severe neuropathy has been reported in few cases. Case 1: this man developed progressive neuropathy at the age of 40. The main clinical features were painful legs, stocking type sensory disturbances for all modalities including proprioceptive involvement, hyporeflexia, distal atrophy and autonomic dysfunction. There was bilateral hearing loss, and a neurogenic bladder. Electromyography (EMG) showed a sensorimotor neuropathy with predominating axonal signs. Muscle biopsy revealed ragged red fibers. Cytochrome C oxidase activity was not expressed. MRI showed mild cerebellar atrophy. Case 2 is the older sister of case 1. She developed a similar progressive neuropathy at the age of 45. Clinical features included neurogenic bladder, and sensory-motor impairment with distal domina. EMG showed axonal neuropathy, involving both upper and lower limbs. Muscle biopsy revealed ragged red fibers. Peripheral neuropathy is rarely caused by mitochondrial disease. Moreover, distal weakness and stocking type atrophy has been reported in very few cases. These cases report shows that mitochondrial disease may be present, even when there is no optic atrophy, nor signs of encephalopathy, nor systemic involvement, in patients with familial neuropathy.

17
AGEING AND POLYNEUROPATHY: AN EPIDEMIOLOGICAL PROSPECTIVE AND CLINICAL STUDY. D Baudoin-Martin, E Laborde, F Viallet, C Creisson. *Aix en Provence, France.*

In a geriatric center, from March to July 1993, two examiners clinically assessed each elderly patient (over 75 years) for weakness, loss of tendon reflex, tactile and vibration sensory changes in limbs and on dysautonomia (pupils, orthostatism). Two abnormalities were necessary to conclude that a polyneuropathy was present. Patients with diabetes, uremic, alcoholic or toxic disease, known monoclonal gammopathy, known inherited neuropathy were excluded. All the 50 selected patients gave their informed consent for the study: 38 women [mean age 85; range 75 to 96] and 12 men (mean age 84; range 75 to 92). The sex ratio was exactly the same as in the normal 85 years old French population. We described 18 (36 %] distal symmetric polyneuropathy: 18 bilateral loss of ankle reflex, 17 impaired vibration sensory of distal limbs, 9 tactile distal limbs sensory changes, 6 abnormal photomotor reflex,4 distal limbs weakness,2 orthostatic hypotension. Centripetal progression of the impairment of vibration sense and loss of tendon reflexes was verified in polyneuropathic patients. 4 out of 18 patients associating loss of tendon reflex, weakness impairment of vibration and tactile sensory were 87, 92 and 96-years old. The 18 polyneuropathic patients (mean age 89 ± 7 years] were significantly older than the 32 others patients [mean age 83 ± 5 years] which were asymptomatic. We concluded that an idiopathic distal symmetric polyneuropathy has been observed in 36 % [18 out of 50). This polyneuropathic group was significantly older than the asymptomatic group. These results must be confirmed on a larger scale of elderly people and further analysed with follow up.

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INFLAMMATORY BOWEL DISEASE (IBD) AND PERIPHERAL NEUROPATHY. V Crespi, G Bogliun, L Marzorati, A Zincone, L D'Angelo, A Liberani, M Merlini, R Rivolta, *Monza, Italy.*

Peripheral nervous system involvement was therefore described during Croon Disease (CD and Ulcerative Colitis (UC). It was alternatively referred to malabsorbtion , immunological derangement, drugs interference. We started in 1991 a prospective study on this topic, and now we report the results of the cross-sectional analysis of the first 40 patients, recruited at the time of the diagnosis or during relapses. Twenty four patients had CD (10 relapses) and 16 had UC (12 relapses). They were submitted clinical evaluation, vibratory detection threshold, conduction velocity tests (CV) 1 motor and sensory limb nerves, SSR and R-R interval variation studies for autonomic function. No patient had clinical evidence of peripheral neuropathy. CV study revealed a single case of mild sensorimotor subclinical neuropathy of unknown cause On the contrary abnormal values were sometimes found for R-R variation (7 cases -18%) so confirming that cardiovascular tests may be affected in IBD. These findings provide some evidence for autonomic dysfunction: however. our research did not support t] hypothesis of a direct linkage between these abnormalities, the intestinal disease and its treatment: we rather think speculate that bowel anatomical changes, motility disorders and abdominal discomfort could interfere with heart rate reflexes.

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INFLAMMATORY NEUROMUSCULAR DISORDERS ASSOCIATED WITH CHRONIC LYMPHOID LEUKEMIA: PCR DETECTS CLONAL CELLS IN MUSCLE AND NERVE. A Creange, J-C Sabourin, I Theodorou, C Vital, RK Gherardi. *Creteil, France*

We describe 5 patients with chronic lymphoid leukemia and neuromuscular disorders (NMD). NMD associated with chronic lymphoid leukemia have been rarely reported and mainly include massive neoplastic infiltration of muscle and nerve structures. Inflammatory myopathies and neuropathies that may be associated with neoplastic lymphoid diseases are considered paraneoplastic. Five patients with chronic lymphoid leukemia developed neuromuscular manifestations: 3 dermatomyositis, 1 mononeuropathy due to leucocytoclastic vasculitis, and 1 inflammatory demyelinating neuropathy with stripping of myelin by macrophages at EM). Phe-

notypic characterization of the lymphoid infiltration in nerve and muscle biopsies was studied by immunohistochemistry on frozen sections and by PCR amplification of the genomic DNA region encoding for immunoglobulin heavy chain (FR3-FR4). Immunohistochemistry showed no monotypic cell population, but PCR amplification showed clonal B-cells rearrangement in 3 cases (2 dermatomyositis, I inflammatory demyelinating neuropathy). Results were equivocal in the case of mononeuropathy and negative in I inflammatory myopathy. Conclusions. Monoclonal B-cells can be detected in biopsy specimens of patients with chronic lymphoid leukemia and inflammatory NMD. This may question the traditional distinction between inflammatory and neoplastic NMDs in patients with lymphoid proliferations.

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MYELIN PROTEIN MRNA EXPRESSION IN DIABETIC NEUROPATHY. AM Conti, E Scarpini, ML Malosio, PL Baron, G Scarlato. *Milan, Italy*

Human diabetic neuropathy results from interaction of metabolic consequences of hyperglycemia, insulin deficiency or both, and from poorly defined genetic or environmental variables. An alteration of the synthesis of myelin specific proteins might be reflected in mRNA level changes. We performed an "in situ" hybridization study of 2 myelin protein transcripts in the peripheral nerves obtained from patients with diabetic neuropathy. Two nerves from age and sex matched normal individuals and two nerves from non diabetic neuropathic subjects undergoing vascular or orthopedic surgery served as negative controls. All specimens were processed blind; standard histology, fibre teasing and electron microscopy were used to establish the normal or pathological patterns of surgical material. The "in situ" analysis showed that myelin protein messages were easily detectable in myelinating Schwann cells with the same distribution in both diabetic and non diabetic patients. However, PO and MBP mRNA contents were slightly higher in nerve sections of 12. subjects with diabetic neuropathy. These findings are consistent with previous data obtained in experimental diabetes and suggest that a phenotypic plasticity of Schwann cells can modulate gene expression of myelin-sheath-specific proteins inducing higher turnover of these proteins in response to diabetic syndrome.

21
INTRAVENOUS IMMUNOGLOBULIN IN THE TREATMENT OF GUILLAIN-BARRE SYNDROME R Chorao, MJ Rosas, I Leite. *Porto, Portugal*

High-dose intravenous immunoglobulin (IVIg) has been recently used as an alternative treatment in the GBS. Some studies have shown that this is a far safer and easier to manage and is as effective as a plasma exchange in this acute disease. The present report is about our experience of treating GBS patients with IVIg during the past year.of the 12 patients admitted to our hospital in 1993 with GBS (ll GBS and l Miller-Fisher Syndrome), 9 fulfilled the generally accepted criteria for the IVIg treatment. They were 4 men and S women aged between 37 and 77 years. In 5 of them we could find an antecedent event: myocardial infarction (l), hepatitis B virus infection (l) and gastrointestinal tract (l) and upper respiratory tract (2) infection. In the period of maximal neurological deficit (which had been reached between the 3rd and 12th days of disease) 6 required mechanical ventilation, l was unable to walk with support and 2 could not walk without support. The treatment was started between the 3rd and 13th days of disease . During the 5 subsequent days, 0.4 g of immunoglobulin was given per kilogram per day. All patients improved and none had complications related to the treatment. In the last follow-up examination (l to l0 months after the beginning of the disease) all patients could walk without support. Based or. our experience and on the previous published results, we comment on the benefits, risks and costs of this treatment in GBS.

22
MAGNETIC STIMULATION OF PHRENIC NERVE IN DIABETIC POLYNEUROPATHY. L Callea, E Donati, C Bargnani, *Brescia; Italy.*

In order to evaluate phrenic nerve conduction in diabetics, we recorded diaphragmatic compound muscle compound muslce action potential (DCMAP) evoked by magnetic stimulation. We studied ten normal subjects (mean age 65 years-range 50-80) and five diabetic patients (mean age 62.8 years-range 48-75) with neuropathic symptoms. Phrenic nerve was stimulated with-butterfly shaped twin coil placed at the posterior border of sternomastoid muscle: the DCMAPs were recorded with surface electrodes at seventh intercostal space bilaterally in the anterior axillary line. Median motor and sensory, tibial and sural nerve conductions were also measured in the diabetic patients. The mean phrenic latency obtained in normals was: 6.90 ms on the right side (range 6.2-7.5, SD 0.40) 6.94 ms on the left side (range 6.4-7.6 SD 0.45). The peripheral latency in diabetics was higher than the control group: 9.94 ms on the right (range 8.55-11.30) 9.96 ms on the left (range 8.59-11.33). Our data suggest that magnetic stimulation of phrenic nerve could be considered a reliable method of investigation in diabetics with neurpathic symptoms, even if further studies to achieve sufficient numbers of controls and diabetic are necessary because the technique may be applied in the diagnosis of diabetic polyneuropathy. We conclude, that magnetic stimulation is an easy, well tolerated, painless and safe technique to evaluate phrenic nerve conduction in diabetic patients.

23
PERIPHERAL NERVE REGENERATION ACROSS GAPS OF DIFFERENT LENGTHS. M Buti, E Verdu, X Navarro, *Bellaterra, Spain.*

We evaluated recovery of muscle! skin and sweat gland (SG) functions in the mouse paw after transection of the sciatic nerve leaving a gap of 2 mm between nerve stumps (group S2), resection with gaps of 4 mm (S4), 6 mm (S6) and 8 mm (S8). Functional reinnervation was assessed by electromyographic recordings, nociceptive responses to pinpricking and silicone molds, repeatedly for three months after operation. Compound muscle action potentials after proximal sciatic nerve stimulation were only recorded in plantar muscles of group S2, from 45 days postoperation. Pinprick responses reappeared in groups S2 from 39 days, and later in groups S4 and S6; the final score decreased with increasing gap length. Reinnervation of only occurred In group S2, and for a few SGs in group S4. A combined functional index of recovery showed an exponential reduction as the gap length increased from 2474 (S2) to 38 (S8) units. These results indicate that the loss of substance in peripheral nerve lesions adversely affects the regenerative capabilities of nerve fibres. Fibres of small calibre showed higher capabilities for regeneration across long interstump distances to distal target organs than large diameter fibres.

24
EFFECT OF NEUROTROPHIC MOLECULES IN AN IN VITRO MODEL OF HUMAN SKELETAL MUSCLE CELLS CULTURED WITH RAT EMBRYO SPINAL CORD EXPLANTS. S Braun, S Einius, P Poindron, JM Warter, *Strasbourg, France*

Neurotrophins and synthetic molecules effects are studied, either in vitro, on purified motorneuron cultures, or in vivo, by means of normal or neurodegenerative animal models. We have developed a protocol allowing testing of molecules in an integrated and functional model of innervated and contracting human skeletal muscles normal or diseased, and cultured in the long term. This model combines several of the advantages of simple in vitro systems (e.g. access to individual cells) and those of in vivo models (e.g. reproduction of complex cellular and molecular interactions). We found that neurotrophins NT3, NT4/5 and in a lesser extent BNDF as well as 2 of the synthetic molecules we tested induced a two a three fold increase of the number of neurites growing out of the spinal cord explants, a 30 to 50 % increase of their length, and up to a two fold increase of the number of end plates per muscle fiber and of the surface of the innervated muscle fibers areas. Using muscles of patients with spinal muscular atrophy muscles, we observed a specific degeneration of the muscular component after 1 to 3 weeks of coculture, suggesting a possible role of skeletal muscle in this neurodegenerative disease. None of the molecules tested, including neurotrophins, could prevent cocultures from degenerating.

25
EXPRESSION OF NERVE GROWTH FACTOR RECEPTOR BY SCHWANN CELLS IN EXPERIMENTAL DIABETES IN RATS AND IN HUMAN DIABETIC NEUROPATHY. J Bradley, RHM King, PK Thomas. *London, UK*

Diabetic sensory polyneuropathy is characterised by a distal axonopathy, initially accompanied by profuse axonal regeneration that later fails. This is not because of loss of parent dorsal root ganglion cells which is relatively slight. A possible explanation would be an alteration in the capacity of peripheral nerve to support axonal regeneration, the main requirement for which being the presence of denervated Schwann cells. Axonal regeneration is impaired in streptozotocin-induced diabetes in rats. Schwann cells associated with axons do not produce nerve growth factor or express nerve growth factor receptors but do so if contact with axons is lost following axonal degeneration. This is likely to support regeneration of sensory axons and is down-regulated once regeneration occurs. In this study

the expression of nerve growth factor receptors by Schwann cells has been investigated immunocytochemically both in human patients with diabetic sensory polyneuropathy and after nerve section in streptozotocin-induced. This was found to take place normally. Failure to up regulate nerve growth factor expression therefore does not appear to explain impaired axonal regeneration in diabetic neuropathy.

26
PERIPHERAL NERVE FUNCTION IN WOMEN WITH HEAVY PHYSICAL WORK. SI Bekkelund, T Torbergsen, SI Mellgren, *Tromsö, Norway.*

The purpose was to study peripheral nerve function in healthy female floor cleaning workers, presumed to be susceptible to cumulative trauma disorders, such as carpal tunnel syndrome. 36 age matched women cleaners and 36 controls (office workers and others with little physical work) randomly selected from an occupational health service were included in the study. The cleaners had a median age of 46 years (range 22-55) compared with 44 (25-55) in the control group. Median duration in the cleaning profession was 10.0 years (5-32). Recording of neurological symptom score (NSS), neurological deficit score (NDS), vibration threshold (VT), temperature and pain thresholds, cardiovascular autonomic tests, nerve conduction velocity (NCV) and quantitative EMG were performed. Median NSS score was 1 (0-7) for the cleaners and 0 (0-5) in the control group (P=0.001). Warm-cold difference limen (in °C) was significantly higher for all extremities in the cleaners with median 6.17 (1.16-14.73) in right index finger and 4.02 (1.37-9.32) in the controls (P=0.0005). Limen in the right big toe was 17.53 (6.36-47.96) in the cleaners compared with 13.83 (4.98-27.71) in the controls (p=0.04). Similar differences were found on the left side. Several of the NCV and EMG data also showed statistically significant differences between cleaners and controls. Among these were NCV parameters in the median and ulnar nerves which were significantly poorer in the cleaners than in the controls. Quantitative EMG showed that a longer duration of and a higher number of phases in motor unit potentials predominated significantly in lower leg muscles of cleaners. The study suggests that a more diffuse peripheral nerve affection occurs in female professional house cleaners and other mechanisms in addition to cumulative trauma may contribute to this.

27
NEURORADIOLOGICAL FEATURES OF VASCULAR DEMENTIA. S Carlomagno, V Parlato, A Santoro, A Lavarone, F Boller, V Bonavita. *Naples, Italy.*

In order to study the correlations between vascular dementia (VaD) and neuroimaging findings we reviewed clinical charts of 136 patients consecutively admitted at the Institute of Neurological Sciences of Naples from 1989 to 1992 suffering from multi-infarct cerebrovascular disease (MICVD). Patients were classified as having (n. 64) or not (n. 72) dementia according to DSM III-R crite ria . CT scan and NMR were evaluated by a neuroradiologist blind of the clinical informations, and classified as showing cortical, subcortical or cortico-subcortical atrophia, multiple ischemic lesions (mainly involving the left or the right hemisphere), leucoaraiosis. All the considered neuroradiological parameters failed to discriminate the two groups of patients, but the occurrence of subcortical atrophy (51.0% in VaD patients vs 35.7% in CVD non demented patients, p<.05). Such findings led us to conclude for a particular involvement of subcortical structures in determining onset of dementia in CVD patients.

28
NEUROLOGICAL AND IMMUNOHISTOCHEMICAL FINDING IN CHURG-STRAUSS SYNDROME. A Engelhardt, H Lörler, S Robeck, C Kluglein, B. Neundörfer, *Erlangen; Germany*

Churg-Strauss'syndrome (CSS, allergic granulomatous angeitis) is a rare type of systemic necrotizing vasculitis. In 92 patients with systemic vasculitis we found only 3 cases with CSS. In contrast, peripheral neuropathy can be found in up to 75% of CSS patients. In a group of 51 patients with vasculitic neuropathy, 5 had CSS. We report herein on 7 female patients with CSS. Mean age was 57.7 y (range 41-72), duration of illness 2.7 y (range 0.26-8.0). All patients had asthma and hypereosinophilia (6-69%), 5 had weight loss. Clinical signs of peripheral nerve involvement were observed in 6 patients. The distribution of peripheral neuropathy was asymmetric (mononeuritis multiplex) in only 2 cases. 4/6 showed a symmetric sensorimotor neuropathy. A combined sural nerve and muscle biopsy was performed in 5 cases with immunohistochemical analysis in 3 cases. Vasculitic infiltrates were found in all examined nerves and in 4/5 muscle biopsies. Among the infiltrating cells CD4 and CD8 lymphocytes predominated. Eosinophils were rare. 2 cases showed intramural IgE producing plasma cells and complement in epineurial vessels. All patients were treated with corticosteroids, 4 cases in combination with azathioprine. 5 patients were observed over a period of 4 years. 4 of these improved and one died. Epineurial necrotizing vasculitis appears to be the most important pathogenic factor of peripheral nerve damage in CSS. Toxic factors produced by eosinophils may have a minor influence.

29
SOMATOSENSORY AND MOTOR EVOKED POTENTIALS IN CERVICAL SPONDYLOTIC MYELOPATHY. G Comi, V Avoledo, T Locatelli, L Leocani, G Galardi, G Magnani, S Medaglini, *Milan, Italy*

Cervical spinal cord MRI shows several types of signal abnormalities, but gives no functional information as somatosensory (SEPs) and motor evoked potentials (MEPs) can offer. The aim of our study was the evaluation of SEPs and MEPs sensitivity in cervical spondylotic myelopathy CSM disease assessed by cervical spinal cord MRI. We studied 30 patients by means of upper and lower limb SEPs and MEPs. The frequency of abnormalities detected by SEPs and MEPs respectively was 69% and 60% for the upper limbs and 70% and 69% for the lower limbs.The sensitivity of SEPs and MEPs was 77% and 68% for the upper limbs and 68% and 85% for the lower limbs. A significant correlation between the degree of clinical involvement and neurophysiological data was found. SEPs and MEPs were both abnormal in 94% of cases. The lemniscal tract was the most frequent damaged structure as regards sensory pathways while a radicular involvement was less frequent. Neurophysiological evaluation showed a good sensitivity and provides an objective information about involvement of long tracts.

30
EVOKED POTENTIALS IN MULTIPLE SCLEROSIS. TS Chkhikvishvili, A Zangaladze. *Tbilisi; Republic of Georgia.*

The auditory brainstem responses (ABRs) and somatosensory evoked potentials (SEPs) were averaged in 78 patients with a diagnosis of possible, probable or clinically definite multiple sclerosis. An abnormality of at least one evoked potentials was found in 100% of the clinically definite cases in 86%, of the probable, and 55 of the possible cases. SEP as well as ABR abnormalities were correlated with a clinical evaluation of the activity of the disease. Their role in monitoring disease progression was estimated. The possibilities of applied electrophysiological methods in determination of pathological loci are evaluated. It is assumed that pathological alterations of temporal and amplitude parameters of the ABR proceed from common mechanisms. The evoked responses were very sensitive in detecting asymptomatic lesions, and can therefore be used in conjunction with clinical date to provide evidence of multiple sclerosis. The data presented, prove that an increase of the stimulus repetition rate did not provoke the ABR abnormality, but worsened already abnormal ABR responses.

31
POTENTIAL FIELD DISTRIBUTION IN FOCAL SPIKE ACTIVITY. M Bratoeva, P Kovachev, D Chavdarov. *Sofia; Bulgaria.*

The aim of the study was to examine the topographical characteristics of focal spike activity in patients with simple partial seizures and to compare them with EEG findings. EEG trials with focal spike activity with different localization and morphology were studied. Also the potential field distributions of the single spike independantly for the positive and negative phases, of the averaged spikes, and of the spikes in an averaged time interval around the maximum, were examined. We used T-and Z-statistics for evaluating the differences in the patterns of distribution. The results showed that for every case there were no significant differences in the patterns of potential field distribution (SD less than 1.9). The latter concerned the single spikes, the averaged ones and the groups of spikes as a whole. In both the positive and the negative maxima, the patterns of potential field distribution were similar. When the potential field distribution is studied in cases with simple partial seizures and focal spike activity, there is a quite constant pattern of distribution. This regular pattern of distribution was found in all trials, supporting that there is no need for analysing extended epochs to find out the regularities of the potential field distribution.

32
CONFIRMATION OF BRAIN DEATH USING TRANSCRANIAL DOPPLER EXAMINATION. N Artemis, D Karacostas, I Milonas, *Thessaloniki, Greece.*

In 22 comatose patients we performed Transcranial Doppler (TCD) examination over a period of I year. Abnormal waveforms consisting of absence of flow, small systolic spikes, oscillating flow or systolic peaks in at least 2 intracranial arteries occurred in 11 patients. All the above mentioned patients met criteria for determination of brain death. An additional patient with low velocities on the initial evaluation finally met criteria for brain death 2 days after the TCD examination. In our study, the TCD method was highly specific (100 %) and sensitive (91,6 %) for recognition of brain death. Our results indicate that TCD examination is a simple, portable and reliable method for confirmation of brain death and can be used as another criterion for this unfortunate event. Additionally the method provides very early signs indicating brain death.

33
MULTIMODAL EVOKED POTENTIALS IN MULTIPLE SYSTEM AND LATE ONSET CEREBELLAR ATROPHIES. J Arpa, R Lopez-Pajares, A Cruz-Matinez, J Sarria, F Palomo, M Alonso, A Rodriguez-Albarino, T Lacasa, J Nos, P Barreiro. *Madrid; Spain.*

The aim present neurophysiological investigation is the assessment of the usefulness of evoked potentials (EPs) in the diagnosis of multiple system atrophy (MSA) and late onset cerebellar atrophy (LOCA, including late onset autosomal dominant cerebellar ataxia, ADCA). Twenty-three cases were clinically examined using scales for cerebellar, pyramidal, parkinsonian, mental status and neuroimaging quantitative evaluations. The patients were classified into four groups. OPCA, striato-nigral degeneration (SND) Sky Drager syndrome (SDS) and LOCA. We have performed visual (VEPs), brainstem auditory ((BSAEPs) and somatosensory (SEPs) evoked potentials in order to establish their validity in making the diagnosis. We also studied correlation between EP's and central motor conduction time (CMC), and electro-oculography (EOG). VEPs detected clinically silent lesions in 5 patients. BSAEPs'central conduction abnormalities were found in 3 cases with OPCA and in all 4 with LOCA. Five out of 11 patients with OPCA and 3 out of 4 LOCA showed SEPs'central conduction abnormalities. LOCA group showed more frequently an abnormal latency and shape of BSAEPs and SEPs. In 46% of OPCA patients SEPs and/or BSAEPs abnormalities were also found, but less frequently than in LOCA. Our results suggest subclinical lesions of large sensory fiber and brain stem structures in those diseases. EP's abnormalities in concert with CMC and EOG appear as possible laboratory tools supporting the clinical diagnosis.

34
TRANSCRANIAL MAGNETIC STIMULATION IN MULTIPLE SYSTEM AND LATE ONSET CEREBELLAR ATROPHIES. A Cruz Martinez, J Arpa, C Villoslada, M Alons and F Palomo. *Madrid; Spain.*

Central motor conduction time (CMCT) after transcranial magnetic stimulation (TMS) of the cortex, electromyography and nerve conduction velocity were performed in 24 patients with multiple system (MSA) and late onset cerebellar atrophy (LOCA) (often OPCA). CMCT was abnormal in 7 patients with OPCA and one with LOCA. CMCT abnormalities (43% of cases) and increased threshold (68%) were more often found within OPCA group than in another multisystem atrophy and LOCA. Reduction in amplitude of the response after TMS was significantly correlated with cerebral hemisphere atrophy. Increased threshold was correlated with upper vermal hemisphere atrophy and enlargement of the fourth ventricle. Thus, cerebellar dysfunction could contribute to increase motor threshold. Electrophysiologic signs of mixed peripheral neuropathy were found in 8 patients. TMS abnormalities were not related to peripheral nerve impairment. Marked variation in CMCT suggests heterogeneityn in these diseases. However, the percentage of CMCT abnormalities in OPCA group suggests that TMS seems to play a role in the neurophysiological diagnosis of these heterogeneous disorders.

35
VISUAL P100 AND P300 IN TREATED WILSON'S DISEASE. A Taghavy, H Hamer, A Kratzer, *Erlangen, Germany*

Cognitive impairments of variable degrees have been observed in Wilson s disease (WD). They respond effectively to d-penicillamine, but the question remains whether there are still subclinical cognitive deficits in treated patients using sensitive electrophysiological techniques. 10 treated patients with WD (6 neurological, 4 non-neurological; 37.2 ± 0.7 y) were investigated by a pattern flash visual "odd-ball paradigm" (P300) and additionally in 7 with pattern reversal visual evoked potentials (P100). The potentials were derived from Oz to Fz (Cz was ground). The parameters were compared with those of age and sex matched controls. Whereas among the P 100-parameters (latencies of N80 and P 100; amplitudes of N80/P100) only a slight but significant lengthening of P100-latency was observed (113.7 ± 7.4 ms versus controls: 108.0 ± 6.3 ms; $p<0.05$), P300-parameters differ more significantly from controls: N250 latency: 292.5 ± 27.0 ms (controls: 266.1 ± 17.4 ms; $p<0.02$); P300-latency: 339.5 ± 34.2 ms (controls: 319.8 ± 10.5; $p<0.02$). The N250/P300 amplitude showed a significant reduction in subgroup of neurological WD only (6.82 ± 4.93 uV versus controls: 14.16 ± 8.85 uV; $p<0.05$). For all differing parameters the neurological WD was more prominent than the non-neurological WD (up to 3 standard deviations from the norm). The results show a more prominent impairment of "endogenous" potentials (P300) in contrast to "exogenous" potentials (P100) indicating subclinical cognitive dysfunction in treated WD -more so in neurological ones.

36
EFFECT OF CATECHOL-O-METHYLTRANSFERASE (COMT) INHIBITION ON PERIPHERAL AND CENTRAL METABOLISM OF [^{18}F]FDOPA IN THE RAT. S. Dethy, T. Pauwels. M. Monclus, A. Luxen, S. Goldman, *Brussels, Belgium*

The PET radiotracer of the presynaptic dopaminergic system, [^{18}F]FDOPA, is metabolised outside the brain by dopamine decarboxylase and COMT. In the presence of carbidopa, [^{18}F]FDOPA is mainly metabolised by COMT. We studied the effects of OR-611 (entacapone), a peripheral COMT inhibitor, on striatal [^{18}F]FDOPA uptake in rats. Rats were treated with carbidopa, entacapone or both before administration of [^{18}F]FDOPA. Blood samples were withdrawn at 3, 5, 15 and 30 minutes; striata and cerebellum were dissected at 30 minutes. Blood and tissue were counted before and after HPLC separation. Radioactivity content per gram of tissue was calculated in striatum and cerebellum to obtain a striatum/cerebellum ratio. Entacapone alone antagonised the appearance of methylated metabolites in plasma, striatum and cerebellum but did not increase striatal [^{18}F]FDOPA availability. When entacapone was added to carbidopa, striatum/cerebellum ratio increased significantly (1.4 versus 1.2 in rats with carbidopa, 1.0 in control) but significant levels of methylated metabolites were found in the brain. In conclusion, entacapone added to carbidopa might increase striatum/cerebellum ratio in human undergoing [^{18}F]FDOPA PET studies. However, appearance of methylated metabolites in the brain could hamper quantification of the PET data.

37
KINETIC PROFILE AND EFFECT ON TREMOR OF PIRIBEDIL IN 13 PARKINSONIAN PATIENTS DURING AND AFTER I.V. PERFUSION. M Ziegler, O Crambes, I Ragueneau, F Arnaud, *Paris & Courbevoie, France*

Piribedil (Trivastal®), a D2 dopaminergic agonist, is effective for parkinsonian symptoms, especially for tremor. The objective of this study was to correlate its therapeutic activity on tremor with plasma concentrations during and after an i.v. infusion of 6 mg. 13 patients presenting an idiopathic Parkinson's disease with resting tremor were included (7 W, 6 M); aged 66 years (52/79); weight 67.4 kg (47/84); mean duration of discase 6.2 years (1/20); 8/13 patients received L-dopa treatment (520 mg/d). Patients treated with b-blockers, MAOI, or with orthostatic hypotension were not included. A three day treatment with domperidone was prescribed before inclusion (30 mg/d). Antiparkinsonian treatments were withdrawn at least one day prior to study initiation. Blood samples, clinical evaluation of tremor (duration, amplitude), BP and HR measurements, and acceptability were performed at time points 0, 5, 10, 15, 30, 45, 60, 75, 90, 120, 180, 240, 360 and 480 min. Four patients were not evaluated: 3 selected patients did not present any evaluable resting tremor at T 0 min, and in 1 patient the infusion was stopped at 15 min because of hypotension. The duration and amplitude of resting tremor decreased significantly during the infusion ($p < 0.001$) ($n = 9$); the effect was maximal for amplitude at T 45 min (-42 %) and for duration at T 60 min (-62 %). A moderate decrease (less than 10 %) of BP was observed (NS). Tremor decreased when piribedil concentration increased ($r = -0,43$) and reappeared after the end of infusion (67 % of the effect disappeared 30 min after the end of infusion). These results on resting tremor were observed for piribedil plasma concentrations between 10 and 30 ng/ml.

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PHARMACODYNAMIC OF SHORT-DURATION RESPONSE AND LONG DURATION RESPONSE TO LEVODOPA IN PARKINSON'S DISEASE.. M Zappia, R Montesanti, R Colao, A Palmieri, D Branca, G Nicoletti, M Rizzo, G Parlato, A Quattrone, *Catanzaro, Italy*

In the present study we evaluated the characteristics of duration response (LnR) LDR in 15 PD patients (mean age 63.3 ± 8.5 years) with similar short-duration response (SDR) lasting effect to an acute oral test (mean duration 6.2 ± 1.6 hours), and considered as stable responders to chronic levodopa therapy. SDR was evaluated after an acute 250 mg levodopa oral test performed on baseline conditions; LDR was examined after the last dose following a fifteen day treatment period with levodopa 250 mg t.i.d. Motor functions were assessed by the Motor Examination of the Unified Parkinson's Disease Rating Scale and by measuring movement time (MT) with a computerised tachystoscope; MT recordings and clinical assessments were detected every two hours (from 8 AM to 8 PM of each day) after the drug intake, no clinical or were . samples were collected hourly for six hours after the drug intake for plasma levodopa analysis. The results showed that LDR to chronic levodopa therapy lasted longer than SDR to an acute test (37.9 ± 14.3 hours vs 6.2 ± 1.6 hours, P 0;01). LDR was negatively correlated with disease severity (r = -0.65, P0.0l), whereas SDR was not; neither LDR nor SDR were correlated with levodopa peripheral pharrnacokinetic parameters. Our findings suggest that LDR to chronic levodopa therapy in PD may depend on indicator of nigrostrial dopamine storage capabilities in PD patients stable responders to chronic levodopa therapy.

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PESTICIDE EXPOSURE ASSESSMENT IN A GROUP OF PARKINSONIAN PATIENTS. N Vanacore; P Zuchegna, V Bonifati, G Meco, *Roma; Italy*

The aims of this research are: a) to define a method for pesticide exposure assessment in analytical studies; b) to characterise neurotoxins likely linked to extrapyramidal system; c) to clinical course of patient exposed to neurotoxins. Eight parkinsonian patients with agricultural occupational exposure to pesticides were studied using a specific questionnaire developed by the Italian Superior Institute of Health. Clinical diagnoses include: two definite Parkinson's Disease (PD), three likely PD and three likely parkinsonism (according to clinical criteria of UK PD Society Brain Bank). Five indices of agricultural work were : total number of pesticide treatments (544.7 ± 263.3); total length of treatments (hours) (1787.9 ± 1393.5); extension of cultivated field (hectares) (5.7 ± 7.9); personal habits and protective equipment adopted (max score 25) (12.1 ± 3.6); mode of pesticides use (max score 10) (7.6 ± 2.4). The correlation matrix was statistically significant between age at onset of symptoms and total number of treatments (r = - 0.816; p < 0.05), and between extension of cultivated field and total number of treatments (r = - 0.723; p< 0.05). Five patients had used pesticides mainly containing diethyldithiocarbamate. One patient had had one episode of acute pesticide intoxication . These preliminary data stress the importance of a more accurate quali/quantitative pesticide exposure assessment in Parkinsonian patients.

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MULTIFACTORIAL ETIOLOGY IN IDIOPATHIC PARKINSON'S DISEASE: A CASE -CONTROL STUDY. J Scholz, H -J Friedrich, A Rohl, G Ulm, P Vieregge. *Lubeck & Kassel, Germany*

An epidemiological study was undertaken among 66 patients with Parkinson's disease (PD) and 72 age -and sex -matched controls regarding familial occurrence of PD or essential tremor (ET) and other causal actors in patients before 40 years of age. PD patients reported less frequent cigarette smoking (OR 0.37), an increased risk of a 1st or 2nd degree relative with PD (OR 7.14) or ET (OR 3.62). Place of living and source of drinking water during the first 15 years of life, number of removals and travels outside Europe before 40th year of age were not different. The same applied to congenital or perinatal abnormalities, and to comorbid diseases.

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PRINCIPAL LIFETIME OCCUPATION AND PARKINSON'S DISEASE: A CASE CONTROL STUDY IN ITALIAN POPULATION. G Savettieri, WA Rocca, F Meneghini, F Grigoletto, L Morgante, A Reggio, G Salemi, R Di Pierri, *Palermo, Messina, Catania, Padova, Italy & Rochester MN, USA*

We investigated the association between occupation or other sociodemographic variables and Parkinson's disease (PD) through a population-based (prevalence) case-control study. Current epidemiologic evidence on the association between occupational exposures and PD is inconsistent. Through a door-to-door two-phase survey (the SNES Project), we iclentified all prevalent cases of PD in three Sicilian municipalities. During the screening visit, we also obtained information on principal lifetime occupation and other sociodemographic variables for each subject in the study population. For all cases (N=62), an adjudication panel reviewed the diagnosis of PD using specificic criteria. We then randomly selected two controls for each case from the general population (N= 124) cases and controls were matched for age (>1 year), sex, and study municipality. Subjects working rmost of their life as farmers were not at increased risk of PD. Also housewifes, fishermen, factory workers, salesmen,craftsmen,clerks,, or with other occupations. PD was not associated with education nor with season of birth. Our findings suggest that occupation is not a risk factor for PD, and does not support the hypothesis that agricultural work and exposure to pesticides play a role in its causation. Our study desi~n reduced the possibility of selection and recall bias but not of incidence-prevalence (survival) bias.

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PROBABLE TRIGGER FACTORS IN PARKINSON'S DISEASE. S Özckmekçi, S Ertan, N Yeni, H Apaydin, G Erkol, G Kiziltan, F Denktas. *Istanbul, Turkey*

It has been claimed that some trigger factors may play a role in the onset of the symptoms of Parkinson's disease after a long preclinical period. The aim of this study is to investigate the existence of some precipitant factors (PF's), such as psychic or physical trauma, systemic disease and surgical operation, in the last 5 years before the beginning of the symptoms, in a group consisting of 287 patients (150 male, 137 female) with Parkinson's disease. PF positive (group 1) and PF negative groups (group 2) have been compared for the age of onset and progression rate. 124 patients (44.2%) had a PF history. The female/male ratios in group 1 and group 2 were 1.13 and 0.77, respectively, which were not statistically significant. The distribution of PFs was as follows: psychic trauma 54.8 %, physical trauma 16.9 %, systemic disease 11.3 % and surgical operation intoxication 17 %. The mean ages of onset of the disease in group 1 and group 2 were 56.8 (11.5 and 65.5 (9.9, respectively. This difference was statistically significant (p<.001). In order to evaluate the progression rate of the disease, we have calculated the mean elapsed time from stage I to III according to the Hoehn and Yahr scale, of the patients with at least 5 years of disease. There was no significant difference between the two groups.

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A CASE-CONTROL STUDY OF NOCTURNAL PROBLEMS IN PARKINSON'S DISEASE. D Ranoux, M Ziegler, J de Recondo, *Paris France.*

Night can be a particularly distressing time for patients with Parkinson's disease (PD), because of sleep disorders, motor disability, pain and bladder symptoms. This case-control study was performed in order to evaluate the prevalence of sleep complaints in a non-selected population of parkinsonian patients compared with controls chosen among patient's relatives and friends fulfilling the following criteria: no parkinsonian features, same age (+/-5 years), same sex, residency in the same region. Seventy-four consecutive parkinsonian patients (45 men and 29 women) and 74 controls participated in this study. Mean age of the PD patients was 65 years and mean duration of PD 10.7 years. They completed a questionnaire about their sleep (delay of sleep initiation, number of nocturnal awakenings, nightmares, duration and subjective quality of sleep, diurnal somnolence) and nocturnal symptoms (pain, dystonia, restless legs, myoclonus, nocturnal akinesia, urinary frequency). Sleep initiation problems were common in PD patients and in controls. Whatever the age and stage of disability, nocturnal awakenings and urinary frequency were more frequent in PD patients than in controls (p<0.001). The subjective appreciation of sleep was not as good and the duration of sleep was not as long in PD patients as in controls. However, this difference was statistically significant only in patients under 65 years of age (p<0.01 and p<0.05 respectively). We can assume that, in older patients, sleep disturbances are in part due to the effect of age whereas in younger patients they are mainly related to the disease process itself.

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PEN-INJECTED APOMORPHINE AGAINST OFF-PHENOMENA IN LATE PARKINSON'S DISEASE. A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY. L Ostergaard, L Werdelin, P Odin, O Lindvall, E Dupont, PB Christensen, E Boisen, NB Jensen, M Schmiegelow, SH Ingwersen. *Copenhagen, Aarhus, Denmark & Lund; Sweden.*

We evaluated the effect, therapeutic dose range and pharmacokinetics of apomorphine, given as subcutaneous injections, in the treatment of off-phenomena in 22 patients with idiopathic Parkinson's disease. At study entry a placebo-controlled apomorphine test was performed, and apomorphine doses were then individually titrated (mean 3.4 mg, range 0.8-6.0 mg)) and compared to in a double-blind cross-over phase. Apomorphine reduced by 51% the mean daily duration of off-periods compared to placebo, as assessed patients, and by 58%, as assessed by the staff. The severity of off-periods was also significantly reduced. After eight weeks of training 13/14 patients were able to inject themselves, and 11/14 patients found that their feeling of freedom had increased. The most common adverse reactions were nausea, subcutaneous noduli and increased frequency of involuntary movements. Pharmacokinetics were linear and did not change with repeated dosage. T_{max} ranged from 5 to 45 min (16 patients).

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DESCRIPTIVE EPIDEMIOLOGY OF PARKINSON'S DISEASE. J Matias-Guiu, R Manzanares, T Canet, R Falip, R Martin, L Galiano, *Alicante, Spain*

The prevalence of Parkinson's disease (PD) has been estimated to be between 10 and 350 cases per 100.000 inhabitants in various populations world-wide. However, there is little information on the risk of PD in Spain. We have conducted a community-based study in the Alcoi's healthy area which aim was to know the descriptive rates of PD. The total population of the studied area is 133.889 inhabitants and the ascertainment of PD cases was performed from June 1st 1986 to May 31, 1991. The diagnosis of PD was established when a history of progressive neurological disorder was found in a patient with at least two of the following: rest tremor, rigidity, bradycinesia and impaired postural reflexes. Patients with secondary causes or pharmacological etiology were excluded. The crude prevalence of PD in Alcoi was 174.7 cases/100.000 inhabitants (238 cases 95% confidence limits 151.6-195.8; adjusted prevalence to standard European population 151.1/100.000 inhabitants; 95% C.L. 127.0-175.2). All PD prevalent patients consisted of 123 men (191.0 cases/100.000 inhabitants. 95% C.L. 158.8-223.2) and 110 females (158.9/100.000 inhabitants. 95% C.L. 129.8-188.0). The annual incidence rate of PD in Alcoi was 31.8 cases/100.000 inhabitants, year (95% C.L. 22.3-41.4, adjusted incidence to standard European population 28.1, 95% CL 19.2-37.1). Sex specific incidence was 32.1 cases/100.000 year for males (95% CL 22.3 -41.4) and was 28.4 cases/100.000 year (95% CL 15.8-41.0) for females. During the study period 58 PD patients died that means a mortality of 8.6/100.000 inhabitants (95% CL 3.6-13.5 ; adjusted mortality rate to standard European population 7.0).

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ULTRASTRUCTURAL CHANGES IN NEURONS OF MOTOR THALAMIC NUCLEI IN CATS WITH PARKINSON-LIKE SYNDROME EVOKED BY NEUROTOXIN MPTP. MY Voloshin, LF Burchinskaya, *Kiev, Ukraine*

Disturbance of excitation conduction through thalamic motor nuclei is considered to be one of the reasons for Parkinson-like motor disorders. In the last years a modeling of this disease by MPTP-induced injury of dopaminergic neurons of substantia nigra has been widely used for the study of parkinsonism pathogenesis. The present work was aimed at elucidating indirect influences of MPTP (5 mg/kg daily for 5 days) on the ultrastructure of ventral lateral thalamic nucleus in cats wit expressed bradykinesia, rigidity and sometimes, tremor. It has been found that in two days after completion of MPTP course the somata and dendrites of the majority of thalamic neurons showed the ultrastructural changes typical for hydropic dystrophy combined with the signs of compensatory and restorative reactions. The dead cells were absent. As for synapses, only single F an SR-types of synapses had initial signs of dark degeneration. The majority of all synapses both on the somata and dendrites displayed hydropic changes from negligible to local destructions. The generalized ultrastructural changes in the blood-brain barrier elements are observed evidencing their dysfunction that entails the hypoxia of brain cells. The data obtained provide evidence for morphological changes related not only to specific disturbance in the striatum-reticular part of substantia nigra-thalamus circuit, but also resulting from direct toxic effect on the whole brain.

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PERIPHERAL IRON METABOLISM IN PATIENTS WITH PARKINSON'S DISEASE. F Cabrera-Valdivia, FJ Jimenez-Jimenez, JA Molina, P Fernandez-Calle, A Vazquez, F Canizares-Liebana, S Larumbe-Lobalde, L Ayuso-Peralta, M Rabasa, R Codoceo. *Alcala de Henares and Madrid, Spain*

To elucidate the possible role of peripheral metabolism of iron in the risk for developing Parkinson's disease (PD), we compared serum levels of iron, transferrin and ferritin and 24 hour urinary iron excretion after a single i m dose of 1 mg/kg of desferrioxamine, in 68 PD patients and their spouses as the control group. All these values did not differ significantly between the groups, they were not influenced by antiparkinsonian therapy, and they did not correlate with age, age at onset and duration of the disease, scores of the Unified PD Rating Scale or the Hoehn and Yahr staging in the PD group, with the exception of the 24 hour urinary iron excretion with the duration of the disease ($r=0.32$, $p<0.05$). These results suggest that peripheral metabolism of iron is apparently unrelated to the risk of developing PD.

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LOW SERUM LEVELS OF SELENIUM IN PARKINSON'S DISEASE. FJ Jimenez-Jimenez, JA Molina, FJ Arrieta, MV Aguilar, F Cabrera-Valdivia, L Ayuso-Peralta, M Rabasa, A Vazquez, P Fernandez-Calle, A Jorge-Santamaria, and MC Martinez-Para. *Alcala de Henares & Madrid, Spain*

Selenium (Se) is an important component of the antioxidant enzyme glutathione-peroxidase. The activity of this enzyme is reduced in the substantia nigra of patients with Parkinson's disease(PD), but the results of studies on erythrocytes are controversial. We compared the serum levels of Se and 24 hour urinary Se excretion (measured by an atomic absorption spectrophotometric method) in 29 PD patients and 30 matched controls. Serum Se levels were significantly lower in PD patients than in controls (34.6±2.35 and 45.2±3.83 μg/l, $p=0.022$) while urinary excretion was similar for both groups (47.1±6.25 and 45.5±5.38 μg/24 h). These values were not influenced by antiparkinsonian drugs, and they did not correlate with age, age at onset and duration of the PD, scores of the Unified PD Rating Scale or the Hoehn and Yahr staging in the PD group. These results might suggest a possible role of low serum se levels in risk for PD.

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EFFECTS OF ALPHA-TOCOPHEROL (VITAMIN E) ON MOTOR FLUCTUATIONS IN PATIENTS WITH PARKINSON'S DISEASE UNDER PROLONGED LEVODOPATHERAPY. J Alarcon, D Mateo, FJ Jimenez-Jimenez, and S Gimenez-Roldan. *Madrid and Alcala de Henares, Spain*

Recent studies suggest that levodopa is toxic against dopamine neurons by generation of reactive free radicals and by formation of some oxidation products. Vitamin E acts as antioxidant for unsaturated lipids and maintains the integrity of biologic membranes. To test whether vitamin E could delay the development of motor fluctuations, we initiated a 4 year study involving 63 patients with Parkinson's disease (PD) on long term levodopa-therapy. They were assigned randomly to group A (31 patients, therapy with vitamin E 600 mg/day) or group B (no therapy with vitamins). These groups did not differ in sex, age, age at onset of PD, and dose and time of exposure to levodopa or dopamine agonists. Group A patients had a higher mean±SEM score in the UCLA scale than those of group B (25.3±3.65 and 15.5±2.86, respectively, $p<0.05$). The percentages of development of motor fluctuations for groups A and B were, respectively: 10% and 19.4% at the 1st year, 33.3% and 40.7% at the 2nd year, 41.2% and 50% at the 3rd year, and 53.8% and 65% in the 4th year. Although the differences were non-significant by an analysis of Kaplan-Meier survival curves, the small size of the study does not allow to reach definitive conclusions about the hypothesis tested. Studies addressed to this point involving a higher number of PD patients seem to be justified.

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ON THE PROBLEM "QUALITY OF LIFE" IN PATIENTS WITH PARKINSONISM. E Gencheva, Tz Tzonev, G Georgiev, P Petkova, *Sofia, Bulgaria* .

Quality of life was evaluated in 52 patients with parkinsonism at age 52 to 68 years (30 males and 22 females), according to the changes in their somatic and mental health. The emotional reactivity (depression, anxiety, frustration) and the ability for professional and social functioning were studied by means of clinical and psychological methods. The results of the study suggest the necessity of including in the therapeutical complex both antidepressive and tranquillizer treatment, along with antiparkinsonian drugs. The therapy should be combined with psychotherapeutic intervention, directed to constructive settling the inner conflict, due to the disease. The psychotherapy could be carried out individually or in the patient's family. Forming an adaptive behaviour in the members of family would help the patients in their social independence and functioning. The investigation shows, that the patients with parkinsonism have a specific style of life (professional disability, social isolation), witch must be treated as a mental disorder itself.

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PERSEVERATIONS EN PARKINSON'S DISEASE : THE ROLE OF FRONTAL LOBES. M Gasparini, N Vanacore N, G Meco- *Roma, Italy*

The term perseveration is generally used to describe any recurrence of experience or activity without the appropriate stimulus. Perseveration on tests requiring memory and cognitive flexibility has been associated with dysfunctions in the regulation/inhibition activity of frontal lobes; it has also been observed in patients with subcortical disorders. In addition to continuous perseveration (the compulsive repetition of a movement) the taxonomy includes recurrent perseveration and stuck-in-set perseveration. In elderly, untreated patients with Parkinson's Disease, stuck-in-set perseveration has been described on the W.C.S.T. and Verbal Fluency. In the present study we have examined the performances on neuropsychological tests of 32 newly diagnosed patients with Idiopathic Parkinson's Disease (14 females and 18 males; age 67.16±5.50; education 7.19±3.50; duration of illness 6.53±4.37). All patients have been treated with L-dopa therapy and evaluated in the "off-phase". ANOVA revealed no significative differences between patients on the I/II and III/IV stage of the Hoehn &Yahr scale. Significative, strong correlations have been found between increase of recurrent perseverations and decrease of mnemonic retrieval on the Rey Complex Figure ($r=-0.588$; $P< 0.0001$) and between increase of stuck-in-set perseverations and number of categories achieved on the Wisconsin Card Sorting Test ($r=-0.864$; $P< 0.0001$). Our data seem to suggest the interference of perseverations on executive functions and on the storage of mnemonical input, probably linked with an abnormal recall of previous, visual memory traces; they also suggest a similar impairment at different stages of Parkinson's disease, without correlations with severity and duration of the illness.

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BONE MASS IN PARKINSON S DISEASE: A STUDY WITH THREE METHODS. G de la Sierra, FJ Jimenez-Jimenez, F Aguado, M Revilla, L Varela, and H Rico. *Alcala de Henares (SPAIN)*

Recent reports suggest the presence of osteopoenia in a high percentage of patients with Parkinson's disease (PD). These data constrasts with previous reports of our group, perhaps due to the different methods used. We studied bone mass in 24 PD patients (13 males, 11 females) and in 80 age and sex-matched controls (40 males, 40 females), who had no other diseases which could affect bone mass, by using different techniques: metacarpal radiogrammetry (CCT), total body bone mineral content measured by dual energy X-ray absorptiometry (TBBMC), and ultrasound bone velocity (UBC). In males, bone mass by CCT did not differ significantly between PD patients and controls, but TBBMC and UBV were lower in the PD group ($p<0.05$ and $p<0.001$, respectively). In females (all of them postmenopausal), bone mass by CCT was significantly higher in the PD group ($p<0.05$), while it was similar by TBBMC and UBV. These preliminary data suggest that the changes reported in bone mass in PD patients can depend on the sex and the study methods.

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ABNORMAL PREMOTOR POTENTIALS IN MOTOR THALAMIC NUCLEI OF PARKINSONIAN PATIENTS. A Feve, JP N'Guyen, N Bathien, G Fenelon, J Veroust, P Cesaro, J D Degos. *Creteil, France.*

Flattening of premotor potentials (MRPs) in patients with Parkinson's disease (PD) or lesions the basal ganglia can suggest the influence of the basal ganglia in the electrogenesis of these MRPs. We postulated that this scalp flattening reflected decreased activity in the pallido-thalamo-cortical loop. MRPs were sought by recording thalamic neuronal activity before a self-paced movement of finger flexion. Eleven patients were recorded; six had PD and five had an essential tremor. A stereotactic electrode had been implanted in the Vim or Vop for treatment of tremor by chronic stimulation. EMG bursts in the flexor digitorum superficialis were used as a trigger for back-averaging with a computerassisted technique. Location of recording was superimposed with Shaltenbrandt's atlas, and amplitudes and latencies were compared between PD and non PD patients. In PD patients, MRPs were recorded only in Vim. In non PD patients, MRPs were recorded in both Vim and in Vop. Amplitudes and latencies were similar in the two groups. Two components were found in the anterior part of the Vin in non PD patients, whereas only one component was found in PD patients. Pallidal inputs are though to project into the upper part of the Vim and in Vop, whereas cerebellar inputs are thought to project into the lower part of the Vim. Two components of MRPs could be generated by these two pathways. The flattening of MRPs on the scalp of PD patients could thus be explained by the decreased activity of the pallido-thalamo-cortical pathway.

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PERSEVERATIVE MOTOR BEHAVIOR IN PARKINSON'S DISEASE. G Egersbach H. Hattig L. Schelosky, J. Wissel, W. Poewe . *Berlin, Germany*

Difficulties in shifting of cognitive sets and perseverative behavior have been shown to be part of the neuropsychology of Parkinson's disease, possibly due to frontal dysfunction. We have tested perseverative motor behavior by assessing ability to generate random movement sequences in 15 patients with Parkinson's disease using the Breidt Perseveration Test Device (PTD). In this experiment subjects are instructed to press one of nine buttons arranged randomly on a metal board without use of systematic or repetitive strategies. The speed of this task that comprises 150 consecutive presses is determined by an acoustic go-signal appearing at 1 Hz frequency. Results were compared with 14 age-matched controls. Patients performance was impaired with intrusion of unwanted systematic strategies suggesting a decreased ability of Parkinsonian patients to generate random movement sequences.

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COMPARISON OF CEREBRAL ATROPHY EVALUATED BY MRI IN PARKINSON'S DISEASE AND MULTIPLE SYSTEM ATROPHY. F Durif, E Albuisson, B Debilly, J Perret, M Tournilhac, P Pollak, Clermont-Ferrand; *Grenoble -France.*

The differential diagnosis between Parkinson's disease (PD) and multiple system atrophy (MSA) may be clinically difficult, especially in patients with a symmetrical akinetic-rigid picture without resting tremor. Radiographic studies report no cerebral atrophy in PD without dementia and infratentorial atrophy. MSA, but few data are available concerning the interest of this atrophy to differentiate PD from MSA. The aim of this study was to compare the cerebral atrophy in 31 patients with PD and in 24 patients with MSA. Contiguous sagittal (T1-weighted) and axial (T2-weighted) sections parallel to the bicommissural plane were performed with a 0.5 T Magniscan imager. Assessment of atrophy was carried out using ventricles, mesencephalon, pons, and total brainstem areas. Cortical and cerebellar atrophies were subjectively assessed. Age and sex were not significantly different between the 2 groups of patients. The total brainstem ($p<0.001$), the mesencephalon ($p<0.05$) and the pons ($p<0.05$) areas were significantly smaller in MSA as well as the cerebellum ($p<0.01$). A progressive discriminant analysis extracted 6 variables in the following order of appearance: total brainstem area, measured cortical atrophy, third ventricle area, lateral ventricle area, global cortical atrophy, and lateral (cella media) ventricle area. Those variables correctly classified 87% of patients ($p<0.002$).

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THE INCREASE OF PARKINSON'S DISEASE MORTALITY IN ITALY (1951-1988) MAY BE DUE TO A COHORT EFFECT. C Magnani, C Mocellini, R Soffietti, D Schiffer, *Torino, Italy*

Parkinson's disease (PD) mortality markedly increased in Italy during 1951-1988 period (males, from 3.3 to 5.4/100,000 population; females, 1.9 to 3.5). In both sexes, age-specific mortality increased threefold in subjects over 75 years and decreased in those under 64 years. The causative factor

of this phenomenon is unclear (a "delayed" death effect due to the introduction of levodopa in therapy, a better case ascertainment, or an increased accuracy of death certificates). In order to verify whether the increase of mortality could be ascribed to an increased risk of dying from PD for specific birth-cohorts, the data have been analysed by means of an age-period-cohort model (StatMed, 1984; 3:113-130). In both sexes, we observed an increase of death risk starting from the cohort born between 1881 and 1885, to a maximum in the cohort born between 1906 and 1910, and a subsequent decrease in the following cohorts. There were no period and age effects. Therefore, the observed increase of PD mortality may be explained by to an higher risk of dying from PD experienced by the cohorts of people born in the first decade of this century. The nature of the factor acting during this period is still unclear.

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NEURONAL CHANGES OF SUBSTANTIA NIGRA IN THE ELDERLY POPULATION. A Cardozo, E Tolosa, FF Cruz-Sanchez. *Barcelona, Spain.*

Substantia nigra neuronal loss has been associated to brain ageing. However other changes may occur prior to cell death. To study these changes, the substantia nigra of 20 patients aged from 20 to 93 years without history of neurological disease were examined using the Golgi method. Three groups were formed according to age: Group A (from 20 to 39), four cases; Group B (from 40 to 69), five cases, and Group C (from 70 to 39), 11 cases. Detailed tracings of neurons from silver impregnated material were made with a drawing tube and several representative neurons were documented by numerous photographs. Three neuronal types were recognised in relation to shape and size: large pigmented cells (Type I neurons); bipolar cells with fusiform shape (Type II neurons) and small cells with radiated dendrites (Type III neurons). Significant abnormalities could be observed in cases of group C compared with neurons from Group A. Nerve cell bodies lost their normal profile, were swollen and showed proliferation of spine-like protrutions. Dendrites become shorter and lost their branches. Nodulations and distorted profile of dendrites could be also observed. Severe loss of spines were found and the remaining ones became thinner and longer. These changes increased with age and were more evident in cell type I and II. Our results may suggest a possible relation between extrapyramidal dysfunction in normal aging and the described neuronal changes.

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SMOKING AND PARKINSON'S DISEASE: A MATCHED CASE CONTROL STUDY. T Canet, R Manzanares, L Falip, L Galiano, R Martin, J Matias-Guiu, *Alicante, Spain*

Many authors have suggested that smoking is a protective factor from developing Parkinson's disease (PD). We have conducted a study using four matched case-control methodology among 94 patients with PD (and 376 controls) to determine whether the possible relationship between smoking and PD. The diagnosis of PD was based on the presence of two or more cardinal signs of the disease and responsiveness to levodopa or dopaminergic agonists. The controls were randomly chosen from healthy people who were attending the hospital. Controls were matched by age and sex. Odds ratio (OR) were calculated using Matntel-Haenszel test. We found that the prior and current use of tobacco was significantly less in PD than controls ($p<0.05$). Consequently, our data confirm the protective relationship betwen the use of tahacco and P.D.

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ODOUR IDENTIFICATION IN PARKINSON'S DISEASE. G Potagas, M Ziegler, N Bathien, P Rondot. *Paris, France & Athens Greece.*

Two simple, clinical, olfactory tests are presented. A population of 80 patients with Parkinson's disease showed a statistically very significant impairment to an odours' identification test, compared to an oge matched population of 40 controls, matched for the age. The results depended on age and the severity of the disease. A simple olfactory stimulius discrimination test did not reveal any difference between populations. The necessity and the possibility of generalization of the olfactory examination in neurology and, through it, the possibility of analysis of olfactory deficits is pointed out. Suprathreshold stimuli and parallel testing of different aspects of olfaction can allow answers to the arising issues: a) Is the olfactory deficit a central, information processing, deficit? b) Which structures can be incriminated for this deficit?

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FAMILIAL PARKINSON'S DISEASE -ANALYSIS OF NINE ITALIAN KINDREDS. V Bonifati, E Fabrizio, N Vanacore, G Meco, *Roma, Italy.*

We selected nine families which include at least two cases fulfilling strict diagnostic criteria for definite or likely Parkinson's Disease (PD), in order to analyse their clinical features and possible models of transmission. Sixty-nine sporadic PD cases served as controls. Among familial cases we ascertained 17 cases of definite PD and 2 cases of likely PD. Age at onset of PD did not differ significantly between the familial and sporadic cases (familial: 59.5±10.3 yrs; sporadic: 60.8±9.2 yrs), nor did other clinical parameters we studied (age, sex, disease duration, Hohen-Yahr stage, symptoms at onset and their distribution, clinical type, l-dopa response, course). Age of onset was also similar between single-generation (n=6) and multigeneration (n=13) familial cases. Affected relatives were distributed in the paternal line in 7 cases, maternal line in 3 cases and in both lines in 1 case in which PD started very early (age 28). There was no correlation among couples of PD relatives between the calendar year-of-onset of the disease; age at onset instead showed a good correlation (r=0.442) which failed to reach statistical significance owing to the limited number of cases. In conclusion, this study confirms that familial PD is clinically not different from sporadic PD. If genetic factors do cause the familial occurrence of PD, then autosomal dominant transmission with incomplete penetrance or multigenic/multifactorial types of transmission are the most suitable models.

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BLOOD SUPEROXIDE DISMUTASE ACTIVITY IN PARKINSONIAN PATIENTS. S Bostantjopoulou, Z Katsarou, G Kyriazis. *Thessaloniki, Greece.*

Increased free radical generation and lipid peroxidation have been implicated in the pathogenesis of Parkinson's disease (PD). Superoxide dismutase (SOD) is an antioxidant enzyme that provides defence against oxygen toxicity. Activity of SOD was assayed in blood lysate and erythrocytes of 17 parkinsonian patients and 17 matched normal controls. Parkinsonian patients were in stage II or III of the disease (Hoehn and Yahr classification) and they were all on antiparkinsonian medication. Mean SOD activity in lysated blood was 107.6±18.5 u/ml in PD patients and 128.8±13.1 u/ml in controls ($p<0.01$). Mean SOD/haemoglobin rate was 739.6±13.6 u/gHb in PD patients and 911.8±55.05 u/gHb in controls ($p<0.0l$),while mean SOD activity in red blood cells was 22.98±3.5 nu/RBC in parkinsonian patients and 26.6±1.5 nu/RBC in normal controls ($p<0.01$). Decreased SOD activity in PD patients may indicate a defect in the antioxidant defense mechanism in PD.

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DELAYED GASTRIC EMPTYING AS A PATHOGENETIC FACTOR OF LATE MOTOR COMPLICATIONS IN PARKINSONISM. H Baas, L Demisch, A Esser, F Zoeller, F Burklin, S Harder, PA Fischer, *Frankfurt, Germany*

We tried to investigate the role of aberratic L-dopa resorption (LR) in late-motor-complications (LMC) in Parkinson's disease (PD) and in the potential development of new therapeutic strategies. Recently gastrointestinal dysfunction has gained increasing interest with respect to LMC in PD. LR is likely to be aberratic in L-dopa non-responders (PD-NR) and in unpredictable on/off-fluctuators. Since LR is directly depending on gastric emptying velocity (GEV), reduced GEV might be an essential pathogenetic factor and improvement of motor response (MR) might be achieved by pharmacogenic acceleration of (GEV). Methods: Three series of investigations were performed. 1: In 24 >12hrs. fasting and drug free PD-pats. (11 responders[PD-R]/13 [PD-NR]) GEV was measured by 99mTc-scintigraphy simultaneously to peripheral Ldopa kinetics (100/25mg L-dopa/benserazide p.o.) and MR. 2: Influence of short/longterm administration of the gastrokinetic domperidone 15mg tdi on L-dopa kinetics and MR was investigated in 14 unselected PD-pats. 3: Influence of domperidone 15mg tdi on GEV, L-dopa kinetics and MR was investigated in 9 severe fluctuators. Results: Ad 1. GEV was abnormal in 11 /13 PD-NR vs. 2/11 PD-R ($t_{1/2elgastr}$ x13.8 ± 6.1 vs. x 42.9 ± 20.2min). GEV correlated

closely with L-dopa kinetics (t1/2elgastr vs. tmax. r=0-64 p<0 01, Spearman rank). Ad 2. Short-/and longterm domperidone lead in PD-NR to normalization of L-dopa kinetics (tmax x60±5.2 to x24.0±8.2 min) but not to improvement of MR. Ad 3. GEV and L-dopa kinetics were abnormal in majority of unpredictable fluctuators. GEV, L-dopa kinetics and MR were improved by domperidone. Conclusion Reduced GEV causes aberratic LR in PD-NR and in unpredictable on/off-fluctuators. Aberratic LR superimposing preexisting wearing-off phenomena might be the essential pathogenetic factor for the development of unpredictable fluctuations. On/off-fluctuators might clinically benefit from pharmalogic stimulation of GEV.

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TIMING OF MENTALLY REPRESENTED ACTIONS IN NORMAL HUMANS AND PARKINSON'S DISEASE (PD), MJ Arcusa, S Hermandez, FJ Claramonte, A Pascual-Leone Pascual,MD Alonso, MD Catala, A Pascual-Leone, *Valencia, Spain*

Mental and actual performance of an action may require activation of common neural structures, but executive structures may not be wholly subordinate to mental movement structures. Slowness of actual movement in PD may not be correlated with abnormal mental imagery. We have studied the timing of mentally and actually performed motor tasks in 7 patients with PD on and off medications as compared with 10 age-matched controls. Subjects completed 2 tasks: Grooved Pegboard Test and walking 15 m at 'natural pace". All were tested 5 times actually performing and 5 times mentally performing each task. The order of the trials was randomised. Subjects timed themselves with a hand-held stopwatch. Normal subjects matched well their mental with their actual performance time. However, PD patients showed significantly shorter mental than actual performance time in both tasks regardless of medication-state. This difference between PD patients and controls was statistically significant and unaccountable by the longer actual performance time in PD off medications. Patients with PD overestimate what their executive motor mechanisms can perform . These results support the structural differentiation of executive and mental imagery motor mechanisms and illustrate the differential disturbance in PD.

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RISPERIDONE IN THE TREATMENT OF PSYCHIATRIC COMPLICATIONS OF PARKINSON'S DISEASE THERAPY. A Alessandri, P Giustini, V Bonifati, G Meco. *Roma, Italy.*

Visual hallucinosis, confusion, and paranoid psychosis are major and increasingly common complications of long term dopaminergic therapy in patients with Parkinson's disease (PD). The addition of dopamine receptor blocking neuroleptics may decrease or abolish the hallucinosis, but the parkinsonian signs are rapidly worsening. Risperidone is a new neuroleptic agent with dopamine and serotonin 5HT2 antagonist activity. Due to its receptor profile, risperidone produces less extrapyramidal side effects than classical neuroleptics. We studied 4 PD patients (3 men and 1 woman: mean age 72.50 yrs; range 66-78). All patients were on levodopa therapy and suffered from visual hallucinosis or confusional episodes of varying severity. They underwent repeated examinations with Unified Parkinson's Disease Rating Scale (UPDRS) Mini Mental State (MMSE) and Brief Psychiatric Rating Scale (BPRS). Risperidone was administered at increasing doses up a total of 0.25-1.25 mg daily. In 2 patients the hallucinosis was markedly attenuated without worsening of extrapyramidal symptoms (respectively at 0.25 and 1.25 mg daily); 1 patient had no hallucinosis improvement or parkinsonian signs worsening (0.25 mg daily); 1 patient dropped out due to worsening of parkinsonian signs in spite of moderate hallucinosis improvement (0.75 mg daily). These preliminary data suggest that risperidone might be useful in the treatment of psychiatric complications during levodopa therapy for PD.

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INTRATHECAL IL-2 THERAPY IN DISSEMINATING CNS TUMORS. A Salmaggi; A Dufour, A Silvani, E Ciusani, A Nespolo, A Boiardi , *Milan, Italy*

CNS tumours disseminating via cerebrospinal fluid (CSF) pathways offer a stimulating opportunity for intrathecal immunotherapy. We treated 3 patients (2 affected by disseminating cerebellar medulloblastoma, 1 by disseminating thalamic glioblastoma) by intrathecal r-IL2 via reservoir. In the first 2 patients, this treatment was preceded by a-IFN. Monitoring of immunological effects of the treatment involved kinetics of CSF and serum TNF-a, IL2s and IL2R and assessment of CSF cells, protein and CSF and PB NK cell activity and CD3-CD56+ cells .While a-IFN treatment elicited marginal effects within the CSF compartment, r-IL2 treatment induced sharp changes in cytokine profile and in NK activity in the CSF. Immunological response to r-IL2 was different during the second cycle: decrease in CSF CD3-CD56+ and NK activity took place in CSF and in PB, in contrast with marked enhancement during the first r-IL2 cycle. Clinical response was satisfactory during the first r-IL2 cycle. Neuroradiological evolution showed regression or stability of CNS disseminating lesions located in the vicinity of the administration catheter, but dissemination in the cerebral ventricles and around cranial nerves was unaffected by treatment.

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ALTERATIONS OF THE BLOOD-BRAIN BARRIER IN HUMAN BRAIN TUMORS: COMPARISON OF RB-82, C-11 METHIONINE AND F-18 FDG USING PET. Roelcke U, Radu EW, von Ammon K, Maguire RP, Leenders KL, *Villigen, Basel, Zurich, Switzerland*

The influence of the blood-brain barrier (BBB) on tracer uptake was investigated in 21 patients with gliomas and meningiomas using PET, 18F-fluorodeoxyglucose (FDG), 18C-methionine (MET), and the potassium analog 82Rubidium (RUB). Tracer uptake was quantitated by 1. multiple time graphical plotting providing tracer distribution volume (VD), net tracer accumulation (ki), and 2. normalized uptake (NU) values. VD, ki and NU of MET in tumors increased from astrocytomas over glioblastomas to meningiomas and were significantly correlated with tumor RUB uptake (Spearman Rank: p<0.005 (VD), p<0.05 (ki), p<0.001 (NU)). NU MET correlated with VD (p<0.001) and ki (p<0.005) of MET. Tumor VD of FDG was in the range of contralateral cortex. Ki and NU values of FDG were highest in glioblastomas. NU of FDG correlated significantly with ki of FDG (p<0.005) but not with VD of FDG. These results demonstrate, that alteration of MET uptake is governed by changes of tracer transport across the BBB, whereas changes of FDG uptake is related to FDG phosphorylation in tumor cells. This has implications for the differential diagnosis of tumor recurrence from radiation necrosis, which both result in BBB alterations.

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BRAIN TUMOR LOCALIZATION WITH EEG MAPPING. M Radionova, D Chavdarov, M Bratoeva, Ch Tzekov, *Sofia, Bulgaria*

Together with the CT and MRI structural diagnosis, important for the treatment of the tumor is the functional localization . We compared the EEG mapping findings with those of CT in 22 patients with intracranial tumors (supratentorial). The EEG mapping investigation included potential field and power parameters in standart and selected frequency bands and probable equivalent dipole localization in selected cases. In 16 patients the mapping distributions in the standart bands revealed localized abnormalities regionally corresponding to that of the CT (+ additional focuses in 7 patients). The investigation in selected frequency bands increases the abnormal findings to 19/22 and the additional power parameters - to 21/22 . In 11 was registrated discharge activity - the dynamic of the potential field distribution in 6 of them indicated the tumor localization. The probable equivalent dipoles of the focal slow waves in three patients with meningeomas showed concentration in areas corresponding to the brain oedema. The EEG mapping increases the detection of localized abnormalities in patients with brain tumors to a degree from 72% to 95% depending on the analyzed parameters and reveals functional engagement of adjacent and distant regions. The dipole localization method IS supplemental to the EEG mapping techniques for the functional tumor localization.

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MENINGEAL CARCINOMATOSIS: CLINICAL FINDINGS AND COURSE IN 5 SELECTED PATIENTS. A Pietrangeli, L Bove, A Pace, L Falqui, B Jandolo. *Rome, Italy*

Meningeal carcinomatosis, is increasingly being recognized. From a group of 20 patients studied in our center from 1988 to 1993 were selected 5 patients that presented signs and symptoms of this pathological condition. All the patients had a leptomeningeal involvement of a solid tumour (breast or lung) with CSF evidence of carcinomatosis without focal metastases. Each patient, except case 5, was given MTX, 10 mg/m2 weekly i.t. by lumbar puncture until the results of CSF cytodiagnosis became nega-

tive. One patient, with lung cancer, had a seizure and complained of headache and diplopia. After 4 doses a CT scan showed hydrocephalus that was treated with ventriculoperitoneal shunt. A month later he died. Another patient, with breast cancer, complained depression and mild cephalgia treated unsuccessfully treated with tricyclic drugs, and diplopia. She improved after i.t. MTX (10 doses). She died 4 months later. A third patient, with breast cancer, had a seizure and complained severe disturbances of vision with papilloedema and delayed VEPs. She improved after i.t. MTX (4 doses) and radiotherapy. After 3 years she is still alive. The fourth patient with breast cancer showed multiple cranial nerve palsies (VI-VII-VIII-IX-X-XI-XII) followed by severe atrophic weakness of the hands. She improved after i.t. MTX (8 doses). She died 3 years later. The last patient with breast cancer complained of headache, neck stiffness and blindness. She was treated, without benefit, with low doses of whole brain radiotherapy and died 2 months later. In this group of patients the efficacy of intrathecally administered Methotrexate (MTX) is confirmed. The treatment improves or stabilises neurological symptomatology and prolongs survival in a patients

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LEUKOSTASIS IN CENTRAL NERVOUS SYSTEM IN ADULTS WITH LEUKEMIAS AND LYMPHOMAS. MORPHOLOGICAL ASPECTS. P Nowacki, C Fryze, B Zdziarska, B Zyluk, H Grzelec, A Potemkowski, *Szczecin, Poland*

The clinical and neuropathological investigations have been done on 133 patients with acute myelogenous leukemia (AML), blasted phase of chronic myelogenous leukemia (BPCML), acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphomas of high malignancy (NHL) Leukostasis in the central nervous system vessels (CNS-L) appeared in: 48.9 % of AML, S4.8 % of BPCML, 4O % of ALL and 41.8 % of NHL. CNS-L depend on the leukocyte counts elevation, the size of CNS vessels and interactions between blasts and blasts-endothelium. It should be skewed that, irrespective of the type of the disease, in cases with leukocyte counts lower than 4OO G/l, CNS-L was observed mainly in medium-sized, thin-walled vessels in white matter, especially in the periventricular region, cerebellum, as well as in the leptomeninges, whereas the cortical microcirculation was much less involved In cases with leukocytosis above 4OO G/l all vessels were filled with blasts and neurological disorders of hyperleukocytosis were demonstrated It was found that the time needed for CNS-L appearance or disappearance was at least 2-3 days. The local abnormalities in cerebral circulation may also be important in the development of CNS-L: vessels completely filled with blasts were found near the vessels without leukostasis. CNS-L does not depend either on the course of hyperleukocytosis during disease or rapid increase of the leukocyte counts.

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MELANOMAS OF THE CNS. Muller B, Reinhard I, Krone A, Warmuth M, Brocker EM, Krauseneck P, *Dresden, Wurzburg, Bamberg, Germany.*

We report a retrospective study on 30 cases of the university hospital and viewed the literature on etiology and multi modal therapy in CNS melanoma. Epidemiology: Despite more than 1/2 of all pts with metastatic melanoma develop CNS-manifestation, only 2/3 rd of CNS melanomas are brain metastases of known systemic origin. 1/6 are of unkown origin (C-MUP), and 1/6 initially present with meningeosis melanotica. In only 1/3 of the patients with C-MUP a systemic melanoma could be identified, or manifested later. In at least 3/30 cases there were clear evidence for a primary intracranial melanoma. For patients with metastatic CNS-melanoma latency to CNS manifestation ranges from 0 to more than 10 years (3/20 pts.). Post mortem studies showed, that CNS-melanoma is accompanied in 75% by meningeosis. There is no prospective therapeutic series for brain metastases of melanoma In 1980 a retrospective series of 80 pts from MDACC/Houston suggested a better prognosis for operated pts and efficacy of radio- and chemotherapy, especially regarding long-term outcome Also in more recent studies the overall survival of operated CNS-melanomas did not improve and ranges from 7-12 months (median). Solitary brain metastases are prognostically more favourable. RT (about 13x3 Gy) seems to delay relapses, but remains to be proven prospectively Chemotherapy has only been evaluated for all metastatic melanomas. DTIC, Nitrosoureas and CDDP are the most effective drugs with response rates of 15-30%. The combination of nitrosourea, DTIC and tamoxifene seems to improve the results to about 35-50% response Since DTIC, nitrosourea and tamoxifene penetrate the BBB, this concept is reasonable for CNS-melanoma, too. We conclude that in pts with CNS-melanomas and acceptable prognosis an active antineoplastic therapy should be considered.

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CEREBRAL METASTASIS OF A RENAL CELL CARCINOMA IN A PATIENT WITHOUT RENAL CELL CARCINOMA. U Meyding-Lamadé, D Krieger, K Sartor, W Hacke. *Heidelberg, Germany.*

We report on an immunosuppressed patient without primary carcinoma developing cerebral renal cell metastasis after heart transplantation. Neurological complications after heart transplantation are mostly due to vascular complications such as prolonged pre-or intraoperative hypotension. Immunosuppressants are known to promote opportunistic infections and malignancies. A 62 year old woman presented with a several week history of fatigue, decreasing alertness and a brachiofacial hemiparesis. She had undergone heart transplantation twelve months before and was on immunosuppressants including azathioprine and cyclosporine. CT and MRI revealed multiple, space-occupying lesions with an irregular ring enhancement at the corticomedullary junction One the right frontal lobe extended through the bone extracranially. Biopsy revealed metastases of renal cell carcinoma The patient had normal kidneys. Past medical history resolved this paradox: the donor was found to have a hidden renal cell carcinoma, only detected on autopsy following transplantation. Conclusion: Tumour cells were transplanted into the recipient along with the heart We propose, the heart already harboured micrometastasis at transplantation, or a few tumour cells within the donors vasculature were not eliminated during preoperative irrigation In the immunosuppressed patient these were likely to grow.

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IMMUNOHISTOCHEMICAL EXPRESSION OF GLUTATHIONE S-TRANSFERASE (GST) AND ISOENZYMES IN 23 HUMAN ASTROCYTOMAS IS RELATED TO HISTOLOGIC TUMOUR GRADE. C Maugard-Louboutin, G Fayet, C Sagan, S Martin, D Ménégalli, Y Lajat, F Resche. *Nantes, France.*

Gst isoenzymes play an important role in cellular detoxification. Gst π expression is correlated to tumour differentiation in numerous human preneoplastic or neoplastic lesions. Few data are available on gliomas, especially for Gst μ. We studied retrospectively Gst π and μ immunohistochemical (IHC) expression in 23 untreated astrocytomas (ua) (10 grade 4, 3 grade 3, 10 low grade) obtained by brain stereotactic biopsy or surgical resections and in 4 non tumoral brains. We analysed tumour specimens for differences in staining intensity (si) and number of immunoreactive cells (nic) according to histologic grade using chi square method. Correlation between the 2 isoenzymes expression was tested with the Spearman non parametric method. Results are the following: 1) Glial tumoral cells immunostaining was observed predominantly in cytoplasm as opposed to normal astrocytes where the nucleus was stained. 2) Gst π was related to ua grade for si ($P = 0.008$) and nic ($P = 0.03$). 3) Gst μ was also related to ua grade for si ($P = 0.008$) and nic ($P = 0.008$). 4) Gst π and Gst μ expression for a single tumour was significantly correlated in most of specimens for si ($P = 0.0001$) and nic ($P = 0.0002$) independently from histologic grade. When a difference was observed, Gst π expression was predominant. Gst π and μ immunohistochemical expression was related to ua grade. These isoenzymes may markers for astrocytoma tumoral progression. Relationship between Gst π and μ isoenzymes expression and gliomas primary chemoresistance remains to be defined.

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PATTERN OF CENTRAL NERVOUS SYSTEM TUMORS IN SAUDI ARABIA. OM Koriech, K Al Moutaery, B Yaqub, S M Al Deeb *Riyadh, Saudi Arabia.*

Between 1983 and 1993, a total of 561 cases on CNS tumours were referred to Departments of Oncology and Neuroscience's. All but 14 brain stem tumours were histologically confirmed. The overall median age was 33 years and the M:F ratio was 2:1. The overall median age was 33 years and the M:F ratio was 2: 1. Gliomas (including oligodendrogliomas) were present in 234 cases (42 %), Pituitary tumours in 79 cases (14 %), Medulloblastomas in 59 (11 %), Ependymomas in 27 (5 %), Malignant meningioma in 20 (4 %), Sympathetic system tumours in 33 (6) Lymphoma in 17, (3 %), Pinealomas in 11 (2 %) and Others in 81 cases). The histological localization, histological grading and types of the gliomas, pituitary adenomas and sympathetic tumours will be presented. All lymphomas

were AIDS unrelated. The clinical presentation was mostly due to increased intracranial tension, reflecting the frequently advanced stage due to delay in presentation. This was followed by focal neurological deficit and or epilepsy, depending on the site of the lesion. The clinical response to radiotherapy and the follow up was extremely variable.

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DTPA-OCTREOTIDE-SPECT EXAMINATIONS TO EVALUATE TrE SOMATOSTATIN RECEPTOR STATUS IN BRAIN TUMORS. K Maier-Hauff, R Jochens, A Wolters, S Venz, M Cordes, *Berlin, Germany*

The aim of this study was to quantify the [^{111}In]-DTPA- Octreotide-uptake in brain tumours by SPECT. We examined 10 patients. (age 21 to 62 years) with brain tumours. The diagnosis was made by MRI and confirmed by histological examination in all patients. SPECT examinations were performed 4 h after administration of appr. 200 MBq [^{111}In]-DTPA-Octreotide. The results were standardized by a calibrating curve. 11 patients. with no brain tumors served as a control group. Two. with pituitary adenomas and four. with meningiomas showed a significantly increased uptake of the tracer ($p<0.001$ vs. control group). One patient with craniopharyngeoma and one with ependymoma also had an increased uptake, whereas one with primary CNS lymphoma and one glioblastoma showed no increased uptake compared with the results of the control group. We conclude that [^{111}In]-DTPA-Octreotide-SPECT is a useful method for the evaluation of the somatostatin receptor status in brain tumours. The calculation of uptake values represents an objective procedure for the quantification of the radioligand binding in neoplastic tissue. However, these preliminary data do not allow differentiation among gliomas.

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Y CHROMOSOME REPLACED BY X CHROMOSOME IN BRAIN TUMOR. BK Hecht, M Chatel, P Gaudray, C Turc-Carel, J Gioanni, N Ayraud, F Hecht. *Nice, France*

Cloned loss of the Y chromosome from diverse types of tumours and benign tissues is well known and not at all understood. We cultured cells from 30 high-grade malignant gliomas 23 males and 7 females) and documented clones with Y loss in 14 (52%) of the specimens from the males. Two unforeseen observations were made. First, clones with Y chromosome rearrangements (deletion, inversion or translocation) were found in association with Y instability and Y loss. Second, clones with XX but no Y chromosome also occurred in tumours from male patients. The XX clones were easily detected in some tumours but in other tumours were only suggested by a single karyotype. Using fluorescent in situ hybridization (FISH) and DNA alpha satellite and painting probes for the identification of the sex chromosomes, we detected small XX clones accounting for less than 5% of the total cells. No XXY cells were seen. The sequence of sex chromosome changes therefore appears to be: Y rearrangement leading to Y loss followed by X isodisomy with a second X replacing the Y chromosome. This sequence of events had not been previously suspected in malignant gliomas.

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CYTOKINES AND ADHESION MOLECULES PRODUCTION IN PATIENTS with SCLEROSIS TREATED WITH ANTI-CD4 MONOCLONAL ANTIBODIES. L Rumbach, E Racadot, M Bataillard, M Billot, J Pariset, J Wijdenes. *Besançon, France.*

Twenty-one MS patients were treated with a murine anti-T CD4 monoclonal antibody (mAb) for 10 days. Cytokines and adhesion molecules were studied before, after the 10 days treatment and 3 months later. The 21 patients were in an "active" form : 5 had a relapsing remitting, 16 a progressive form. In each patient, cell counts (CD3, CD4, CD8, CD20, CD56, CD45RA, CD45RO), anti-CD4 mAb levels, soluble(s) CD4 and CD8 antigens, sTNF receptor, INFγ, IL1⟨, IL6, ICAM-1, sE-Selectin were determined in blood, sometimes in CSF. Two hours after the 1st infusion, we observed a dramatic decrease in all lymphocyte subsets ; CD3 and CD4 cells remained low until the 3rd month. INF⟨, IL1⟨ sCD8, sCD4, ICAM-1, sE-Selectin levels did not change during treatment. TNF◊ and IL6 levels increased notably after the 1st infusion ; after 24 hours normal values were observed. CSF levels were not modified, as sTNF◊ R. Mechanisms responsible for the TNF◊ and IL6 increase are not elucidated ; they may be responsive for the clinical side effects as they only occurred in patients with secondary effects. In vitro capacity of secretion are under study to determine anti-T CD4 mAb effects. Elucidation of these mechanisms may prove to be beneficial in the intervention of symptoms in MS and in other immunological treatment.

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ANTIGANGLIOSIDE ANTBODIES EN SERA OF MS PATIENTS. Rio J Montalban AL Fernandez, I Duran, M Tintoré, I Galan, N Acarin, *Barcelona, Spain.*

Multiple sclerosis (MS) is an autoimmune disorder, but an unique antigen has not been found. We tried to study antibodies against gangliosides (AGA) in sera of MS patients and to investigate relationships between AGA, subtypes of MS differentiated by the clinical course into relapsing remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS). Eighty two patients (50 females, mean age 35.5±10.5 years) with MS who fulfilled the criteria of clinically definite disease (62.2 % RRMS, 15.2 % SPMS, 23.6% PPMS), 80 patients with systemic lupus erythematosus and 56 healthy controls were studied. A modification of previously described ELISA techniques was used to estimate serum IgG and IgM antibodies anti-GMl and anti-GDla., 45% of the patients had high levels of AGA. Anti-GMl was found in 40% of MS patients and anti-GDla in 30.5%. IgG was the isotype more commonly found. A correlation between presence of AGA and progressive disease ($p=0.02$) and between anti-GDla and PPMS ($p=0.003$) was found. We conclude that the incidence of AGA in MS patients is elevated. In contrast with the results of others a strong correlation between AGA and progressive disease is showed in our study.

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COMPREHENSIVE NEUROCOGNITIVE ASSESSMENT IN MULTIPLE SCLEROSIS. A LONGITUDINAL STUDY. S Rapaport, E Kott, M Huberman, D Shechter, *Kfar Saba, Israel*

Cognitive linguistic impairment occurs in MS patients. The objective of the following study was to assess cognitive functions over 3 years. A motor free battery consisting of 15 neuropsychological measures whose administration in a two hour limit, does neither rely on fine visual acuity, motor speed nor motor coordination was administered. The tests evaluated speed on information processing, sustained attentional skills, memory functions, visual spatial functions, language, higher level reasoning skills and affective state. 34 patients with definite MS were tested. Results: Memory disturbances were the most. consistent impairment. Impaired verbal short term memory, difficulties in tracking and recording verbal information and consequently disturbed short term recall ability. The same patients also performed poorly on attentional measures. Long term verbal memory skills appear to remain intact. The follow up retest, data 12 and 24 months generated, similar findings indicating a consistent pattern of memory impairment over time.

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CRANIAL PLUS SPINAL CORD MR EXAMINATION IN MS: RESULTS OF 26 CASES. R Karabudak, M Kilinc, S Boyacigil, A Cila. *Ankara, Turkey.*

The spinal form is probably the most common variety of Multiple Sclerosis (MS). Prior to MRI, no method existed for visualisation of spinal cord lesions. MRI is proved to be more sensitive than EP and CSF studies. The aim of the present study was to evaluate whether brain and the spinal MRI together could provide further support for the correlation between the location of the plaques and the degree of the clinical disability. We carried out a combined cranial and spinal MRI examination study on 26 clinically definite MS patients. It was possible to demonstrate intrinsic spinal plaques reliably in the majority of patients. MRI was positive for the presence of additional plaques within the spinal cord in 15 of 26 patients. Most lesions detected in the cord were found in the cervical region (12 of 15 cases). MRI correlations between the location and the clinical disability were difficult to establish. However, the relation was categorised " certain n in 42%. The EDSS scores of the spinal cord MRI (+) patients were significantly high. Spinal MRI may provide additional evidence for dissemination, before clinical signs of dissemination, which may take many years, occur.

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INEVITABLE BACKWARD FALLS IN A WOMAN WITH PROTRACTED PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY. JM Polo, S Setien, R Sanchez, J Pascual, J Figols, A Zubimendi, J Berciano. *Santander, Spain.*

We report on the case of a patient with prolonged progressive multifocal leukoencephalopathy (PML), manifested for 4 years only with recurrent unavoidable falls. Most patients with PML show relentless subacute and usually fatal clinical progression, but deviations from the typical picture have been reported. These deviations may have theoretical and practical importance. A 49-year-old woman presented in May 1988, with recurrent backward falls, 8 years after renal transplantation. Even minor back-directed stimulus caused inevitable falls, apparently due to loss of postural reflexes in that direction. EEGand somatosensory evoked potentials were normal, and MRI showed multiple small lesions of increased signal intensity confined to white matter in both hemispheres. In spite of several therapeutic attempts her condition remained stable, seriously disturbing her everyday life. In 1991, a second MRI revealed no changes. By July 1992, she had developped visual impairment, progressing to almost complete blindness. Repeated MRI showed an increase in previous lesions with extensive parieto-occipital leukoencephalopathy. Her condition deteriorated in the last 5 months of life when she developped progressive rightsided hemiparesis and left weakness, speech difficulties progressing to aphasia, and finally increasing mental impairment. The brain showed the typical features of PML. The present case illustrates the variability of PML which is another cause of cryptogenic falls in middle-aged women.

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INCREASED MIXED LYMPHOCYTE RESPONSE OF CEREBROSPINAL FLUID T-CELLS TO AUTOLOGUS BLOOD T-CELLS IN MULTIPLE SCLEROSIS. ZG Nadareishvili. *Tbilisi; Republic of Georgia.*

Thirty-two patients with clinically active multiple sclerosis (MS) and 14 healthy persons (controls) of age 16-42 years were studied. Mixed lymphocyte reaction (MLR) between the cerebrospinal fluid (CSF) and autologous blood T-Cells was performed in 2 variants: 1. CSF T-Cells stimulators and blood T-Cells responders; 2. blood T-Cells stimulators and CSF T-Cells responders. Stimulators T-Cells were treated with Mitomycin C. CSF and blood T-Cells were cultured for 7 days and during the last 18h H-thymidine was added. MLR values were expressed as delta counts per minute (delta cpm). MLR was nonsignificantly increased in MS compared with control in the first variant. A significantly ($p<0.01$) increase of MLR was found in the second variant in patients with MS (6000different800 delta cpm) when compared with healthy persons (2700different800 delta cpm). Increased mixed lymphocyte response of CSF T-Cells is a result of both a high HLA-DR expression at the stimulator cells surface and less ability of responder cells in recognizing self antigens.

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DEVIC'S DISEASE VERSUS MULTIPLE SCLEROSIS. R Massot, R Marés, F Gallecho, C Richart. *Tarragona, Spain*

Since Devic's original description of the neuromyelitis optica, exactly a century ago, controversy has existed as to its independence with regard to multiple sclerosis. We present a case of a 16 year-old-woman, who developed bilateral optic neuritis and cervical myelopathy, throughout a year. Initial symptoms were severe loss of sight which she did not regain. Three subsequent relapses with tetraparesis improved significantly with prednison. Clinical findings and several magnetic resonance (MR) failed to reveal any cortical, brainstem or cerebellum lesion. Spinal MR showed a pronounced enlargement and cavitation of the cervical and upper thoracic cord. One CSF gave 160 leukocytes, 190 mg% protein; two IgG and immunoelectrophoresis were normal. Several characteristics of this patient are described in Devic' 8 disease: 1/ Signs were severe and limited to the optic nerve and spinal cord. 2/ MR showed a dilation with tumour-like appearance and cavitation of the cervicodorsal cord. 3/ CSF with important pleocytosis, high protein and normal immunoelectrophoresis. However, the several relapses with good clinical and MR recovery, point to a demyelinative lesion without necrosis, and these features suggests a multiple sclerosis. These results underline the overlapping and close relationship between the two disorders. The etiologic knowledge will resolve this nosologic challenge.

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VITAMIN B12 LEVEL IN THE SERUM IN MULTIPLE SCLEROSIS. MA Hernandez, MR Garcia JN Lorenzo, C Leon, M Muros, J Togores, *Tenerife Spain*

A relation between multiple sclerosis (MS) and vitamin B12 deficiency has been described recently. The significance of this observation remains unclear although demyelination is a prominent feature of both conditions. Serum vitamin B12 level was determined in 37 patients, 20 females and 17 males, mean age 37 years (range 23-64 years). 37 patients with clinically definite MS (Poser criteria1983). Patients who were taking steroids, immunosuppresive therapy or vitamin B12 were not included. The median serum vitamin B12 level was 634 ± 299 pg/ml with a range 217 ± 1608 pg/ml. No patients with MS had an abnormal serum vitamin B12 level. Three patients (8%) had a level between 200-300 pg/ml. In the relapsing-remitting forms (22 patients) the median serum vitamin B12 level was 676 ± 357pg/ml and in the remitting-progressive was 583 ± 192 pg/ml. In the males with MS the median serum vitamin B12 level was 561 ± 205 pg/m and the females was 696 ± 349 pg/m. In conclusion, we have not found an association between clinically definite MS and vitamin B12 deficiency. Further investigations will be necessary to understand the possible relation between MS and vitamin B12 deficiency

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COGNITIVE IMPAIRMENT AND MRI FINDINGS IN MULTIPLE SCLEROSIS. K Kutluk, G A Damlacik, B Tekinsoy, O Obuz, B Baklan,E Idiman, K Genc, *Izmir,Turkey*

The aim of this study is to investigate the correlation of cognitive defects and quantitative analysis of MRI findings in Multiple Sclerosis. Neuropsychological tests were performed in 50 definite MS patients and 30 healthy individuals. The main functions studied were orientation, mental control, language, verbal and visual memory, visuospatial skills and abstracting ability. Quantitative MRI measurements were done mainly to assess periventricular and discrete lesions, confluence, atrophy of corpus callosum, ventricular index, total lesion score, width of IIIrd. ventricle. Verbal and visual memory defects were common. There was no impairment in abstraction, naming, visuospatial perception. The severity of the cognitive defects did not significantly correlate with the Kurtzke Expended Disability Status Scale. Total lesion scores and linear measurements of IIIrd ventricle were higher in patients with cognitive dysfunction,but this was nonsignificant. No significant changes were foun in the measurements of corpus callosum,ventricular index and ratio of signal intensities. The result of the studies trying to correlate the cognitive impairment and MRI findings in MS patients are controversial This study shows that there may not be a consistent relation between the cognitive defects and MRI findings although a quantitative system is used to measure the lesion score.

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NITRIC OXIDE SYNTHASE IN EXPERIMENTAL AUTOIMMUNE NEURITIS (EAN) AND EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE). J Zielasek, S Jung, B Schmidt, R Gold, FY Liew, KV Toyka, HP Hartung. *Wurzburg, Germany; London, UK*

The cytokine-inducible form of nitric oxide synthase (iNOS) has been implicated in the pathogenesis of EAE. We studied the effects of the in vivo administration of NOS inhibitors in Lewis rats with EAE or EAN. Treatment with N-monomethylarginine (NMMA, 2x100 mg/kg p.o.) led to a significant attenuation of adoptive-transfer (AT)-EAN (d 5 mean score + SD NMMA 4.7±1.1, n=7; control 6.9+0.5, n=6; $p<0.05$; score from 1=mild disease to 9=severe disease). Other inhibitors (N-nitroarginine, nitro-arginine-methyl ester) had little or no effects in AT-EAN. In myelin-EAN, NMMA had no reproducible effect. None of the inhibitors had significant effects on myelin basic protein (MBP)-induced EAE or AT-EAE. However, aminoguanidine, a selective inhibitor of iNOS, significantly enhanced MBP-EAE (d 13 mean score+SD AG 6.2+2.2; control 3.8+2.3; n=6 per group, $p<0.05$), but not myelin-EAN. By immunohistology, we found iNOS immunoreactivity in the inflammatory infiltrates of the central nervous system of rats with EAE and the peripheral nervous system of rats with EAN. Thus, the administration of NOS inhibitors may modify the disease course of EAE and EAN, but in a complex and, in part, paradoxical way.

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MAJOR HISTOCOMPATIBILITY COMPLEX CLASS-I AND CLASS-II ANTIGENS IN TURKISH PATIENTS WITH MULTIPLE SCLEROSIS. E Idiman. Z Gulay, B Baklan, K Genc, G Damlacik, N Yulug. *Izmir, Turkey*

Various studies have reported the importance of genetic factors in multiple sclerosis (MS). Particularly, the major histocompatibility complex coding for HLA-A, B, C (Class I) and D (Class II) antigens has been positively associated with MS. The strongest association in Caucasians is the HLA-DR2 allele and MS severity has been associated with this allele. But in particular ethnic groups, there have been reports of HLA-MS associations with other than DR2, or of no association. We studied the HLA types of 100 unrelated Turkish MS patients, 69 women and 31 men, mean age: 33.2 years. The control group for the HLA typing consisted of 50 healthy kidney donors. 94 patients were definite and 6 patients were probably MS. Patients were classified into 3 groups: relapsing-remitting, secondary progressive, and primarily progressive. In 10 patients EDSS score was more than 5 and in 90 patients EDSS score was 5 or less than 5. Patients and controls were typed for HLA-A, B, DR and DQ antigens by the standard lymphocytotoxicity assay. In MS patients. we found an association with HLA-A1 (P<0.02), HLA-B8 (P<0.01), and HLA-DR2 (P<0.01). In our study the highest relative risk was associated with HLA-B8.In relapsing-remitting group (83 patients) an association with HLA-B16, B22 and DR4 was highly significant when compared with relapsing-remitting and progressive group. In patients those of EDSS score were high an association with HLA-A26 and HLAB59 found. In Caucasians, population studies have demonstrated an association with HLA-A3, B7 and especially DR. We found an association with HLA-DR, but not with A3

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CHARACTERISTICS OF HEADACHE IN PATIENTS WITH EPILEPSY. D Zekin, D Baltadjiev, K Sabev; *Sofia, Bulgaria* .

Purpose of the present study is to assess the diagnostic significance of the headache characteristics in patients with epilepsy. 8O patients (44 men aged 13 to 7O years, and 44 women aged 15 to 65 years) with clinically verified epilepsy were examined for headache attacks. Each patient received a neurological examination and an EEG screening with hyperventilation and photostimulation. Headache was established in 28 women (63.6%) and 14 men (38.8%). 23 patients (28.75%) with headache had generalized seizures, 12 patients (15%) had partial seizures. The results were analyzed with mathematical methods for measuring the information value of a given symptom. The obtained results showed the diagnostic significance of headache, especially in epilepsy with partial seizures and vegetative symptomatics. This statement is of great importance for the early diagnosis and correct treatment of epilepsy patients.

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THE PREVALENCE OF MIGRAINE IN HONG KONG: A POPULATION-BASED TELEPHONE STUDY. KS Wong, TW Wong, TS Yu, R Kay. *Shatin, Hong Kong.*

We performed a population-based random telephone study of the prevalence of migraine in Hong Kong. In 1992, 2240 (85.5%) households were successfully interviewed. There were 372 patients with more than two attacks of headache in the past twelve months. Their headaches were then classified according to the International Headache Society criteria. The prevalence of migraine was 1.02% (95% confidence interval: 0.79 - 1.25%). Migraine with aura, Migraine without aura and Migraine disorder not fulfilling IHS criteria represent 31%, 12% and 57% respectively. The prevalence rate for female and male were 12.66/1000 and 5/1000 respectively (2.5: 1). Most of the patients described their attacks as 1 to 2 attacks per month (52%), moderate (63%), unilateral (61%) and throbbing (51%). The main precipitating factors were mental stress (81%), physical exertion (65%), menstruation (49%) and weather (41%). Phonophobia (53%) was the commonest associated symptoms but nausea (45%) and photophobia (42%) were also very common. Our study confirmed that Chinese has a very low prevalence of migraine but the clinical characteristics are quite similar to other countries.

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NEUROLOGICAL COMPLICATIONS OF PRIMARY BILIARY CIRRHOSIS. A prospective clinical study. A Joutel, R Poupon, P Giral, MG Bousser, E Roullet, *Paris, France*

Several neurological disorders of unknown mechanism have been reported in patients with primary biliary cirrhosis (PBC), including peripheral neuropathy, progressive ophthalmoplegia, transverse myelitis and multiple sclerosis (MS). However neurologic involvement in PBC has not been the subject of any systematic evaluation. The goals of this study were to estimate the frequency of neurological manifestations in PBC and to assess their relation to the Sjögren's syndrome present in up to 90 % of patients with PBC. Twenty-five patients were randomly selected from a French PBC cohort and examined by a neurologist. They were asked for neurological and sicca symptoms and a detailed history was taken. All patients were women aged 35 to 75 years (mean: 53.8). Seventeen patients (68 %) had xerostomia, xerophtalmia, or both; 14 patients (56%) had neurological symptoms or signs (sicca symptoms (SS): 12/14), and 11 had none (SS: 5/11). Eight patients, all with SS, had distal symmetric lower limb sensory symptoms and signs consistent with peripheral neuropathy; 4 other patients had isolated neurological Signs (absent tendon reflexes, distal sensory loss, ptosis) and 2 had sensory symptoms only. In addition, 2 patients without neurological manifestations had a first-degree relative with MS. In this purely clinical study we found a high prevalence of neurological manifestations in PBC, which may be related to the presence of the Sjögren's syndrome. This unsuspected finding needs further evaluation which is in progress.

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APOMORPHINE EFFECTS ON MIDDLE CEREBRAL ARTERY FLOW VELOCITIES IN MIGRAINE WITHOUT AURA. C Roberti, EM Zanette, F Chiarotti, P Barbanti, L Brusa, R Cerbo. *Rome, Italy*

Aim of this study was to investigate the effects of apomorphine on the middle cerebral artery (MCA) flow velocity, in patients suffering from migraine without aura. For this purpose a transcranial Doppler (TCD) was performed in 22 migraine patients (16 F, 6 M, mean age 33 yrs) and 20 controls (10 F,10 M, mean age 28 yrs), and systolic, diastolic, mean velocity and pulsatility index were recorded on the MCAs in basal conditions and every 10 minutes for 1 hour after the administration of 0.5 mg of apomorphine s.c. Blood pressure, heart rate and pC02 were also recorded. The test was performed twice, with and without pretreatment with domperidon, a blocker of the peripheral dopamine receptors. No variations of blood pressure, heart rate and pC02 were found. The values of flow velocity were in the normal range, both in migraine patients and in control subjects, during the test. However the ANOVA showed a significant increase of diastolic and mean velocity and a significant decrease of pulsatility index both in patients and controls, with and without domperidon pre-treatment. These data suggest that apomorphine, administered subcutaneously, with or without domperidon pretreatment, determines a vasodilatation both in migraine patients and controls, but none of the subjects complained of headache.

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THE USE OF TRICYCLIC ANTIDEPRESSANTS IN THE INITIAL CONTROL OF DRUG INDUCED REBOUND HEADACHE. A Prusinski, *Lodz, Poland*

Drug induced rebound headache constitutes an important problem in clinical practice, and the treatment of which is difficult. The condition consists of everyday persistent headaches that appear after longer uncontrolled use of simple analgesics and/or ergotamine in patients with migraine or tension headache. The basic procedure in this condition is the discontinuation of the drugs used. However the discontinuation of the analgesic produces the increase in head pain, accompanied by the withdrawal symptoms. This may prompt significant drop out during the initial phase. Effective additional treatment during this phase is therefore very important. Different drugs -amitriptyline imipramine, dihydroergotamine, methylergonovine etc. -were proposed. This study presents the efficacy of opipramol (anxiolytic and antidepressant) in the treatment of drug rebound headache. 17 patients (all women, mean age -43.2 yrs), with unequivocal diagnosis of drug induced headache, persisted for about 2 years, were treated by the author. The patients took from 3 to 10 doses of simple analgesics. The current treatment consisted of the institution of opipramol for 7 days (orally; the doses increased from 25 mg daily -to 50 mg t.i.d.), and next -of withdrawal the analgesic with the continuation of opipramol treatment for 6 -8 weeks. In 9 patients the headache disappeared, in 5 there was no effect of opipramol (which was connected with the reluctance to the discontinuation of the painkillers), and the rest 3 patients resigned from the treatment proposed.

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SPONTANEOUS INTRACRANIAL HYPOTENSION AND VI CRANIAL NERVE PALSY. M Pondal, R Canton, Erodriguez, J Dominigo. *Madrid, Spain.*

Spontaneous intracranial hypotension (SIH), is a reported syndrome of spontaneously occurring postural headache associated with low CSF pressure. We present two patients with SIH. Both cases in addition to the postural headache, neck stiffness, nausea and vomiting, they also presented, after the onset, diplopia and VI cranial nerve palsy, bilateral in one of them. In the two cases were demonstrated a low opening pressure in lumbar puncture, a CSF leakage in a radionuclide tomographic cisternography by SPECT and a pachymeningeal enhancement in the MRI. An extensive diagnostic workup, including brain angiography and CSF examination, excluded other possible condition. The headache is a consequence of the low CSF pressure producing displacement of pain-sensitive structures, but the other symptoms are presumably from hydrostatic changes among intracranial fluid compartments that occur at low CSF pressure. In summary, the appearance of a VI cranial nerve palsy besides the cardinals symptoms of SIH, don't exclude the diagnostic.

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SUCCESSFUL PROPHYLAXIS OF SEVERE BASILAR MIGRAINE WITH NIMODIPINE. J M Polo, J Pascual and J Berciano. *Santander, Spain.*

objective. To determine the usefulness of nimodipine for preventing severe basilar migraine. Background. The treatment of basilar migraine is controversial; conventional anti-migraine drugs may be of little use or even contra-indicated. Patients Methods. Six women and one man, aged 12-27 years, with basilar migraine according to International Headache Society criteria were treated with oral nimodipine. All the patients suffered from recurrent episodes of loss of consciousness with or without accompanying prodromal symptoms. Three patients had been unsuccessfully treated with a variable combination of conventional anti-migraine drugs. Daily dosage of nimodipine ranged from 9O to 18O mg. in three or four divided doses. Results. All seven patients experienced an immediate cessation of neurological attacks shortly after oral nimodipine administration, and this responsc remained as long as the treatment was maintained. In fact, in three patients migraine became nimodipine-dependent, attacks recurring when the drug was temporarily interrupted or decreased. In one 1 8-year-old woman two prolonged coma episodes, also related to drug interruption, resolved with intravenous nimodipine administration Conclusions. our results suggest that nimodipine is a useful drug for treating severe basilar migraine attacks. Further controlled studies are needed to confirm these seemingly satisfactory results.

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MIGRAINE AND TENSION TYPE HEADACHES. Pereira Monteino JM and X, *Porto, Portugal.*

In order to establish a score for classification of primary headaches based on Amman t of points rather than the criteria of the International Headache Society (IHS), we performed a stepwise logistic regression analysis of a 2008 population-based study at Oporto (Portugal) in May 1992. In our series we obtained a prevalence of 8.8% for migraine, 62.5% for tension-type headaches, for combined migraine and tension headache 12.1%, and 5.3% for other headaches. Based on the results of stepwise logistic regression, we built a score ranging from zero to eleven points (unilateral=1, pulsating=1, aggravated by exercise=1, severe=1, moderate=1/2, nausea=3, photophobia=2, phonophobia=1, duration superior to 4 hours=1/2 and frequency < 120 per year=1/2). Scores from 0 to 4 are tension-type headaches and scores from 6 to 11 are migraine; scores 4.5, 5 and 5.5 are intermediate forms corresponding to a combination of two types of primary headaches. We define four levels of disability O (none), I (mild), Il (moderate) and lll (severe) based on severity and frequency. Different levels of disability imply different therapeutic modalities (O and I -symptomatic therapy and Il,lll-prophylactic therapy). In levels II and lll they are: 97.6% of chronic-TTH, 52.9% of migraine with aura, 39.6% of migraine without aura and 17.4% of episodic-TTH. Using our score we found 92% in concordance with IHS classification in primary headaches.

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ASSOCIATION OF MIGRAINE WITH0UT AURA WITH THE HLA-DQA1*0301 ALLELE. J Pardo, A Carroacedo, F Barros, M Lema, J Castillo, M Noya, *Santiago de Compostela, Spain*

The influence of immunologic factors in migraine has been suggested. Most of studies are limited to the investigation of class I specificities with conventional techniques and association with the HLA system was not found. We thus studied DNA polymorphisms to evaluate the possible relationship between migraine and class II HLA molecules. Thirty-five Galician patients (NW Spain) suffering migraine with aura, 50 without aura and 178 Galician healthy people underwent the determination of HLA-DQAl by heteroduplex analysis using polymerase chain reaction followed by SDS-PAGE in miniaturized non-denaturing gels and dot-blot with ASO probes. Calculation of allele and genotype frequencies, Hardy-Weinberg equilibrium, Woolf index and comparison of population studies by means of chi-square test was made in each of these 3 groups. RESULTS: We have found an association between migraine without aura and the HLA-DQAl*0301 allele ($p<0.01$). There were no difference between the group of patients presenting migraine with aura and the control sample ($p=0.5$). We conclude that the association between migraine without aura and the HLA-DQAl*0301 allele indicates an implication of class II HLA molecules (chromosome 6) in this disorder and also a different immunogenetic basis for migraine with and without aura.

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ALCOI 1992 QUESTIONNAIRE: A VALIDATION Of A QUESTIONNAIRE FOR HEADACHE. L Galiano, A Melchor, I Montiel, R Martin, R Falip, J Matias Guiu. *Alicante; Spain*

Taking into account the non existence of a validated questionnaire in Spain, we performed a validation of a self-administered questionnaire in order to conduct a later study of the prevalence of headache in the general population. All headache disorders were classified according to the operational diagnostic criteria of the IHS. The questionnaire consisted of fifteen multiple-choice questions about headache frequency, duration, location, severity, character of pain, associated symptoms, etc. Thirty-four people accepted to participate in the study, 17 headache patients and 17 healthy volunteers. 9 (52.9%) with migraine without aura (MOS), 5 (29.4%) tension-type headache (TTH) and 3 (17.7%) cluster headache (CH). Firstly, each subject was invited to answer the questionnaire and later to a general physical and neurological examination focusing on headache by a neurologist expert on headache. The mean age was 37,2±8,6 for patients and 31,4±6,3 for controls. We obtained a sensitivity of 82% and a specificity of 65%, a positive and negative predictive values of 70% and 79% and a Kappa index of 0.48, for all headache disorders, being of 100% and 94%, 90%, 90% and 0.71 respectively for MOS, 100% and 100%, 100%, 100% and 1 for CH and 40% and 71%, 29%, 80% and 0.10 for TTH. Our results confirm that a self-administered questionnaire is not a satisfactory tool in diagnosing headache disorders, according to the IHS criteria.

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INTERMITTENT CEREBRAL DISTURBANCES WITH HIGH DOSES OF SUMATRIPTAN. TM Kloss, M Keidel, M Jacob, HC Diener, *Essen, Germany*

Sumatriptan is a selective SHT-1 agonist for the treatment of cluster and migraine attacks. It leads to vasoconstriction of intracranial blood vessels. We report a 67-year old women suffering from migraine with aura, chronic renal failure, mild hypertension and diabetes mellitus, who developed cortical visual symptoms and was treated with high doses of sumatriptan over 4 weeks for presumed migraine aura. Sumatriptan dosage was 300 mg/d for 1 week, orally, followed by subcutaneous injections of 6 mg/d for another 3 weeks. Under therapy intermittent hemianopsia, disorientation, parietal lobe signs, disturbances of word-finding and seizures developed. Cranial MRI showed a parietal and occipital edema in the left hemisphere; also, disturbed regional cerebral perfusion was shown by SPECT and was normalized after injection of acetazolamide. The patient recovered completely after sumatriptan was discontinued. In the following six months the patient showed no CNS signs or symptoms. It is most likely, that the early symptoms were due to an incipient cerebral ischemia. Aura symptoms may be triggered by cerebral ischemia. The treatment of sumatriptan in a patient with contraindications and in an inadequate dose may have worsen cortical perfusion. Since the principal mechanism sumatriptan clearance is by metabolism and studies on sumatriptan in renal failure it can not be decided whether the pathophysiological process was triggered in this case by sumatriptan accumulation or by an interaction of the drug with vascular risk factors.

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SPECT AND EEG ABNORMALITIES IN MIGRAINE. F Idiman, B Baklan, H Durak, E Idman, V Ozturk, E Metin, M Yilmaz, *Izmir, Turkey.*

Migraine is a trigemino-vascular system disorder. However, it is not known whether migraine is primarily a perivascular or a neurogenic in-

flammation. The studies in this subject are increasing. In this study, we wanted to investigate neuronal dysfunction in migraine by Tc99m-HMPAO brain SPECT and topographic EEG mapping during ictal and interictal periods. We studied 40 migrain patients (27 females, 13 males) during the interictal period and 10 of 40 were also studied during the ictal period. In the interictal period, both SPECT -and topographic EEG mapping abnormalities reached 60 %. The most common SPECT abnormality was hypoperfusion over the posterior regions (75 %). Topographic EEG mapping studies showed slow wave abnormalities (88) and lateralisation of alpha frequency band power (56 %). In the ictal period, all of the 10 patients (100 %) demonstrated both SPECT and topographic EEG mapping abnormalities. Most of the previous literature studying interictal EEG or SPECT showed normal findings, whereas ictal findings were positive. We demonstrated that interictal abnormalities are evident in the majority of patients. Our findings indicate that migraine is not only a paroxysmal, but also a chronic disorder.

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IS OPHTHALMOPLEGIC MIGRAINE A MIGRAINE RELATED DISORDER. JM Gerard, R Bouton, D Decamps, AG Herbaut, F Delecluse, M Cavenaile, L Divano. *Mons, Belgium*

Introduction: Ophthalmoplegic migraine is a rare cause of a third nerve palsy. We present a case whose radiological and therapeutic features are unusual for the diagnosis of migraine.
Case report: A 12-year-old boy had sudden left side headache. Three days later he experienced left ptosis and diplopia. The patient had suffered two similar episodes in the six previous years. Subcutaneous injection on Sumatriptan had no effect on both migraine and ophthalmoplegia. The condition resolved in eight weeks. The brain CT scan and the left internal carotid angiography were normal. Biology and spinal fluid were normal. (Gd -DTPA) Magnetic resonance demonstrated nodular enhancement at the origin of the left third nerve in the interpeduncular cistern. Follow up demonstrated complete resolution of this enhancement. Discussion: The clinical history and evaluation of our patient is consistent with the diagnosis of ophtalmoplegic migraine. An enhanced nodular lesion of the third nerve has been previously reported by Mark et al (1). This is the first report showing that the enhancement with gadolinium resolved concomitantly with the clinical improvement. Nevertheless, the nodular lesion of the third nerve was persistent. The significance of this nodular aspect as well as the enhancement is still unclear. The regression of this enhancement and the unresponsiveness after the injection of Sumatriptan may suggest that the ophtalmoplegic migraine has a different physiopathology when compared to other types of migraine.

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COMPARISON OF SUMATRIPTAN WITH THE USUAL ACUTE TREATMENTS OF MIGRAINE. G Chazot, F Boureau, J Emile, L Bertin, H d'Allens. *Lyon, Paris & Angers, France.*

A series of 246 migraineurs (IHS definition, 1 to 6 severe attacks per month) were randomised into a multicenter, cross-over study comparing sc. sumatriptan 6 mg administered by auto-injector (SUM) with the usual acute migraine (UTs). Patients were treated with either SUM or with UTs prescribed by their physician for 2 months or up to 12 attacks, and then crossed-over to the alternative treatment for the same duration. UTs were: analgesics (including combinations): 49%; ergotamine: 24%; NSAIs: 19%; DHE: 7%. Rescue medication was allowed 2 hours after the first dose. Headache was assessed on a 4-point self-rating scale (0: none, 1: mild, 2: moderate, 3: severe). Other symptoms were assessed as present or absent. Quality of life (QoL) was assessed before the study and at the end of each period using a validated migraine-specific questionnaire. 217 patients were eligible for the cross-over analysis. At 2 hours post-dosing, an average of 78% of attacks per patient were successfully relieved (3/2(1/0) by SUM, compared with 34% for UTs ($p<0.001$) and 63% of attacks per patient were completely relieved (grade 0) by SUM compared with 15% for UTs ($p<0.001$). SUM treated patients used rescue treatment for 19% of their attacks, compared to 59% for UTs ($p=0.001$). Results for patient's preference were: SUM: 85%, UTs: 10%, no preference: 5% ($p<0.001$). SUM was significantly superior to UTs for all other efficacy end-points ($p<0.001$). QoL improvement was 3 times higher in SUM treated patients than in UTs treated patients ($p<0.0001$). Tolerability of both treatments was good. In patients with severe migraine attacks, subcutaneous sumatriptan is superior to the usual acute treatments for both the relief of all migraine symptoms and the improvement of quality of life.

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HEADACHE IN TRANSIENT ISCHEMIC ATTACKS (TIAS). JM Ferro, I Costa, *Lisboa, Portugal.*

Method: In a hospital-based prospective stroke database the presence and location of headache occurring during TIA were recorded. Results: 59, out of 205 registered TIAs, reported headache during the neurological event. The more frequent localization of the headache were diffuse 9; bifrontal 7; bioccipital 2; hemicranial ipsilateral 5; hemicranial contralateral 5. Headache location had no significant relation with the affected vascular territory. Age, sex, risk factors, duration of the TIA, mechanism of the TIA (cardioembolic, artery-to-artery embolism, large vessel occlusion, perforator disease), presence of arterial stenosis, infarct detected by CT, clinical symptoms and vascular territory were similar in TIA patients with and without headache. The only significant difference found was a lower proportion (16%) of current smokers among TIA subjects without headache (28% vs 12%; CI = 27%-4%). Conclusions: The presence and location of headache during a TIA cannot be satisfactorily explained by the characteristics of the cerebrovascular event or the underlying pathology. Smoking may decrease the likelihood of headache during a TIA.

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EVENT-RELATED POTENTIALS (ERPs) IN MIGRAINE PATIENTS. R Cerbo, F Carletto, A Pietrangeli, T Catarci, A Padovani, B Iandolo, GL Lenzi. *Rome, Italy*

Event-related potentials (ERPs) consist of cortical activity evoked by either acoustic, visual or somatic stimuli and are useful in testing CNS cognitive functions. Ach, NA, 5HT and DA are probably involved in mediating or modulating ERPs responses. Altered ERPs have been reported in migraine patients in pain-free periods. We have evaluated acoustic P300 ERPs of 8 migraine patients (age range 2350 years), by means of brain mapping technique. All patients were evaluated pain-free, before and after 4 months treatment with 5 mg flunarizine (4 patients) or 10 mg dihydroergocriptine (4 patients). All patients with anxiety and/or depression were excluded from the study. Five healthy volunteers served as controls. We measured P300 latency after acoustic stimuli and recorded it through surface electrodes. All migraine patients showed a significantly longer latency of P300 wave as compared to controls, as already reported in the literature. our interest was to study the P300 wave after treatment with two drugs, namely flunarizine and dihydroergocriptine, which are known to have two opposite actions on DA systems. Three patients, studied so far, showed a marked decrease in P300 latency after treatment with flunarizine (1 patient) or dihydroergocriptine (2 patients), together with a significant reduction of both frequency and intensity of migraine. These preliminary results suggest that the study of P300 latency may be useful to better understand the mechanism of action of prophylactic drugs for migraine.

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PLATELETS DO NOT PLAY A PRIMARY ROLE IN MIGRAINE PATHOGENESIS. MG Buzzi, M Bartoli, M Bonamini, F Pulcinelli, R Cerbo, P Pignatelli, GL Lenzi, M Russo, PP Gazzaniga, *Rome, Italy*

Platelets which are known to be the main reservoir of circulating serotonin have been widely studied in migraine patients. The involvement of serotonin in migraine has been recently revised due to the pharmacological activity of antimigraine drugs sumatriptan and dihydroergotamine. They bind with high affinity to 5HT1 receptors possibly located on trigeminal sensory fibbers. Platelet membrane glycoprotein CD62 expression, which is present only on activated platelets, and the "in vitro" aggregation responses to Platelet Activating Factor (PAF), Arachidonic Acid (AA) and Collagen, were evaluated in venous blood from female migraine patients (n=11, mean age 32.4 yrs) during headache-free period. Patients were not under preventive or aborting treatment for at least 7 days. Healthy volunteers served as controls (n=13, mean age 31.6 yrs). Platelet CD62 expression was assayed using a fluorescent monoclonal antibody (MoAb). The "in vitro" platelet aggregability responses were evaluated in Platelet Rich Plasma (PRP), using the aggregation technique according to Born. No significant difference as concerns both platelet membrane CD62 expression and the aggregometric patterns in response to PAF, AA and Collagen, was observed between migraineurs and normal subjects, thus suggesting that platelets do not play a primary role in migraine pathogenesis.

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HEADACHES IN THE EMERGENCY ROOM. J Barros, J Pinheiro, AP Correia, JM Pereira Monteiro *Porto, Portugal*

Headache is a common complaint in patients presenting to the emergency department (E.D.). one percent of E.D. visits in the U. S.A. are primarily for headache. Because headache is a very common symptom, it is important to separate the benign from more serious condition variety. The aim of this work was to evaluate the causes of headaches as the main reason for entering an contact with E.D. of a European University Hospital. We reviewed 22,973 E.D. records and selected 310 records(1.35%) where headache has been the main reason for the Headache was the main reason for the visit. The mean age of the patients was 41 years (SD-20.9), and 63% were females. Nineteen percent were previously observed by another doctor; in E.D. 44% were examined by 2 or more doctors. Neurologists or neurosurgeons examined 52% all total patients. Brain CT scan was performed in 18%, X-ray of skull in 8%, and lumbar puncture in 8%. The final diagnosis was: acute exacerbation of chronic headaches in 46%, acute post-traumatic headaches in 9%, headaches associated with systemic diseases, toxic or metabolic disorders in 9%, headaches associated with intracranial disorders in 7%, acute sinus headache or other extracranial lesions in 7%, and a no specific diagnosis was made. Nine percent of the patients were admitted to the inpatient department, and 12% were referred to the outpatient department. Conclusion: although symptomatic headaches accounted for only about 1% of admission in our ED they should be taken seriously. Physicians should be trained to make a diagnosis based on the International Headache Society (IHS) criteria, which permit identification of idiopathic headaches and headaches due to potentially serious conditions.

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CHANGES IN VON WILLEBRAND FACTOR AND PLATELET ACTIVITY IN MIGRAINE. JC Alvarez-Cermeno; G Avello, JL Sastre; A Vecino; JM Cesar. *Madrid, Spain*

We tried to study an implication of endothelial activation in the pathogenesis of migraine attacks. A neurogenic inflammation of vessel wall has been proposed in the pathogenesis of migraine attacks. In that case, endothelial cells could secrete Von Willebrand factor (VWF), a hemostatic protein stored in them. VWF antigen (VWF:Ag) studied according to Laurell, VWF ristocetin cofactor (VWF:RCo) measured following Weiss and platelet aggregation were studied in both attack and interattack phases of 13 patients with migraine without aura. A similar increased platelet aggregation was observed in both phases while VWT:RCo and the response to high and low concentrations of ristocetin were normal. We found increased levels of VWF:Ag during the migraine attack (130.2 -75X) versus the period free of pain (72.4 + 29%, p<O.OI). CONCLUSION: Inactive components of VWF are released from endothelial cells during the migraine attacks suggesting an endothelial role in the pathogenesis of this disorder.

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ALTERED CHRONOBIOLOGICAL PRODUCTION OF MELATONIN AND CORTISOL IN CLUSTER HEADACHE. M Leone, B Stankov, D D'Amico, C Maltempo, F Moschian, F Fraschini, G Bussone. *Milan, Italy.*

Cluster headache (CH) is a highly distinctive primary headache characterised by shortlasting head pain attacks occurring for days or months (cluster periods). These attacks usually start at the same hour of the day or night in the same patient. The typical cyclic occurrence of cluster attacks suggests the involvement of rhythm regulating centres, located in the hypothalamus, in the pathogenesis of this headache. In this study, the circadian secretion of plasma melatonin and cortisol was investigated in 12 CH patients during a cluster period; 7 age-sex matched healthy subjects were the control group. Blood was sampled each 2 hours during a 24-hour period. 24-hour production (mesor) of melatonin was significantly reduced and mesor of cortisol significantly increased in CH patients (40±6 and 7.8±0:3 respectively; mean±SEM) compared to controls (23±2.4 and 10±0.5; P<0.02 and P<0.03). In the control group the hour of melatonin peak (acrophase) and cortisol acrophase were correlate (P < 0.03, r=.86~, while such a correlation was absent in CH patients. No relationship was found between the peak of the two hormones and timing of cluster attacks. These findings show a derangement in the chronoregulatory centres located in the hypothalamus of CH patients, supporting a central pathogenesis for this headache form.

107
STROKE IN PATIENTS OVER AND UNDER 75 YEARS OF AGE: A COMPARATIVE STUDY JM Molto, E Fernandez, A, Morento Fernandez-A Barreiro, J Sicilia, P Castejon, *Murcia, Spain*

Longer survival in Eastern countries represents an increased risk of stroke. The aim of our study is to compare a group of patients with ischemic stroke aged over 75 with a younger group. We have prospectively analysed over a period of 10 months (March to December 1993) a total of 415 consecutive patients with stroke (either or hemorrhagic), 108 over 75 y (25.7%), with a mean age of 79.6y±3.8 and a male/female ratio 2:3, and 313 were younger than 75, with a mean age of 63.1±8. with a male/female ratio 3:2 (p<.05). Every patient had at least are brain CT. Statistical analysis includes parametric and non parametric tests. the percentage (proportion) versus of ischemic hemorrhagic events was similar in both groups. non valvular atrial fibrillation (29.2% vs. 8.5%), consciensness disorders as clinical presentation (43% vs. 21,7%), urinar tract infections (18.5% vs. 8.3%) and fatal outcome in the first week (11.4% vs. 4.5%) were commoner in older patients (p<.05). These data confirm that short-term prognosis is worse in patients over 75, However we found no significant difference in major clinical complications that could account for it. This aspect must be addressed in future works.

108
EFFECT OF ALMITRINE-RAUBASINE COMBINATION ON FUNCTIONAL RECOVERY IN PATIENTS WITH ISCHEMIC STROKE. B Mihout, M Malberin, V Salzman, D Guez, J Bogousslavsky,on behalf of the study group. *Rouen, Courbevoie, France & Lausanne, Switzerland*

From a registry of 2,000 patients, 90 patients were included in a multicenter double blind randomised trial within 15 days after a first ischemic stroke in the middle cerebral artery territory. Patients were aged over 40 years, with similar educational level, 30<N score<65 (normal vigilance), and without previous history of stroke or TIA. They received 6 month treatment with almitrine-raubasine combination (80 mg per day) or placebo. An intention-to-treat analysis was performed; the main criteria were N score and Barthel score, the secondary criteria were MADRS, Wechsler Memory Scale subtests (similarities, block design), quality of life visual analogue scale. There was no significant difference between the 2 treatments (mean age: 70±11; sex ratio M/F: 0.52); 70 % of the patients ((28) improved with the active treatment while 63 % ((35) with the placebo (Barthel score). A covariance analysis taking into account age, sex, depression score, number of vascular risk factors, presumed aetiologies, stroke location, and initial level of main criteria showed some influence on the degree of recovery for the active treatment for sex, etiology and initial level of N score and Barthel score.

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TRANSCRANIAL DOPPLER SONOGRAPHY OF BASAL CEREBRAL. ARTERIES: FLOW VELOCITY STUDY IN NORMAL SUBJECTS. G Meneghetti, C Baracchini, G Bozzato, B Marini, *Padova, Italy*

A series of 218 patients (98 females, 120 males; age range 80-92 years; average age 56 yrs) without neurological deficits, with no vascular risk factors were examined in our laboratory by Transcranial Doppler sonography (TCD). Significant stenosis of carotid and vertebral extracranial arteries were excluded by Duplex scanner ultrasounds. We recorded the mean blood flow velocities (Vm) of the following arteries: middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA-P1 segment), along with the Pulsatility Index (PI) of the MCA. Our study has shown a 6 % decrease/10 years for MCA Vm, a 4.1% decrease/10 years for ACA Vm and a 5.9% decrease/10 years for PCA Vm. All of these values were statistically significant (p < 0.05). The PI of the MCA increased with age in the following manner: 0.67-0.72-0.86-1.10 every 10 years from 40 to 80 years of age. Regarding age dependence of PI, PI increased 20.8% /10 years for MCA. A side-to-side difference analysis for Vm demonstrated: MCA r=0.994; ACA r=0.825; PCA r=0.986. The conclusions of our study are: mean flow velocities decrease significantly in all examined vessels with increasing age. There seems to be a threshold value for age (50 years) after which the Vm decrease is greater. The PI of the MCA increases with age, this being an expression of blood vessel sclerosis. No significant side-to-side differences have been found as far as the Vm's are concerned: however, the ACA shows a lower order of correlation mostly due to the asymmetry of the anterior portion of the circle of Willis.

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TRANSTHORACIC AND TRANSOESOPHAGEAL ECHOCARDIOGRAPHY IN THE DIAGNOSIS OF THE CARDIAC SOURCE OF CEREBRAL EMBOLISM. T Mendel, A Czlonkowska, T Pasierski, H Szwed, *Warsaw, Poland.*

We have studied 70 patients in age 14-82 ys, mean 54, 22 women, with recent stroke of presumed embolic origin and no significant stenosis found in extracranial Doppler, with transthoracic (TTE) and biplane transoesophageal (TEE) echocardiography. TTE showed mitral valve prolapse in 14, left ventricular thrombus in 4 and atrial septal aneurysm in 4 patients. TEE revealed in addition communication between both atria in 23 (10 small atrial septal defects and 13 patent foramen ovale) and atrial septal aneurysm in 5 subjects interatrial communication was present in 57 % patients with mitral valve prolapse and 78 % patients with atrial septal aneurysm. The clot within left atrial appendage was seen in 7 and spontaneous contrast without clot in additional 2 patients only with TEE. Among patients with positive atrial findings 88 % were in atrial fibrillation. Ulcerated plaques was seen in ascending aorta in 1 and in aortic arch in 43 (61 %) subjects. Tiny filamentous strands of so far unknown embolic potential were present on mitral valve in 22 and on aortic valve in 10 patients. Conclusion: Combined thoracic and biplane transoesophageal echocardiography have high positive diagnostic yields in patients with recent stroke of presumed embolic origin. The known association between mitral valve prolapse and embolic stroke may be the high prevalence of interatrial communication in this group of subjects. The role of fibrin deposits on mitral and aortic valves in etiology of cerebral embolism deserves further observation.

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HYPERGLYCAEMIA AND STRESS HORMONE RESPONSE IN THE PHASE OF STROKE PROGNOSTIC VALUE. J Marta-Moreno, J Lopez-Delval, E Mostacero, F Morales, *Zaragoza, Spain.*

We studied the relation of hyperglycaemia after stroke with stress hormone response and outcome in diabetics and non diabetic patients. In a prospective study, we studied the relation of hyperglycemia, stress hormone response and outcome in 136 patients hospitalised with an acute stroke. Admission and fasting blood glucose levels-glycosylated haemoglobin, 24-hour urinary catecholamines (total catecholamines, epinephrine, norepinephrine and dopamine) and cortisol on days 2 and 3 after onset; outcome measures (mortality. Glasgow, Canadian Neurological Scale and Barthel scores) and CT lesion type, site and size were studied. The patients were classified in two groups: diabetics and non-diabetics. For all subjects there was a significant relation between poor outcome and survival with high glucose level and cortisol concentration . When the patients were grouped, plasma cortisol and epinephrine correlated with glucose level in all subjects, and cortisol in non diabetics patients. but there was not relation in diabetics. Glucose was not correlated with outcome in diabetics, but cortisol was . Conclusions: hyperglycemia after stroke in non diabetics is a stress , glycemia prognostic value is linked to diabetic condition and that cortisol and dopamine are a predictor of outcome in stroke.

112
ISCHEMIC STROKE REVEALING UNRUPTURED INTRA-CRANIAL ANEURYSM, REPORT OF TWO CASES. MH Mahagne, A Rogopoulos, F Bertrand, P Bedoucha, M Lanteri-Minet, M Chatel, *Nice, France.*

Distal embolization of a clot from an enraptured intra-cranial aneurysm is a rare cause of stroke. The diagnosis requires the arteriographic evidence of an aneurysm and distal embolization in the same territory. We present two cases of transient ischemic attack (TIA) in young adults, revealing an enraptured aneurysm. Case 1: A 28 years-old woman with a past history of common migraine had a during atypical migrainous attack. She complained of weakness and dysesthesias in the right arm. The symptoms lasted several hours. The radiological imaging revealed an infarct in the posterior cerebral artery (PCA) territory, and an aneurysm in the basilar artery. All other aetiologies have been excluded. The follow-up, after embolization of the aneurysm has been good, with no recurrence of neurological signs. Case 2: A 33 year-old black woman was admitted for sudden onset of right hemiplegia and dysarthria; she had been complaining of regressive weakness in her right leg a few hours prior to the onset. CT scanner showed cortical and sub-cortical hypodensities in left middle cerebral artery (MCA) territory, angiography disclosed a left MCA aneurysm (M1-M2). All others etiological studies were negative. The frequency of association between enraptured aneurysm and TIA or stroke is not well known. The majority of cases concerns carotid or MCA aneurysms, PCA aneurysms are less common and basilar ones exceptional. It is important to consider this association for therapeutic management. Moreover, some studies have shown that transient neurological signs may precede the rupture of aneurysm. This risk points out the need of a complete and rapid screening of TIA.

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THE CONTRIBUTION OF THE CEREBELLUM TO LANGUAGE PRODUCTION EVIDENCE FROM A CASE OF 5 YEARS GIRL WITH CEREBELLITIS. D Riva, C Zorzi, N Milani, *Milano, Italy*

We report the case of 5 year-old girl with normal language and behavioural development before the illness who was affected by a severe viral cerebellitis. When the disturbances of the consciousness recovered a complete absence of language become evident, while the comprehension of language was not impaired. When the mutism disappeared she was able to produce some words only aphonically. After months she could speak with slow rhythm with monotonous modulation , but no particular phonetic disturbances were evident. While the intelligence was still in the normal range, she could produce spontaneously or in a constraint situation only telegraphic language. Furthermore she was able to maintain the sequentiality of the discourse only under continuous adult guidance. Single word recognition or naming were normal. Free verbal fluency was very poor, while categorial verbal fluency was good. The findings are discussed as the results of the diaschisis of the cerebellar\frontal loops with the loss of the strategies in processing and programming language production.

114
ARTHROGRYPOSIS DUE TO CONGENITAL MYASTHENIC SYNDROME. J Vajsar, G Ronen, D Macgregor, L Becker. *Toronto, Canada*

Two children, ages 6 and 5.5 years, presented in neonatal period with hypotonia, multiple joint contractures, ptosis, extraocular weakness, bulbar symptomatology and respiratory distress. The symptoms were characterized by fluctuations and episodic exacerbations necessitating respiratory support. The development in both children has been delayed and they have not achieved independent walking, although one child underwent bilateral tenotomies. Biochemical and metabolic investigations, EMG, nerve conductions, including slow rate repetitive nerve stimulation, were all normal. Acetylcholine receptor antibodies in serum were absent. Single fibre EMG with axonal stimulation showed prolonged mean jitter in the tibialis anterior and extensor digitorum muscles, with more than 2 abnormal individual jitter values in each muscle. Muscle biopsy demonstrated normal pattern and morphology of muscle fibers, as well as normal immunohistochemical staining for cholinesterase. However, electron microscopy revealed abnormalities in motor endplates. There was atrophy with flattening of the primary synaptic clefts and paucity of the side branches. Both children have improved clinically on Pyridostigmine therapy. Arthrogryposis congenital multiplex due to congenital myasthenic syndrome, as diagnosed in our children, has been reported in only one case so far (Smit and Barth, 1980). The diagnosis can be established by the characteristic clinical history, neurological examination and electrophysiological and pathological findings. Clinical improvement can be achieved with anticholinesterase therapy.

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CLINICAL ASPECTS OF CONGENITAL MUSCULAR DYSTROPHY. E Szwabowska-Orzeszko, S Jozwiak, R Michalowicz, W Szaplyko *Warsaw, Poland*

A term "congenital muscular dystrophy" (CMD) has been widely used for a group of infants with weakness, usually associated with hypotonia from birth, and a muscle biopsy showing striking pathological changes similar to a muscular dystrophy. Despite of some clinical modifications CMD is regarded as a distinct genetic entity, with an autosomal recessive pattern of inheritance. We observed 4 children with CMD. In all of them the condition was present from birth with marked hypotonia and associated weakness affecting the limb, trunk and facial muscles. In one child contractures of various muscles were present at birth, in others developed later. Intellectual development remained normal. Electromyography a myopathic pattern. PK was moderately elevated in all children. Muscle biopsies

showed a dystrophic process and a remarkable replacement of muscle by adipose tissue. Brain US or CT scan was normal in all except for one child with perinatal asphyxia. The condition remained relatively static and children could pass some motor milestones, although at a very delayed time.

116
SIDE DIFFERENCE IN OCCURRENCE OF EPILEPSY IN HEMIPARETIC FORM OF CEREBRAL PALSY. J Susseve, Z Seidl, J Faber, J Obenberger. *Prague; Czech Republic.*

51 children with hemiparetic form of cerebral palsy were investigated. Patient's history, side of the lesion, occurrence of epilepsy and level of mental functions were correlated. We found out uniformly negative influence of hypoxia / asfyxia / and reanimation, EEG changes were present in all patients, one half of these no doubt of epileptic origin. There in an interesting coupling of low clinical occurrence of epilepsy with the left cerebral hemisphere involvment. In case of the right cerebral hemisphere involvment, focal but even epileptic EEG manifestation occurs without clinical epilepsy with much higher significance, than on the left side /p=0.046 in X2 test/. Morever the nonepileptic children with right hemispheric involvment were of normal intellect, but whenever clinical seizures occured, the intellect lowered down rapidly, what was not the case in children with left hemisphere involvment combined with epilepsy.

117
SIMULTANEOUS POLYSOMNOGRAPHIC RECORDINGS OF SYMPATHETIC SKIN AND SKIN LASER DOPPLER FLOWMETRY IN INFANTS DURING QUIET SLEEP. R Springer, RT Bax, T Eckardt, GV Czettritz, P Emmrich, *Munich, Germany.*

In studies conducted on high risk infants for sudden infant death syndrome (SIDS) apnoeas are assessed according to their duration and accompanying clinical phenomena. Furthermore the sympathetic activity seems to be important for the classification of these infants. Therefore skin blood flow using laser doppler flowmetry (LDF) and sympathetic skin activity (SSA) were measured simultaneously. We report our first results of the rate during quiet sleep and the activity associated with apnoeas. Polysomnographic recordings of 11 term infants were analysed (mean conceptional age 49.6 weeks) using the following tests LDF, SSA and EEG, EOG, actogramm, ECG, respiration, Sao2. observation extended over 20 h of quiet sleep periods. Additionally 80 apnoeas longer than 6 sec (d= 7.25 sec, SD 1.2 sec) were recorded. During periods of quiet sleep the SSA-frequency was O.67 per minute (O.13-1.7) and LDF-frequency O.86 (O.23-2.1). during the 80 apnoeas 45 SSA reactions and 54 LDF reactions were observed. A simultaneous reaction of LDF and SSA was identified in 39 of the 80 apnoeas. This indicates an increased sympathetic activity associated with apnoeas. Furthermore the results show an equally close relationship between LDF and SSA. Whether the above results are relevant to the evaluation of apnoeas in high risk infants for SIDS is yet to be shown.

118
CLINICAL REPORT OF 10 CASES WITH CONGENITAL MUSCULAR DYSTROPHY. S Vlaski-Jekic, V Petrova, *Skopje, Macedonia.*

Ten patients with congenital muscular dystrophy (CMD), diagnosed by clinical and electrophysiological findings, CPK serum level and dystrophical histopathological patterns with neither necrosis nor regeneration, are reported . Eight of them were males; two were twins-sisters, The patients age ranged from eleven month to twenty years. All of them showed muscle hypotonia and weakness at birth. Muscle weakness was generalized, more severe proximally than distally. In seven cases the muscle weakness was moderate. In the other three cases it was severe and disabling, one showing severe involvement of axial and chest musculature which exposed him to recurrent pneumonia. The neck and face muscles were involved in three cases . Nine patients had multiple joint contractures; five of them had vertebral deformities of different degree as well. Significant motor delay was present in all cases. In nine of them intelligence was normal, one patient was mentally retarded. Clinical improvement was noticed in only one patient . Seven cases had stable muscle weakness but slow progression of muscle contractures. Two patients were severety disabled, one having died at the age of eleven due to respiratory failure. CPK was normal in four cases, slightly elevated in five cases, and high in one. There were myopathic characteristics of electromyogram in all cases.

119
LATE PROGNOSIS OF THE VISUAL FUNCTIONS IN CHILDREN TREATED FOR INTERNAL HYDROCEPHALUS. S Cherninkova, TGudeva, C Tzekov, *Sofia , Bulgaria*

The disorder of the visual functions in patients with internal hydrocephalus is a result of the elevated intracranial pressure, of direct compression of the optic nerves and the chiasma by the dilated third ventricle, rarely of ischemia, or disturbed cerebral hemodynamic. A total of 102 children with internal hydrocephalus were investigated and surgically treated at the Clinic of Neurosurgery, University Alexander Hospital , Sofia, for a period of 12 years (1978-1990). Thirty-eight children were followed up for over 10 years after the first operation due to in eternal hydrocephalus . The studies were performed by routine ophthalmologic methods. The paresis of oculomotor nerves, optic atrophy, syndrome of the aqueduct of Sylvius, setting sun syndrome, nystagmus are frequent manifestation of the internal hydrocephalus. An improvement of many neuro-ophthalmological symptoms is found after more than 10 years (dilated and slowly reacting pupils to light, upward gaze paralysis, lid retraction). An increase of the optic atrophy in our group after a period of 10 years probably is-a result of elevated intracranial pressure particularly in disturbed function of the shunt.

120
THE NEUROPSYCHOLOGICAL EFFECTS OF PHENOBARBITAL DISCONTINUATION IN CHILDREN. D Riva, M Devoti, S Franceschetti, *Milano, Italy*

In spite of the long use of phenobarbital (PB) as antiepileptic drug, its influence on cognitive behaviour has been little studied in adults and in children. In this study we present the results of the neuropsychological assessment of children who were candidates for PB discontinuation . Selection criteria were 1) antiepileptic monotherapy with PB; 2) age between 5 and 16; 3) disappearance of seizures that had lasted at least 2 years; 4) normal EEG lasting no less than 1 year. The selection criteria excluded at least the influence of EEG and seizures on cognitive functions. The 8 selected children were evaluated using a neuropsychological battery assessing verbal and non verbal intelligence, attention and spatial and verbal memory, before and 6 months after the PB withdrawal. Results show that PB slightly affects general cognitive performances and that only certain time consuming and attention tasks improve in a significant way after discontinuation. These results emphasise the relative innocuity of PB on cognitive performances and its influence on attentional ones.

121
COGNITIVE ACTIVATION AND ITS CORRELATES IN BRAIN ELECTRIC ACTIVITY OF CHILDREN. S Mientus, P Vienna. *Berlin, Germany; Vienna, Austria.*

EEG-coherence was computed from 19 scalp electrodes, with the reference of linked earlobes, from 34 healthy children in the age of 13 years. The children were subdivided under psychological aspects into three groups. They were asked to explore a three dimensional labyrinth with closed eyes. While various wave patterns of the EEG are related to distinct behavioural states, which are referred as synchronised or desynchronised activities, one may expect the occurrence of high-amplitude oscillations with relatively slow frequencies or on the other hand a lower amplitude related to faster waves. We found both: A decrease in α1-amplitude on the entire cortex and an increase of slow frequency (δ, ϑ)-amplitudes. The phenomenon of an increase in slow frequency-amplitude shows significant differences between the groups. On the other hand we could prove an increase in slow frequency coherence for all groups, even there are differences in the extent of coherent activity. These results are conform to the model of resonance suggested by Basar (1988) and Steriade (1990) and would support the two-comportmental model of cortico-cortical association from Thatcher (1986).

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ALLOGENIC MIXED LYMPHOCYTE REACTION OF CHILD'S AND MOTHER'S T-CELLS IN IDIOPATHIC EPILEPSY. Y Vashtang, V Malashkhia, *Tbilisi, Georgia*

We investigated allogenic mixed lymphocyte reaction (MLR) of mother and child T-cells in 21 patients with idiopathic, 31 patients with symptomatic epilepsy and 12 healthy persons (controls). We used the microvariant of MLR . MLR valves are expressed as delta count per minute (cpm).

Results: T-lymphocytes of child (responders)+ mothers T-lymphocytes (stimulators) blocked by mitomycin C was: in idiopathic epilepsy 12780 ± 1145 Δcpm; in symptomatic epilepsy 5165± 1170 Δcpm: in normal controls-5360 Δcpm. Conclusion: in idiopathic epilepsy allogenic MLR is higher (p<0,01) than in symptomatic epilepsy an controls. That indicates incompatibility of children and mothers' and mother an child, if the placental barrier is disrupted, probably may cause the damage of the brain of foetus an may be the risk factor for the development of idiopathic epilepsy. We conclude that the course of epilepsy is more severe when there is a great difference between the HLA-D antigens.

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ELECTROPHYSIOLOGICAL STUDY IN METACHROMATIC LEUKODYSTROPHY. M Tazir, S Assami, D Oulbani, M Ait Kaci Ahmed, *Algiers, Algeria*

We report on an electrophysiological study of 15 patients with the late infantile form of metachromatic leukodystrophy (LD). Nerve conduction velocity (NCV), brainstem auditory evoked responses (BAER) and somatosensory evoked potentials (SEP) were performed in all patients. MNCV were all decreased to between 9,5m/s and 25m/s. BAER were abnormal in all patients with alteration of the wave form. Prolongation of the I-V interwave latency was noted in the early stage of the disease. SEP were altered in 14 patients with increased latency and decreased amplitude of cortical components. The diagnostic of L.D. was confirmed by enzymatic analysis in all cases. We conclude that electrophysiological study is helpful in the diagnosis of L.D. and useful in detecting the disease in early stages.

124
CITALOPRAM FOR POST-STROKE PATHOLOGICAL CRYING. G Andersen, K Vestergaard, J O Riis, *Aalborg, Denmark*

The effect of the selective serotonin reuptake inhibitor citalopram on uncontrolled crying in stroke patients was investigated in a double-blind placebo-controlled crossover study of sixteen consecutive patients (median age 58.5 years, range 40-83 years). The patients entered the 9 week study a median of 168 days (range 6-913 days) post stroke arid were treated with citalopram 10-20 mg daily for a 3-week period. Crying history was determined from semi-structured interviews and diaries kept by the patients. Psychiatric assessment was made using the Hamilton Depression Scale (HDS) and unwanted effects were measured using the UKU side effect scale. In 13 patients in whom frequency of crying could be assessed, the number of daily crying episodes decreased by at least 50% in all cases during citalopram treatment vs. 2 patients during placebo treatment (p<0.005, McNemar's test), the effect being immediate (1-3 days) and dramatic in 11 (73%) and slightly slower in 4 (27%). There was a concomitant significant decrease in depression rating from HDS 8.9 to 5.3 (p<0.005, Wilcoxon's test). Citalopram was well tolerated, the few side effects being mild and transient (p: n.s.). We conclude that serotonergic neurotransmission plays an important role in post-stroke pathological crying and that the selective serotonin reuptake inhibitor citalopram is an effective and well tolerated treatment.

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CLINICAL AND NEUROPHYSIOLOGICAL CORRELATIONS IN COMPLEX PARTIAL SEIZURES (CPS). D Chavdarov., M Bratoeva, M Radionova, *Sofia, Bulgaria*

In order to examine the correlation between the clinical and neurophysiological findings in CPS, the dominating symptomatology was compared to the EEGmapping data. The existence of affective, psychosensory and autonomic symptomatology correlates with abnormal findings in both the temporal and the parietal cortical projections; ideational symptoms or speech arrest engage the temporal, as well as the frontal areas; in cases with visual hallucinations abnormalities were found in the occipital areas; the psychomotor automatisms obligatory show bitemporal discharges or slow wave activity. The dynamic of the distribution of the abnormal EEG phenomena show different but specific for each patient spreading pattern. The results imply that CPS engage in a complicated manner the temporal lobe and different areas. It seems that CPS with obligatory qualitative changes in consciousness involve spatio-temporally greater brain zones than the discrete cortical areas in focal bursts and more restricted areas than in absence or generalised tonic-clonic seizures. That is why the CPS do not exactly coincide with the definition of focal discharges; they are a more restricted form than the generalised seizures.

126
INTEGRINS LFA-1 AND MAC-1 CAN MEDIATEICAM-1 DEPENDENT CELL ADHESION IN VASCULITIC NEUROPATHY. M Corbo, R Nemni, S Previtali, A Quattrini, S Iannaccone, N Canal. *Milan, Italy.*

Cell adhesion molecules are important in focusing inflammatory and immune responses by mediating interactions amongst leucocytes, endothelial cells and accessory cells. LFA-1 (CDlla/CD18) expressed by lymphocytes, and Mac-1 (CD11b/CD18) expressed predominantly by monocytes, are the two ligands which bind to ICAM-1, an adhesion molecule recently found to be involved in inflammatory and immune responses. We studied by immunocytochemistry the expression of ICAM-1 in sural nerve biopsies from patients with axonal neuropathy with or without vasa nervorum vasculitis (VNV). We used monoclonal antibodies to characterise the mononuclear cell subsets and to identify the presence of integrins LFA-1 and Mac-1 in the inflammatory infiltrates. In the nerves with VNV ICAM-1 was intensely expressed on the endothelial cells and on vascular smooth muscle cells. In some patients with axonal neuropathy and no evidence of VNV, expression of ICAM-1 was generally restricted to the endothelium but was still more marked than in controls. In the inflammatory infiltrate we found a large number of LFA-1 and Mac-1 expressing cells consisting, mostly, of T cells and monocytes. Our findings suggest that the interaction between ICAM-1 and its natural ligands on leukocytes may play a role in the pathogenesis of VNV.

127
THE INTERPRETATION OF PAIN RELIEF AND SENSORY CHANGES FOLLOWING SYMPATHIC BLOCKADE. PLI. Dellemijn, RR. Allen, WC McKay, M.C. Rowbotham, *San Francisco, U.S.A.*

The diagnosis of sympathetically maintained pain (SMP) is assumed if substantial pain relief occurs following sympathetic blockade. We evaluated of pain relief and sensory changes following sympathetic blockade by local anaesthetic stellate ganglion block (SGB) and intravenous phentolamine infusion (Phl). Sympathetic blockade by SGB and PHI was carried out in 24 patients (16x PHI, 15x SGB) with presumed SMP of an upper extremity. Quantitative sensory testing (QST), infrared thermography, and autonomic signs were used to monitor both procedures. All patients developed a Horner's syndrome with SGB, and autonomic signs with PHI. Greater pain relief was achieved with SGB, but similar results were achieved in 6 out of 7 patients who underwent both procedures. None of the pretreatment variables such as history and physical exam, skin temperature (asymmetry) or (abnormal) thermal thresholds, nor changes in skin temperature predicted pain relief from either SGB or PHI. For PHI, pain relief correlated with the magnitude of decrease in systolic blood pressure. After SGB, changes in QST suggesting a partial deficit in thermal sensation correlated with pain relief. The diagnosis of SMP cannot be made on the basis of the history and physical examination alone, thus a sympatholytic procedure may be helpful. When SGB produces pain relief but PHI does not, systemic absorption of local anaesthetic and/or sensory blockade by spread to somatic nerves may be the reason. PHI appears to be a less sensitive but more specific test than SGB, and both may be needed to support the diagnosis of SMP.

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CHEMILUMINESCENT DETECTION OF BLOTTED PCR PRODUITS (CP-PCR) OF TWO CAG DYNAMIC MUTATIONS (HUNTINGTONS DISEASE AND SPINOCEREBELLAR ATAXIA TYPE 1). S Castellvi-Pel, T Matilla, I Banchs, H Kruyer, J Corral, M Mila, X Estivill. *Barcelone, Spain.*

Trinucleotide repeat sequences have been up to now implicated in six neurological diseases: myotonic dystrophy, fragile X syndrome, spinobulbar muscular atrophy, Huntington's disease, spinocerebellar ataxia type 1 and FRAXE mental retardation. Such peculiar stretches of repeated nucleotides have been considered as dynamic mutations since they show instability of copy number through generations and its mutation rate is related to the copy number of repeats. We have applied a non-isotopic PCR assay based on the chemiluminescent detection of blotted PCR products (CB-PCR), for two of these diseases (Huntington's disease, HD, and spinocerebellar ataxia type 1, SCA1), which gives an accurate sizing of alleles and allows a rapid analysis of "at risk" individuals. The system involves PCR of the samples, separation of alleles on polyacrylamide gels, Southern blotting and hybridisation with specific primers 3' labelled with fluorescein (Fl)dUTP as probes. CB-PCR retains the isotopic sensitivity for accurate allele determination, avoids isotopic manipulation, and provides the advantages of safety, long-term storage of probes and recycling of hybridization solutions.

129
X-LINKED SPASTIC PARAPLEGIA (SPG2) AND PELIZAEUS-MERZBACHER DISEASE ARE ALLELIC DISORDERS AT THE PROTEOLIPID PROTEIN (PLP) LOCUS ON CHROMOSOME Xq21-22. P Saugeir-Veber, A Munnich, D Bonneau, JM Rozet, M Le Merrer, O Boespflug-Tanguy. *Paris; France.*

Three forms of X-linked spastic paraplegia (SPG) have been recently recognized according to clinical and genetic criteria. One locus (SPG1) has been mapped to Xq28 while two clinically distinct forms have been mapped to Xq22 (SPG2). On the other hand, a rare X-linked dysmyclinating disorder of hte central nervous system, pelizaeus-Merzbacher disease (PMD), has been mapped to chromosone Xq21-q22. This disease has been ascribed to mutations in the proteolipid protein gene (PLP) which encodes two myelin proteins, namely PLP and DM20. While narrowing the genetic interval containing the SPG2 gene in a three-generation pedigree, we found that PLP was the closest genetic marker with respect to the disease locus. For this reason; we considered PLP as a major candidate gene in this disease. We have found that a point mutation in exon 3B of an affected male (H139Y) segregated with the disease (Zmax=6.63 at O=0.00) and resulted in a mutant PLP but a normal DM20. It appears therefore than SPG2 and PMD, which have been described as distinct clinical entities, are in fact allellic disorders at the PLP locus.

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LANDAU-KEFFNER SYNDROME: FIVE PATIENTS INCLUDING TWO SIBLINGS. AN ASSESSMENT OF CLINICAL, LABORATORY FINDINGS AND EFFICACY OF ANTIEPILEPTICS. M Eraksoy. A Gokyigit, O Oktem, M Barlas, G Demir, H Ozcan, A. Caliskan. *Istanbul; Turkey.*

We present five patients, including two siblings, with Lanbau-Kleffener Syndrome (LKS) which is characterized by acquired aphasia associated with seizures and paroxysmal EEG abnormalities. All patients were male; the age of onset of aphasia ranged from 3 to 5 years. Three patients presented with verbal auditory agnosia, the others presented with epilepsy. Three patients had two episodes of transient aphasia. Aphasia persisted in two others. The EEG abnormalities were present in all patients, one of them showed a very similar feature to electrical status epilepticus during slow sleep (ESES). CT and MRI scans were normal. Single photon emission tomography (SPECT) could be performed only in two cases. One of them was normal, the other patients had two SPECTs which were performed at 6 months intervals. The first SPECT showed hyperperfusion over the left basal ganglia, thalamus and parieto-temporal regions but the last SPECT was normal. Corticosteroids and antiepileptics, especially clonazepam were given to all patients. EEG abnormalities dramatically improved after small dose of clonazepam (1mg/day) but clinical improvement was not observed in the early period. Our series show that the clinical picture can vary at onset as well as during the course of the disease, and that the outcome of the aphasia is unpredictable, while epilepsy and EEG abnormalities usually regress.

Symposium 2
Epilepsy:
Basic Mechanisms and Surgical Management

Chairmen: G. Franck, Liège, Belgium; SD Shorvon, London , UK.

GENETIC APPROACHES TO BASIC MECHANISMS OF EPILEPSY. RM Gardiner, *London, UK*

Inherited forms account for about 20% of all patients with epilepsy and are particularly common in children. Epilepsy is a component of the phenotype in over 100 mendelian disorders, but the most common genetic epilepsies display a 'complex' non mendelian pattern of inheritance. These include several well-defined syndromes such as juvenile myoclonic epilepsy, (JME), absence epilepsy and benign childhood epilepsy with centrotemporal spikes. The basic neurobiological basis of these common familial epilepsies is entirely unknown, but recent advances in genetics and molecular biology have provided new methods for investigation of human inherited diseases known only by their phenotype. Two principal strategies exist: positional cloning and candidate gene analysis. Intensive activity in the field of molecular neurobiology has led to the cloning of a number of candidate epilepsy genes, including in particular genes encoding proteins such as ion channels which play a direct role in mediating neuronal excitability. Of these, the voltage gated K+ channels and inhibitory neurotransmitter receptors represent promising classes of candidate epilepsy gene.
HBK2, a human brain specific voltage-gated potassium channel gene, has been analysed in 31 patients with JME using direct sequencing and mutational screening by detection of single strand conformation polymorphism (SSCP) and heteroduplex analysis. HBK2 is a member of the human shaker gene family. Genomic sequence data for the HBK2 gene was provided by Professor Olaf Pongs, Hamburg. The open reading frame encodes a 528 amino-acid sub-unit with six putative membrane with spanning domains (S1-S6) and a hydrophobic H5 or P region believed to line the ionselective pore. There are no introns.
Nested PCR was used to amplify specific regions of the gene from genomic DNA. The highly conserved and functionally important S4-S6 region which encompasses the site of two shaker mutations (Sh5, Shksl33) was analysed initially. Amplification products were sequenced using solid-phase dideoxy methodology. Homozygous wildtype sequence was found in all but one of the 31 patients investigated. One proband, however was heterozygous for a silent base substitution (ACG-ACC) in codon 422. All other affected individuals in the family were heterozygous for this sequence change. Although this point mutation does not alter an aminol acid it gives rise to a region of dyad symmetry creating stable secondary structure which may have functional consequences by altering transcription. This sequence change is readily detectable by heteroduplex analysis and screening of 100 control subjects excluded its occurrence as a population polymorphism. Sequencing of the remainder of the HBK2 coding region in family members revealed no further deviation from wildtype in this kindred. The residual coding region of HBK2 was screened in the 31 probands using both SSCP and heteroduplex analysis. No abnormalities were identified. In combination these methods should detect a high proportion of any sequence variations present. These observations exclude the coding region of HBK2 as the site of a common mutation predisposing to JME.
Most recently, mutations in the a subunit of the glycine receptor have been reported in patients with hyperekplexia, a neurological disorder with some features in common with epilepsy. This is the first human disease associated with mutations in a neurotransmitter receptor. Mutations were identified in exon 6 in four of seven families studied. A further eight families have been ascertained, and work is in progress to screen GLRA1 in affected individuals.

ANATOMICAL IMAGING: MRI. Simon Shorvon, *London, UK*

The application of MRI to the investigation of epilepsy has proved as important as the introduction of EEG in the 1930s. The primary role of MRI is to provide anatomical data and in this sense is complementary to EEG, which is an investigation of function. There are various clinical applications for MRI structural imaging in clinical practice: (1) MRI can reliably detect and quantify hippocampal atrophy and sclerosis. Our understanding of the importance of hippocampal damage in various aspects of clinical epilepsy has been greatly enhanced, and the pre-surgical assessment of temporal lobe epilepsy has been rendered simpler and more precise. (2) MRI can visualize previously undetectable congenital disturbances affecting the cortical ribbon, especially neuronal migrational defects and cerebral dysplasia. These lesions are found to underlie epilepsy in many cases who, prior to MRI, were thought to have cryptogenic seizures. Indeed, these congenital lesions are amongst the most commonest structural causes of epilepsy; frequently encountered examples include macrogyria, polymicrogyria, heterotopias and dysembryoplastic neuroepithelial tumours. (3) MRI can visualise small foreign tissue lesions such as hamartomata, cavernous haemangiomata and small gliomas, especially in the middle cranial fossa. (4) MRI allows more precise stereotactic surgical treatment by directing stereotactic planning and allowing accurate intracranial electrode placement. The co-registration of pre- and post-surgical imaging also allows the outcome of surgery to be related to the site and extent of resection.
Advances in MRI continue to be made. These include new postprocessing techniques such as 3D rendering, 3D reformatting, volume measures, fractal and textural measures; each has important applications in the analysis of volumetric images of the brain in epilepsy. New data acquisition methods include EPI which will allow per ictal serial imaging, and new sequences (including FLAIR and other methods for cortical imaging) which show abnormalities in patients with normal conventional imaging. New quantitative methods include the measurement of T2 values and T2 mapping, which provide adjunctive structural information.

FUNCTIONAL AND BIOCHEMICAL IMAGING WITH POSITRON EMISSION TOMOGRAPHY (PET) IN PARTIAL EPILEPSY. B Sadzot, *Liège, Belgium.*

Complex partial epilepsy (CPE) is the most prevalent form of epilepsy in adults Thirty percent of Patients with CPE are not controlled by their medication and could benefit from surgical resection of their epileptic focus. Localization of the epileptic focus is a prerequisite for a surgical success. PET with 18F-fluorodeoxyglucose (18FDG) rPvpa interictal glucose hypometabolism on the side of the epileptic focus in more than 70 % of these patients. In temporal lobe (TL) epilepsy resistant to drug treatment, 1 8FDG-PET is abnormal in more than 80%, and the most hypometabolic area is located in the TL corresponding to the surface and the intracranial EEG focus. The hypometabolism often extends to the ipsilateral frontal and parietal lobe as well, and sometimes to subcortical structures. No metabolic difference can be found between patients with a seizure onset restricted to the hippocampus from those with a seizure onset involving the hippocampus and the adjacent neocortex as indicated by intracranial EEG. Even when the seizure focus includes the hippocampus, hypometabolism is usually more pronounced in the lateral temporal cortex than in the mesial part of the temporal lobe on the transversal planes. More recently however, with our new tomograph, we have been able to obtain coronal reconstructions which facilitates the visualisation of biochemical changes in the internal part of the temporal lobe. Quantitative analysis of these coronal planes reveals that the degree of glucose hypometabolism is, on average, the same in the internal, basal and lateral part of the temporal lobe. Patients with extratemporal epilepsy are less likely to have an abnormal 1 8FGD-PET. When present, lobar glucose hypometabolism is a strong indicator of the lobe of seizure onset.
It is also possible with PET to image several neuroreceptor systems that could play an important role in controlling neuronal excitability. Until recently, in vitro biochemical studies on brain samples resected during surgery in patients with intractable partial seizures have failed to show any consistant changes in neurotransmitters. PET has the advantage to allow in vivo human studies and intra-individual comparisons (focus vs non focus). For example, altough the role of the opioid peptides in seizure mechanisms has been extensively documented in animal models of epilepsy, change in this system of neurotransmission has not been demonstrated in human epilepsy. It has been found with PET that the binding of 11 C-carfentanil, a potent mu opiate receptor agonist, is increased in the temporal neocortex on the side of the epileptic focus in patients with CPE, suggesting changes in mu opiate receptor affinity, density or occupancy at distance from the epileptic focus. By contrast, 1 1C-diprenorphine binding, reflecting mu as well as non-mu opiate receptor subtypes, was not significantly modified.
There are also strong arguments to suggest that the GABA inhibitory neurotransmission system is modified in epilepy. We have recently begun combined PET studies with 1 1C-flumazenil followed by 1 8FDG in patients suspected to have temporal lobe epilepsy. 11 C-flumazenil is a potent benzodiazepine receptor antagonist suitable for imaging these receptors in vivo; measurement of its uptake is an indirect way to assess GABA receptors. This protocol allows for the direct comparison between glucose metabolism and benzodiazepine receptors. More than 20 patients included in a presurgical evaluation for resistant complex partial epilepsy have been explored with combined PET; they have not yet been investigated yet with intracranial EEG. In each case, the 1 8FDG and the 11 C-flumazenil scans are abnormal in the temporal lobe suspected to include the epileptic focus. The degree of glucose hypometabolism is similar in the hippocampus and in the temporal cortex while the decrease in 11C-flumazenil binding is predominant in or limited to the hippocampus. Both 1 1C-flumazenil and 18FDG PET are extremely sensitive in temporal lobe epilepsy patients but the area of decreased 1 1C-flumazenil binding is spatially more restricted and could therefore have a closer relationship with the epileptic focus than the area of glucose hypometabolism. This point will be clarified when some of these patients have intracranial EEG recordings. Furthermore, the pattern of 1 1C-flumazenil binding in extra-temporal lobe epilepsy must be determined to establish the specificity of our findings.
Combined with other non invasive techniques (EEG, neuroradiology), PET appears extremely useful in the non invasive presurgical exploration of patients with CPE and is now an indispensable step in that process. Receptors, imaging might prove even more valuable than metabolic studies.

EPILEPSY: SURGICAL MANAGEMENT. Heinz-Gregor Wieser, *Zurich, Switzerland*

Surgical therapy of the epilepsies consists of « curative (causal) » and « palliative » procedures. Causal therapy is in essence a resective surgery and depends in the concept of a « primary epileptogenic zone », which is not necessarily synonymous with the « lesional zone ». Palliative therapy is in the spread of the seizure discharges (e.g. anterior callosotomy). a third category of surgical procedures intends to modify the excitability subsystems only, by increasing the inhibitory output. Historically cerebellar stimulation, and more recently, stimulation of the putamen and thalamus should be mentioned in this context. Transplantation (grafting) is in its infancy, but has aroused considerable interest. Following Rasmussen's a concept of 1st, 2nd and 3rd order localisation, presurgical evaluation of surgical candidates must answer the following questions: (a) Where do the attacks begin in the brain, (b) what is the extent and location of the potentially epileptogenic cortex contiguous with the site of the origin or the seizure, and (c) how much of the potentially epileptogenic cortex must be removed in to achieve the maximal likelihood or a satisfactory reduction of the seizure tendency with the least possible risk or producing an unacceptable neurologic deficit. We review the presently performed types of epilepsy surgery and the results.

Symposium 3
Ethical Issues in Neurology

Chairmen: PK Thomas, London, UK; A Portera-Sanchez, Madrid, Spain.

ETHICS IN ANIMAL RESEARCH. KA Hossmann, *Cologne, Germany*

The use of animals for biomedical research has come under increasing criticism in many countries all over the world. Attacks of animal protectionists against researchers and research institutions have been most violent in the United States and Great Britain, but occasional outbursts of aggressive actions have been reported from many other countries with advanced standards of biomedical research. In Germany, the public uneasiness with animal experiments has led to restrictive legislation which is in serious conflict with the constitutionally confirmed freedom of scientific research. According to this legislation, each experimental intervention including "terminal" investigations in anaesthetised rodents, requires governmental approval. The application has to specify all details of the experimental interventions, and any deviations from this application bear the risk of the life-time loss of the applicant's license to perform animal experiments. The governmental agencies are assisted by ethical committees in which on third of the members must be selected from the lists of animal welfare groups. The time from application to approval lasts rarely less than three months, and pending decisions have been reported for up to several years. Although this legislation has been passed against the vehement protest of all medical schools and research organisations of the country, further restrictions are presently under discussion.
This development is not readily explained by a violation of ethical principles by animal experiments. As long as the killing of animals for human needs is not seriously called in question, justification of animal experiments depends on the comparison of the ethical importance of the research goal in relation to that of animal welfare. German legislation therefore requires the individual ethical assessment of each individual experimental protocol. In principle this procedure is fair but in practice it has led to a serious strangulation of biomedical research because the bureaucratic procedures are the same regardless of whether the experiment is an ethically debatable investigation an awake primate or a one-stage pilot experiment in the anaesthetised rat.
Since similar developments are likely to occur in all other countries of the European Community, the biomedical societies should take the initiative for a legislation that protects the interests of both scientific research and animal welfare. Considering both the positive and negative experiences made in Germany, such a legislation should consider the following points: 1) Animals for experimentation should be bred and kept under conditions that conform to their species-specific behaviour. 2) All personnel doing animal experiments be educated and licensed. 3) One-stage acute animal experiments)that are performed and terminated under surgical anaesthesia, should be reported but should not require individual approval as long as they are carried out by licensed personnel. 4) All other experiments should require approval by a government-appointed ethical committee, consisting of representatives of biomedical research, health care, human sciences and animal welfare groups. The decision should be made in less than six weeks. 5) As a guideline for the ethical committees, a list of ethically acceptable experiments should be compiled and regularly updated by the governmental authorities.

Harmonization within Europe would be of great benefit and should be reached as soon as possible.

ETHICS IN NEUROGENETICS. AE Harding, *London, UK*

Molecular genetic techniques have made an impact on neurological practise, leading to improved diagnosis and genetic counselling neurological disorders. The application of these techniques has, however, identified both expected and unexpected ethical difficulties. Apart from the specific issues of genetic testing, dilemmas arise relating to confidentiality, ownership of DNA samples, the use of stored samples, an distinshing between research an clinical results. There are essentially three types of genetic test: diagnostic, predictive: and prenatal. For diagnostic tests, the possibility of a genetic disease should be discussed with the subject in the case of positive results, it is essential to take into account the potential needs of relatives in terms of information and genetic advice, as identification of a genetic basis for a seemingly disorder has implications for a seemingly sporadic has implications for the whole family. Most experience with predictive tests for adult onset neurological disorders come from Huntington's disease (HD), and this can usefully be applied to the application of presymptomatic and prenatal testing have been published in an attempt to deal associated ethical issues; these, importantly, take into account views of lay HD organisations, it is essential that individuals wishing to be tested understand the variable manifestations and natural history of the relevant disease. The implications of a positive result need to be discussed in detail during pre-test counselling, in relation to emotional reactions in the immediate post-test period and the longer term, life insurance, employment and effects on partners, parents, children, and other relatives, inappropriate use of predictive tests may be requested by physicians, family members, or others such a insurance companies, employers, or adoption agencies. The decision to take a predictive test should be the sole choice of the individual concerned. It is generally thought that testing not to be performed on subjects under the age of majority but that they should be allowed to make an informed decisions about after this age. Other ethical problems which have arisen in presymptomatic testing, for HD and other diseases, include refusal to give blood samples by key relatives, unintentional risk alteration in family members, testing monozygous twins, and requests for tests from subjects with a 25% risk (i.e. who have an affected grandparent) which could provide unwanted information for their parent at risk. It is generally held that the applicant's right to be tested should take priority, but this issue needs careful consideration. The demand for prenatal tests for inherited neurological disorders is determined mainly by severity to the disease. Prenatal tests can assess whether or not the foetus carries the relevant mutation, but not severity of disease, which can diction making hard in this context. DNA is ideally analysed from chronic cillus sample obtained at 8-10 weeks gestation and result are thus available in time for a first trimester abortion. It is advisable to assess informativeness before conception, although human nature dictates that this is not always practical. Testing is inappropriate unless the couple concerned is committed terminating high risk pregnancies. Continuation of pregnancies shown to be at high risk for example, raises the possibility of the child having had an unsolicited presymptomatic test. This situation should be avoided by adequate pre-pregnancy counselling. All prenatal tests are potentially harmful to the pregnancy and should not be undertaken unless the result will be acted on

ETHICAL CONSIDERATIONS IN THE MANAGEMENT OF THE TERMINALLY ILL. A Steinberg, *Jerusalem, Israël*

Many ethical, religious, social and legal dilemmas are involved in the care of dying patients. Major changes and developments in recent years have greatly intensified these moral problems . In order to enhance the ability of the health-care providers to attain morally sound decisions an to evaluate the decision-making process concerning the dying patient, it is important to pay attention to the following four majors factors; relevant medical data, including diagnosis, short and long term prognosis, therapeutic options, the possible benefits an burdens of each therapeutic option, and the most appropriate placement or the patient; patient -physician relationship, in particular, the establishment of a mechanism for a mutual decision-making process between the health-care providers and the competent patient, or the most appropriate surrogate when the patient is incompetent; institutional and departmental rules an regulations; a complementary, and occasionally an alternative system to the principles approach is the casuistry approach. The relevant ethical principles include the following: value of life, quality of life, nonmaleficence, beneficence, autonomy, paternalism, justice, an physician's integrity. From a practical point of view three major categories are discussed: treatment, and the decision-maker.

The patient: Several categories of patients require different types of decisions. They include the following: currently competent; currently incompetent, but previously competent. The treatment, there options in treating a terminally ill patient: to prolong every life by all available means, no matter what the prognostic is; active euthanasia, namely acting actively in a way that will cause direct and immediate death; and passive euthanasia. According to this approach, when treatment is deemed to be futile it is morally acceptable to forego certain treatments, based on selective criteria a proposed ordinary treatment versus extraordinary; natural vs artificial; appropriate vs inappropriate. The decision-maker, the patient himself, provided he is competent, or that his wishes are well known, the responsible physician, a medical team, a surrogate, i.e., close relative or friend, a spiritual leader, an institutional ethics committee, a court of law, the legislature.

ETHICAL PROBLEMS IN ACUTE NEUROLOGY. H van Crevel, *Amsterdam, the Netherlands*

Acute disorders are common in neurology. In the Netherlands, of the 105.000 yearly neurological hospital admissions, 26% concern stroke, 13% head injury, 5% tumours and 4% infections. Do Not Resuscitate (DNR) orders are also part of acute neurology, as are many consultations in other departments, e.g. the intensive care unit. In many situations, diagnostic and therapeutic decisions with important consequences for the patient must therefore be made rapidly. These decisions require balancing expected benefit harm. They are based on clinical knowledge interconnected with value judgments; value judgments are often concealed in clinical terms. Prognosis is a cornerstone of clinical decisions. Advances have been made in prognosis of neurological disorders, but predicting prognosis in individual patients with 100% certainty is seldom possible. Moreover, it should be realized that prognostic measures may contain value judgments. Outcomes should expressed in terms that patients care about. Ethical problems in acute neurology are complicated by the fact that the patients are often comatose or otherwise incompetent. Advance directives are helpful but usually lacking. Relatives may know the patient's preferences, but they may also substitute their own opinions. The value that people attach to life with severe mental and (or) physical disability is personal, and clinicians should be careful not to substitute their own opinions without questioning. Some important ethical principles (beneficence, nonmaleficence, autonomy, justice) are acknowledged in general. However, clinicians should realize and accept that these may collide in specific situations. Some "ethical pain" is therefore unavoidable. It should be recognized that in seriously ill patients both the decision to withhold or withdraw treatment and the decision to continue treatment may need ethical justification. These issues should be addressed before life-threatening complications arise, in order to avoid escalation which is later regretted. Discussion of these choices benefits from the adoption of a system of well-defined categories of treatment; vague terms like "no heroics" are unhelpful. Some consensus has been reached about the management of patients with a locked-in syndrome and for those in a vegetative state and these situations will be discussed. Other problems, such as severe hemisphere strokes in elderly patients, are more controversial. DNR orders show large variation in practice, the causes of which will be explored. Intensivists may ask the neurologist whether treatment should be stopped, with the false implication that it is a decision based on neurological facts only.
Summarizing, ethical problems are frequent in acute neurology and they are difficult. To meet these problems, more knowledge is needed: about outcomes, about patient preferences and about the validity of judgments made by relatives. Clinicians should be trained in ethical reasoning, the same way as they are trained in diagnostic reasoning in relation to specific patient situations. Patients should be encouraged to make advance directives.

Oral Session 15 - Headache

1
ALTERED CHRONOBIOLOGICAL PRODUCTION OF MELATONIN AND CORTISOL IN CLUSTER HEADACHE. M Leone, B Stankov, D D'Amico, C Maltempo, F Moschian, F Fraschini, G Bussone. *Milan, Italy.*

Cluster headache (CH) is a highly distinctive primary headache characterised by shortlasting head pain attacks occurring for days or months (cluster periods). These attacks usually start at the same hour of the day or night in the same patient. The typical cyclic occurrence of cluster attacks suggests the involvement of rhythm regulating centres, located in the hy-

pothalamus, in the pathogenesis of this headache. In this study, the circadian secretion of plasma melatonin and cortisol was investigated in 12 CH patients during a cluster period; 7 age-sex matched healthy subjects were the control group. Blood was sampled each 2 hours during a 24-hour period. 24-hour production (mesor) of melatonin was significantly reduced and mesor of cortisol significantly increased in CH patients (40±6 and 7.8±0:3 respectively; mean±SEM) compared to controls (23±2.4 and 10±0.5; P<0.02 and P<0.03). In the control group the hour of melatonin peak (acrophase) and cortisol acrophase were correlate (P<0.03, r=.86~, while such a correlation was absent in CH patients. No relationship was found between the peak of the two hormones and timing of cluster attacks. These findings show a derangement in the chronoregulatory centres located in the hypothalamus of CH patients, supporting a central pathogenesis for this headache form.

2
GENETIC HETEROGENEITY OF FAMILIAL HEMIPLEGIC MIGRAINE. A Joutel, MG Bousser, A Ducros, K Vahedi, J Julien, P Labauge, N Pinsard, G Ponsot, F Gouttiere, JL Gastaut, O Delrieu, V Besançon, E Tournier-Lasserve. *Paris; France.*

Familial hemiplegic migraine (FHM) is an autosomal dominant subtype of migraine with aura, characterized by the occurrence of a transient hemiplegia during the aura. We previously localized one FHM gene on chromosome 19 bylinkage analysis conducted on 2 large FHM pedigrees. We established the most lokely location of this gene within a 30 cM interval between D19S216 and D19S215 loci. We have now collected ten families which fulfill the "International Headache Society" criteria for FHM. Each of these families includes at least ten informative meiosis. Linkage analysis of these families using chromosome 19 microsatellite markers spanning the FHM locus showed clear evidence of linkage in 5 of these families. We are able to exclude linkage to chromosome 19 in the rest of these families. These data early establish genetic heterogeneity of FHM. FHM families linked to chromosome 19 have been used to reduce the size of the interval containing the FHM locus. The size of one of the linked families was large enough to conduct genetic mapping by linkage analysis of another FHM affected gene. These data will be presented at the meeting.

3
INTERMITTENT MUSCLE ACHE, PARTICULARLY IN THE SUBOCCIPITAL/PARACERVICAL (COATHANGER) REGION IN AUTONOMIC FAILURE - FREQUENCY IN ASSOCIATED NEUROLOGICAL CONDITIONS AND RELATIONSHIP TO POSTURAL HYPOTENSION. CJ Mathias, K Bleasdale-Barr, G Smith, NMF Murray, P Hawkins, M Pepys, PK Thomas. *London, UK*

Patients with autonomic failure (AF) are often aware of, or complain about, moderate to severe aching in the suboccipital/paracervical (coathanger) region. The frequency of pain in muscles in the "coathanger, buttock and calf region was determined in two groups; pure AF (PAF=21) and Shy-Drager syndrome (SDS= 19, multiple system atrophy). Comparisons were made with neurological disorders without autonomic failure, (parkinsonian = 20, cerebellar = 6, and miscellaneous disorders, = 15). In 81 % of PAF and 47 % of SDS, standing and walking caused a "coathanger" pain, which was relieved by sitting or lying down in all PAF and 56 % of SDS. Posturally associated buttock pain occurred in 14 % of PAF and 11 % of SDS. Calf pain related to postural change occurred with similar frequency in all groups (10-21 %). Postural hypotension was greatest in PAF (145±5/86±4 to 83±5/51±4 mmHg), less in SDS (161±4/93±3 to 118±6/78±3 mmHg) and did not occur in the other groups. Muscle ache, probably due to ischaemia, occurred in the "coathanger" region in all PAF, but only in half SDS; in whom the postural fall was less. Suboccipital /paracervical muscles maybe more susceptible because of their position (above the heart), and continuous activity to maintain the head position. Recognition of "coathanger" ache as a symptom of low perfusion pressure in AF should aid management and reduce unnecessary investigations.

4
RESPIRATORY CHAIN AND MITOCHONDRIAL DNA IN MIGRAINE. T Klopstock, A May, P Seibel, E Papagiannuli, HC Diener, H Reichmann. *Wurzburg, Essen, Germany.*

Cerebral infarction, most often in the posterior cerebral regions, occasionally complicate migraine. Stroke-like episodes in the posterior cortex and migrainous headache with vomiting are also characteristic features of the MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes). Depression of mitochondrial enzyme activities has recently been shown in muscle and platelets of migraine patients. Several studies employing phosphorus 31 magnetic resonance spectroscopy have shown a defective energy metabolism in brain and muscle of these patients. We measured the activities of the respiratory chain enzymes in isolated platelet mitochondria and analysed the mitochondrial DNA in lymphocytes of 22 migraine patients. There was no significant difference between patients and controls for the complexes I to IV of the respiratory chain. Southern blot and PCR analysis of mitochondrial DNA failed to detect any large-scale deletions or point mutations at nt3243 (MELAS) and nt8344 (MERRF). Our data do not support the hypothesis that there is a generalised respiratory chain defect in migraine nor that some cases of migraine might be monosymptomatic forms of a MELAS syndrome. We cannot exclude, however, the possibility that migraine might be associated with a brain-specific mitochondrial dysfunction.

5
TRANSCRANIAL DOPPLER EVALUATION OF PATIENTS WITH MIGRAINE. C Gurses, C Aykut, S Aktan. *Istanbul, Turkey.*

Patients with migraine were studied with during transcranial doppler (TCD). We investigated vascular changes in patients during attacks and during headache-free periods. We examined total 36 migraineurs (31 female, 5 male) with a mean age of 34.2 years (17-56).TCD was done on only 7 patients without an aura both during attacks and during headache free periods. During attacks the mean flow velocity in the left middle cerebral artery (MCA) was lower than in the right MCA (P<0.05).Thirteen patients with unilateral headaches without an aura were studied in headache free periods with TCD. There were no statistical differences between the 2 hemispheres. 20 patients had headaches more than once a week. The remaining 16 patients had headaches less than once a week. The mean flow velocity (MFV) and the diastolic velocity (DV) increased in patients with headaches occurring more than once a week (P<0.05). The mean velocity decreased during attacks in 7 patients without aura. The decrease of the mean flow velocity represents vasodilatation. Patients with an increased frequency of headaches in headache free periods had high MCA velocity, pulsatility index (PI), DV in TCD findings. Our results suggest that TCD is a useful associated method to investigate the pathogenesis of migraine and to monitor drug's given as prophylactic agents.

6
EFFECT OF SUMATRIPTAN IN NITROGLYCERIN-INDUCED HEADACHE IN MIGRAINE PATIENTS. R Cerbo, MG Buzzi, G De Vuono, F Fiacco, GL Lenzi, *Rome, Pozzilli, Italy*

The mechanism of action of sumatriptan in aborting migraine attacks is still under debate. Studies in rats suggest an action on 5-HT1 autoreceptors on sensory fibers innervating cephalic blood vessels. Doppler sonographic studies in humans do not show any significant effect in large vessels although sumatriptan constricts isolated blood vessels and reduces blood flow in A-V shunts. Clinical efficacy of sumatriptan (6 mg.s.l.) was studied following nitroglycerin (NTG) s.l. (5 mg) in 10 migrainous sumatriptan-responders (patients free of symptoms in <30 min after sumatriptan administration in spontaneous attacks) and in 5 healthy volunteers without familiarity for migraine. NTG induced early headache in 9 out of 10 patients studied. Sumatriptan was given 10 min. after the onset of pains and headache completely disappeared after a mean interval of 45.2 min from drug administration. Seven patients developed delayed headache. Sumatriptan was uneffective on delayed headache. No healthy volunteer developed early or delayed headache. The sumatriptan inhibition of sensory fibers activation induced by distended vessels is uneffective on pain control in experimental headache. The lack of pain relief of NTG-induced delayed headache following sumatriptan administration suggests that the mechanism of action of the drug is not vasoconstriction and that NTG-induced headache is different from spontaneous migraine attacks.

7
PLATELETS DO NOT PLAY A PRIMARY ROLE IN MIGRAINE PATHOGENESIS. MG Buzzi, M Bartoli, M Bonamini, F Pulcinelli, R Cerbo, P Pignatelli, GL Lenzi, M Russo, PP Gazzaniga. Pozzill, *Rome, Italy*

Platelets which are known to be the main reservoir of circulating serotonin have been widely studied in migraine patients. The involvement of serotonin in migraine has been recently disputed due to the pharmacological

activity of antimigraine drugs sumatriptan and dihydroergotamine. They bind with high affinity to 5HT1 receptors possibly located on trigeminal sensory fibers. Platelet membrane glycoprotein CD62 expression, which is present only on activated platelets, and the "in vitro" aggregation responses to Platelet Activating Factor (PAF), Arachidonic Acid (AA) and Collagen, were evaluated in venous blood from female migraine patients (n=11, mean age 32.4 yrs) during headache-free period. Patients were not under preventive or aborting treatment for at least 7 days. Healthy volunteers served as controls (n=13, mean age 31.6 yrs). Platelet CD62 expression was assayed using a fluorescent monoclonal antibody (MoAb). The "in vitro" platelet aggregability responses were evaluated in Platelet Rich Plasma (PRP), using the aggregation technique according to Born. No significant difference of platelet membrane CD62 expression and the aggregometric patterns in response to PAF, AA and Collagen, was observed between migraineurs and normal subjects, thus suggesting that platelets do not play a primary role in migraine pathogenesis.

Oral Session 16 - Infection of the Nervous System

1
CYTOMEGALOVIRUS MULTIFOCAL NEUROPATHY IN AIDS. CLINICAL PATTERN, DIAGNOSIS AND RESPONSE TO THERAPY IN 15 CONSECUTIVE CASES. E Roullet, V Assuerus, J Gozlan, G Said, M. Baudrimont, C Jacomet, O Picard, W Rozenbaum, *Paris, France*

In a retrospective study we identified 15 consecutive HIV-positive patients with a definite diagnosis of CMV-MN based on 1) markedly asymmetric neuropathy; 2) fewer than 100 CD4+ cells per mm3; 3) exclusion of other causes of neuropathy; and 4) characteristic CMV cytopathic changes on neuromuscular biopsy (2 cases), positive CSF culture for CMV (2 cases), or clinical improvement on anti-CMV therapy, given for concurrent extra-neurologic CMV disease (8 cases) or neuropathy (3 cases). First symptoms were numbness and paresthesiae, which were often painful and showed a patchy multifocal distribution. After a mean of 11 weeks (range: 1 to 10 months), the patients developed moderate to severe sensorimotor asymmetric neuropathy. Extra-neurologic CMV infection occurred in 10 cases before diagnosis. Electrophysiological studies showed an axonal neuropathy and CMV DNA was detected in CSF by the polymerase chain reaction (PCR) technique in 90 % of patients tested. Fourteen patients showed a marked improvement 1 to 4 weeks after starting ganciclovir or foscarnet on an open treatment basis. During follow-up on maintenance therapy (13 patients), the neuropathy relapsed in 3 cases, probable or confirmed CMV encephalitis occurred in 8, and 12 patients died. In HIV + patients CMV-MN can present as a mild and smouldering sensory multifocal neuropathy in which PCR detection of CMV DNA in CSF may be a useful diagnostic marker.

2
SIGNIFICANCE OF DNA IN SITU HYBRIDIZATION FOR EARLY DIAGNOSIS OF HERPES SIMPLEX ENCEPHALITIS. M Nueckel, P Osschmann, CR Horning, W Dorndorf, *Giessen, Germany*

Recently the polymerase chain reaction (PCR) evolved to the diagnostic method of choice in herpes simplex encephalitis (HSE), however, requires specialised personal and laboratory equipment. Therefore we evaluated the diagnostic significance of DNA in situ hybridization (DISH), which can be easily performed within a day in every routine laboratory. Using a new commercially available DISH kit with a digoxigenin labelled cDNA probe we investigated 8 patients (4 HSE, 4 controls). In the HSE patients (3 male, 1 female, aged to 31-62 years) the diagnosis was proven by CSF, clinical and neuroradiological findings (all cases) and PCR (3 cases). The control group (3 males, 1 female, 23-67 years of age) comprised 3 cases of neuroborreliosis and 1 case of viral meningitis of unknown origin. Additionally positive control slides by the kit manufacturer (paraffin preparations of HSV-infected culture cells) were used. The DISH revealed in all HSE patients a positive result by staining HSV-DNA mainly located in the nuclei and less in the cytoplasm of lymphocytes and monocytes of the CSF. The percentage of positive CSF cells ranged from 10 to 80% (median 47,5%), furthermore a different intensity of staining could be recognised. We conclude that the DISH seems to be a reliable method for the rapid, early and specific diagnosis of HSE.

3
APPLICATION OF PCR TO THE DIAGNOSIS OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATY IN AIDS PATIENTS. R Caldarelli-Stefano, E Omodeo-Zorini, G E Rivolta, R Maserati, A Cagni, P Ferrante. *Milan, Pavia, Monza, Italy.*

Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disease due to the reactivation of JC Virus (JCV) in immunosuppressed subjects. In order to perform the " in vivo " diagnosis of PML we have set a Nested Polymerase Chain Reaction (PCR) to detect both JCV DNA and BK virus (BKV) DNA in cerebrospinal fluid (CSF) and urine from AIDS patients. JCV and BKV share a high genomic homology, but the amplified region contains a Bam HI site, present only in JCV genome. We have examined CSF and urine collected from 16 AIDS patients with different neurological disorders including neurotoxoplasmosis (5) AIDS - dementia complexe (6) cryptococcosis (3) and PML.(2). JCV-DNA was detected only in the two PML cases, both in urine and CSF. The other 14 patients had no JCV-DNA in the CSF, while 3 of them had JCV-DNA in the urine. Moreover in 2 other patients BKV DNA was detected in the urine, but not in CSF. Our results indicate that the finding of JCV DNA in CSF could be a specific marker of PML and that PCR is a useful method for the diagnosis of PML in AIDS patients.

4
NEUROVIRULENCE IN EXPERIMENTAL HERPES SIMPLEX VIRUS ENCEPHALITIS: IN VIVO STUDY BY MRI OF DIFFERENT STRAINS OF HSV AND DISEASE COURSE. U Meyding-Lamadé, W Lamadé, Th Heb, G Gosztonyl ,K Sartor, G Daral, W Hacke. *Heidelberg, Germany.*

The goal of this experimental study was to establish a sensitive and physiologic model of herpes simplex virus encephalitis (HSVE). Different strains of Herpes Simplex viruses (HSV) were examined as to virulence and neuroinvasiveness in vivo. Time course of disease was monitored. Thus far morphological changes of experimental HSVE have never been monitored in vivo. 40 mice (BALBc, SJL) were intranasally inoculated with an infectious dose of wild-type strain HSV- 1 strain F and deletion mutant HFEM. Serial clinical evaluations and follow-up cranial MRI examinations were correlated with genetics and neuropathology. 96% of the mice developed cerebral abnormalities on MRI, resembling human HSVE. Areas of increased signal intensity on T2-weighted sequences and focal pathological contrast enhancement were mostly found in the frontal and temporal lobe and thalamic and cerebellar region. All animals with neuropathologically proven HSVE showed MRI abnormalities, for up to 8 months. The intraperitoneal apathogenic strain HFEM proved to be neuroinvasive as well as neuropathogenic. Encephalitis of intranasally inoculated mice resembles morphologically human HSVE. With an in vivo MRI monitoring system a phenotypic correlation of genotypic differences could be demonstrated. Disease course, neurovirulence, neuroinvasiveness and therapeutic strategies may be examined using this in vivo monitoring system.

5
CLINICAL VALUE OF POLYMERASE CHAIN REACTION IN DIAGNOSIS TO TUBERCULOUS MENINGITIS. C Fresquet, J Haas, B Storch-Hagenlocher, B Wildemann. *Heidelberg; Germany.*

The prognosis of tuberculous meningitis (TBM) depends on early therapy based on rapid diagnosis. The conventional methods detecting Mycobacterium (M.) tuberculosis in the CSF are not entirely reliable, more over the results may not be available before several weeks. Polymerase chain reaction (PCR), a sensitive and rapid method based on in vitro amplification of specific DNA sequences could be a very useful for rapid diagnosis of TBM. We investigated 61 CSF specimens from 49 patients. After cell lysis and DNA preparation following a standard protocol, we performed a half-nested PCR with primers able to detect M. tuberculosis as well as M. fortuitum and other mycobacterial subspecies. The specificity of the PCR products was checked by sequencing. We evaluated our data in 42 patients according to clinical features and the bacteriological results. PCR detected 4 (80%) of 5 cases of highly probable TBM. In 7 (18.9%) of 37 patients with other bacterial (2) or aseptic (3) meningitis or other diseases (2) PCR amplified mycobacterial DNA. These sequences were highly consensus (>84%) with M. fortuitum, probably due to cross-contamination. In conclusion PCR is a rapid method of high sensitivity and specificity of about 80% in TBM diagnosis. Detection of cross-contamination with M. fortuitum must be avoided by appropriate primer.

6
BK VIRUS ASSOCIATED ENCEPHALITIS IN AN IMMUNOCOMPETENT PATIENT. R Voltz, G Jager, L Fuhry, R Hohlfeld. *Munich, Germany.*

A 34 year old HIV negative, previously healthy man developed an encephalopathy with severe agitation, confusion and seizures. This clinical picture persisted for eight weeks and then gradually resolved over 3-4 months. Repeated lumbar puncture showed elevated protein levels ranging from 61 to 74 mg% and normal cell counts. There was no evidence of intrathecal immunoglobulin production. Blood serology was negative for HIV, syphilis, Lyme disease, mycoplasma, HSV IgM, FSME IgM, coxsackie, HCV, HBV, toxoplasma, influenza A and B, parainfluenza 1-3, LCM virus, Q fever, VZV IgM, except for elevated IgM and subsequently elevated IgG titers for polyoma virus. Later in the course there was evidence of intermittent CMV hepatitis with elevated liver enzymes and a transiently positive IgM response to CMV. PCR analysis of the CSF was repeatedly negative for CMV, but was positive for BK virus at the height of the clinical picture. MRI scanning showed increased signal intensity in the cerebral white matter without Gd enhancement, which would be atypical for CMV encephalitis, and later reversed to normal. Our observations suggest that BK virus may induce an encephalitis even in immunocompetent patients, and that diagnostic tests for BK virus should be included in the screening program for encephalitis.

Oral Session 17 - Epilepsy (1)

1
RELAXOMETRY AND VOLUMETRICS OF HIPPOCAMPUS IN THE PREOPERATIVE EVALUTION OF INTRACTABLE TEMPORAL EPILEPSY. W Van Paesschen, RA Grunewald, JS Duncan, A Connelly, GD Jackson, S Sisodiya, AA Raymond, SD Shorvon, DR Fish, JM Stevens, *London, UK*

We measured T2 values (Neurology 1993; 43 1793) and volumes (Brain 1992; 115 1001) of the hippocampus in the preoperative evaluation of 36 patients with intractable temporal lobe epilepsy. Twenty seven (75%) patients had abnormally increased hippocampal T2 values and hippocampal volume loss ipsilateral to the seizure focus The diagnosis of hippocampal sclerosis (HS) was pathologically confirmed in all 20 patients who underwent temporal lobectomy so far T2 ratios (R/L) correlated with volume ratios (L/R) (r=0 84). Nine patients (25%) had normal or mildly abnormal hippocampal T2 values and volumes. Four had a temporal tumour identified on routine MRI scans, while the other five had no abnormality on the MRI. Two of these were operated one patient had a vascular malformation not recognised on MRI, and one had a normal hippocampus. Two of the 5 patients (40%) with normal MRI versus 4 of the 27 patients (] 5%) with HS required depth electrodes as part of the preoperative evaluation. In conclusion, T2 values and volumes of hippocampus accurately predict the presence of HS in patients with intractable temporal lobe epilepsy In the subgroup with normal T2 values and volumes, pathology other than HS is present. Quantitative MRI appears to decrease the need for invasive EEG studies

2
LOCALIZATION OF FRONTAL FOCI WITH [11C] FLUMAZENIL PET. I Savic, S Pauli, JO Thorell. *Stockholm, Sweden*

With the presently available non invasive methods only about 50% of frontal lobe foci are correctly localized. In an attempt to develop a new approach, six patients with frontal lobe seizures were investigated with PET and the benzodiazepine (BZ) receptor antagonist [^{11}C]flumazenil. Seven healthy men served as controls. The reference methods were seizure semiology, intracranial/scalp EEGs and in four cases the [^{18}F]FDG PET. The focus region was determined visually, from the uptake images of [^{11}C]flumazenil and the PET images representing regional BZ receptor density, as the area with maximally reduced ligand concentration/BZ receptor density in relation to the homotopic reference region. When the values from this area were outside the 95% confidence interval for the corresponding control values, and the percent difference in relation to the homotopic region was higher than the corresponding differences for all the other homotopic pairs in the same subject, the visually selected region was defined as the PET focus. The BZ receptor images offered a correct localization in all six, and the [^{11}C]flumazenil uptake images in five of the patients. The [^{18}F]FDG PET depicted 50% of the seizure onset regions.

3
THE INTERACTIONS OF VALPROIC ACID WITH CARBAMAZEPINE IN EPILEPTIC CHILDREN. MR Delgado, H Liu, RH Browne. *Dallas, Texas, USA*

In two groups of epileptic children receiving carbamazepine (CBZ) therapy, with (n=31) or without (n=57) valproic acid co-medication (CBZ+VPA), the drug interactions of VPA on the concentrations, concentration ratios and level/dose ratios of CBZ and its metabolites were investigated Serum total and free CBZ10, 11-epoxide (CBZ-E) concentrations were significantly increased in CBZ+VPA patients, together with higher CBZ-E/CBZ concentration ratios and CBZ-E level/dose ratios These results reflect accumulation of CBZ-E The decreased concentration ratios of trans-10, 11-dihydroxy-10, 11-dihydro-CBZ (CBZ-H)/CBZ-E observed in CBZ+VPA patients suggest an inhibition in the biotransformation from CBZ-E to CBZ-H Significant negative correlations were found between serum VPA level and CBZ-H/CBZ-E concentration ratios, indicating that the inhibition of CBZ-E hydrolysis may depend on the concentration of VPA (total, or free CBZ H/CBz-E concentration ratio). Patients with CBZ+VPA had significant higher free fractions of CBZ and CBZ-E than monotherapy patients, suggesting a protein binding displacement by VPA VPA concentration also showed significant positive correlations with CBZ level/dose ratios, implying decreased elimination of CBZ with increased VPA

4
AMINO ACID CONCENTRATIONS IN THE HUMAN PUTAMEN DURING POSTNATAL DEVELOPMENT AND AGING. ME Kornhuber, J Kornhuber. W Retz, P Riederer, *Munich & Würzburg, Germany.*

Neurochemical data on the human brain is scarce. This is also true for neurotransrnitter amino acids. Therefore, we have studied the amino acids in the human putamen with postnatal development and aging. 45 autopsy specimens (age at death 0.1 to 95 years) were weighed, homogenized and deproteinized after appropriate storage and the amino acids measured by HPLC. The results clearly demonstrate specific alterations. The excitatory amino acids, glutamate and aspartate, increase steeply during the first year to reach a plateau and remain fairly constant thereafter. These alterations go in parallel with the development of neurons, synaptic contacts and neurotransmitter receptors. By way of contrast, Glutamine shows an early decrease, a plateau and an increase with old age. Taurine and phosphoethanolamine decrease throughout life in about an exponential manner.

5
CLINICAL AND NEUROPHYSIOLOGICAL CORRELATIONS IN PATIENTS WITH REFRACTORY PARTIAL EPILEPSY AND INTRACRANIAL STRUCTURAL LESIONS. F Boon, J de Reuck, L Calliauw, I Hoksergen, E Thiery, J Caemert, D Decoo, A Desomer, *Gent, Belgium.*

Twenty patients with a mean duration of refractory seizures of 17 years and an intracranial, intra axial, structural lesion, detected by neuro imaging were enrolled in a presurgical protocol including video-scalp-EEG monitoring, neuropsychological assessment and positron emission tomography (PET). Five patients underwent invasive monitoring with depth and subdural electrodes. Lesions were mainly located in the temporal lobe (55%). Most patients (90%) presented complex partial seizures. Clinical seizure characteristics correlated well with lesion location in 55% of patients. Interictal EEG, that showed focal epileptic activity in 85% and focal slowing in 30% of patients, lateralized concurrently with the side of the lesion in 85%, and localised concurrently with the lobe of the lesion in 65% of patients. Octal EEG lateralized correctly in 70% and localised correctly in 50% of patients. Neuropsychological assessment lateralized and localised congruently in respectively 47% and 41% of patients. In 81% of cases interictal PET showed focal and congruent interictal hypo metabolism. Invasive EEG findings were congruent with lesion location in 3/5 patients but extended well beyond the area of the lesion in 2/5 patients. Complete surgical removal of the lesion, regardless of other findings, resulted in a >90% reduction of seizures without neurological deficit in 12/13 patients after average follow-up of 14 months.

6
LAMOTRIGIN IN LENNOX GASTAUT SYNDROME: AN EEG CONTROL STUDY. Y Chevalier, A Grinspan, E Hirsch, J Moszkowski, C Marescaux, *Strasbourg, France*

Three open studies including 11 to 24 patients and based on clinical criteria have suggested the effectiveness of Lamotrigin in Lennox-Gastaut syndrome. This syndrome associates generalised tonico-clonic seizures, atonic seizures, but also myoclonic jerks, atypical absences and nocturnal tonic seizures, which are often difficult to identify. We proposed a new study based on both clinical and EEG quantification of the seizures. A 24-hour video-EEG recording was performed before and after 4 and 12 months of treatment. In addition, the patient's family was asked to complete a diary about the patient's seizures. Lamotrigin was added to the previous treatment, which remained unchanged. EEG analysis was performed by .m independent investigator, blind to the experimental conditions. The aim of this methodology is to evaluate, using objective criteria, the actual effect of Lamotrigin. Sixteen patients are now included in this study. Twelve of them have been followed for more than 4 months and, in six of them, seizures have significantly decreased. Results of the blind analysis of EEG will be discussed.

7
NOCTURNAL SEIZURES IN ADULTS: A BENIGN PARTIAL EPILEPTIC SYNDROME. BA Yaqub. *Riyadh, Kingdom of Saudi Arabia*

We evaluated the clinical characteristics and the electroencephalographic (EEG) findings by long video-split EEG monitoring in 64 successive patients with definite nocturnal seizures. Mental state, neurological examination, neuro-imaging and EEG background were normal in all patients. Classification of seizures was possible in 42 out of 64 (66%) patients according to the revised Classification of Epilepsies and Epileptic Syndromes by the Commission on Classification and Terminology of the International League Against Epilepsy (1989). Out of those 42 patients, 33 (79%) had partial epilepsies while 9 (21%) had generalised epilepsies. The response to anti-epileptic drugs was excellent with only 4 (6%) having one seizure per year; 2 of them were on 2 anti-epileptic drugs while the others were free of seizures on a single drug during the 2 years of follow up. It seems that nocturnal seizures in adults form a distinctive benign partial epileptic syndrome.

Oral Session 18 - Epilepsy (2)

1
SUCCESSFUL TREATMENT OF GELASTIC EPILEPSY BY RESECTION OF HYPOTHALMIC HAMARTOMA. JM Valdueza, MJA Puchner, O Dammann, A Vortmeyer, H-D Herrmann. *Hamburg, Germany*

Hypothalamic hamartoma have been shown to be the main cause of gelastic epilepsy.. Our report summarises the experiences gained in the treatment of gelastic epilepsy in four patients from a series of six cases with hypothalamic hamartoma (two boys and two girls, aged four to six years at the onset of the gelastic fits). Other symptoms included behavioural abnormalities and generalised seizures in 3 cases, and precocious puberty and associated developmental defects in one case. MR imaging was performed in all cases revealing a mass of 1.5 to 2 cm in diameter with broad attachment to the mammillary bodies in all cases, and a displacement of the floor of the third ventricle in three cases. There were three non responders to medical treatment. Surgical resection was performed without morbidity and yielded good to excellent results when considering the severity of the epilepsy and behaviour abnormalities in two patients. Due to a mild degree of epileptic activity in one patient, no surgical treatment was recommended. In the fourth patient, carbamazepine alone was effective in controlling the seizures. We think that with introduction of MRI technology and laser-assisted microsurgical techniques, a surgical approach to the hamartoma itself is a valuable therapeutic modality for the management of severe cases if medical control was not achieved.

2
COMPUTERIZED BRAIN ATLAS DEMONSTRATES BRAIN DISTORSIONS IN PATIENTS WITH PRIMARY GENERALIZED EPILEPSY. I Savic, S Pauli. *Stockholm, Sweden*

Morphological analyses of brains from patients with primary generalized epilepsy (PGE) indicate the existence of migrational disturbances, especially in the cerebellum and the frontal lobes. Conventional MRI is however normal in these patients. We have used a computerized anatomical brain atlas to detect possible brain distortions that could be an effect of the reported microdysgenesis in PGE. Nine patients with PGE were compared with eight healthy men, eight patients with partial nine with secondary generalized epilepsy. A11 the subjects had normal CT scans and NMRs. The antiepileptic drugs were phenytoin and/or carbamazepine. The contours of the brain atlas were first adapted to each subject's NMR images, using parameters for the form, size and rotation of the brain. The values for each parameter were then compared between the four investigated groups (one way ANOVA with Bonferroni correction). In contrast to other groups, the patients with PGE had significantly ($p< O.O5$) smaller brains in the cranio-caudal direction, with a disproportionally small caudal part. Their brains were also antero-frontally elongated in relation to the posterior part. Conclusion: The findings are consistent with the previously reported microscopic cerebellar changes in PGE. The study shows a new approach to detect anatomical abnormalities when the conventional NMR is normal.

3
DYNAMIC COMPUTERIZED DISPLAY OF EPILEPTIFORM DISCHARGES. W Peterson. *Washington; USA.*

Three dimensional spacial display of paroxysmal discharges appears to be a useful as a method of evatualing the focus and propagation of epileptiform discharges. Dynamic computerized display of focal epileptic discharges has been investigated in 10 patients with complex partial seizures and focal Electroencephalogram (EEG) epileptiform discharges. Focal epileptiform discharges were digitally recorded and based on the eccentric dipole model three dimensional simulated paroxysmal discharges were mapped onto 3 dimensional computer representations of the brain. The temporal evolution of these discharges allowed for viewing the development of paroxysmal discharges topographically and sequencially. Localization of cerebral electrical potential sources remains a central problem for electroencephalography. The application of dynamic computerized display of cerebral potential may prove to be a useful technique in the evaluation of patients with epilepsy and other disorders of the cerebrum.

4
EFFECT OF SODIUM VALPROATE ON CENTRAL BENZODIAZEPINE RECEPTORS IN PATIENTS WITH IDIOPATHIC GENERALISED EPILEPSIES. MJ Koepp, MC Prevett, JS Duncan, V Cunningham, DR Fish, DJ Brooks, *London, UK*

We tried to determine the effect of sodium valproate (VPA) on cerebral central benzodiazepine receptors (BZR) in patients with idiopathic generalized epilepsy (IGE). In a cross-sectional study patients with IGE receiving VPA had a mean 8% reduction of 11 C-Flumazenil volume of distribution (11 C-Fmz-Vd) (Prevett et al 1992). In a longitudinal study we calculated 11C-Fmz-Vd in 5 patients with IGE, aged 19-56 years, using tracer alone high specific 11C-Fmz-PET scans. The first scan was performed when the patient was not taking VPA and the second four weeks after the addition of VPA up to the clinically indicated dose. Vd before and after treatment were compared in each patient and with a group of 5 age-matched controls. The addition of VPA was associated with a reduction of 11 C-Fmz-Vd. Conclusion: These preliminary results suggest the possibility that chronic VPA therapy results in downregulation of the GABA-BZR complex, which may be relevant to the mode of action of the drug.

5
INSIGHTS INTO THE MECHANISMS OF ACTION OF THE ANTIEPILEPTIC DRUG GABAPENTIN. AN IN VITRO STUDY USING PRIMARY NEURONAL CULTURES. A Pomes, C Sunol. *Barcelone, Spain*

Gabapentin is a new anticonvulsant drug. In this work we have investigated the effect of gabapentin on GABA inhibitory neurotransmission related to the $GABA_A$ receptor: the binding site of the picrotoxinin convulsing drug by using t-[^{35}S]butylbicyclophosphorothionate (TBPS) and the GABA-induction of Cl- flux by measuring the^{36} $^{CR}Cl^-$ uptake. The study has been performed using in vitro neuronal systems (primary neuronal cultures from cerebellum and neocortex) which express the $GABA_A$ receptor. Gabapentin (10^{-8}-10^{-3} M) did not modify the binding of TBPS to primary neuronal cultures either from cerebellar granule cells or from neocortical cells. When GABA was added to the incubation buffer, a statistically significant decrease of the binding of TBPS was observed and this

decrease was reverted by the GABA antagonist bicuculline. Gabapentin neither modified the effect of GABA nor the effect of GABA + bicuculline Gn the TBPS binding. GABA neurotransmission was quantitatively assessed by studying the GABA-induced $^{36}Cl^-$ uptake in neuronal neocortical cells. Short incubation (5s) of primary neuronal cortical cultures with 5-30 IIM GABA increased the basal $^{36}Cl^-$ uptake by 130- 230% and this increase was completely abolished by bicuculline and picrotoxinin. Gabapentin neither modified the GABA induced $^{36}Cl^-$ uptake nor the blockade of this increase by picrotoxinin. These results indicate that the action of gabapentin is not related to an interaction with the $GABA^A$ receptor at the picrotoxinin recognition site and that the anticonvulsant properties of this drug are not mediated by an enhancement of Cl- fluxes induced by GABA.

6
RELEVANCE OF EPILEPTIC FOCUS AND MORPHOLOGICAL SUBSTRATE FOR MEMORY PERFORMANCE IN PATIENTS WITH TEMPORAL. HF Durwen, *Bochum, Germany*

Depending on the lateralisation of the epileptic focus patients with temporal lobe epilepsy show material specific memory deficits. However, it remains unclear until now, whether the impairment is determined by the epileptogenic neuronal alteration or by possibly underlying morphological substrates. In order to test this hypothesis we investigated 26 patients with intractable complex partial seizures of left temporal lobe origin using a German version of the AVLT (Auditory Verbal Learning Test). Patients with temporomesial or neotemporal localisation of the epileptic focus as well as morphological lesions in the same locations but with different distribution were compared using ANOVA for statistical analysis. The results show that particular steps of memory processing are significantly influenced by the localisation of the epileptic focus ($p < 0.01$), whereas the localisation of the morphological lesion has no such effect. Patients with temporomesial localisation of the epileptic focus showed significant impairment. These findings suggest that the epileptogenic alteration of the neuronal network in particular region of the temporal lobe rather than a circumscribed morphological lesion is important for memory performance in temporal lobe epileptics.

Oral Session 19 - Multiple Sclerosis (3)

1
MULTIPLE SCLEROSIS, AZATHIOPRINE AND RISK OF CANCER A 25 YEAR EXPERIENCE. Ch Confavreux, J Grimaud, P Saddier, T Moreau, P Cortinovis-Tourniaire, G Aimard, P Adeleine, *Lyon, France*

There is still concern about induction of cancer when using azathioprine as treatment in multiple sclerosis. This issue has been addressed systematically trough the Lyon Multiple Sclerosis Database which is in usage since 1976. Among the 1310 cases of the database, 23 developed a cancer, 16 solid tumors, 2 skin epitheliomas, 1 secondary liver adenocarcinoma, and 4 primary hematopoietic neoplasms. There was no case of multiple cancers. Incidence of azathioprine treatment was 61% in the cancer group vs 49% in controls (Odds ratio = 1.7; 95% CI: 0.6, 4.6; p = 0.29). Cumulative doses of treatment was splitted using different cutpoints. Conditional logistic regression did not show increasing relative risks of cancer with increasing cumulative doses of azathioprine treatment. Results obtained from total duration of azathioprine were similar. In conclusion, although the duration/dose effect of azathioprine treatment on cancer development was suggestive, it did not reach statistical significance, even using 10 years of treatment duration and 600 g of cumulative dosages as cutpoints. These findings should be considered in evaluating the benefits/risks ratio of azathioprine in the treatment of multiple sclerosis.

2
CORRELATION BETWEEN CHANGES IN DISABILITY AND MRI ACTIVITY IN MULTIPLE SCLEROSIS; A FOLLOW UP STUDY. M Filippi, DH Miller *(London-UK)*; DW Paty *(Vancouver-Canada)*, L Kappos *(Basel-Switzerland)*, F Barkhof *(Amsterdam, The Netherland)*, DAS Compston *(Cambridge)*, CM Wiles *(Cardiff)*, AJ Thompson, WI McDonald *(London-UK)*

Previous longitudinal studies have reported little or no correlation between changes on brain magnetic resonance imaging (MRI) and the clinical status of multiple sclerosis (MS) patients, perhaps because of small numbers of patients and short follow up periods. The aim of this study was to correlate changes in disability and MRI activity in a large cohort of MS patients followed up for 2 to 3 years. Two unenhanced brain MRI scans were obtained 24 to 36 months apart in 281 clinically definite MS patients. The number of new and enlarging lesions present on the second T2-weighted scan were counted and correlated by the Spearman Rank Correlation Coefficient (SRCC) with changes in disability rated using Kurtzke's EDSS. The numbers of new (SRCC=0.13, p=0.02) and enlarging (SRCC=0.18, p=0.002) MRI lesions and their sum (SRCC=0.13, p=0.02) all correlated with changes in disability over the follow up period. The strongest correlations came from patients with relapsing-remitting MS. The present study's cohort size and duration of follow up approximate the requirements of large scale clinical treatment trials. The results suggest that MRI monitoring of disease activity in such a context is clinically relevant.

3
MORTALITY AND DISABILITY IN MULTIPLE SCLEROSIS IN WESTERN NORWAY. R Midgard, T Riise, G Kvale, H Nyland, Molde, *Bergen; Norway.*

The trend in age-adjusted average annual incidence, mortality and disability pension rates for multiple sclerosis from 1966 to 1991 were examined in an ethnically stable county in Western Norway. The incidence rate increased from 4.22/105 in 1966-68 to 6.03/105 in 1987-89 [p=0.003]. The mortality rate in the county rose from 0.91/105 in 1966-68 to 2.73/105 in 1987-89 [P=0.01] while the national mortality rate increased from 1en patients reported on persistent symptoms related to the peripheral nervous system at the time of follow-up. Frequent subjective complaints were paresthesias in feet and hands, unsteadiness of gait and muscle cramps in the lower extremities. Careful neurological examination revealed neuropathic signs in 23 patients. The presenting clinical signs are mainly sensory disturbances due to large fibre dysfunction and decreased tendon reflexes restricted to the lower extremities. Vibration perception threshold w.11/105 to 1.88/105 in the same period [p=0.16]. The incidence rate of disability pension recipients due to MS increased from 3.62/105 in 1966-68 to 5.04/105 in 1987-89 [P=0.31]. The first year of reception of disability pension was taken as an indirect measure of disability. The point prevalence rates of disability pension recipients due to MS by the end of each year were significantly different when comparing the rates in the county [1967: 26.2/105, 1991: 72.9/105] to the national rates [1967: 34.5/105, 1991: 58.6/105](p=0.002).

4
COMPARATIVE STUDY OF NMR AND IMMUNOHISTOLOGICAL FINDINGS IN ADOPTIVE TRANSFER EAE. SP Morrissey H Stodal, U Zettl, R Kiefer, A Haase, H Lassmann, HP Hartung, KV Toyka, *Wurzburg, Germany & Vienna, Austria.*

Over the last decade increasing evidence accumulated that Magnetic Resonance Imaging (MRI) is the investigation of choice in Multiple Sclerosis (MS), and is increasingly used to monitor the disease activity in therapeutic trials. Of particular interest is the relationship of pathological Gd-DTPA enhancement - as a MRI marker of opening of the blood-brain barrier and inflammatory infiltrates in the CNS. We studied an animal model of MS, adoptive transfer Experimental Allergic Encephalomyelitis (AT-EAE) in Lewis rats and correlated pre- and post-GD-DTPA MRI of the brain using fast T1-maps with clinical and histological findings. MRI of the brain was performed over the whole course of the disease. Results: Significant T1changes were observed even before onset of clinical signs (as early as 4-8 hours post injection). In EAE rats on day 3,5 +7 a widespread, non-focal significant decrease of T1values was observed in the brainstem and midbrain. The MRI changes broadly correlated with the number of inflammatory cells (T-cells and macrophages) and with the intensity and extent of the albumin stain. Conclusion: Our data suggest that pre- and post-GD-DTPA T1-changes as evidenced in AT-EAE in Lewis rats broadly parallel the histological findings of infiltrating inflammatory cells and albumin extravasation.

5
VASCULAR CELL ADHESION MOLECULE -A NOVEL APPROACH TO DETECT ENDOTHELIAL CELL .ACTIVATION IN MS IN VIVO. R Mobner, K Fassbender, A Schwartz, M Hennerici, *Mannheim, Germany*

A hallmark of multiple sclerosis (MS) is perivascular inflammatory infiltrates, which are present in acute lesions. It is now becoming clear that vascular endothelium plays a central role in controlling leukocyte immi-

gration into tissues. Control of leukocyte migration into inflammatory lesions is exercised by adhesion molecules present on activated vascular endothelium. Pivotal among these are E-selectin and the vascular cell adhesion molecule-1 (VCAM-1), which are found on very few cell types other than endothelium activated by infectious agents or cytokines. We determined the presence of the soluble form of these adhesion molecules (sE-selectin and sVCAM-1) in serum and CSF of patients with multiple sclerosis and viral encephalitis using enzyme-linked immunosorbent assays. MS patients with active, gadolinium enhancing MRI lesions had significantly higher sVCAM-1 serum levels than did control subjects ($P<0.05$). Patients with viral encephalitis had significantly higher levels of sVCAM-1 in serum ($P<0.02$) and cerebrospinal fluid ($P<0.02$) than controls. sE-selectin levels showed no significant variations. These results show that activated vascular endothelium controlling leukocyte migration into brain lesions can be demonstrated in MS patients in vivo by determining sVCAM-1. Furthermore, sVCAM-1 is useful as a monitor of inflammatory activity in central nervous system inflammatory disease.

6
ACUTE MYELITIS: A LOCALISED FORM OF ACUTE DISSEMINATED ENCEPHALOMYELITIS. SM Al Deeb, B Yaqub, GW Bruyn, N Biary. *Riyadh, Kingdom of Saudi Arabia.*

We present 31 patients (20 men, 11 women; mean age 30 (18-51) years) with acute quadriparesis or paraparesis with sensory and sphincter disturbances which frequently occurred after flu-like or febrile illness. Mental state, cranial nerves and cerebellar functions were normal. The lesions were cervical or upper thoracic in 11 (35%), mid-lower thoracic in 17 (55%) and in the conus in 3 (10%). CT myelography showed abnormalities in 3 out of 10, suggesting an intra-medullary tumour, and MR showed cord swelling in 12 out of 21 patients with enhanced, scattered, high intensity lesions on T1, over a long area. Brain MR was normal. CSF showed mild pleocytosis and mild to moderate rise in protein with normal IgG index and no oligoclonal bands. Pattern shift visual and brainstem auditory evoked potentials were normal. Somatosensory evoked potentials were either normal (12/20) or severely abnormal (8/20) with loss of cord and brain potentials. Extensive CSF and blood screen failed to identify any infectious aetiology. The outcome was complete remission in 10 (32%), marked improvement with minimal deficit in 8 (26%), moderate improvement with independent mobility in 6 (19%), slight or no improvement with severe spasticity and spasm in 6 (19%), one death being due to pulmonary embolism in an obese patient. Follow-up for a period of 1 to 10 years revealed no relapses. Although these patients form a special disease entity, they are apparently related to a localised form of acute disseminated encephalomyelitis rather than to multiple sclerosis (MS) in view of the monophasic attacks, the male preponderance, manifestation after febrile episodes, normal IgG-index, and the occurrence in an area of low MS prevalence.

7
TAP2 GENE POLYMORPHISM CONTRIBUTES TO THE GENETIC SUSCEPTIBILITY TO MULTIPLE SCLEROSIS. G Semana, H Teisserenc, M Alizadeh, P Loiseau, G Edan, B Birebent, J Yaouanq, B Genetet, O Sabouraud, DJ Charron. *Paris, Rennes; France.*

The aim of this study is to analyse TAP1 and TAP2 membrane transporter gene involvement in the susceptibility to multiple sclerosis (MS). These two genes are located within the HLA class II region and their products are involved in endogenous antigen processing. A population of 116 unrelated MS patients was compared to a control population of 46 subjects and to a control population of 79 HLA DR15 subjects. TAP1 and TAP2 alleles (4 for TAP1, 8 for TAP2) were typed by PCRSSO technique. An additional mutation of TAP2 generating two variants (I/J) was analysed. Results: Comparison of TAP1 and TAP2 allele frequencies in MS and controls showed no significant allele variations. Analysing TAP2-I and TAP2-J mutations revealed an increased frequency of TAP2-J in MS patients (gene frequency 33 % in MS vs 11,4 % in controls - $p < 10\text{-}6$). We have then compared TAP2-I /-J allele distribution in DR15 positive MS ($N = 54$) and controls (N-79). This comparison showed that TAP2-J allele frequency is at least doubled in MS population (40,8 % vs 19,6 % - $pc < 10\text{-}3$), suggesting that J mutation is not in linkage disequilibrium with HLA-DRB1 *1501. Conclusion: The present study showed that TAP2 gene and particularly a specific variant TAP2 J characterised by a mutation at nucleotide 1158 is involved in susceptibility to MS. Further calculations suggests that TAP2-J allele is acting as additional susceptibility marker conferring a higher RR to develop the disease.

Oral Session 20 - Multiple Sclerosis (4)

1
MYELIN ASSOCIATED GLYCOPROTEIN MEDIATES OLIGODENDROCYTE BINDING TO AXONS. CE Shaw, DAS Compston, *Cambridge, UK.*

Myelin associated glycoprotein (MAG) is a member of the immunoglobulin superfamily of adhesion molecules (Williams and Barclay, 1988). It is expressed by oligodendrocytes in a periaxonal location early in myelination (wood 1984) An axonal ligand for MAG has yet to be identified and its role in mediating glial-axonal interactions is unclear. By coculturing rat oligodendrocyte progenitors with purified dorsal root ganglion (DRG) neurones as an in-vitro model of CNS myelination (Wood 1984) we have shown that the regional expression of MAG on oligodendrocytes is influenced by axonal contact. The change in distribution from a diffuse pattern over the cell body of those cells not in contact with axons, to being confined to discrete foci along those oligodendrocyte processes unsheathing axons, suggests that MAG is binding to axons. By using a chimerical protein containing the extracellular domain of MAG bound to fluorescent Covaspheres, we have shown binding of the MAG protein to the growth cone and distal portion of DRG axons. MUC-18 a related myeloma associated glycoprotein did not bind to axons. In co-culture MAG was detectable only after the initial ensheathment of axons had occurred. We conclude that MAG has an axonal legend and that it may have a role in the maintenance of glial/axonal contact.

2
SHORT-TERM EFFECTS OF 2-CHLORODEOXYADENOSINE (2-CDA) IN REMITTING-RELAPSING MULTIPLE SCLEROSIS (MS). C Stelmasiak, J Solski, J Nowicki, B Jakubowska, M Ryba, P Grieb. *Lublin & Warsaw, Poland*

2-CDA (cladribine) is a new potent antileukemic and immunosuppressive nucleoside with limited side effects. Clinical improvement and disappearance of oligoclonal antibodies from CSF were reported in 4 progressive MS patients following treatment with this drug (cf. Beutler, Lancet 340:952, 1992). The present study has been undertaken to test safety, tolerability and short-term effects of 2-CDA in remitting-relapsing MS. The drug was donated by the Foundation for the Advancement of Diagnostics and Therapy (Warsaw). Ten patients were treated by 1/2 of maximal tolerated dose established for oncohematologic applications (0,14 mg/kg orally or 0,07 mg/kg subcutaneously once daily for 5 consecutive days). Courses were repeated every 4 weeks. Clinical status and blood counts were monitored monthly. We observed progressive mild leucopenia due to moderate lymphopenia. No infections, thrombocytopenia or other side effects occurred. on average, a slight improvement in neurological status was noted, in Kurtzke scale from 4.5 at the entry to 3.05 after the third course ($p<0.05$). Treatment of remitting-relapsing MS with 2-CDA deserves further evaluation in longer follow-up and in controlled studies.

3
TUMOR NECROSIS FACTOR GENE REGION POLYMORPHISMS AND MULTIPLE SCLEROSIS. A Garcia-Merino, K Usuku, E Yunis, C Alper, SL Hauser, *Madrid, Spain; San Francisco and Boston, USA.*

Tumor necrosis factor-a (TNF) and lymphotoxin (LT) are closely related cytokines with a profound role in inflammation and immune regulation. Both seem to be relevant in experimental autoimmune demyelination. In multiple sclerosis (MS), there is also evidence supporting the involvement of those cytokines in disease pathogenesis. TNF and LT genes map between class III and class I of the major histocompatibility region (MHC). To investigate whether the MHC association with MS might be related to genetic variability in the TNF region, polymorphisms of three microsatellites (A, B, and C) flanking the LT gene were analyzed by PCR amplification in 39 multiplex MS families with 91 patients out of a total number of 235 individuals. The presence of some TNF alleles was in linkage disequilibrium with some HLA extended haplotypes, in particular B7-DR15-DQw6, overrepresented in MS families. However, analysis of frequency showed no differences in chromosomes from healthy siblings and in patient-derived chromosomes for alleles of the three microsatellites. Our data suggest that there is no association between MS and TNF or LT genes.

4
HLA, GM, KM, AND BF ALLOTYPES AND SEVERITY OF MULTIPLE SCLEROSIS. Ch Confavreux, T Moreau, P Adeleine, H Betuel, L Gebuhrer, JP Salier, G Aimard. *Lyon, France.*

The genetic factors in susceptibility to multiple sclerosis (MS) are now well demonstrated (race, twin, immunogenetic studies). In contrast, the study of genetic influence on the severity of MS has led to conflicting results. We studied the prevalence and the influence on severity by actuarial methods of the HLA system. the immunoglobulin allotypes Gm, Krn and the complement ailotype Bf in 355 MS patients. We selected from the LYON-MS database cases with definite MS according to Poser's criteria. HLA-A (16 antigens tested), HLA-B (20), HLA-C (7) and HLA-DR (12) were performed serologically. Gm (6 antigens tested), Km. Bf (4) allotypes were determined for 118 patients. The time to reach DSS3 (according to the Kurtzke's Disability Status Scale) defined the moderate disability and DSS7 the severe disability. The antigens over represented (A30, B7, DR'7) or under represented (A3 1, C6) in this MS population were not severity factors. In contrast, HLA-A10 and DR11 had only a tendency to be indicators of a poor prognosis and HLA-B 12 a better one. In conclusion; the immunogenetic markers cannot be used as a definitive factor for prognosis. Particularly, the susceptibility antigens were not indicators of severity.

5
LEBER'S HEREDITARY OPTIC NEUROPATHY MITOCHONDRIAL DNA MUTATIONS IN MULTIPLE SCLEROSIS. N Robertson, H Kellar-Wood, GG Govan/ DAS Compston, AE Harding, *Cambridge and London, UK*

The occurrence of a multiple sclerosis (MS)-like illness in patients, particularly females, who have a Leber's hereditary optic neuropathy (LHON) mitochondrial DNA (mtDNA) mutation at bp 11778 suggests a possible contributory role for mitochondrial genes in genetic susceptibility to MS. We screened 307 unrelated MS patients, ascertained from population surveys, for the pathogenic LHON mutations at bp 11778 and 3460 of mtDNA, and also studied 20 patients with prominent and early optic nerve involvement. Neither of the LHON mtDNA mutations occurred in the 307 unselected MS patients. Three of the cases selected on the basis of severe optic nerve involvement had either the 11778 (one) or 3460 (two) mutations, the latter not previously described in association with an MS-like illness. All were women and none had affected relatives. We conclude that these LHON mutations do not contribute to genetically determined susceptibility in typical MS patients, although a mitochondrial genetic component in the aetiology of MS remains possible. A subgroup of MS patients, particularly females with severe optic neuropathy, may harbour a LHON mutation and we suggest that mtDNA analysis is appropriate in such patients.

6
COP-1 MULTICENTER TRIAL IN RELAPSING REMITTING MULTIPLE SCLEROSIS: 3 YEAR FOLLOW UP. The COP-1 Multicenter Clinical and Research Group Study. *Tel Aviv, Israel.*

COP-1 is a mixture of synthetic polypeptides cross-reacting with myelin basic protein and suppressing experimental autoimmune encephalomyelitis. In a previous controlled trial in relapsing-remitting (RR) multiple sclerosis (MS) COP-1 reduced the relapse rate and the progression of disease. We report preliminary results of a 3 year follow-up of patients with RR-MS enrolled in an open multicenter phase III trial. Admission criteria included an Expanded Disability Status Scale (EDSS) score of 0 to 6 and at least 2 relapses in the previous 2 years. COP-1 was administered subcutaneously 20 mg/day. Of 247 patients enrolled 7.6% dropped-out due to adverse effects and 14.4% withdrew voluntarily or were lost to follow-0up. For patients treated for at least 2 years, the annual relapse rate few from 1.36 ± 0.60 prior to treatment to 0.35 ± 0.51 ($P<0.05$),with 55% still relapse free. Over 70% did not deteriorate in either EDSS score or electrophysiological parameters. Injection site reactions were the most common side effects (34% of the patients) followed by transient systemic reactions, including dyspnea (15%) and vasodilatation (15%). The routine laboratory data remained unchanged. These results support the potential benefit and safety of COP-1 treatment in RR-MS.

Oral Session 21 - Cerebrovascular Disorders (3)

1
SUBARACHNOID HEMORRHAGE IN FIRST AND SECOND DEGREE RELATIVES OF PATIENTS WITH SUBARACHNOID HEMORRHAGE. JEC Bromberg, GJE Rinkel, A Algra,. J van Gijn, *Utrecht, The Netherlands.*

Aggregation of subarachnoid haemorrhage (SAH) within certain families has frequently been described but it is unknown whether relatives of patients with SAH are at increased risk of SAH. We studied the frequency of SAH among first and second degree relatives in a prospectively collected series of 165 patients with recent SAH. Histories and, where possible, medical documents were retrieved for all first and second degree relatives. For deceased family members the history was taken from a next of kin. Strict criteria were applied for the diagnosis SAH. Of 1267 first degree relatives, 9 had suffered a definite and 4 a possible SAH. Of 3541 second degree relatives, 4 had suffered a definite and 12 a possible SAH. The hazard ratio for definite SAH in first degree relatives when compared with second degree relatives was 5.9 (95% CI: 1.8-20), $P_{COX} = 0.003$. The difference between the cumulative incidences is significant: $P_{LeeDeSu} = 0.0002$. The hazard ratio including possible SAH was 2.2 (95% CI: 1.0-4.8), $P_{COX} = 0.043$, the $P_{LeeDesu} = 0.016$. The incidence of SAH in second degree relatives was similar to that in the general population. These data show that first degree relatives of patients with SAH have a two to six times greater risk of SAH than the general population.

2
DISSECTION OF CERVICAL ARTERIES: LONG-TERM COURSE. D Leys, T Moulin, T Stojkovic, D Chavrot, S Begey for the DONALD group *Lille, Besançon, France*

The long-term course of cervical artery dissections (CAD) remains unknown. The aim of the study was to evaluate the rate of stroke recurrence in the territory of CAD. Secondary end-points were (i) any stroke or transient ischemic attacks (TIA), (ii) death, (iii) recurrent CAD, (iv) headache or cervical pain, (v) recanalisation. Outcome events were validated by a neurologist. We included 109 consecutive patients admitted for CAD and discharged alive. Five patients (4.6%) dropped-out. The remaining 104 consisted of 46 females (44.2%) and 58 males (55.8%), aged 13 to 80 years (median; 42). The median follow-up was 35 months. CAD were located in carotid arteries in 62 patients (bilateral in 2), vertebral in 40 (bilateral in 1), and both in 2. The presumed causes were trauma in 33 patients, elastic tissue disease in 4, fibrodysplasia in 11 and unknown in 56. Eighty-eight patients received heparin and 16 had antiplatelet drugs at the acute stage. Ninety three patients had no outcome event; 76 (73 %) were independent (Barthel's index = 100); 3 patients had TIAs in the same territory and 2 had a recurrence of stroke; 5 patients died from other causes; 3 patients with elastic tissue disease had recurrent CAD within 1 year;

3
CLINICAL COURSE OF 56 PATIENTS WITH SPONTANEOUS CAROTID-CAVERNOUS SINUS FISTULAS TREATED WITH COIL EMBOLIZATION C Klotzsch, K Kaiser-Rub, HC Nahser, 'P Berlit, *Essen, Germany.*

A clinical, neuroimaging and laboratory study was performed to evaluate the pathogenesis and the clinical course before and after treatment of spontaneous carotid-cavernous fistulas (CCF). Corresponding to the classification of Barrows, 9 patients with type A, 8 with type B, 4 with type C and 36 with type D fistulas were included. Thirteen were men, 44 were women. The mean age was 61.4 years. The patients were treated with arterial and/or transvenous coil embolization; 2 had incomplete occlusion and 6 presented with recidivation. Vascular risk factors were present in 42% with arterial hypertension, 25% with hyperlipidemia and 12% with diabetes. 37% had coronary heart disease and 5% ischemic cerebral infarction. Elevated cardiolipine-IgM autoantibodies were found in 25%. The mean interval between the onset of first symptoms and diagnosis was 6.9 months. Chemosis and/or conjunctival hyperemia and protrusion of the bulb were found in 79% as the initial symptoms. 56% had diplopia, 30°/0 vision loss, 45% complained tinnitus and/or headache. After treatment conjunctival hyperemia, Chemosis and protrusion improved in 78% as the first clinical symptom. In the subsequent follow-up the cranial nerve palsies improved in 42%. The early clinical diagnosis of spontaneous CCF and subsequent coil embolization improves the outcome siginficantly and reduces the risk of persistent cranial nerve palsies.

4
HIGH FLOW EXTRACRANIAL-INTRACRANIAL BYPASS; A NEW TREATMENT FOR PATIENTS WITH SYMPTOMATIC OCCLUSION OF THE INTERNAL CAROTID ARTERY? CJM Klijn, CAF Tulleken, LJ Kappelle, J van Gijn. *Utrecht, The Netherlands.*

The risk of recurrent ischaemic stroke in patients with a TIA or minor stroke and an occlusion of the internal carotid artery is estimated at 5-8% per year. Since the negative results of the extracranial-intracranial (EC-IC) bypass study, which was published in 1985, secondary prevention by means of aspirin is the only treatment of proven value for these patients. In the department of neurosurgery of the University Hospital Utrecht, The Netherlands, a new promising 'high-flow' EC-IC bypass has been developed. With this new technique a branch of the external carotid artery is connected with the distal part of the ICA by means of an arterial or venous transplant. The final anastomosis of this new bypass is made with a laser catheter; therefore it is not necessary to occlude the recipient artery. After extensive testing on animals, to date eight patients with symptomatic ICA occlusion have been successfully treated with the new EC-IC bypass. No recurrent events have occurred during a follow-up of 2-21 months. one patient with not only an occlusion of the ICA but also a severe stenosis of the contralateral ICA, developed an infarct in the contralateral hemisphere during the operation. Currently, we are preparing a pilot study in which patients are randomised between 'high-flow' EC-IC bypass surgery (plus medical therapy) and medical treatment alone. The predictive value of vasomotor reserve capacity, assessed by transcranial Doppler, magnetic resonance spectroscopy and single photon emission computed tomography will also be studied in this pilot study.

5
DETERMINATION OF CAROTID ARTERY BLOOD FLOW VELOCITY AND VOLUME FLOW WITH MR TECHNIQUES: EVALUATION OF NORMAL SUBJECTS AND PATIENTS WITH CAROTID ARTERY DISEASE. KW Neff, M Daffertshofer, J. Kother, M Hennerici, A Schwartz. *Mannheim, Germany.*

Magnetic resonance angiography (MRA) has superseded conventional imaging methods for revealing vascular structures intra- and extracranially. Additionally the high sensitivity of MR flow detection provides the potential for the non-invasive measurement of blood flow velocity and volume flow by dynamic MR presaturation bolus tracking and phase-contrast cine MR imaging. In 30 healthy volunteers and patients, the common carotid artery (CCA) and the internal carotid artery (ICA) were examined. Blood flow velocities were measured by duplex sonography and flow-sensitive gradient-echo sequences with dynamic MR presaturation bolus tracking. Volume flow was calculated by fitting the approximately parabolic flow velocity profile and three-dimensional integration. In patients with carotid artery disease pre- and poststenotic reduction of flow was worked out in dependence of the stenosis, which was estimated by DSA and duplex B-scan. Correlations for dynamic MRA bolus tracking and ultrasound results were rs = 0.99 ± 0.03 for systolic peak velocities and r_d = 1.03 ± 0.04 for diastolic maximum velocities in the CCA. Equally good correlations were obtained for the ICA. Dynamic MRA bolus tracking measurement of blood flow velocity is highly correlated with conventional ultrasonographical results. In patients with carotid artery disease pre- and poststenotic flow reduction highly depends on the stenosis, especially for volume flow determination. Initial clinical results for phase-contrast cine MR imaging proved this correspondingly.

6
FOCAL ISCHEMIA AND REPERFUSION INJURY IN RAT BRAIN: EFFECTS OF EITHER SUPEROXIDE DISMUTASE, NIMODIPINE OR MONOSIALOGANGLIOSIDE GM1. PRELIMINARY STUDY. JM Roda, F Carceller, E Diez-TeJedor. *Madrid, Spain.*

This study was performed to analyse whether either superoxide dismutase (SOD), nimodipine or the monosialoganglioside GM1 reduce infarct volume after focal cerebral ischemia, by means of our previously described experimental model, which allows the impregnation of the cerebral tissue with a hypothetic protective substance during ischemia and reperfusion. Four groups of five Long Evans rats each were subjected to focal cerebral ischemia. Groups 1 (control),2,3 and 4 received intra-arterial injection (IAI), through the external carotid artery, either of isotonic saline, nimodipine, SOD or GM1, respectively. Quantification of the volume of the cortical infarction was carried out applying an unbiased stereological method. Values were 191.6±36.97 cc, 110.32±44,77 cc, 109.74±29.53 cc, and 143.5±23.52 cc for groups 1,2,3 and 4, respectively. Values were significantly lower in groups 2 and 3 than in group 1 (Dunnett test; $p<0.01$). We conclude that the (IAI) of nimodipine or SOD reduces the volume of cerebral cortical infarction in rats subjected to focal cerebral ischemia, probably because of partial blockade of reperfusion injury.

7
CLINICAL COURSE AND PROGNOSIS OF MASSIVE CEREBELLAR INFARCTION. CR Hornig, DS Rust, O Busse, A Laun. *Giessen & Minden; Germany*

Case record forms, CT scans, surgery reports, and angiograms of 52 patients with space occupying cerebellar infarction defined by CT criteria were re-evaluated with regard to clinical course, aetiology, therapeutic management, mortality, and functional outcome. Clinical deterioration in most cases started on the third day after the stroke and a comatose state was reached within 24 hours. Sixteen patients were treated medically, 30 by suboccipital craniectomy (22 plus ventriculostomy, 12 plus tonsillectomy) . Ten patients primarily had a ventriculostomy, in 4 cases this had to be supplemented by craniotomy because of continuing deterioration. Twenty-nine patients made a good recovery, 15 remained disabled, and 8 died. Even comatose patients had a 38 % chance of good recovery after decompressive surgery. Age about 60 years (P=0.0043), and probably initial brainstem signs (P=0.0816) and a late clinical stage (P=0.0893) were linked with a fatal or disabling outcome. In conclusion decompressive surgery should be the treatment of choice of massive cerebellar infarction causing progressive brainstem signs or impairment of consciousness .

Oral Session 22 - Cerebrovascular disorders (4)

1
ENDOTHELIN-1, ANGIOTENSIN-II, AND ATRIAL NATRIURETIC FACTOR IN ANEURYSMAL SUBARACHNOID HEMORRHAGE. O Corabianu, A Berbinschi, C Chastang, J Cophignon, M Haguenau, JM Ketelslegers, *Paris, France & Bruxelles, Belgium*

We prospectively measured by radioimmunoassay blood and cerebrospinal fluid (CSF) levels endothelin (ET)-1, angiotensin (A)-II, two potent vasoconstrictors and atrial natriuretic facto (ANF), a vasodilator peptide, in 17 patients with aneurysmal subarachnoid hemorrhage (SAH), during the first week after the bleeding. These levels were compared with controls an correlated with the occurrence of cerebral vasospasm. Mean plasma ET-1-like and ANF-like immunoreactivity levels in patients with SAH were highly elevated during the whole stud period, while mean plasma A-ll-like immunoreactivity levels were in the normal range at onset and became significantly elevated at day 7 ($p < 0,03$). Compared to controls, patients with SA had normal CSF ANF-like immunoreactivity concentrations, higher CSF ET-1-like immunoreactivity levels and their mean CSF A-ll-like immunoreactivity levels significantly higher at onset ($p < 0, 01$) tended to remain elevated at day 7 ($p = 0, 06$). There was no correlation between the concentrations of neuropeptides and vasospasm. We conclude that in aneurysm SAH (1) ET-1, A-II and ANF are not predictors of vasospasm and (2) an imbalance between CS ET-1-like and ANF-like immunoreactivity levels on one side and ANF-like immunoreactivy concentrations on the other, may play a role in the pathogenesis of vasospasm.

2
LYMPHOCYTIC INFILTRATION AND EXPRESSION OF THE INTERCELLULAR ADHESION MOLECULE-1 (ICAM-1) IN PHOTOCHEMICALLY INDUCED ISCHEMIA OF THE RAT CORTEX. S. Jander, M Kramer, M Schröter, OW Witte, G Stoll; *Dusseldorf; Germany*

The contribution of immune mechanisms to focal ischemic brain damage is unknown. We have analysed leukocyte infiltration and the expression of the intercellular cell adhesion molecule-1 (ICAM-1) in photochemically induced focal ischemia of the rat parietal cortex by immunocytochemistry. T lymphocytes were seen around superficial and parenchymal vessels between day 1 and 2 after, lesion induction thereby preceding macrophages which appeared at day 2 or 3. Subsequently, both cell types increasingly infiltrated the borderzone of the infarct. T cells reached their peak during the first, macrophages during the second week. The core of the infarct was infiltrated with a delay of about 10 days. By lymphocyte subtyping the vast majority of infiltrating lymphocytes could be identified as CD 5-/CD 8+ natural killer cells. ICAM- 1 was expressed transiently in the rim

around the lesion during the first week after lesion induction. Core-infiltrating macrophages during the second week were largely ICAM- 1 negative. Lymphocyte-dependent cytotoxic mechanisms and upregulation of adhesion molecules may be important pathogenic factors and targets of experimental immunotherapy in focal ischemic brain injury.

3
CIRCULATING ADHESION MOLECULES IN ACUTE ISCHEMIC STROKE. K. Fassbender, R. Möbner, M. Hennerici; *Mannheim, Germany*

Expression of adhesion molecules which mediate endothelial adhesion and activation of leukocytes is essential in leukocyte mediated reperfusion injury. Circulating selectin-type (sELAM- l, sL-Selectin) and immunoglobulin-type (sICAM- 1 and sVCAM- 1) adhesion molecules have been studied in acute stroke. Soluble adhesion molecules have serially been determined at hours 4, 8, and lO and days l, 3, and 5 in serum of 20 patients with acute acute stroke in relation to functional and neurological outcome. Compared to healthy controls, levels of these molecules were significantly increased ($P<0.05$) at hour 8 until day 5 in patients with acute stroke. Maximal concentrations were found at hour 8 (sELAM-l), hour lO (sICAM-l, sL-Selectin), and at day 1 (sVCAM-l). Levels slowly decreased until day 5. A significant correlation between initial levels of VCAM- 1 and functional outcome was observed. The pattern of increase of circulating adhesion molecules in acute stroke points toward their early synthesis at sites of cerebral ischemia. The resulting adhesion, activation and passage of leukocytes into the CNS represents a key event in reperfusion injury in acute stroke.

4
INTERLEUKIN LEVELS IN THE CEREBROSPINAL FLUID OF STROKE PATIENTS. V Barak, I Sarova-Ponchas, Holon, *Tel Aviv, Israel*

Production of interleukines (IL) were found to play a role in brain ischemic events. Increase of cytokines were documented also in the cerebrospinal fluid (CSF) of age related stroke (proven diagnostically) patients. We examined IL levels in the CSF of 20 stroke patients (mean age 54 ± 12.4 years) 12-48 hours after the event and compared it to a control group of 20 others (mean age 51 ± 9.8 years). No significant differences were found between the CSF tumor necrosis factor, CSF-IL 2 and CSF-IL 1β in groups. The IL 2 receptor (IL 2R) level, different in both groups, was also non-significant. The mean levels were 74.8 ± 36.6 ug/ml in the stroke patients and 74.8 ± 36.6 ug/ml controls. Subgroup of five patients, all suffering from central nervous system vasculitis caused by stroke, demonstrated a very high level of IL 2 (281 ± 162 ug/ml) with a similar statistical significant measurement as compared with the other stroke patients ($p<0.05$) and the healthy controls ($p<0.001$). In three patients, the cerebrovascular symptoms were the presenting symptom of system collagen disease. High CSF-IL 2R may be a specific finding in stroke patients secondary to brain vasculitis.

5
SPONTANEOUS PARTIAL BRAINSTEM HEMORRHAGES. A REVIEW OF 25 CASES WITH INITIAL BENIGN COURSE. P Le Coz, F Woimant, M Haguenau, B George, JJ Merland, J Cophignon, M Haguenau, *Paris, France*

Level of consciousness at admission and size of bleeding usually y predicted the out come of patients with brainstem hematomas that were considered as benign when patients survived the acute event. We reported 25 patients (17 men and 8 women), aged from 25 to 8 years, all explored with CT scan or MRI. Neuroimaging showed limited (or partial) brainstem haemorrhages which most often laterally located with preferential or exclusive pontine involvement. 5 patients had isolated mesencephalic hematomas. No medullary hematoma was observed. Half of patients had no consciousness impairment during the course. Clinical picture consisted mainly of oculomotor signs isolated or less commonly associated with long-tract findings. Half of patients were hypertensive. In one case, angiography revealed a small arteriovenous malformation (AVM). All patients had a good to excellent recovery even when surgical treatment for acute hydrocephalus (2 cases) was required in emergency. In 3 cases, rebleeding occurred several years later: one patient (with AVM) died, another one was operated of a cavernous angioma diagnosed by MRI. Conclusion: Partial brainstem haemorrhages defined upon neuroimaging are mostly benign even if initial neurological manifestations are serious. Recurrences are rare but may do search underlying etiology.

6
BEHAVIOURAL AND HISTOLOGICAL STUDY OF PIRACETAM IN FOCAL CEREBRAL ISCHEMIA IN RATS. E Chleide, W Deberdt. *Braine-l'Alleud, Belgium*

The cerebroprotective effect of piracetam was studied in a model of focal cerebral infarction in rats. The infarct was produced by intravenous injection of a photosensitive dye, rose bengal (30mg/kg), and by focal illumination of the intact skull surface for 10min with a cold white light stereotactically positioned above the hindlimb right sensorimotor neocortex. Behavioural tests were performed 1 week before infarction and 1, 2, 3, and 4 days after infarction. It consisted in evaluating sensorimotor function (tactile/proprioceptive limb placing reactions), locomotion on an elevated beam and limb grasping behaviour. Infarcted rats exhibited severe deficits of the contralateral hindlimb both in tactile/proprioceptive placing reactions and in locomotion on the beam. The grasping behaviour remained unaltered after stroke. Treatment with 400 or 1600 mg/kg piracetam (i.p.) given 30min after the cortex illumination was ineffective both at behavioural and histological levels. In contrast, the dose of 800mg/kg significantly reduced the infarct size in piracetam-treated rats (5.72mm^3) compared to vehicle-treated rats killed at +96h (7.77mm^3). This effect was repeatedly observed in 2 supplementary groups. Moreover, these animals made significantly less hindlimb placing deficits in the beam test on the 2nd day. Further studies are required to determine the effects of piracetam on cerebral stroke but the present results suggest that piracetam may be of clinical use as an anti-ischemic agent.

Oral Session 23 - Muscle Disorders (1)

1
MUTATIONS IN MITOCHONDRIAL ENCODED TRNAASN AND tRNALeu ARE ASSOCIATED WITH CHRONIC PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA (CPEO) AND KEARNS-SAYRE SYNDROME (KSS). H Reichmann, T Klopstock, P Seibel, KV Toyka, *Würzburg, Germany*

KSS and CPEO are related neuromuscular disorders characterized by external ophthalmoplegia with ptosis. Genetically, almost 50 % of the patients show large scale deletions of the mitochondrial genome. This fact explains the decreased activity of the mitochondrial encoded oxidative phosphorylation enzymes in affected tissues of these patients. Among the seven patients studied extensively three presented large scale deletions of the mitochondrial genome. Additionally, the mitochondrial genomes of four patients harbouring not any portion of deleted mitochondrial DNA were characterized by RFLP analysis and DNA sequencing. Three presented a mutation in the mitochondrial tRNALeu-gene at nucleotide position 3243 (A to G transition), which previously had been associated with the MELAS subgroup of mitochondrial encephalomyopathies (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes). Another patient, however, classified as CPEO, showed a novel heteroplasmic mitochondrial DNA mutation in the tRNAAsn gene. The mutation occurs at a position which is highly conserved between species during evolution. These findings together with the analyses of mtDNA from humans with different ethnic background support the assumption that the mutation in the mttRNAAsn gene is associated with the disease. Furthermore our results imply that the pathogenesis in patients with KSS or CPEO is due to an impaired protein synthesis in mitochondria.

2
MOLECULAR CHARACTERIZATION OF PEARSON'S SYNDROME AND MITOCHONDRIAL MYOPATHY IN TWO SIBLINGS. J Casademont., A Barrientos, F Cardellach, F Cervantes, JM Grau, X Estivill, J Montoya, C Rozman, A Urbano-Marquez, V Nunes. *Barcelona, Spain*

Mitochondrial diseases are clinically heterogeneous multisystem disorders, usually sporadic or maternally transmitted. Pearson's marrow-pancreas syndrome is a disorder involving the hematopoietic system, exocrine pancreas, liver, and kidneys. It is thought to be due, in most cases, to deletions of one population of mtDNA, arising either during oogenesis or early development of fertilized eggs. A case of Pearson's syndrome has recently been described who developed signs of mitochondrial encephalomyopathy resembling Kearns-Sayre syndrome, and heteroplasmy with one population of mtDNA deleted by 4.9 kb. We describe two siblings with Pearson's

syndrome who complained of mild muscle weakness in their late childhood. Histochemical and biochemical muscle biopsy studies disclosed the presence of ragged-red fibers and a defect in complex I, III, and IV of their mitochondrial respiratory chain. Southern-blot analyses were normal, but PCR studies and direct sequencing showed multiple mtDNA deletions, which were also present in their mother. We conclude that this family probably represents a further example case of the rare mitochondrial diseases with autosomal inheritance.

3
IMPAIRED MITOCHONDRIAL PROTEIN SYNTHESIS IN MYOBLASTS HARBOURING THE MERRF TRANSFER RNA LYSINE 8344 MUTATION. MG Hanna, I Nelson, JA Morgan-Hughes, AE Harding, *London, UK*

The transfer (t)RNA lysine mitochondrial DNA mutation is commonly associated with the MERRF phenotype but the molecular pathogenesis of this disorder is unclear. To elucidate the effects of this mutation we have studied clonal primary myoblast cultures, harbouring varying amounts of mutation, established from a patient with the MERRF phenotype. Mitochondrially encoded protein synthesis and transcription were studied in these clones. We observed a progressive decline in protein synthesis with increasing proportion of mutant mtDNA. Further- more, there was evidence that mitochondrially encoded proteins were differentially affected, particularly affecting cytochrome oxidase subunits. These data provide direct evidence that, in cells from an affected tissue, the MERRF mutation mediates its effect by impairing mitochondrial protein synthesis.

4
METABOLIC MYOPATHY IN CHRONIC FATIGUE SYNDROME 31p-MRS AND MITOCHONDRIAL FUNCTION STUDIES. RJM Lane, LC Archard, AHV Schapira, JM Cooper, PRJ Barnes, GJ Kemp, DJ Taylor *London & Oxford, UK*

CFS patients studied by 31P-magnetic resonance spectroscopy occasionally show abnormally rapid intracellular acidification in muscle relative to phosphocreatine utilisation during aerobic exercise, and some studies have indicated that defective glycolytic function and mitochondrial abnormalities may occur. 31/96 (32%) CFS patients had abnormally high plasma lactate responses to sub-anaerobic threshold exercise testing (SATET). 5 patients were studied subsequently by MRS and muscle biopsy for quantitation of mitochondrial function. 4 patients showed abnormally rapid intracellular acidification during aerobic exercise and 1 also had an abnormal resting MRS spectrum suggestive of mitochondrial cytopathy. In all cases, defects of complex I activity were present and in one, additional complex IV abnormalities were demonstrated. CFS is a heterogeneous condition in which evidence of metabolic myopathy may be found occasionally.

5
ADULT CASE OF MULTIPLE ACyL CoA DEHYDROGENASE DEFICIENCY STUDIED BY P-MRS: SUCCESSFULL TREATMENT BY RIBOFLAVIN. A Toscano, B Garavaglia, G Vita, B Barbiroli, C Antozzi, C Rodolico, M Aguennouz, R Lodi, S Iotti, C Messina, S Di Donato, - *Messina, Milan & Bologna, Italy*

A 47-year-old man with a 20-year history of muscle weakness and fatigability, and several episodes of sudden hypotonia presented with waddling gait, and proximal myopathy. CK was elevated (8000 U/l) as well as serum lactate and pyruvate before and after exercise test. Muscle biopsy showed a vacuolisation of most type 1 fibres because of abnormal lipid accumulation. Total and free carnitine was low in muscle, whereas it was normal in blood and urine. The 24-hour urinary excretion showed increased lactic, ethylmalonic, glutaric and 2-hydroxyglutaric acids, a pattern compatible with glutaric aciduria type II. Muscle homogenate oxidised pyruvate and succinate normally but the oxidation of palmitate, butirate and octanoate was markedly low. In isolated muscle, mitochondrial activities (citrate synthase corrected) of SCAD., MCAD and LCAD were respectively 38%, 62% and 71%. Western blot analysis with antibodies against purified SCAD, MCAD and ETF to detect cross-reacting material (CRM) in patient's mitochondria, showed a 50% reduction of CRM-SCAD and normal amounts of MCAD- and ETF-CRM. In vivo ^{31}P-MRS evidenced that the brain phosphorylation potential was remarkably low (67; n.v. 83)7.4). A deficient muscle mitochondrial respiration was also shown by a very low rate of phosphocreatine resynthesis during recovery after exercise. After 2 months of riboflavin treatment (100 mg/day), a dramatic improvement of patient's muscle strenght was evident.

6
INFANTILE.MYOPATHY.ASSOCIATED WITH TISSUE SPECIFIC DEPLETION OF MITOCHONDRIAL DNA: A MOLECULAR GENETIC STUDY. C Mariottu, G Uziel, F Carrara, M Mora, S Di Donato, M Zeviani, *Milano, Italy*

Abnormalities of the mitochondrial DNA (mtDNA) associated with human disease include maternally inherited mutations, sporadic large-scale rearrangements and forms inherited as mendelian traits. The latter include either qualitative (e.g. multiple mtDNA deletions) or quantitative (e.g. tissue-specific mtDNA depletions) changes. We present here the results of a morphological, biochemical and molecular genetic study carried out on a patient affected by a presumably familial mitochondrial encephalomyopathy of childhood associated with mtDNA depletion. The propositus, a male infant, was born from consanguinous parents. He suffered since birth of a progressive neuromuscular disorder characterised by psychomotor delay, hypotonia, muscle weakness and wasting, deep-tendon arcflexia and spastic posture. High levels of lactic acid in blood and cerebrospinal fluid suggested a mitochondrial respiratory chain defect. Muscle biopsy showed ragged-red and cytochrome c oxidase-negative fibres, lipid accumulation and dystrophic changes. Multiple defects of respiratory complexes were detected in muscle homogenate, but cultured fibroblasts, myoblasts and myotubes were normal. Southern-blot analysis showed markedly reduced levels of mtDNA in muscle, while lymphocytes, fibroblasts and muscle precursor cells were normal. Sequence analysis of the mtDNA D-loop and of the origin of replication of the mtDNA light strand failed to identify potentially pathogenic mutations of these replicative elements in the proband's muscle mtDNA. Our findings indicate that mtDNA depletion is due to a nuclear encoded gene and suggest that the gene abnormality underlying defective mtDNA propagation occurs during the late stages of muscle differentiation, possibly after the innervation of the muscle fibres.

7
LYSIS OF THE THICK MYOSIN FILAMENTS DURING ORAL CORTICOSTEROID THERAPY. B Mahe, N Milpied. *Nantes, France.*

Two female patients were treated for acute leukemia by a bone marrow transplantation followed by daily high dose oral corticosteroids. They rapidly developed a generalized flaccid tetraparesis, of muscular type, with a slight increase of serum creatine kinase activity. A muscle biopsy was performed. The picture was that of an acute Isis of the myofibrillar network in the muscle fibres, especially of the thick myosin thick filaments. There was no inflammation and, in particular, nothing to suggest a graft-versus-host disease . The features are the same as those described after acute curare/steroid infusions, but neither the drugs used here nor their administration were the same. the effect of pregraft treatment on muscle metabolism and the ionic abnormalities induced by the steroid, may be relevant in the causation of the acute myopathy in these 2 patients.

Oral Session 24 - Muscle Disorders (2)

1
SPORADIC AND FAMILIAL INCLUSION BODY MYOSITIS: MOLECULAR CHARACTERIZATION OF T CELL RECEPTOR ON MUSCLE-INFILTRATING T LYMPHOCYTES. P Bernasconi, R Mantegazza, E Torchiana, O Simoncini, F Cornelio, MC Dalakas, *Milan, Italy; Bethesda, USA*

Polymyositis (PM) and inclusion body myositis (IBM) are inflammatory myopathies characterized by cytotoxic T lymphocyte infiltrates whose T cell receptor (TCR) repertoire and rearrangements in IBM patients' muscles were investigated by RT-PCR. Five IBM sporadic cases and 4 members of an IBM family were analyzed and compared to PM, DMD and normal subjects. The following TCR Vα/Vβ rearrangements were found in sporadic IBM patients: Vα1-2-7-8-10-12-13-15-19 (Vα12 in 80%, Vα8 and Vα13 in 60% of the patients); Vβ1-2-5.1-5.2-6-7-11-12-13 (Vβ2 in 80% and V1 in 60% of the patients). No functional rearrangements were found in familial IBM. These preliminary results suggest that a limited TCR repertoire (Vα12-Vα8-Vα13-Vβ1-Vβ2) is present in sporadic IBM different from that of PM patients (Vα1-Vα5-Vβ1-Vβ15 Mantegazza et al, J Clin Invest 91: 2880-2886, 1993). Whether the restricted TCR reper-

toire observed in sporadic IBM is related to the b-amyloid expression is unclear, because it was not detected in familial IBM. In the latter the TCR characteristics may indicate no reactivity to conserved antigenic structure.

2
INTERACTIONS OF γ/δ T CELLS AND CULTURED MUSCLE CELLS: RELEVANCE TO THE PATHOGENESIS OF γ/δ MYOSITIS. N Goebels, D Michaelis, G Häcker, R Hohlfeld. *Munich, Germany*

Recently, a distinct subtype of polymyositis, γ/δ myositis, has been identified (NEJM 324:877881), in which gamma-delta T cells (γ/δ T cells), a rare subtype of T cells, destroy muscle fibers expressing the 65 kD heat shock protein (hsp). Epitopes shared between mycobacterial and eukaryotic hsp are known as potential target antigens of γ/δ T cells. In this study we investigated interactions of myocytes with γ/δ T cells in an in vitro model. We analysed the expression of different types of hsp in cultured human myocytes. Furthermore, we studied the susceptibility of different cell types to lysis by γ/δ T cells in relationship to hsp expression. No extracellular hsp expression was detectable in human myoblasts, TE671, Raji and K562 cells. only Daudi cells constituitively expressed extracellular hsp 65. All cell lines showed intracellular expression of hsp 27 kD, 65 kD, 72 kD and 90 kD. Hsp 72 kD was inducible in human myoblasts and TE 671. Activated γ/δ T cells lysed all target cell types. Freshly isolated γ/δ T cells were not cytotoxic. Cytotoxicity was not influenced by hsp induction. Our results indicate that hsp related myocytotoxicity is not an intrinsic property of γ/δ T cells and support the concept that γ/δ myositis is mediated by clones of γ/δ T cells that recognise an autoantigen on muscle fibers.

3
ADULT SKELETAL MUSCLE SODIUM CHANNEL MUTATION IN AN ITALIAN PARAMYOTONIA CONGENITA (PC) FAMILY. G Meola, V Sansone, L Ptacek, *Milan, Italy & Utah, USA*

We report on a mutation in an S4 segment of the adult skeletal muscle sodium channel in a clinically defined Italian family that results in the paramyotonia congenita (PC) phenotype with dominant autosomal inheritance and temperature-related symptoms, present since childhood in all family members affected. Neurological examination of the proband (a 52-year-old woman)revealed general hypertrophy more evident in both gastrocnemius slight myotonic phenomenon after percussion of the thenar eminence. Electrophysiological tests showed myotonic and paramyotonic discharges in all affected members. Muscle biopsy gave evidence of aspecific neurogenic involvement, with type II fibre atrophy. Potassium loading test did not induce stiffness and was not associated with increase in serum K+. Genetic analysis of the family using the single-strand conformation polymorphism technique demonstrated an aberrant banding pattern that co-segregated with the disease in this family. Sequencing of the aberrant band revealed a G-A transition at position 4420 in this sodium channel protein responsib le for the PC phenotype. Further investigations intw these naturally ocurring mutations will contribute to a better understanding of channel gating as well as of channel malfunction in the periodic paralysis to diagnostic and therapeutic capabilities.

4
MOLECULAR STUDY OF SPANISH FACIOSCAPULOHUMERAL DYSTROPHY WITH CHROMOSOME 4 MARKER P13 - E11. JJ Vilchez, A Gonzalez, F Palau, T Sevilla, C. Diaz. *Valencia; Spain.*

Fascioscapulohumeral dystrophy (FSHD) is an autosomal dominant myopathy with an estimated prevalence of 4-5/100,000. Linkage studies in different populations (Dutch, English) have assigned the FSHD locus to 4q35 region. We report the preliminary results of molecular studies with the marker p-13E11 in a series of Spanish FSHD families. Up to now we have investigated 68 members from 9 families and one sporadic case. Of these, 22 were symptomatic, 6 abortive and 41 were healthy. DNA were digested with EcoRi and hybridised with the probe p13E-11. This probe is closely linked to FSHD gene and detects the mutation as a de novo DNA rearrangement characterised by the presence of fragments < 28 KB. The rearrangement has been detected in the sporadic case and in all families except one. However, in some affected members the rearrangement was not apparent. We conclude that most of FSHD Spanish patients presents a mutation located in 4q35 region. Nevertheless, due to difficulties in define the size of alleles and the recombinant events observed with the o-13E-11, it is recommended that the study be combined with other flanking markers of the FSH gene.

5
ANALYSIS OF CDR3 REGION OF TCR SUGGESTS THAT A CONVENTIONAL ANTIGEN IS THE TARGET OF MUSCLE INFILTRATING T LYMPHOCYTES IN POLYMYOSITIS. R Mantegazza, P Bernasconi, E Torchiana, F Baggi, F. Andreetta, FCornelio, *Milan, Italy*

Polymyositis (PM) is an inflammatory myopathy, characterized by mononuclear cellular infiltrates. Immunocytochemical analysis revealed a predominance of cytotoxic lymphocytes at the endomysium, suggesting a cytotoxic activity against an unknown muscular antigen. The infiltrating T lymphocytes were characterized for their T cell receptor (TCR) repertoire by reverse transcriptase-PCR. Four TCR families were preferentially expressed: Vα1 (73.3%), Vα5 (60%), Vβ1 (86.6%), and Vβ15 (100%). As this oligoclonality might be due to the action of a superantigen or a conventional antigen, the molecular organization V-(D)-J of the Vα/β families was analyzed. Vβ15 transcripts showed a restricted expression of Jβ2.1 or Jβ2.2 segments with a consensus motif EQF in the CDR3 region. Vα1 transcripts revealed random Jα1.4 rearrangements but the same consensus motif was detected in their CDR3 region. Vα1 sequences were paired with random Jα segments (Jα1.4, 1.7, 6.1, 9.14, 16.4 and 17.1) but no conserved aminoacidic residues were identified in the N-J region. In conclusion the molecular results support the hypothesis that the T cell infiltrates in PM are driven by a conventional antigen expressed on the muscle surface.

6
DETECTION OF PROTEOLYSIS IN MUSCULAR DYSTROPHY BY 1H NMR SPECTROSCOPY. O Boespflug-Tanguy, G Bielicki, A Tanguy, M Zanca , JP Renou, *Clermont-Ferrand & Montpellier, France.*

In order to identify specific markers of different myopathic processes, we compared the muscle IH NMR spectra of 12 myopathic affected patients (6 progressive muscular dystrophies, 1 acquired myositis, 4 congenital and 1 mitochondrial myopathies with those of 10 control patients. Muscle fragments were protein free extracted and analysed with the help of ID and 2D IH NMR Spectroscopy in a high field, high resolution spectrometer. comparison of COSY water suppressed spectra lead us to identify a signal present only in the 6 muscles from progressive muscular dystrophy affected patients, identified as the signal of the 3-methyl-histidine, marker of contractile proteins degradation. None of our 6 patients express a significant signal of 3 methyl-histidine in urine, confirming that urinary 3-methyl-histidine cannot permit to evaluate muscle 3 methyl histidine production. Possibility to detect 3 methyl histidine by in Vivo IH NMR Spectroscopy is under evaluation with animal models of proteolysis in which we have found the characteristic 3-methyl-histidine signal by 1 NMR Spectroscopy analysis of muscle fragments (cancerous rats and myopathic mutant mice dy/dy

Oral Session 25 - Child Neurology

1
HYPERARGININEMIA, A QUARTER OF A CENTURY LATER: ANOTHER TREATABLE INBORN ERROR OF METABOLISM? PP De Deyn, B Marescau, BA Pickut; on behalf of the Hyperarginimenia Research Group. *Antwerp, Belgium.*

Data regarding all 49 hyperargininemic patients presently diagnosed world-wide are presented with emphasis on the neurological complications and their proposed pathogenes. Typically, episodes of irritability, poor appetite, periodic vomiting and lethargy, in some cases progressing to seizures and coma, develop on weaning from breast feeding or on changing from formula to cow's milk. Motor and mental deterioration is observed at ages varying from 3 months to 4 years. Outcome ranges from normal intellectual and motor function to severe mental retardation and pronounced pyramidal tract signs. Pyramidal tract symptomatology, often restricted to the lower extremities, presented in 84 % of patients. Seizures were observed in 76 % of cases and occurred in the absence of hyperammonemia. Failure to thrive was observed in 66 % of cases and occasional findings were ataxia, athetosis, spinal deformities, microcephaly and intermittent hepatomegaly. Accumulation of arginine in serum is the hallmark of the disease. Arginase deficiency in red and white blood cells, liver and stratum corneum confirms the diagnosis. Argininuria was only present in

62 % and lysine-cystinuria was present in 55% of patients. Hyperammonemia is only periodically observed, less pronounced and even absent in certain cases. The important accumulation of guanidine compounds (secondary catabolites of arginine) is demonstrated in biological fluids and tissues including brain. The treatment of choice is the administration of essential amino acid mixtures without arginine, with or without stimulation of alternative pathways for excretion of waste nitrogen. All patients with mental (retardation) deterioration, spasticity and epilepsy should be screened by urinary Guanidino compound analysis or serum amino acid analysis

2
STIMATION OF THE RISK OF CONGENITAL MYOTONIC DYSTROPHY ACCORDING TO THE MATERNAL EXPANSION. AM Cobo, JJ Poza, L Martorell, JL Emparanza, A Lopez de Munain, M Baiget, Marti-Masso JF. *San Sebastian, Spain*

objective. To estimate the maternal risk of having a congenital myotonic dystrophy (CMD) child according to the maternal expansion.Patients and methods. We analysed the expansion size in 124 affected mother-child pairs (42 mother-CMD and 82 mother-DM children).Results. The mean maternal expansion in the congenital cases was three times higher [700 $(CTG)_n$] than in non congenital cases [236 $(CTG)_n$] (t Student, $p<0.001$). When the maternal expansion is in the 50-300 (CTG) n range, 90% of the children are non CMD. In contrast, when the maternal expansion is greater than 300 $(CTG)_n$, 59% of the children are CMD. In consequence, the risk of giving birth to a CMD child is 14 times higher for the mothers with a $(CTG)_n$ greater than 300.Conclusion. The risk of giving birth to a CMD child always exists for the affected mothers. However, our data demonstrate that such a risk is considerably higher if the maternal expansion is greater than 300 $(CTG)_n$.

3
TREATMENT WITH DOCOSAHEXAENOIC ACID PATIENTS WITH DISORDERS OF PEROXISOME BIOGENESIS. M Martinez, *Barcelona; Spain.*

Patients with Zellweger's syndrome and other disorders of peroxisome biogenesis have extremely low levels of docosahexaenoic acid (DHA) in the brain and retina. A clinical trial started three years ago to test the possible beneficial effects of DHA when administered orally in the form of ethyl ester to patients with disorders of peroxisome biogenesis. Two children diagnosed with neonatal adrenoleukodystrophy and infantile Refsum's disease were treated; both patients had very low DHA levels in red blood cells (RBC) and plasma. Treatment with 250 mg/day of pure DHA ethyl ester rapidly normalized blood DHA concentrations, and increased plasmalogen levels in both patients. In one of the patients, there was also a decrease in the ratio 26:1/22.0 and a clear neurological improvement. The therapeutical effect of DHA is particularly clear in those patients that start the treatment very early in life. in two such patients, plasmologen levels have increased markedly in RBC and a virtual normalization of the two ratios 26:0/22:0 and 26:1/22:0, diagnostic of the disease, has been observed in plasma. Neurologically, the milestones of development are processing rapidly after only a few months of DHA therapy. A marked visual improvement is clear in both patients. MRI has evidenced normalization of the characteristic dysmyelination images present in one of the patients. The results obtained so far suggest that DHA plays an important role in the pathogenesis of peroxisomal disorders. We think that DHA therapy must be assayed in all peroxisomal patients with a DHA deficiency, and started as soon as possible.

4
CONGENITAL MYOPATHY WITH DYSTROPHIN DEFICIENCY. ABERRANT mRNA SPLICED FORMS AND ABSENCE OF Dp 116. GP Comi, E Ciafalon, A Bardoni, N Bresolin, A Prelle, P Ciscato, F Fortunato, G Felisari, R Garghentino, A Roses, G Scarlato, *Milan, Bosisio Parini, Italy & Durham, NC, USA.*

Dystrophin (Dys) gene structure, transcription and expression were investigated in a 9 years old patient with congenital myopathy, multiple dysmorphisms and severe mental retardation. The patient who was born prematurely from a mother with high CK levels, was hypotonic at birth. Psychomotor development was delayed. At 6 months, he had epicantus, gothic palate, hyporeflexia, macroglossia, and transverse palmar creases. CK were 7,165 IU. Karyotype was normal. At age 3 years, Gowers'sign was present, he had ten don retractions and dysphasia. EEG was dysrhythmic. He was mentally impaired at age 9. The EMG was myopathic, while sensory and motor conduction velocities were normal. Muscle biopsy showed complete Dys absence by Western blot and immunohistochemical analysis. No deletions were found by PCR analysis of 32 DMD gene exons, including exons 68,69,70. Dys mRNA analysis from exon 67 to the 3' end demonstrated, instead of the normal fragment, 6 abnormally spliced transcripts. Sural nerve biopsy was investigated for the presence of Dpll6. No signal was detected with Dys COOH-terminus antibody by immunohistochemistry and Western blot analysis. The probable site of mutation in this patient affects muscle and nerve Dys isoforms. Congenital myopathies with dysmorphic features, severe mental retardation, and deficiency of Dys and Dpll6 might be caused by 3' end mutations of the DMD gene.

5
PATHOGENY OF LANDAU-KLEFFNER SYNDROME AND RELATED DISORDERS CONTRIBUTION OF POSITRON EMISSIO TOMOGRAPHY. P Maquet, G Franck, E Hirsch, MN Metz-Lutz, C Marescaux, *Liège Belgium & Strasbourg, France.*

The Landau-Kleffner syndrome (LKS) and the syndrome of continuous spike-and-wave discharges during sleep (CSWS) appear in children and combine an acquired deterioration of one or several higher cerebral functions, spike and spike-wave discharges on EEG recordings, and eventually, behavioural disturbances and epileptic seizures. Their pathogenic mechanism remains unknown. We analysed retrospectively 19 studies of cerebral glucose metabolism (11 sleep and 8 waking studies) performed between 1986 and 1993 in 6 children (5 LKS, 1 CSWS; follow up studies in 3 patients), using PET and [^{18}F]fluorodeoxyglucose method. Results. Cortical metabolic abnormalities always predominate over associative cortices. The temporal lobe is always involved, sometimes bilaterally (3 patients). Metabolism is lower in the thalamus than in the cortex, a metabolic pattern characteristic of the brain in maturation. The thalami always remains symmetric despite the important asymmetries observed within the cortex. Conclusions. LKS and CSWS are caused by a focal or multifocal dysfunction of associative cortical areas during brain maturation. As cortico-thalamic neurones do not appear to participate to the pathological processes (thalamus symmetry), it is suggested that the pathogeny primarily involves maturing cortico-cortical circuitry.

6
ONTOGENETIC STUDY OF NEUROTENSIN AND NEUROTENSIN RECEPTOR IN INFANTS WITH RADIOIMMUNOASSAY, BINDING AND RADIOAUTOGRAPHY. A. Coquerel, F Pfaff, M Dussallant, G Gaudriault,N Zsurger, V Le Cam-Duchez, A Berod, JP Vincent, J Tayot, W Rostene, *Rouen, Nice, Paris,. France.*

Neurotensin (NT) is a neurotransmitter associated with dopaminergic, thermal and algesic and respiratory controls. Like opiates it could be implicated in the Sudden Infant Death Syndrome (SIDS). Between birth and 15 months old we studied NT maturation with : (i) Radioimmunoassay (RIA) in CSF and in discrete brainstem areas (ii) NT Receptor (NTR) analysis from whole brain and specific areas (thalamus, caudate, substancia nigra (SN), pons and medulla) with specific ligands; (iii) with the same ligands we obtained radioautographies of various brain areas including cortex, basal ganglia and brainstem: We found: (i) CSF NT level is increased in SIDS vs same age alive infants. In brainstem, excepted SN, highest values are observed in the medial part and the retroolivar part of the upper medulla: (ii) NT receptor(s) (NT-R) are only of the high affinity type ($Kd = 0.24 \pm 0.07$ nM) from neonates until 15 months. The Bmax increases from 0 to 2 months and then decreases slowly to adult value; the combination of RIA and Binding analysis on numerous punches did not show any parallelism between NT and NT-binding sites. (iii) Radioautographies display numerous binding sites of the high affinity type in brainstem: SN and ventral tegmental area (as in adults) We conclude that NT & NTR expressions are both dramatically increased during the first months of life. The NTR is only of the High affinity type and the time course of NTR Bmax variation is synchronous with the incidence curve of SIDS.

7
CAN JUVENILE, PURE, PROGRESSIVE SPASTIC PARAPLEGIA BE DUE TO PROTEOLIPOPROTELN GENE MUTATIONS. G Giraud, C Minault, J Vallée, F Cailloux, O Boespflug-Tanguy, *Clermont-Ferrand, France*

A 10 year-old boy developed at 30 months an isolated, slowly progressive spastic paraplegia (SP). Cerebral MRI and central evoked potentials revealed a myelin defect restricted to the CNS. Classical causes of progressive leukodystrophies were ruled out by extensive explorations and different arguments led us to analyse the proteolipoprotein (PLP) gene, a gene already involved in Pelizaeus-Merzbacher disease (PMD) 1) among the 50 PMD families we analysed, the affected uncles of 2 index cases expressed a pure form of SP, (3) one pure and 2 complicated forms of X-linked SP have been localized in a region closed to the PLP locus, (4) in a large family of complicated X-linked SP, in which PLP exon III mutation has been reported, one of the 9 affected males expressed a pure form of the disease. DNA analysis of this affected boy and her mother revealed a point mutation in intron IV of the PLP gene (28 nucleotides from the 3' end of exon IV) which was not found in 100 unrelated chromosomes. Correlation between this mutation and the disease is under investigation as well as linkage studies in 8 families affected by X-linked pure form of SP.

Oral Session 26 - Clinical Neurophysiology

1
THE CEREBRAL ACTIVATION PATTERN DURING INHIBITED, SENSORY-GUIDED, VOLUNTARY AND IMAGINED SACCADES. L Law, OB Paulson, *Copenhagen, Denmark.*

An important element of adaptive behaviour is the ability to direct visual attention to explore the visual environs by centralising image of object of interest on the visual environment by centralising images of objects of interest on the fovea. Nine healthy volunteers performed saccadic eye movement in five conditions twice during measurements of the regional distribution of counts using H_2O^{15} and positron emission tomography (PET). Eye movements were sensory-guided and paced by three light diodes at a 1 HZ frequency an all cases exempt baseline. 1 Beeline: Central gaze fixation: 2 Saccade suppression: Central gazefixation. without saccades; 3 Reflexive saccades: Imagined reflexive saccades, central gazefixation. Using a paired T-statistic, significant increases ($p< 0.005$) were found in the supplementary motor area(SMA), bilateral frontal eye field (FEF)and bilateral parietal lobe (PL) when comparing reflex volitional and imagined saccades with baseline. Increments were from 2.1 to 4.1 normalised counts (nCBF). Additionally the right FEF and PL were significantly activated ($p < 0.01$), 1.4 and 1.5 nCBF respectively during suppression of unwanted visuo-motor activity. This study emonstrates the involvement of areas involved in motor planning, visual exploration and visual attention connected to the oculomotor system.

2
COMPARISON OF RATES OF MUSCLE ACTIVITY ASSOCIATED WITH ESSENTIAL TREMOR WITHIN AND BETWEEN LIMBS. TC Britton, *London, UK*

This study addresses the question of whether the oscillatory mechanism responsible for the segmentation of EMG activity in one muscle is the same as that responsible for the segmentation of EMG activity in other involved muscles. Simultaneous polymyographic recordings were made from up to 24 muscles in 18 patients with hereditary essential tremor. Upper limb tremor was always associated with segmentation of EMG activity in forearm muscles and often associated with segmentation of EMG activity in upper arm and intrinsic hand muscles, particularly for larger amplitude tremors. The rate of segmentation of EMG activity in proximal muscles was the same as or at least very similar to that in distal muscles of the same limb. This indicates that the motoneurone pools of involved muscles within the same limb are subjected to the same oscillatory drive. The rate of segmentation of EMG activity in involved muscles of different limbs of the same individual was never the same. The oscillatory drive to the motoneurone pools of involved muscles in one limb therefore differs from that to the motoneurone pools of involved muscles in other limbs. However on group analysis there was a significant correlation between the rates in different limbs, indicating that the oscillatory mechanisms responsible for tremor in different limbs are not entirely separate. These results emphasize the importance of central mechanisms in essential tremor and could be explained by the existence of a single central oscillator with a broad frequency spectrum.

3
THE NEUROPHYSIOLOGICAL EVALUATION OF SPASTIC PATIENTS BEFORE AND DURING INTRATHECAL BACLOFEN. I Dones, D Servello, F Molteni, G Mariani, G. Broggi, *Como Italy*

The intrathecal administration of baclofen is, at present, the most effective treatment of spasticity when resistant to oral therapy. Clinical evaluation of spasticity according to the Ashworth scale together with the subjective assessment of muscle strenght is not sufficient to exactly assess the ratio between spasticity and muscle strenght and thus the indication to that treatment and the proper daily dosage of intrathecal baclofen a patient may need .Five patients of different age and diagnosis disease, all affected by severe spasticity (grade 4 or 5 on the Ashworth scale) were evaluated before and during a test with the administration of a bolus of intrathecal baclofen (the peak effect of baclofen was scored as two dregrees lower than before test). Patients were tested by means of isokinetic ergometry and functional EMG. A system for the evaluation of passive and voluntary movements was studied and used to evaluate these patients (Technogym) and the speed and pattern of movements together with the EMG of agonists and antagonists muscles was measured in both lower limbs of all patients. Although few patients were evaluated the preliminary results indicate that this battery of tests is able to find some useful parameters that make the clinical follow up of patients under treatment with intrathecal baclofen objective in order to find the right daily dosage with which these patients can really improve their motor performance.

4
SYNAPSE ELIMINATION IN BOTULINUM TOXIN- PARALYSED RAT MUSCLES. SM Hassan, FGI Jennekens, G Wieneke, H Veldman, *Utrecht, The Netherlands*

In order to determine the fate of the superfluous neuromuscular junctions formed during the course of botulinum toxin- induced paralysis, we quantified the change in length of the nerve- muscle contact area following toxin injection in rat calf muscles. Quantification was performed in longitudinal sections of soleus and gastrocnemius muscles at time points ranging between 0 and 28 weeks post- injection. The measured areas were those positive for synaptophysin (a synaptic- vesicle marker) to ensure that they represented actual nerve- muscle contact areas. The results show that, after an initial marked increase, the length of the junctional area decreased rapidly between the 10th and 14th week post- injection, and rather slowly thereafter. At 28 weeks post- injection the junctional area in treated animals was still larger than in age- matched controls. Ultrastructural observations indicate that synapse elimination begins as early as 4 weeks post-injection, simultaneous with the extension of sprouts and formation of new junctions. Our results also demonstrate that the soleus and gastrocnemius muscles follow a different time course during synapse formation and elimination, suggesting that muscle fibres regulate their own innervation. It is concluded that synapse elimination is a slow process, as 6 months post- injection it was not yet complete.

5
POSTEXCITATORY INHIBITION EVOKED BY TRANSCRANIAL MAGNETIC STIMULATION IS IMPAIRED IN PATIENTS WITH ISCHEMIC LESIONS. C Fritz, H-J Braune, *Marburg, Germany*

Following transcranial magnetic stimulation during sustained muscle contraction a temporary suppression of motor activity can be observed. In the present study we analysed this postexcitatory inhibition (PI) in 25 healthy subjects and 30 patients with previous stroke. The patient group was divided in 3 subgroups according to the degree of impairment. Magnetic stimulation was performed at the vertex, recording electromyographic activity via surface electrodes placed on the m. abductor digiti minimi on both sides. In the control group there was no statistically relevant interside-difference of the PI duration whereas a markedly interindividual variation was found. In 4 patients with minor stroke showing no motor disturbances anymore (group I) we found a significant ($p<0,05$) prolongation of the postexcitatory inhibition recorded from the affected side compared with the sound side. This interside-discrepancy was even more pronounced in 7 patients (group II) with minor clinical signs of hemiparesis

(p<0,01) and 12 patients (group III) with moderate hemiparesis (p<0,01). Our findings suggest that the measurement of the PI elicited by transcranial magnetic stimulation is a useful and sensitive neurophysiologic parameter in the management of stroke. Especially in the subgroup of patients revealing no clinical signs of central motor impairment, PI measurement was sensitive to detect subclinical motor function disturbances.

6
A PET STUDY OF REMEMBERED SACCADES IN NORMAL SUBJECTS. EPO Sullivan, IH Jenkins, DJ Brooks, L Henderson, C Kennard. *London; UK.*

We investigated the role of the frontal lobes in remembered saccades. Seven right handed male volunteers were studied using H2 15O activation positron emission tomography (PET). The saccadic task consisted of a target being flashed at one of five horizontal eccentricities (>15 degrees). After a delay of up to 1000 milliseconds a buzzer sounded and the fixation light was extinguished to trigger a saccade to the remembered location of the target. In the rest state subjects listened to the buzzer with eyes closed. Comparison of regional cerebral flow in the two conditions showed significant activation (p<0.001) in the remembered saccade task, both in the frontal eye fields (FEFs) and the supplementary motor area (SMA) in the frontal lobes. The prefrontal cortex was not seen demonstrated. Other areas significantly activated included basal ganglia, midbrain, thalamus, parietal area 7, and striate and extrastriate cortex. Conclusion: 1) The preeminent role of the FEF and SMA in the production of remembered saccades compared to other frontal lobe areas has been demonstrated. 2) The presence of a cortico-striatal pathway involved in remembered saccades has been confirmed.

Oral Session 27 - Motor Neuron Disease

1
CENTRAL MOTOR CONDUCTION TIME IN AMYOTROPHIC LATERAL SCLEROSIS. Ch Brunholzl, D Claus. *Erlangen, Germany.*

In 57 patients with amyotrophic lateral sclerosis the diagnostic and prognostic value of transcranial magnetic stimulation was studied. Stimulation was done using a circular high power coil positioned over Cz for recordings from the abductor digiti minimi muscle (ADM), and over Fz for recordings from the anterior tibial muscle (TA) bilaterally. Central motor conduction time (CMCT) was normal in 44% (n=25) of patients at the time when the diagnosis was established. In 56% (n=32) CMCT was abnormal to one or more target muscles. Mean time of survival after diagnosis was 17.5 ± 7.7 months in patients with normal CMCT, and 14.7 ± 8.8 months in patients with abnormal CMCT. This difference was not significant. Motor disability of patients was scored by three degrees. Abnormalities of CMCT did not correlate with the degree of disability. 13 patients were re-examined after 3 to 17months. Mean CMCT to the ADM as well as to the TA did not significantly change. Only 3 initially normal values to the ADM became abnormal despite progression of the disease. In conclusion, abnormal CMCT does not provide prognostic information.

2
A PREDICTIVE MODEL OF THE RATE OF PROGRESSION IN AMYOTROPHIC LATERAL SCLEROSIS. J Pascual Calvet, Jm Soler Insa, A Pou Serradell, *Barcelona, Spain.*

To evaluate the progression of amyotrophic lateral sclerosis (ALS) wtried: a) to define different profiles in the progression of the disease in a population of patients, b) to find if these differences are related with any factor from a clinical rating scale, c) to create a predictive model of survival based on the results of the clinical rating scale. Between 1987-1991, 26 patients who shared diagnostic antenna of ALS were prospectively studied. Clinical evaluation using the Baylor Rating Clinical Scale was done every three months until death. Statistical analysis included: descriptive, cluster, Person's correlation coefficient, discriminate, survival analysis and multiple linear regression. A total of 108 successive clinical evaluations were performed. Cluster analysis including time of follow-up and survival at the end of the study permits to reveal a group of seven patients who lived over 40 months. By means of discriminate analysis this group could be separated according to clinical evaluation in 83% of cases. A predictive model of the duration of the illness based on the clinical rate of progression could be obtained . We conclude that it is possible to define a predictive model of survival based on the clinical progression rate obtained from a functional clinical scale.

3
CU/ZN SUPEROXIDE DISMUTASE IN SPORADIC AMYOTROPHIC LATERAL SCLEROSIS. F Coria, I Rubio, MA Garcia, C Bayon, J Duarte, AP Sempere, LE Claveria, I Blanco, *Segovia Spain*

Mutations of the Cu/Zn superoxide dismutase (SOD-1) gene segregate with amyotrophic Lateral Sclerosis (ALS) in several families. To test whether abnormalities of this enzyme are also pathogenetically relevant in sporadic ALS, we studied four autopsied cases by means of immunohistochemical, biochemical and molecular genetic methods. Six autopsied cases without neurological disease where used as controls. SOD-1 antibodies labelled most neurons and axons in the spinal cord and peripheral nerves. Specific labelling was also observed in oligodendrocytes, Schwann cells, and endothelial cells. In ALS, SOD-1 immunostaining of neurons and axons was decreased or unchanged, but was increased in reactive microglia. Densitometric measurements in immunoblots of spinal cord extracts showed a twofold increase of SoD-1 is ALS, as compared to controls. Single stranded conformation polymorphism analysis of polymerase chain amplified exons of the SOD-1 gene disclosed no apparent mutations. These studies suggest that: 1) SOD-1 in the spinal cord is expressed by cells other than motor neurons, indicating that additional factors are required to explain the selective impairment of motor neurons in familial ALS; 2) The increase of SOD-1 in the spinal cord of sporadic ALS may be a secondary phenomenon due to proliferation of microglial cells expressing high amounts of this enzyme; and 3) familial and sporadic ALS are pathogenetically heterogeneous conditions.

4
THE SIGNIFICANCE OF AGE IN SURVIVAL OF AMYOTROPHIC LATERAL SCLEROSIS. M Ferrarini, D Testa, C Cazzaniga, M Farinotti, G Filippini. *Milan, Italy.*

The clinical records of 405 patients admitted to the Institute because of motor neuron disorders from January 1, 1971 to December 31, 1985 were reviewed by one of us (D.T). Three hundred-seventy-nine (231 men and 148 women) met the criteria of amyotrophic lateral sclerosis (ALS). By September 30, 1993, 320 of these patients (191 men and 129 women) deceased; they form the basis of this study. The mean age of disease onset was 55.9±11.3 years. Mean disease duration was 3.7±3.3 years for men and 3.4±2.8 years for women. Older patients had a much shorter mean survival than younger patients. Mean survival for onset age ≤ 40 years was 5.7±4.9 years, compared with 2.5±2.1 years for patients older than 65 years (p<0.0001). The risk of death among the older patients was about three fold higher than the risk among the younger patients. Mean survival was shorter among patients with bulbar onset, than among those with spinal onset and the relative risk associated with bulbar onset was 1.5 (95% CI 1.1-2.0). These results suggest that onset age, but not sex, is the most significant predictor determining survival in ALS. In familial ALS the importance of age of onset is striking.

5
BRITISH MOTOR NEURON DISEASE TWIN STUDY. CH Hawkes, A Graham, A McDonald, *Ipswich and London, UK.*

We tried to evaluate genetic and environmental factors in MND by population-based twin and case-control study. Dominant inheritance is relevant in only 5-10% cases MND. The cause in the majority of sporadic cases is unknown. Using the "death discordant" method, twin pairs were identified from death certificates, 1979 -1989. Living cotwins were visited at home and zygosity ascertained by the method of Magnus (1983). An environmental questionnaire was administered and analysed by conditional logistic regression modelling. Results 75 pairs were identified; 24 monozygotic (MZ) and 51 dizygotic (DZ). Four MZ probands from two concordant pairs were found initially, giving a MZ proband concordance rate 17.4%. Two of these probands were discarded because they had familial MND. The correlation of liability for MND among MZ twins was 0.717 (S.E. 0.13). No DZ concordant pairs were found. The coefficient of genetic determination ("G") for MND was 0.60 (range 0.38 - 0.85). The case-control

data revealed elevated Odds Ratios (OR) for "regular vehicle maintenance" [OR = 7.0; CI 1.3 - 89.9] and "occupational paint usage" [OR = 3.75; CI 1.1 - 17.1]. Conclusions The genetic analysis supports multifactorial aetiology for sporadic MND i.e. a single gene defect is excluded. The twin case-control study suggests that exposure to petroleum and solvent based chemicals may be causally important.

6
LATE FUNCTIONAL DETERIORATION FOLLOWING PREVIOUS POLIOMYELITIS - A CONSECUTIVE SERIES. RS Howard, E Chroni, FW Heatley, GT Spencer., *London UK*

Many patients with previous poliomyelitis develop 'post polio syndromes (PPS)' in which late functional deterioration follows a period of relative stability. The frequency with which PPS can be attributed to clearly defined causes remains uncertain. We undertook a review of newly referred patients with previous poliomyelitis consecutively seen over two years. There were 88 patients (35 male: 53 female, mean age 51.6 (20-81) yrs) who had acute paralytic poliomyelitis at a mean age of 8.2 yrs (1-42). Thirteen patients were ventilated during the acute illness and 60 had extensive and severe weakness. Following recovery 17 were wheelchair bound and 15 mobile with severe disability. Eighty patients (91 %) were aware of functional deterioration developing at a mean of 39.6 yrs (18-76) after the original illness. Several factors were present in many patients. Functional change included joint pain and limitation (32), cervical or lumbar spine pain (22), impaired mobility (16), increasing limb weakness (9) and dyspnoea (8). Functional impairment was associated with joint problems (73), obesity (10), respiratory abnormalities (10), neurological disorders (10), depression (5) and general medical factors (5). Treatment of the bone and joint abnormalities included provision of appropriate orthoses or supports (46), surgical procedures (18) with physiotherapy and hydrotherapy. Other treatments included weight loss, ventilatory support and pain relief. In the present consecutive series progressive postpolio muscular atrophy was not noted. Functional deterioration was common and associated with orthopaedic, neurological, respiratory and general medical factors which are potentially treatable.

7
GENETIC ANALYSIS OF 23 FRENCH FAMILIAL AMYOTROPHIC LATERAL SCLEROSIS : ABSENCE OF SUPEROXIDE DISMUTASE Zn/Cu GENE LUTATION. B Moulard, W Camu, M Dhib*, M N'Diaye*, A Malafosse, V Meininger , M Billiard, M Baldy- Moulinier, *Montpellier, Paris, France*

Recently, superoxide dismutase Zn / Cu (SOD 1) gene mutations have been identified in different familial amyotrophic lateral sclerosis (FALS) families linked to 21 chromosome. The mutations are found especially in SOD 1 exons 1, 2, 4, 5 in 40 per cent of these FALS families cases. We analysed 23 probands from French FALS families, diagnosed with Escorial's criteria. The exons 1, 2, 4 have been sequenced after PCR amplification of the genomic DNA obtained from these 23 patients. If one considers that about 15 per cent of the FALS families are linked to the 21 chromosome and that about 40 per cent of these pedigrees present SOD 1 mutations, one would expect that our sample should contain a maximum of 2 patients with mutation. Therefore, the absence of mutation in exons 1, 2, 4 of the SOD I gene in our sample may be due to different FALS phenotypes, which could imply genetic heterogeneity between European and American FALS pedigrees.

Oral Session 28 - Peripheral Neuropathy (3)

1
IMMUNOLOCALIZATION OF ANTI-SULFATED GLYCOLIPIDS MONOCLONAL ANTIBODIES IN DEMYELINATING PERIPHERAL NEUROPATHIES ASSOCLATED WITH LGM GAMMOPATHY. A Ben Younes-Chennoufi, JM Léger, ML Harpin, B Chassande, P Bouche, N Baumann. *Paris, France.*

Antibodies to sulfated glycolipids have been mainly reported in patients with demyelinating polyneuropathies and IgM monoclonal gammopathies of undetermined significance (MGUS). We report here our results on 40 cases of demyelinating peripheral neuropathy associated to IgM monoclonal antibodies. Study has been perfomed by ELISA, immunodetection on thin-layer chromatography and by immnohistochemistry methods. We showed that in 33 cases of the 40 studied, the IgM reacted at high titer with the HNK-1 epitope carried by two sulfated glucuronyl glycolpids (SGPG/SGLPG). In 16 of those, the IgM reacted also at high titer with sulfatide. Immunohistochemistry study performed on frozen unfixed sections, from biopsies of human sural nerve, showed that IgM directed to both SGPG/SGLPG and sulfatide, were mainly localized on myelin, but IgM reacting only with SGPG/SGLPG bound essentially to Schwann cells and to some fibroblasts. This was evidenced by an anti-Schwann cells anbtibody (S-100) and anti-human fibroblasts. These findings suggest a variability of the monoclonal IgM anti-SGPG/SGLPG and a difference in the fine structure of the epitope recognized by the IgM. Immunohistochemistry showed a correlation between the difference in the fine structure of the epitope and the difference in the pattern of immunolocalization of these IgM on peripheral nerve. Clinical data showed that anti-antibodies are mainly associated to sensory demyelinating neuropathies and that intensity of pain is only observed in patients with anti-sulfatide antibodies.

2
SPECIFICITY, ISOTYPE AND DURATION OF ANTI-GQ1B ANTIBODIES IN AUTOIMMUNE PERIPHERAL NEUROPATHY. HJ Willison, J Veitch, B Herron, A AlMemar, Glasgow, *Southampton & Plymouth, UK.*

Miller Fisher syndrome (MFS) is associated with anti-GQ1 b ganglioside antibodies which cross-react with GT1a. 14/14 typical MFS cases were all anti-GQ1b positive, 6/14 were also anti-GD3 and GD1b positive and 1/14 was positive for with GD1b or GD3. One highly informative case with ataxia and areflexia without ophthalmoplegia had no anti-GQ1 b or GT1 a antibodies but had high titre antibodies to GD1 b and GD3. This suggests that the sensory manifestations of MFS could be mediated by antibody binding to GD1b and /or GD3 rather than GQ1 b. We have also identified 2 cases of chronic ataxic sensory neuropathy with intermittent ophthalmoplegia who have monoclonal IgM paraproteins reactive with disialosyl moieties common to gangliosides including GD1 b, GD3 and GQ1 b. These antibodies also have anti-Pr cold agglutinin activity and are persistent over many years. The IgG subclass distribution of MFS-associated anti-ganglioside IgG antibodies shows remarkable restriction to IgG1 and IgG3, subclasses typically associated with T-cell dependent responses to protein antigens. In all serial cases studied, antibody levels fall or disappear with clinical recovery. These data indicate that distinct clinical phenotypes of sensory neuropathy can be segregated serologically on the basis of the fine specificity pattern, isotype and duration of anti-ganglioside antibodies.

3
SOLUBLE ICAM-1 AND E-SELECTIN IN IMMUNE NEUROPATHIES. HP Hartung, K Reiners, M Michels, RAG Hughes, F Heidenreich, JJ Archelos, J Zielasek, KV Toyka. *Würzburg, Dusseldorf, Germany & London, UK*

Mononuclear cell infiltration of nerves is a key pathological feature of a number of immune neuropathies. In some patients with GBS autoreactive T cells can be retrieved from blood. How T cells access peripheral nerve is unknown. We determined serum levels of the soluble adhesion molecules ICAM-1 and E-selectin in 126 patients with GBS, 13 patients with vasculitic, 36 with metabolic, 12 with MGUS-associated neuropathies, 54 patients with other neurological disorders (OND), and 15 healthy controls. Quantitation was done by two-sided ELISAs. sICAM-1 (274 ng/ml) and sE-selectin (43 ng/ml) were increased in GBS (vs. 172 and 20 ng/ml in OND). Raised levels declined as patients recovered. There was no relationship to preceding C.jejuni infection or the presence of glycolipid antibodies. E-selectin levels were also increased in vasculitic neuropathies (47 ng/ml). Cytokine-mediated upregulation of ICAM-1 and E-selectin on leukocytes/endothelial cells may be important in homing and attachment of immunocompetent cells to endoneurial endothelial cells and their immigration into nerve. Further studies are warranted to precisely define the role of these molecules in the pathogenesis of GBS and vasculitic neuropathies.

4
BENIGN ANTI-Hu-ASSOCIATED PARANEOPLASTIC SENSORY NEUROPATHY. I Bonaventura, M Uchuya, R Rene, JY Delattre, F Graus. *Barcelone, Spain & Paris, France*

Paraneoplastic sensory neuropathy(PSN) usually runs a subacute progressive clinical course leaving the patient with severe sensory dysfunction in weeks a months. In the present study we describe four patients with PSN, positive anti-Hu antibodies, and a very mild clinical course. The 4 patients(3M/1 F) had a median age of 50 years(range:40-72). In 3 of them, a small-cell lung cancer was diagnosed. One patient presented with clinical and neurographic evidence of sensory multineuritis. In another patient, symptoms were restricted to the arms with paresthesias and minimal involvement of joint position sense, mainly affecting the right hand. Two patients developed a mild, distal, sensory neuropathy. The PSN remained stable or progressed very slowly without any treatment for a median of 20 months(range:5-45) and remained so after treatment with immunoglobulins(1 patient), chemotherapy(2) or both therapies(1). All patient were ambulatory and independent until death from the tumour(1 patient) or last assessment. The median follow-up is 43 months(range:16-48). These patients emphasize that a paraneoplastic origin and the subsequent detection of anti-Hu antibodies should be considered in patients with mild, very slowly progressive sensory neuropathies. The possibility of benign forms of PSN must be entertained in the design of protocols of treatment for this neuropathy.

5
β4 INTEGRIN EXPRESSION IN NORMAL AND PATHOLOGICAL HUMAN NERVES. A Quattrini, L Feltri, R Nemni, SS Scherer, L Wrabetz, N Canal, *Milan, Italy & Philadelphia, USA*

Adhesion molecules play an important role in developing and regenerating peripheral nerve. Integrins are cell surface receptors that can mediate adhesion of cells to extracellular matrix. Schwann cells (SC) must deposit and interact with their basement membranes in order to form myelin. Recently, the expression of B4 integrin in myelinating SC was shown to be axon-dependent and associated with the outer membrane adjacent to the basement membrane, suggesting that B4 may play an important role in myelination. To assess whether integrins may be a diagnostic and prognostic marker for peripheral neuropathies, we have examined the expression of B4 in axonal and demyelinating human neuropathies by means of indirect immunofluorescence. In normal nerves, B4 immunoreactivity is located in endothelial cells, perineurial cells and at lower levels in SC. In diseased nerves, B4 immunoreactivity was present in varying patterns depending on the type of neuropathy. In axonal neuropathy, we found a variable endoneurial staining for B4 and the expression may be correlated with the amount and duration of axonal damage. In demyelinating neuropathy, we observed a remarkably increased expression of B4, suggesting that B4 integrin expression may be a diagnostic marker in the distinction between primary demyelinating and primary axonal neuropathies.

6
ANTI-β-TUBULIN ANTIBODIES IN PATIENTS WITH CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY. IN van Schaik, M Vermeulen, PA van Doorn, A Brand, *Amsterdam & Rotterdam, The Netherlands.*

High titer anti-β-tubulin antibodies were recently reported to occur in over 50% of sera from patients with chronic inflammatory demyelinating polyneuropathy (CIDP). It was concluded that these antibodies may help to distinguish CIDP from other neuropathies. We studied sera of 43 patients with CIDP, obtained during the active phase of the disease for the presence of anti-,B tubulin antibodies by Western blotting. In three patients anti-B-tubulin antibodies were present, one patient had high titers of anti-GM1 antibodies as well. All three patients had anti-neuroblastoma cell line antibodies. The differences between the results obtained can partly be explained by differences between patients since there was also a difference in the occurrence of anti-GMl antibodies. Another difference was the technique used to detect the antibodies. We used Western Blot methodology, whereas the high frequency of antibodies was demonstrated with an ELISA technique. ELISA can be considered as more sensitive, at the price of more false positives, whereas Western blotting maybe less sensitive but more specific. This study shows that the high frequency of selective high titer anti-B-tubulin antibodies in CIDP patients could not be confirmed.

POSTER SESSION 4

1
EARLY THYMECTOMY AND IV IG TREATMENT IN MYASTHENIA GRAVIS. S Tekin, C Aykut, S Aktan, N Afsar, *Istanbul; Turkey.*

Myasthenia gravis is an autoimmune disease characterized by the dysfunction of neuromuscular transmission. Production of polyclonal antibodies against acetylcholine receptors causing structural changes in the postsynaptic membrane is responsible in the etiopathogenesis of the disease. Early thymectomy, removing the source of antibody production, has been shown to be effective in 63% of the myasthenic patients. Recently, the role of high dose immunoglobulins is under discussion. In this study, the results of early thymectomy in four patients with generalised myasthenia were evaluated. All four patients were women aged two patients had radical thymectomy including mediastinal fatty tissue resection and the other two patients had simple thymectomy. Pathologically two patients found to have thymoma and others thymic. hyperplasia. Serum acetylcholine esterase levels of all patients showed dramatic decline in the following six months postoperatively. Due to intercurrent infections two patients received IV Ig treatment with a dose of 1000 mg/kg/day for two consecutive days in a month. Two patients showed total remission where as other two patients needed half doses of previous drug treatment. IV IgG is used (2000 mg/kg) in two patients and acute clinical improvement is observed. These results seemed to be correlated with the recent literature.

2
THYMUS IN THYMOMA-ASSOCIATED MYASTHENIA GRAVIS: NO ANTI-ACHR ANTIBODY PRODUCTION AFTER TRANSPLANTATION INTO SCID MICE. A Sarropoulos, R Hohlfeld, H Wekerle, S Spuler (née Schönbeck). *Munich & Martinsried, Germany*

The SCID mouse model of myasthenia gravis (MG) allows studies of the role of the thymus isolated from the rest of the immune system. (Schonbeck et al. J Clin. Invest. 90: 245, 1992). Here, we applied the SCID mouse model to thymoma-associated MG. Small fragments of a total of 4 thymomas (3 cortical thymomas and 1 well differentiated thymic carcinoma) and extrathymomal thymus tissue were transplanted under the kidney capsule of 43 SCID mice. At regular intervals, the concentration of anti-acetylcholine receptor antibodies (AchR abs), anti-striated muscle antibodies and anti human IgG were measured in the serum of the transplanted SCID mice. Further, the transplants were analyzed histologically and immunocytochemically. No anti-AchR abs or anti-striated muscle abs were produced by the thymoma transplants or by the transplants derived from restthymus. In one case, in which the restthymus showed lymphofollicular hyperplasia, ab production was noted in all mice. Human IgG was secreted by all transplants derived from restthymus but never from thymoma transplants. By immunocytochemistry, it was demonstrated that all cellular components of human thymus were conserved in the transplants. B cells were present in the restthymus but never in the thymoma-derived transplants. In contrast to hyperplastic thymus, thymomas and extrathymomal thymus tissue are not a major site of autoab production in MG. This could explain why MG symptoms are relatively resistant to thymectomy in thymoma-associated MG. Even if not a major site of ab production, the thymoma may still play an important role in the induction of MG.

3
BOTULINUM A TOXIN DOSAGE AND INJECTION SITES IN THE TREATMENT OF BLEPHAROSPASM AND FACIAL HEMISPASM. R Schönhuber, R Pentore, *Bolzano, Italy*

Botulinum A toxin injection into hyperactive muscles is the treatment of choice for benign essential blepharospasm (BEB) and facial hemispasm (HF). So far no standardisation of dosage and injection technique has been agreed. To find out the best dosage and injection technique we assessed retrospectively 60 treatment sessions (28 patients: 11 BEB and 17 HF). We compared side effects and benefits as perceived by the patients themselves treated with 2 dosages (5 and 10 MU BOTOX) and 2 injection techniques (injection at 3 sites into the lower part of the orbicularis oculi only or with 2 more sites above the eye). Five treatments (4 in BEB) were not followed by any benefit, independently from site and dosage. Side effects were found in 15 out of 60 treatments (8/35 HF and 7/25 BEB), most frequently ptosis and/or diplopia (9/60). These side effects were independent from dosage, but more frequent with injections made above the eye (1/23

vs 8/37). From our data no conclusion can be drawn on the best dose. However, since higher doses bear the risk of more side effects, we suggest low dose injections into the lower part of the orbicularis oculi, until prospective randomised clinical studies are done.

4
CONGENITAL MYASTHENIC SYNDROME WITH PARTIAL ACETYLCHOLINESTERASE DEFICIENCY: CLINICAL, ELECTROPHYSIOLOGICAL, MORPHOLOGICAL AND BIOCHEMICAL STUDIES IN TWO SIBS. A Pou Serradell, J Pascual, JM Espadaler, B Eymard, M Fardeau. *Barcelona; Spain & Paris; France.*

A 43-year-old female and her brother, a 41-year-old-male had weakness and fatigability since childhood and the male patient developed myopathic features. None benefited from anticholinesterase therapy. Test for AChR-antibodies were negatives. Electrophysiological studies showed myogenic patterns, abundant jitter, block phenomenous, repetitive response to a single nerve stimulus. AChE was partially absent from the deltoid motor endplates by histochemical and electron cytochemical criteria. Biochemical studies: Partial absence of the EP-specific 16 S AChE. EPs were reduced in size and number. Electron micrograph showed nerve terminals reduced in size being applied against only fraction of the postsynaptic resion; the postsynaptic folds showed focal degeneration. Ultrastructural localisation of the AChR was normal. Underlying muscle fiders (great predominance of type I) showed vacuoles containing electrodense material. In conclusion, patients with autosomal recessive inheritance of a partial deficiency in AChE are described. Clinically, they present a more benign phenotype compared with cases with congenital total absence of AChE. It is likely that other patients with unexplained fatigue may have similar defects in AChe activity.

5
MYASTHENIA GRAVIS. BREATHING PATTERN. IM Pino, E Diez Tejedor, F Garcia Rio, A Frank, C Prados, L Gomez, J Munoz. *Madrid. Spain.*

The aim of this study is to evaluate the breathing pattern in patients with mild and moderate generalised myasthenia gravis (MG). We studied 24 MG patients, who were divided into two groups. Group M1 (IIa or mild generalised MG) included 13 subjects, eight females and five males (aged 23 to 64° and group M2 (IIb or moderate generalised MG) composed of 15 patients, eleven females and four males (aged 23 to 69). our control group was constituted of 15 healthy persons distributed similarly in sex and age. Spirometry and maximal respiratory pressures in basal conditions were performed in all subjects. Inspiratory occlusion pressure in the mouth at the first 0.1s (P0.1) was measured by the method of Whitelaw. Statistical comparison of three groups was treated with analysis of variance coupled with pairwaise mean comparisons using the Bonferroni test. Results: No difference was detected for parameters of breathing pattern between group M1 patients and control subjects. Subjects of group M2 compared with the control group have a lower VT(0.39 ± 0.04 VS 0.55 ± 0.07 I; $p < 0.001$), Ti (1.09 ± 0.19 vs 1.70 ± 0.41 S; $p< 0.01$). and Ttot (2.66 ± 0.40 VS 3.65 ± 0.78 S; $p < 0.05$). When the M1 and M2 groups are compared, a lower VT (0.51 ± 0.07 VS 0.39 ± 0.04 I; $p < 0.001$), Ti (1.44 ± 0.33 VS 1.09 ± 0.19 S; $p< 0.01$) and Ttot (3.40 ± 0.61 VS 2.66 ± 0.40 S; $p < 0.001$) is observed. Conclusion: Breathing pattern is not modified in mild MG. Moderate MG is characterised by a more rapid shallow breathing pattern.

6
ACQUIRED CHRONIC DEMYELINATIVE POLYNEUROPATHY - A RETROSPECTIVE STUDY. C Bouchard, G Said, *Le Kremlin Bicêtre, France*

We report on a retrospective study of clinical, electrophysiological and morphological features of 95 consecutive patients (64 men, 31 women; mean age 51 ± 18 SD) with acquired chronic demyelinative polyneuropathy (ACDP). Patients were classified according to criteria for chronic inflammatory demyelinative polyneuropathy (CIDP) modified from Dyck et al (1993). Thirty one patients had definite forms, 38 probable, 31 possible. Patients with monoclonal gammopathies, HIV infection, identified hereditary or metabolic disorders were excluded. Seven patients had associated hepatitis, 3 had simultaneous CNS involvement, 10 had serious psychiatric manifestations and 4 had epilepsy. On average, the polyneuropathy had progressed over 15 months, less in the 16 patients in whom an infectious event preceded manifestations of peripheral neuropathy ($p<0,05$). Inaugural manifestations included weakness in 75% of the patients, paresthesiac in 68 %, pains in 36 %. The course was relapsing in 14, progressive in 39 cases, more or less stable in the others. At the time of referral, only 17/95 patients had no motor deficit; weakness predominated in the lower limbs in the others. Postural tremor was present in 7 patients. On morphological examination of nerve biopsy specimens, 64 patients had purely demyelinative lesions, 18 had mixed, axonal and demyelinative, lesions. In 5 patients the lesions were predominantly axonal. In the others the nerve specimen was nearly normal. Inflammatory infiltrates were present only in 3 percent of the nerve biopsy specimens, suggesting that acquired chronic demyelinative neuropathy was more appropriate that CIDP to qualify this entity.

7
THE KYPHOSCOLIOTIC (ky) MOUSE: A MODEL FOR STRUCTURAL NEUROMUSCULAR JUNCTION DISEASES. RJM Lane, MJ Barrett & GR Coulton *London UK*

Kay mouse mutants exhibit a neuromuscular disease in which predominantly slow twitch muscles undergo extensive post-natal necrosis and regeneration, the regenerated fibres being smaller and weaker than normal, resulting in spinal deformity. The most striking pathological feature is extensive motor nerve sprouting and complete loss of normal end-plate structure. Studies of the distribution of junction-associated proteins (JAPs) such as AChR and 43kD protein by histochemistry and northern blotting, suggest that loss of AChR clustering is not the primary lesion in Kay but that the mutation affects protein(s) which maintain junction integrity and function. We have mapped the Kay locus to a region of mouse Chr 9 syntenic to human Chr 3p, close to but recombinant with genes encoding a number of JAPs (laminin, collagen-7, dystroglycan) but all such candidates have subsequently been eliminated, suggesting that the genetic lesion affects a hitherto unidentified JAP.

8
RESPIRATORY DRIVE IN THE MYASTHENIA GRAVIS. F Garcia Rio, E Diez Tejedor, J Casadevall, A Frank, R Alvarez Sala, P Barreiro, JM Pino Garcia. *Madrid, Spain.*

The aim of this study is to evaluate the central ventilatory drive in patients with mild and moderate generalised myasthenia gravis (MG). Methods: We studied 24 MG patients, who were divided into two groups. Group MI (IIa or mild generalised MG) included 13 subjects, eight females and five males (aged 23 to 64) and group M2 (IIb or moderate generalised MG) composed of 15 patients, eleven females and four males (aged 23 to 69). our control group was constituted of 15 healthy persons matched for sex and age. Spirometry and maximal respiratory pressures in basal conditions were performed in all subjects. Inspiratory occlusion pressure in the mouth at the first 0.1 s (P0. 1) was measured by the method of Whitelaw. Statistical comparison of three groups was treated with analysis of variance coupled with pairwaise mean comparisons using the Bonferroni test. Results: The P0.1 was higher in group MI than control subjects (2.44 ± 0 71 cmH2O vs 1.53 ± 0.2 cmH2O; $P<0.05$). Subjects of group M2 compared with the control group have a higher P0. 1 (2.18 ± 0.71 cmH2O vs 1.53 ± 0.2 cmH2O; $P<0.05$). This P0.1 increase is inversely related to the deterioration of muscle effort measured by MIP ($r=0.68$; $P<0.05$). Interestingly, P0. 1 is not greater in the group M2 compared to M 1. Conclusions: We proved that the central ventilatory drive is increased in form grade of the disease. Nevertheless, when the disease progresses (IIb grade), the central ventilatory drive fails to increase.

9
MYSTHENIA GRAVIS ASSOCIATED WITH TONIC PUPIL AND HYPERTHYROIDISM. MJM Dupuis, R Mezt, D Jean, E Maes, *Ottignies, Belgium*

A 33 year-old female patient with Basedowis disease associated with myasthenia gravis and unilateral tonic pupil (Adie's pupil) is presented. Hyperthyroidism was diagnosed in 1983. Exophtalmia with left ptosis was noted since August 1991; diplopia developed in December 1991. Left mydriasis was first demonstrated in February 92, associated with bilateral external ophtalmoplegia. In March 92 fluctuating tetraparesis was noted; decrement after repetitive stimulation, positive AChR antibody titer and response to anticholinesterases proved myasthenia gravis. Instillations in

the eyes of pilocarpine revealed a postganglionic abnormality. Adie's pupil without other symptoms of dysautonomia was diagnosed. Myasthenia but not the pupillary signs improved after thymectomy and partial thyroidectomy. The 3 diseases are probably due to associated autoimmune disease. It is the second case of myasthenia gravis and tonic pupil association.

10
THE EFFECTS OF 4-AMINOPYRIDINE ON COGNITIVE FUNCTION IN PATIENTS WITH MULTIPLE SCLEROSIS: A PILOT STUDY. RCF Smits, HH Emmen, FW Bertelsmann , BM Kulig, AC van Loenen, CH Polman. *Amsterdam, The Netherlands.*

Recent studies have demonstrated that 4-aminopyridine (4-AP) has a favourable effect on the disability of certain patients with MS, mainly for motor and visual functions. In our experience, improved memory and attention functions have also been reported by patient being treated with 4-AP. These subjective impressions have, however, until now not been confirmed by objective findings. The study employed a randomized, double-blind, placebo-controlled, cross-over design. Twenty patients with clinically definitive MS were randomized to receive either oral 4-AP for 2 weeks followed by oral placebo for 2 weeks or oral placebo for 2 weeks followed by oral 4-AP for 2 weeks. The mean outcome criterion was the Brief Repeatable Neuropsychological Battery of Rao. Although a trend for improved performance with 4-AP was found in two of the tests used, we were unable to demonstrate significant effects of 4-AP on neuropsychological performance of MS patients. This might be explained either by the fact that 4-AP has no effect on this aspect of central nervous system function or by methodological aspects induced by study design, the sensitivity of the tests used or the analysis of the tests results.

11
THE TREATMENT OF MULTIPLE SCLEROSIS (MS): 4-AMINOPYRIDINE (4-AP). R de Waal, CH Polman, FW Bertelsmann, HAM van Diemen, JC Koetsier, *Amsterdam, The Netherlands*

Potassium channel blockers can be effective in the treatment of MS; a direct comparison between the two agents available for human use (4-AP, DAP) has not been made before. To compare the efficacy and toxicity of 4-AP and DAP in MS, 14 non-responders to 4-A were treated with DAP in a four week open label trial with doses up to l ,0 mg/kg body weight (mean dose 56 ,4 mg), while responders to 4-AP were treated in a randomized double blind, double cross-over study with 4-AP (mean dose 23 mg) and DAP (mean dose 46 mg). The side effects of 4-AP mainly consisted of dizziness, acral paraesthesias and gait disturbance. These complaints were mild and no patient withdrew from the study. The side effects of DAP consisted of acral paraesthesias, nausea and abdominal pain. These complaints were dose-limiting and in some patients more serious: 2 of 3 patients with abdominal pain withdrew from the study after 3 weeks (daily dose 50 mg). In the cross-over study 3 patients (all in DAP phase) discontinued the study, because of subjective deterioration. 4-AP was more effective than DAP, especially for ambulation, fatigue and overall daily functioning. These results suggest that 4-AP is superior to DAP in the treatment of MS.

12
METHYLPREDNISOLONE REDUCES THE EXACERBATION RATE AND PROGRESSION OF MULTIPLE SCLEROSIS. D Ince, N Afsar, S Tekin, C Aykut and S Aktan. *Istanbul; Turkey.*

Etiology of multiple sclerosis is mainly based on auto immunity, hence immunesuppressive agents are mandatory in its treatment. Methylprednisolone has been used successfully in acute attacks but there is nothing certain about tne treatment modalities preventing the disease progression. In this study, methylprednisolone has been given 1000 mg intravenous (IV) monthly for prophylactic manner. Fifteen "clinically definite multiple sclerosis" patients have been evaluated with Kurtzke expanded disability scale (EDSS) and exacerbation rate. As pre-results of first six months, a statistically significant decrease was found in EDSS and exacerbation rate ($p<0.05$, $p<0.001$, Stuart Maxwell test). Fifteen multiple sclerosis patients have been grouped as remission and exacerbation, and chronic progressive group. Methylprednisolone was given 1000 mg IV monthly for the remission exacerbation group and it was given 1000 mg IV three days monthly for the chronic progressive group. We evaluated the EDSS and acute attack rates of these two groups separately and as a whole. In this study, 1000 mg methylprednisolone IV monthly administration was used as prophylactic therapy to reduce the progression and the attack number. In the first six month period, successful results have been obtained. For demonstrating the long term response of methylprednisolone,we planned to continue the administration following two years.

13
DISEASE ACTIVITY AFTER STOPPING CHRONIC INTERFERON (IFN)-ALPHA-2a TREATMENT IN MULTIPLE SCLEROSIS. R Ferri, L Durelli, M R Bangioanni, B Ferrero, A Riva, B Bergamasco. *Torino, Italy*

Chronic IFN-α therapy reduces exacerbation rate and MRI signs of disease activity in remitting-relapsing (R/R) MS, but information about the need for the chronic drug administration is lacking. The aim of this study was to evaluate the long lasting effects of systemic high dose r-alpha$_{2a}$-IFN therapy in R/R MS after stopping treatment. Twenty R/R MS patients received 9 million IU a 2α-IFN (Roferon, Roche) (n=12) or placebo (n=8) every other day for 6 months. Clinical evaluations were performed monthly, and serial MRI and lymphocyte IFN-γ production were studied before, at the end of treatment, and 6 months later. Clinical relapses or new or enlarging lesions at MRI occurred in 2/12 IFN treated and in 7/8 placebo treated patients ($p<0.005$) during treatment, and in 6/12 previously IFN-treated and in 6/8 previously placebo treated patients ($p=0,37$) during the subsequent 6 months without therapy. Baseline IFN-γ production of 19.10 ± 7.12 IU/ml decreased to 3.03 ± 0.66 IU/ml ($p<0.04$) at the end of IFN-α treatment, and thereafter increased to 17.70 ± 7.31 IU/ml 6 months after stopping treatment. IFN-γ production was almost always unchanged in the placebo group. Conclusion: High dose systemic r-alpha$_{2a}$-IFN treatment was associated to clinical, MRI, and immunologic signs of reduced disease activity only during drug administration, but all signs of disease activity returned to baseline after stopping treatment.

14
THE USE OF ALTERNATIVE TREATMENTS IN MULTIPLE SCLEROSIS. A 5-YEARS FOLLOW-UP STUDY. E Stenager, EN Stenager, L Knudsen, K Jensen. *Odense, Denmark*

Previous cross-sectional studies have demonstrated that patients with multiple sclerosis (MS) frequently use alternative, i.e. unauthorized non-medical treatments. In this study 49 patients (22 males, 27 females) with definitive MS were examined and interviewed over a 5 year interval to determine the extent of the use of alternative treatments, and whether the use influenced the natural course of MS. Using clinical course, Kurtzke Disability Status Scale and patients self-assessment as parameters, and comparing patients with and without use of alternative treatments, it was concluded that alternative treatments did not alter the clinical course. The use of alternative treatments declined over the 5 years. The use of alternative treatments could be interpreted as an indicator of psycho-social difficulties in MS patients.

15
IMMUNOADSORPTION THERAPY FOR SEVERE DEMYELINATING RELAPSES IN MALIGNANT MULTIPLE SCLEROSIS. AN OPEN-LABEL STUDY. C De Andres, F Anaya, S Gimenez-Roldan. *Madrid, Spain.*

Plasma exchange has been reported to benefit acute relapsing multiple sclerosis (MS) through the potential removal of circulating soluble factors such as gamma interferon, tumour necrosis factor and relapses-trigger peptides. Though equally effective, immunoadsorption may cause a lesser incidence of side-effects than plasma exchange. We report marked benefit from immunoadsorption therapy in 3 definite, relapsing-remitting malignant MS patients in whom high doses of corticosteroid therapy failed to provide any benefit during severe exacerbations of the disease . Two 27-year old women went into a locked-in state and a 29-year old man developed tetraparesis and signs of brainstem dysfunction during severe relapsing episodes. They all were suffering from definite relapsing-remitting MS with laboratory support; disease duration was of 4-6 years and they were experiencing an average of 2-3 relapses per year. During the exacerbation they all required nasogastric feeding, developed respiratory difficulties and scored 8.5 to 9.5 in EDSS. High-dose intravenous methylprednisolone pulses in all 3 patients failed to provide any benefit while their clinical sta-

tus persisted unchanged for 6-18 weeks. They received 6 immunoadsorption sessions over 3 weeks. They started to improve 2-3 days after the first immunoadsorption session and was kept steadily thereafter, 2 patients becoming ambulant while EDSS scores changed to 6, 7 and 6.5, respectively. Serum immunoglobulins, fibrinogen and C3-C4 levels decreased gradually during the procedure. Mitoxantrone (1 patient) or cyclophosphamide plus iv ACTH (2 patients) was given following the immunoadsorption treatment sessions. All 3 patients remained stabilised during 14-31 months of follow-up. Our observations support the view that immunoadsorption therapy may be of value in the treatment of severe, corticosteroid-resistant MS relapses and deserve a controlled study in a larger series.

16
VISUAL EVOKED POTENTIALS IN MULTIPLE SCLEROSIS PATIENTS WITH THE OPTIC FORM OF MULTIPLE SCLEROSIS AND WITH SUBCLINICAL LESIONS OF THE OPTIC NERVE. V Dimova, S Cherninkova. *Sofia, Bulgaria.*

A group of 140 patients with MS were diagnosed in the Neurology Clinic, Alexander University Hospital, Sofia ,on the basis of complex clinical, neurophysiological, CSF and immunological investigations. Eighty two of the patients were investigated at different stages after optic neuritis . In 58 patients there were no anamnestic and clinical data of a lesion of the optic nerve or visual pathways. In the group with the optic form of MS (82 patients) an abnormal latency of the P 100 component was found in 97,6%. In the remaining 58 patients without symptoms of a lesion of the optic nerve, in 62,1% the latency of the P 100 component was also delayed , but the changes were not as marked . In the group of patients with the optic form of MS the abnormally delayed latency of P 100 component was combined with an abnormality of the amplitude and duration of P 100 potential in some patients. Most patients were followed clinically and neurophysiologically for period of 3-5 years.

17
MULTIPLE SCLEROSIS LIKE DISORDER ASSOCIATED WITH LEBER'S HEREDITARY OPTIC NEUROPATHY IN MALE HARBOURING THE MITOCHONDRIAL DNA11778 MUTATION. NK Olsen, AW Hansen, S Norby, AL Edal, T Rosenberg. *Odense & Copenhagen, Denmark*

The purpose of this report is to draw attention to a possible common pathogenesis of Leber s hereditary optic neuropathy (LHON) and a multiple sclerosis(MS)-like disorder in a male. LHON is characterised by acute or sub acute, severe bilateral visual loss in young adults is a mitochondrial genetic disease, and therefore exclusively maternally transmit as opposed to X-linked diseases, descendants of male patients are unaffected. Three mitochondrial mutations have been found to be associated with LHON, namely a substitution of base pair 11778,3460 and 14484.An MS-like disorder has recently been described in 8 female LHON patients, yet not in males .(LHON was diagnosed in a 31 yr old man and in 3 matrilinear relative all harbouring the 11778 mutation. The patient later developed sequential sensorimoto symptoms in the right and left limbs, trunk and face. Evoked potentials were abnormal, and CSF exhibited oligoclonal bands. Brain MRI showed widespread white matter lesions. It is concluded that mitochondrial genes are important in the pathogenesis of LHON which may be immunologically mediated. The same mechanism may underlie MS-like changes. A complicated genetic interplay may be significant in the phenotypic diversity. The combination of LHON and an MS-like disorder is demonstrated in both series.

18
SPINAL CORD MRI IN MULTIPLE SCLEROSIS: LESSONS FROM FAST SPIN ECHO PULSE SEQUENCE (STIR). JW Thorpe, BE Kendall, WI McDonald, DH Miller, *London, UK*

Recent advances in the design of imaging sequences and receiver coils have greatly enhanced the ability of MRI to detect the spinal lesions of multiple sclerosis (MS), whilst still relying predominantly on differences in transverse relaxation time (T_2) to provide contrast. The short tau inversion recovery fast spin echo pulse sequence (fast STIR) combines the synergistic T, and T_2 contrast mechanism of conventional STIR with the reduced imaging time of fast spin echo (FSE). We have compared fast STIR with T_2-weighted FSE in evaluating the spinal cord lesions in 17 patients with multiple sclerosis, 2 patients with acute transverse myelitis and 12 healthy controls. Intrinsic lesions were seen only in patients. Twenty-five of the sixty-two lesions identified were more clearly demonstrated by fast STIR, 23 by FSE. However, signal-to-noise and contrast-to-noise ratios were higher in all cases on FSE, suggesting other mechanisms must play a part in lesion conspicuity, including the brightness of surrounding structures and the choice of window settings. Such factors should be considered in comparative studies of this kind.

19
INTER-OBSERVER CONCORDANCE OF BRAIN MRI LESION VOLUME MEASUREMENTS IN MULTIPLE SCLEROSIS M Filippi, MA.Horsfield, P Reganati, C Baratti, S Bressi, A Campi, V Martinelli, N Canal, G Comi, *Milan, Italy & Leicester, UK.*

Quantitative assessment of magnetic resonance imaging (MRI) lesion loads in multiple sclerosis (MS) is the best way to evaluate the natural history of the disease and the efficacy of treatments. Since such studies usually need multicenter cooperation in which many observers might be involved, this study was planned to evaluate the Inter-observer concordance of lesion volume measurements. Brain MRI scans (1.5 T machine, SE 2000/50, 5 mm contiguous axial slices) were obtained for 8 clinically definite MS patients and were evaluated independently by 3 observers. The abnormalities were measured both by a quantitative semi-automated technique and by an arbitrary scoring system. The Kendall's coefficient of concordance was high for both the assessments of brain MRI abnormalities, perhaps because the observers have been working together for a long time, but was higher for the quantitative assessment (arbitrary scoring system: W=0.98, chi^2=20, $p<0.003$; semi-automated method: W=0.92, chi^2=19.44, $p<0.006$). These data indicate that quantitative assessment of lesion volumes in MS not only allows more objective results to be obtained, but also gives a high inter-observer concordance.

20
HYPERPROLACTINEMIA IN MULTIPLE SCLEROSIS. F Idiman, E Idman, B Baklan, V Ozurk, S Yeil, *Izmir, Turkey*

A number of studies have indicated a strong influence of the hypothalamus and endocrine factors on immunological and inflammatory processes. Among the endocrine factors, prolactin appears to be a potent immunomodulator capable, of enhancing humoral and cell-mediated immunity. Therefore, in order to clarify hormonal abnormalities in multiple sclerosis (MS), serum prolactin levels were measured in 50 patients with MS and 30 healthy subjects. The presence of hypothalamic lesions was also studied by magnetic resonance imaging (MRI). Serum prolactin levels were found to be significantly higher in MS patients than in healthy controls in both sexes. Group I (relapsing-remitting form), Group II (progressive forms), group III (relapsing-remitting and progressive forms) had higher prolactin levels than normal controls. The most important difference between MS normal control was found in the progressive group. The patients who had greater disability on Kurtzke's scale did not show any difference four the lower disability group. The results of the present study indicate that prolactin may play an important role in immune functions and high prolactin levels can modify immune function in multiple sclerosis.

21
BRAIN MRI CORRELATES OF COGNITIVE IMPAIRMENT IN PRIMARY AND SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS. M Filippi, V Martinelli, M Rodegher, G Sirabian, M Alberoni, A Campi, M Rovaris, G Comi, *Milan, Italy.*

Brain magnetic resonance imaging (MRI) and 14 neuropsychological tests, exploring frontal functions, short and long-term memory, visuo-spatial skills, attention and language, were obtained in 14 patients with Primary Progressive Multiple Sclerosis (PPMS) and 17 patients with Secondary Progressive MS (SPMS). Patients were considered to be cognitively impaired when at least 3 neuropsychological tests were abnormal. MRI was performed with a 1.5 T machine and the lesions were counted and sized for 16 anatomical regions. The clinical features were similar in the two groups. Cognitive deficits were found in 9/17 SPMS patients and in 1/14 PPMS patients ($p=0.01$). Patients with SPMS had higher total ($p=0.004$), periventricular ($p=0.008$) and non-periventricular ($p=0.004$) lesion loads on MRI than patients with PPMS. Non-periventricular lesion load was greater for SPMS patients with cognitive impairment than for those without such deficits ($p=0.005$). Our results indicate that both neuropsychological and brain MRI abnormalities are more marked in patients with SPMS. Since physical disability was similar for the two groups, this

suggests that disability in PPMS is predominantly caused by spinal cord involvement.

22
CLINICAL FEATURES OF ITALIAN PATIENTS WITH FAMILIAL MULTIPLE SCLEROSIS. M Eoli, L La Mantia, A Salmaggi, E Manetti, M Zaffaroni, C Milanese, *Milan, Italy*

As early as the in 19th century Multiple Sclerosis (MS) was noted to occur in families and heredity implicated as a possible cause. Today there is an increasing evidence that genetic factors have a role in determining MS susceptibility. However the well known association between the disease and HLA has been repeatedly shown in population studies but not confirmed by linkage analysis. This discrepancy might be explained by a possible heterogeneity between sporadic and familial cases. Therefore we compared the following clinical characteristics (age of onset, clinical course, initial symptoms, sites of involvement, progression of disability as a function of time) in 53 familial MS coming from 25 Italian families with two or more first-degree relatives affected by the disease with 15O sporadic MS cases regularly attending our Institute. We failed to demonstrate clinical heterogeneity between sporadic and familial MS. Furthermore the interclass correlation analysis of our 25 affected first degree relatives suggested that clinical features of MS are not correlated among relatives and no heterogeneity is present among different families.

23
COGNITIVE FUNCTION IN MULTIPLE SCLEROSIS. E Stenager, L Knudsen, K Jensen. *Odense, Denmark*

The aim of the study was to examine the association between cognitive function, Kurtzke Disability Status scale (DSS) and Beck Depression Inventory (BD) in multiple sclerosis (MS) patients examined over a 5 year interval. In the study 49 patients (22 males, 27 females) in the age-interval 30-45 years participated. The course was chronic progressive (CP) in 45 and relapsing/remitting (RR) in 4 patients. For the group as a whole, a significant deterioration was found in Trail making A and B (Wilcoxon, matched-pairs, $p<0.02$), symbol digit modalities test, auditive verbal learning test, story recall and recurring figurs test (Wilcoxon, matched-pairs, $p < 0.00l$). Dichotomising the group into CP and RR, a significant deterioration was found in CP patients. The deterioration in cognitive function was independent of sex and BD. Logistic regression with deterioration in DSS as dependent and deterioration of cognitive test as independent variables showed a weak association with story recall (Chi-square; $p<0.05$). It is concluded that cognitive function and DSS deteriorate significantly in CP patients, but the deterioration in cognitive function is independent of DSS, sex and BD.

24
IN VITRO ADHESIVENESS TO ENDOTHELIAL CELLS OF PERIPHERAL BLOOD MONONUCLEAR CELLS FROM PATIENTS WITH MULTIPLE SCLEROSIS. A Dufour, M Eoli, A Salmaggi, E Corsini, L La Mantia, C Milanese, A Nespolo. *Milan, Italy*

Migration of peripheral blood mononuclear cells (PBMNC) across the endothelia of cerebral venules is a key step in the pathogenesis of demyelinating lesions in MS. We undertook a preliminary to compare in vitro, the adhesiveness of PBMNC isolated from peripheral blood (bp) of from 6 patients with chronic progressive MS and 6 healthy controls to human umbilical cord vein endothelial cells (HUVECs). After incubation of EC with or without pro-inflammatory cytokines (TNF-α, IFN-γ) PBMNC were added to endothelial cells (EC) in the presence or absence of monoclonal antibodies directed to both chains (CD11a and CD18) of the LFA-1 heterodimer. Evaluation of the proportion of adhering cells was performed by cytofluorimeter analysis after trypsinisation of cell monolayers. No clearcut differences emerged between patients and controls when adhesiveness of PBMNC to unstimulated ECs was considered. After stimulation of ECs with IFN-γ, lymphocyte adherence increased dramatically both in patients and in controls, while only a slight increase was seen in the monocyte population. Inhibition of EC-cytokine-stimulated adhesion showed that lymphocytes from MS patients were inhibited to a lesser extent than controls. This suggests that adherence of lymphocytes from MS patients to activated endothelia may be mediated by other molecules than CD11a and CD18, as opposed to controls.

25
USE OF THE FATIGUE DESCRIPTIVE SCALE IN MULTIPLE SCLEROSIS. P de Castro, M Carreno, J Iriarte. *Pamplona Spain*

Evaluation of fatigue in multiple sclerosis (MS) patients is a difficult task. In a previous paper we depict an scale considering quantitative and qualitative aspects of fatigue. This scale was defined as the Fatigue Descriptive Scale (FDS). The aim of this work was to analyze fatigue in MS patients, and to compare Descriptive Scale with the Fatigue Severity Scale of Krupp. One hundred patients (69 women, 31 men) suffering from clinically definite MS, category 1a by Poser's criteria, were examined for fatigue using the FDS and the FSS. Age was 37,511,3 years (16-66); duration of the disease was 8,5 ± 6,9 years (1-30).Results: Sixty-nine patients referred faligue (45 spontaneously, 24 when questioned). The descriptions of fatiguc were classified according to our scale. Forty-nine defined the symptom as fatigue at exercise, 17 as asthenia and 3 as worsening of other symptoms. Fatigue by itsell own produced same limitalion in 40 patients; work was limited in and patients; social relation, in 17 patients; selfcare was difficult in 1 patient. Thirty-two patients suffered fatigue daily. FDS Global score was 4,68 ± 4,15. FSS was 3,19 ± 1,78. FDS and FSS of Krupp were highly correlated ($p < O,OI$) .Conclusions: Fatigue is very frequent in MS patients. The Descriptive Fatigue Scale is useful to classify modality the, periodicity and the severity of the fatigue in MS. FDS and FSS are correlated.

26
SACCADES IN FRONTAL AND PARIETAL LESIONS. D Kompf, W Heide, *Lubeck, Germany.*

Using infra-red reflection oculography we recorded spontaneous, reflexive, and intentional visually guided saccades as well as exploratory, memory-guided and anti-saccades in patients with unilateral dorso-medial or -lateral frontal ($n = 15$) or posterior parietal lesions ($n = 15$). Results were compared with an age-matched normal control group ($n = 30$). In frontal lesions visually guided saccades had normal latencies and amplitudes, whereas in parietal lesions latencies were significantly increased - particularly in the overlap paradigm - and amplitude gain decreased. Remembered saccades had increased latencies in frontal and decreased amplitude gain in parietal lesions. In a predictive and antisaccade tests frontal patients had deficits in suppressing reflexive and anticipatory saccades into the contralateral visual hemifield, with an error of 30% to 70% particularly if lesions included the frontal eye fields. In visual exploration tasks there was in both groups a preference for the ipsilateral hemifield, more pronounced in frontal lesions; this unilateral visual exploration deficit was most obvious when subjects had to scan an abstract visual scene (coloured squares). Frontal oculomotor areas (FEF, PrC, SMA) play a major role in the cortical control of volitional saccades as well as in the volitional suppression of reflexive saccades. The posterior parietal cortex, however, is crucial for the initiation and visuo-spatial programming of saccades to visual targets. Remembered saccades are successively controlled by the posterior parietal cortex (early selective visuo-spatial program), the Pl C (spatial memorization) and the FEF (triggering).

27
THE DISABILITY SPECTRUM OF MULTIPLE SCLEROSIS IN ICELAND, 1900-1990. JEG Benedikz, H Magnusson, CM Poser, G Guomundsson. *Reykjavik, Iceland, Boston, USA.*

In a total population survey of MS in Iceland 1. Jan. 1900 - 31. Dec. 1989, improving case ascertainment has shown the number of mild cases to be well in excess of that generally reported. Several autopsy studies have indicated that asymptomatic MS may equal that detected clinically. We suggest that severe disease may bc a relatively uncommon expression of a more widespread and usually milder disorder. The first survey of MS in Iceland took place in the late 1950 s, since then the data is prospective, prior to this retrospective. All patients have been examined by one or more neurologists. Total number of patients 323, women 205, men 118. Alive 31.Dec. 1989: Total 252, women 163, men 89. Kurtzke's revised disability scale has been applied: Benign 0-3, moderate 4-6, severe 7-9. Results: 1) The average annual incidence is 2.5 - 4.5 per 100.000 from 1930 - 1990, remaining stable at 4.0 - 4.5 per l00.000 from 1970, clearly reflecting the improved case ascertainment associated with the increasing number of neurologists. 2) The number of benign cases shows a consistent increase from 5% in 1940 to 70% by l990, severe cases accounting for 80% reducing to 16% over the same period. 3) After 20 years disease duration, 80% of patients still have benign MS, 16% have become severe. Conclusion: Preliminary studies indicate that a benign form of MS is considerably more common than generally realised.

28
CELLULAR IMMUNE FUNCTION IN PATIENTS WITH MULTIPLE SCLEROSIS. J Barado, P Echaniz, A Lopez de Munain, E Cuadrado. *San Sebastian. Spain*

We aimed to look insight the following questions: a) Is the analysis of blood lymphoid subsets clinically useful in the management of patients with Multiple Sclerosis (MS)? b) Is there any difference in the spectrum of cytokines produced by T cells from patients which differ in the clinical course of MS?. Thirty eight patients with established MS were staged according the neurologic disability index proposed by Kurtzke. All of them were in clinical remission and did not receive any drug at the time of blood drawing. The "naive" and "memory" subsets Or CD4+ and CD8+ subpopulations and cells expressing activation markers (CD25, CD38, DR and LFA-1) were quantified b/ flow cytometry in the peripheral blood. Proliferative responses to BMP were analysed in blood mononuclear cells and purified CD4+ cells from 20 patients, and secretion of cytokines IFNg, IL4 and TNFa was also analysed in whole blood, PBMC, and CD4+ cells stimulated with the immunodominant BMP 84-102 peptide. Results and conclusion: Peripheral blood lymphoid subsets did not differ quantitatively from normal controls. Forty percent of patients displayed proliferative response to BMP and these responses correlated with the Kurtzke index by regression analysis (R = 0.443. Cytokine synthesis by CD4+ cells in response to BMP 84-102 peptide suggests imbalance of cytokines spectrum towards a higher activity of TH-1 cells in this disease since, synthesis of IFNg and IL4 correlated with the Kurtzke index in the regression analysis (R = 0.38 and R = -0.54 respectively).

29
THE RELATIONSHIP BETWEEN COGNITIVE AND PSYCHIATRIC DISTURBANCES, AND THE MRI AND CLINICAL FINDINGS IN MULTIPLE SCLEROSIS. B Baykan-Kurt, O Oktem-Tanor, S Bahar, R Konyalioglu, A Tumac, S Gok, H Gurvit, G Gursoy, M Eraksoy, *Turkey*

In this study our aim was to investigate the relationship between MRI and clinical findings, and the cognitive and psychiatric disturbances in our multiple sclerosis (MS) outpatient group. We randomly selected 29 MS patients, with an average age of 33.5(10.7 and a mean disease duration of 7 years (min: l, max: 35 years). All had definite MS and all but 5 patients had a remitting-relapsing course. All had low EDSS scores (EDSS:2(1.2). Within a period of 8 weeks all of them underwent an extensive outpatient evaluation, MRI investigations, neuropsychological testings (NPT) with a comprehensive battery. Additionally 23 volunteers from the group were also evaluated at the psychiatry department with a set of scales. Fourteen cases (48 %) were found to have mental dysfunction, especially more prominent in the memory processes. Statistical analysis (Kendall tau) showed a significant correlation between neuropsychological dysfunction scores and some of the MRI parameters such as corpus callosum atrophy ($p<0.005$), the width of the cortical sulci ($p=0.005$) and the size of the ventricles($p<0.02$). Also the total MRI plaque score and the total periventricular plaque score were found to be significantly related to total memory dysfunction scores. The correlation of memory dysfunction with plaques in temporal lobes were significant ($p<0.05$), but frontally localised plaques did not have any significant effect on so called frontal dysfunction. Psychiatric evaluation showed that 48% of the patients had some form of psychiatric disturbance which did not correlate with NPT and MRI scores.

30
TOXICITY OF AMYOTROPHIC LATERAL SCLEROSIS SERA ON PURIFIED RAT SPINAL MOTONEURONS IN VITRO. W Camu, CE Henderson, *Montpellier, France.*

We have developed a rapid and reliable method to purify embryonic rat spinal motoneurons (MNs). This technique named "panning" is based upon the motoneuronal specificity, in the rat spinal cord, of the monoclonal anti-$p7^{SNGF-R}$ antibody since the 15th embryonic day (EIS). Using these purified MNs in culture, we analysed the influence of the sera from 38 amyotrophic lateral sclerosis (ALS) patients and 22 subjects with other neurological disorders (controls). At low concentrations (1%) there is a significant toxicity of ALS sera (vs controls, $p < O.OOS$, ANoVA). The individual analysis shows that 2S% of the ALS sera can be considered as highly toxic (mean below the 9S% confidence interval). There is no correlation between the toxicity and clinical criteria (sex, age at onset and ALS duration). As all the sera were previously dialysed the toxicity cannot be attributed to an excess of excitatory amino acids. No toxicity could be observed with the IgGs purified from the most toxic sera. However, these sera were not toxic when applied on purified MNs from chicken embryos (E6) in the same conditions, suggesting a species specificity. This toxicity of ALS sera may be useful for the understanding of ALS etiopathogenesis.

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ANTIRETROVIRAL SEROREACTIVITIES IN SPORADIC AMYOTROPHIC LATERAL SCLEROSIS (ALS) ME Westarp, H Perron, R Hoff-Jörgensen, H Rasmussen, S Schraff, HH Kornhuber, *Ulm, Germany; Lyon, France; Copenhagen, Denmark*

We tested 32 ALS patients (n= 101 sera) and 93 with other neurological diseases as controls (n= 144 sera) for pep tide reactivity to six synthetic peptides (10-14 aa). Peptides had been selected according to circumscript homologies with human spuma retroviral and/or maedi-visna lentiviral sequences. We identified significant IgG reactivities in 18/101 ALS sera and 6/144 control samples ($p<0.01$ Fisher's exact test), or 8/32 ALS patients versus 2/93 control patients ($p<0.01$ Fisher's exact test). ALS patients or sera with anti-spuma retroviral activity did not excel in these synthetic pep tide assays. In a blocking ELISA with visna viral antigens, the majority of ALS patients (28 out of 30, or 47 sera out of 50) reduced the binding of specific anti-visna antibodiesi 3 out of 12 simultaneously tested visna-reactive patients recognised one of the selected synthetic pep tides. Immunoblotting six ALS sera against a human immunodeficiency virus type-2 antigen, three ALS patients identified bands in the 10 to 56 kD range. One of these three had recognised a decapeptide homologous to visna virus envelope and ciliary neuronotrophic factor. IgG seroreactivities against different retrovirus-associated antigens suggest an altered antiretroviral immune response in sporadic ALS.

32
BRAIN AND SPINAL CORD MRI IN MOTOR NEURONE DISEASE. IW Thorpe, IF Moseley, CH Hawkes, WI McDonald, DH Miller, *London, UK*

Pathological studies in motor neurone disease (MND) have on the whole shown more extensive changes within the spinal cord than the brain. Previous MRI reports have, however, concentrated on the brain findings. We have carried out spinal cord MRI in addition to brain imaging in 11 patients with MND. In all cases sagittal T1- and T2-weighted images of the cord were obtained, as well as T2- or T2*-weighted axial images through the cervical region. The sagittal images were unremarkable. However, in 9 cases axial imaging revealed high signal within the anterolateral part of the cord. T2-weighted axial images of the brain revealed pathologically increased signal within the posterior limbs of the internal capsules in 5 patients, with variable extension rostrally to the corona radiata and caudally to the cerebral peduncles. Marked low signal within the motor cortex was seen in 3 patients. Only one patient had normal imaging of brain and cord. We conclude that spinal cord as well as brain MRI frequently demonstrates characteristic abnormalities in MND, probably related to Wallerian degeneration within the pyramidal pathways. MRI may be of considerable diagnostic value in patients with suspected MND.

33
DECREASED CSF LEVELS OF HOMOVANILLIC ACID IN ALS. D Testa, AM Colangelo, V Fetoni, E Parati, *Milan Italy.*

In amyotrophic lateral sclerosis (ALS) diminution of dopaminergic neurons of the substantia nigra and low levels of homovanillic acid (HVA) in the cerebrospinal fluid (CSF) have been reported. We measured the CSF levels of HVA in 24 ALS patients (15 men, 9 women, aged 53.9(8.9) with an illness duration of 12.4 ± 12.1 months. The CSF levels of HVA were measured by high-pressure liquid chromatography with electrochemical detection. CSF HVA levels were lower in ALS patients (34.1 ± 21.8 ng/ml) than the control group (54.5 ± 2O.7 ng/ml; $p<O.05$). The diminution was not related to the age, duration or type of onset of the disease (bulbar or spinal). We also measured the CSF levels of 5-hydroxyindoleacetic acid in ALS patients (34.2 ± 21.5 ng/ml). They were not different from the controls (29.9 ± 11.3 ng/ml). Abnormalities of detoxification mechanisms have been suggested in Parkinson's disease. Similarly, in ALS excess of free toxic radicals could cause dopamine system imapairment.

34
PERSONALITY PROFILE IN ALS: PRELIMINARY DATA. D Testa, L Austoni, A DiGiovanni, *Milan, Italy.*

We investigated the psychological features of a group of patients affected by amyotrophic lateral sclerosis (ALS) and tried to correlate them with the degree. of disability and cognitive impairment. Seven men and 3 women (mean age 55.2 years) entered the study, with a mean illness duration of 16 months . The mean disability score measured by the Norris scale was 76.5.

The following psychological interviews were given: Beck Depression Inventory, Spielberger State Anxiety Inventory; Cognitive Behavioural Assessment (N, P, E scales of schedule 5 and Fear Survey Schedule-FSS). Cognitive deficits were assessed by MMSE, digit span, short tale, Corsi's block tapping task and supra-span learning, similarities from WAIS, Wisconsin card sorting test (WCST, short form). We found high FSS scores which were not related to the significant WCST number of perseverative errors or the degree of disability. There were no evidence of any characteristic personality profile in our ALS patients. Depression and anxiety were not characteristic features as well as adjustment difficulties. The most important finding was the fear for being socially rejected.

Abstract 35 is printed on p. S162.

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HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN AND CYCLOPHOSPHAMIDE IN AMYOTROPHIC LATERAL SCLEROSIS. N Meucci, E Nobile-Orazio, G Scarlato G, *Milan, Italy*

The of amyotrophic lateral sclerosis (ALS) is not known but there is some evidence an immunological involvement. Since high-dose intravenous immunoglobulin (IVIg) therapy may be effective in autoimmune neuromuscular diseases, we treated 4 men with ALS (aged 29, 50, 53 and 64) with IVIg and oral cyclophosphamide (CTX) for 3 to 12 months. All patients had signs of upper and lower motor neuron impairment and three of bulbar involvement. They had been affected for 5 to 13 months. had slightly increased titers of anti-GM1 or asialoGM1 serum IgM and none had a monoclonal gammopathy. Patients were treated with IVIg, 0.4g/Kg/day for 5 consecutive days, followed by monthly 2-day infusions at the same daily dose, and with oral CTX, 2 mg/kg/die. Treatment efficacy was evaluated by comparing the clinical progression of the disease before during treatment, by means of the Rankin and Appel scales and the MRC scale for muscle strength. In none of the patients treatment seemed affect the progression of the ; in two, treatment was suspended after 3 months of continuously rapid progression while in two, no modification in the rate of progression was observed after 8 to 12 months of therapy. No major side effect was reported The lack of a beneficial effect in our patients does not seem LO justify further controlled studies with IVIg and CTX in ALS.

37
ENZYMES OF LYSOSOMAL ORIGIN IN THE PLASMA OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS). G Goi, A Lombardo, C Bairati, E Aversa, P Ferrante, D Caputo. *Milan, Italy*

The levels of lysosomal enzymes β-D-galactosidase (GAL), β-D-glucuronidase (GCR), N-acetyl-β-D-glucosaminidase (NAG) were evaluated in the plasma of ALS patients and of healthy controls. Change of plasma levels of these enzymes have already been showed in neurological diseases, furthermore alterations of NAG isoenzymatic pattern have been reported in ALS. Plasma of 12 ALS-patients and 12 age-matched healthy controls was collected and stored immediately in 30% ethylene glycol. The lysosomal enzymes were measured by a fluorimetric method using a liquid stable standard. The separation of NAG isoenzymes has been carried out by chromatofocusing on PBE 94 according to a procedure set in our laboratory. Results and conclusion: No differences have been observed between ALS patients and controls regarding the GAL, GCR and total NAG levels. However, in ALS patients increased levels of I and B+I NAG fractions and a decrease of the fraction A have been showed. In particular, a statistically significant increase ($p<0.01$) of fraction I has been observed in ALS patients. This fraction is an intermediate isoenzymatic form, and is the most sensible NAG fraction to metabolic alterations.

38
CEREBROSPINAL FLUID LEVELSOF GLUTAMATE IN AMYOTROPHIC LATERAL SCLEROSIS. C Ferrarese, L Canafoglia, M Frigo, N Pecora, R Riva, L Frattola. *Monza, Italy*

Although modifications of glutamate metabolism have been demonstrated in brains from ALS patients and believed to induce excitotoxic neuronal damage, studies on cerebrospinal fluid (CSF) levels of glutamate in ALS patients are controversial, since this transmitter is rapidly metabolised in CSF. In the present study we aimed to investigate possible modifications of CSF levels of glutamate in ALS patients, using a new method of sample processing and analysis which reliably indicate in vivo levels of this aminoacid in CSF (Ferrarese, Ann. Neurol., 33:316,1993). CSF samples from 10 ALS patients and 10 age-matched controls, affected from peripheral neuropathies, were collected in perchloric acid, to inactivate CSF enzymes, and immediately neutralised, to avoid glutamine hydrolysis. Levels of glutamate, aspartate, GABA and glutamine were determined by reverse-phase HPLC analysis with fluorimetric detection and precolumn derivatization with ophtaldialdehyde (OPA). Glutamate levels were significantly reduced in ALS patients, compared to controls. Glutamate decrease was unrelated to disease severity, assessed by the Norris scale, or to duration of disease. Levels of glutamine and other neurotransmitters were unchanged respect to controls. The early and specific decrease of glutamate levels in CSF may reflect selective degeneration of glutamatergic systems in ALS, which might be linked to excitotoxic damage.

39
ANTI-GLYCOLIPID ANTIBODIES IN MOTOR NEUROPATHIES AND LOWER MOTOR NEURON SYNDROMES. M Carpo, E Nobile-Orazio, M Gamba, N Meussi, S Barbieri, G Scarlato. *Milan; Italy*

Pure motor neuropathies, including multifocal motor neuropathy with (MMN) or without (MN) conduction block (CB), are often difficult to distinguish from lower motor neuron disease (LMND) on a clinical and electrophysiological ground. This distinction is however important for their different responses to immunotherapy. Anti-glycolipid antibodies have been variability associated with these diseases but their specificity is unclear. To determine whether a specific pattern of anti-glycolipid response could be related to these different forms we measured IgM and IgG antibodies to GM1, asialo-GM1, GD1a, GD1b and GM2 by ELISA in the sera of 10 patients with MMN, 7 with MN without CB and 14 with LMND. Antibody reactivities were confirmed by overlay HPTLC. High antiglycolipid antibodies (>1/1,280) were found in two patients with MMN (20%), three with MN (43%), but only one with LMND (7%). Both patients with MMN had selectively high titers of anti-GD1a antibodies, patients with MN had high anti-GM1 antibodies associated with one or more of the other glycolipids (asialoGM1 in one, asialoGM1/GD1a/GD1b in one, GD1a/GD1b/GM2 in one). While the patient with LMND had a selective reactivity with GM1. In conclusion, even if no constant pattern of reactivity with the various glycolipids tested was associated with the different forms, the higher frequency of these antibodies in motor neuropathies than in LMND may help identifying patients with treatable motor syndromes.

40
IgG SUBCLASS DEFICIENCY IN PATIENTS WITH ALS: A DEFECT IN BURSAL LYMPHOCYTE DIFFERENTIATION OR IN CHROMOSOME 14. B Ostermeyer, BM. Patten. *Houston, Texas, U.S.A.*

In order to get clues about T-cell independent versus T-cell dependent immune mechanism in ALS, we measured IgG subclasses in 25 ALS-patients. Sixteen patients had deficiency of T-cell dependent expressed IgGl or IgG3 or both with essentially normal levels of T-cell independent expressed IgG2 and IgG4. Ten of these patients had no prior treatment and 5 out of these 10 had normal total IgG. Six patients had some immunosuppressive treatment before measurements of subclasses were done and all of them had deficiency of total IgG. Eight out of 14 patients who underwent a d-xylose breath test, had evidence of small bowel overgrowth, which was confirmed by cultures of duodenal aspirate. IgGl and IgG3 are T-cell dependent antibodies against protein antigens with close linkage on chromosome 14. The findings suggest a defect in IgG subclass expression in ALS.

41
LEUCINE DOES NOT PREVENT GLUTAMATE NEUROTOXICITY IN PRIMARY CULTURED RAT CEREBRAL NEURONS. S Abeta, N Inoue, H Matsui, Y Yoshino, *Tokyo & Yokohama, Japan.*

The neurotoxicity of glutamate has during recent years been proposed as a factor in the pathogenesis of amyotrophic lateral sclerosis (ALS). Also, branched-chain amino acids have been proposed as possible therapeutic compounds for this devastating disease. This study was undertaken to investigate whether leucine has any protective effect on cultured neurons exposed to glutamate. Primary cultures of cerebral neurons were prepared from foetal rats, by means of an established technique. For the assessment of glutamate neurotoxicity, photomicrographs were taken before and after glutamate exposure both with phase-contrast and with bright field following incubation in trypan blue, a dye normally not taken up by healthy cells. The activity of lactate dehydrogenase released from damaged cells was

also measured. Exposure to glutamate in various concentrations was carried out, and leucine was added in advance to culture dishes. Glutamate neurotoxicity was confirmed, but no protective effect of leucine was observed. Although possible clinical benefit of branched-chain amino acids in ALS can not be excluded, leucine does not prevent glutamate neurotoxicity in cultured cerebral neurons.

42
BENIGN MONOMELIC AMYOTROPHY OF LOWER LIMB: A RARE ENTITY WITH A CHARACTERISTIC MUSCULAR CT. A Uncini, A Di Muzio, C Delli Pizzi, A Lugaresi, M Ragno, D Gambi - *Chieti & Ascoli Piceno, Italy*

Six patients presented with amyotrophy confined to a single lower limb and characterised by insidious onset, slow progression and later stabilisation. Wasting was out of proportion with disability and there were no sensory, pyramidal tract or bulbar signs. All cases were sporadic, and there was no history of poliomyelitis anti-ganglioside antibodies, motor and sensory conductions were normal. Quantitative EMG and muscle biopsy revealed neurogenic features also in clinically unaffected limbs. Muscular CT showed selective or predominant, asymmetrical involvement of posterior leg muscles and caput longus of biceps femoris. We deem that monomelic amyotrophy of lower limb is a clinically localised variant of spinal muscular atrophy with a particularly benign course. Although in the early stage there are no clinical or laboratory findings which allow differential diagnosis with other motor neuron diseases, the history of an amyotrophy clinically localised for more than 3 years to a lower single limb and the characteristic muscular CT pattern suggest the diagnosis since the first observation and indicate a favourable prognosis .

43
CENTRAL NERVOUS SYSTEM INVOLVEMENT IN GUILLAIN BARRÉ SYNDROME. NA Losseff, NA Fletcher, RS Howard, J Thorpe, DH Miller, NP Hirsch. *London UK*

We describe 16 consecutive cases of Guillain Barre syndrome (GBS). The mean age at presentation was 43.2 years (17-71). The following clinical characteristics were present: Prodromal illness (9 patients), areflexic limb weakness (14), Miller Fisher variant (MFV)(2), bulbar weakness (12) and ophthalmoplegia (8). Six patients had features suggestive of CNS involvement (decreased conscious level 3, extensor plantar responses 2, meningism 1). In 3 there was pre-existing neurological disease (cerebrovascular 2, multiple sclerosis 1), 3 had encephalopathic features of the prodromal systemic infection (Epstein-Barr virus, mycoplasma, adenovirus) and 3 had metabolic abnormalities. MRI scan showed periventricular white matter lesions and EEG showed diffuse slow activity in 3 patients respectively. Ten patients had no signs of CNS involvement; 2 of these had MFV and GQbl antibodies, and 4 had coexisting cerebrovascular disease with MRI abnormalities. Spinal cord MRI was normal in all 8 patients studied. This study suggests that clinical CNS involvement may occur in patients with GBS, but when present it is usually due a pre-existing disease and infectious or metabolic factors rather than inflammatory demyelination.

44
INSULIN RESISTANCE IN KENNEDY'S SYNDROME. A G Droogan, R Harper, SA Hawkins, .VH Patterson, P Bell, *Belfast, Ireland*

Kennedy's syndrome is a motor system degeneration with endocrine features including gynaecomastia, testicular atrophy, and reduced fertility. Diabetes mellitus is an infrequently reported association with the disease and has been noted in patients and in unaffected family members. We studied peripheral insulin action in five patients with genetically confirmed Kennedy's syndrome and compared the results with findings in five age- and weight-matched healthy males. Patients and controls were examined after a 12 hour overnight fast. Peripheral insulin action was assessed by means of a two hour euglycaemic clamp at an insulin infusion rate of lmU/kg/min. Basal glucose and insulin values were similar for the two groups. A highly significant decrease in the whole body glucose disposal rate was seen during the final of the insulin infusion in patients with Kennedy 's syndrome, compared with normal subjects: 19.9b3.4 (standard error) µmol/l versus 27.0b4.7 µmol/l, p<0.05. This marked decrease in glucose disposal rate remained significant when adjustment was made for 24-hour urinary creatinine excretion rate to correct for the difference in muscle mass between patients and controls. These findings suggest that insulin resistance is a feature of Kennedy's syndrome and this may contribute to the increased risk of diabetes mellitus in these patients.

45
THE MANAGEMENT AND OUTCOME OF SEVERE GUILLAIN BARRE SYNDROME. RS Howard, DR Fish, NP Hirsch, NMF Murray; DH Miller. *London, UK*

Seventy nine patients with Guillain-Barré syndrome admitted to a neurological ITU between 1985 and 1992 were studied retrospectively. The mean age was 49.8 yrs (16-86) and the time between the first neurological symptom and admission to ITU was 10.2 days (0-62). Admission was precipitated by a combination of respiratory failure requiring ventilatory support (73.4%), bulbar weakness (57.0%), autonomic features (11.4%) and general medical factors (10.1 %). Specific treatments included plasma exchange (65.8%), intravenous gamma globulin (13.9%) and methylprednisolone / placebo (12.7%). Significant complications included lower respiratory tract infections (45.6%), hyponatraemia (25.3%), dysautonomia (19.0%), urinary tract infection (12.7%) and cognitive disturbances (8.9%). Four patients died during the acute illness. The duration of nadir correlated with the duration of ventilation (R=0.657, P<0.001), duration of ITU stay (R=0.834, P<0.001) and outcomes at 3 months (R=0.546, P<0.001), 6 months (R=0.620, P<0.01), 1 year (R=0.646, P<0.001) and 3 years (R=0.516, P<0.01). However the time to nadir, as an indicator of rapidity of deterioration, did not correlate with any outcome. The duration Or ventilation correlated with outcomes at 3 months (R=0.414, P<0.01), 6 months (R=0.464, P<0.01) and 1 year (R=0.612, P<0.001). The low mortality in this series suggests that specialised intensive therapy units will continue to have an important role in the management of acutely ill patients with Guillain-Barré syndrome.

46
HEREDITARY NEUROFIBROMATIS TYPE 7. AAJ Soeterboek, PJ Koehler, *Heerlen, The Netherlands*

We tried to assess the possibility of hereditary transmission of neurofibromatosis (NF) type 7. Eight different types of NF have been discerned by Riccardi. NF-7 or late-onset NF is characterised by the occurrence of neurofibromas in or beyond the third decade and the absence of cafe-au-lait spots, Lisch nodules and most of the other characteristics of NF-1. NF-1 and 2 have been proved to be autosomal dominant disorders. Hereditary transmission of NF-7 has not been reported until now. We report on a 24-year old woman presented with a neurofibroma of the right sciatic nerve. Physical examination did not reveal any abnormalities, in particular no signs of NF-l were present. MR-scan of the brain was normal. CT-scan of the abdomen demonstrated a retroperitoneal tumour, probably a neurofibroma. Family examination was performed and two additional family-members with NF-7 were found: 1) Neurofibromas in neck and chest had been demonstrated in the probands' father from the age of 24 years on. No signs of NF-1 were present; 2) The brother of patients' father had been operated for radicular neurofibromas compressing the spinal cord at the age of 51 years. This may be the first example of heritability of late-onset NF (NF-7).

47
GENETIC LINKAGE ANALYSIS SUGGESTS THAT CARDIOMYOPATHY IS ESSENTIAL FOR FRIEDREICH'S ATAXIA DIAGNOSIS. P Smeyers, E Monros, J Lopez-Arlandis, M Urtasun, J Vilchez, F Palau. *Valencia, Alcoi & San Sebastian, Spain.*

Friedreich's ataxia (FRDA) is a neurodegenerative disorder with autosomal recessive inheritance. FRDA locus has been assigned to chromosome 9q13 by linkage analysis, and genetic homogeneity has been demonstrated. Most of FRDA patients show cardiomyopathy. However, there is no definitive evidence to include cardiomyopathy as an essential criterion for FRDA diagnosis. We have performed linkage analysis in 12 families with at least 2 affected siblings and electrocardiographic and/or echocardiographic examinations available. Linkage analysis were carried out by using the FRDA-linked marker loci D9S15, D9SllO, D9S5, and FDI. Extended haplotypes were constructed in patients, parents, and normal siblings. No family but one (LF-AF60) showed recombinant events. In family LF-AF60 two recombinations were evident which suggested no linkage to the FRDA locus. Both affected siblings from this family showed normal

ECG, whereas abnormal EKGs were detected in at least one sibling from each of the other 11 families. We propose that heart disease is essential to define FRDA phenotype.

48
LEBER'S HEREDITARY OPTIC NEURORETINOPATHY (LHON): MARKED RECOVERY OF VISION DESPITE MULTIPLE mtDNA MUTATIONS. A Salmaggi, F Carrara, M Zeviani. *Milan, Italy.*

Leber's hereditary optic neuroretinopathy (LHON) is a cause of visual loss, most frequently in young men. Several point mutations of mitochondrial DNA (mtDNA) have been associated with LHON, all involving mtDNA-encoded subunits of the respiratory chain. The most frequent mutation is a A→G transition at nucleotide 11778. other mutations have been described, including three G→A transitions (A15257, A7444, A3460) and two T→C transitions (C3394 and C4160). Additional nucleotide changes (A15812, C14484, A13708, A5244, G4917, C4216) have been found in linkage disequilibrium among themselves, with the A11778 mutation and with the LHON phenotype, suggesting a synergistic role, with each additional change presumably increasing the probability of blindness. However, most of these "secondary" mutations are also found in significant percentages of the general population and no conclusive data have as yet been provided to support the "synergistic" hypothesis. We describe a LHON patient carrying two "major" and several "minor" mtDNA mutations, in whom slowly progressive, spontaneous clinical recovery began 18 months after onset of visual loss and continues at the present time, 3 years later. This does not support the existence of a cumulative effect of multiple "minor" LHON mutations in the phenotypic expression of the disease.

49
FRAGILE X SYNDROME CGG MUTATION THREE FAMILIES WITH AN ATYPICAL STATUS FOR FMR-1 GENE. M Mila, S Castellvi-Rel, A Sanchez, J Rosell, R Gine, M Villa, X Estivill. *Barcelona, Spain.*

Fragile X syndrome (FXS) is the most common form of inherited mental retardation, with a prevalence of 1 in 1500 males and 1 in 2500 females. We have studied the p(CCG)n repeat in 40 families using Southern blotting (StB12.3) and PCR. In three families atypical segregation of p(CCG)n mutation was observed. In family 298 both parents were carriers of theFMR-1 premutation and one of their daughters had dysmorphic traits, mental retardation and fragility at Xq27.3 (3%), and the molecular study determined that she was a compound heterozygote with both premutated and mutated alleles. In family 241 we found a male carrier of the full mutation, but with the CpG island adjacent to FMR-1 gene unmethylated, and phenotypically normal. This case agrees with the lack of methylation of the FMR-1 mutation, which is associated with higher cognitive functioning In males. In family 269 we carried out a prenatal diagnosis in a female carrier of the premutation with the following results: normal karyotype (46,XX), only one band at 2.8 kb (Southern blotting), but two normal PCR alleles (17/38). This findings allows that some extraembrionary tissues are not methylated and, therefore, Southern blotting and PCR are both necessary in prenatal diagnosis of FXS.

50
DIFFERENTIATION OF ADULT PHENOTYPES OF X-LINKED ADRENOLEUKODYSTROPHY (ALD). W Koehler, AJ Kumar, D Edwin, HW Moser. *Berlin, Germany and Baltimore, USA.*

Awareness and definition of the great variability in the natural course of ALD is important for prognostic considerations and the evaluation of therapeutic interventions. 164 adult patients (119 males, 45 symptomatic females) underwent MRI imaging of the brain. In 30 patients (20 males, 10 females) MRI of the spine was also performed, and showed atrophy of the thoracic cord in 90% of the men and 80% of the women. Brain MRI studies were normal in 54% of the men and in 80% of the women.. In these patients, referred to as "pure AMN", the demonstrable pathology is confined to the spinal cord and peripheral nerves. Among the 54 men with abnormal brain MRI, the abnormalities were confined to the ascending and descending long tracts in 16 (Adreno-leuko-myeloneuropathy type 1, ALMN 1), in 32 patients long tract involvement was combined with diffuse involvement of the cerebral hemisphere white matter (ALMN 2) in a pattern that resembles that seen in the childhood cerebral form of ALD. Six of the patients belonged to the adult cerebral phenotype, in which there is widespread diffuse involvement of cerebral white matter, particularly the corpus callosum, without preceding evidence of spinal cord or peripheral nerve pathology. 3 of the patients showed changes that resembled those seen in olivopontocerebellar degeneration. Correlation with clinical findings indicate a gradation of severity and rate of progression, with pure AMN and ALMN 1 being less severe and having better prognosis than ALMN 2 and the adult cerebral phenotype.

51
KENNEDY'S DISEASE: CLINICOPATHOLOGIC CORRELATION IN AN ITALIAN KINDRED. D Guidetti, A Ferlini, L Motti, M Bondavalli, MC Patrosso, E Ghidoni, *Milan, Italy*

An increase in the number of (CAG)n repeats in the first coding exon of the androgen receptor (AR) gene has been strongly associated with Kennedy disease (KD or spinal and bulbar muscular atrophy). It is an X-linked hereditary disorder characterised by chiefly proximal muscular atrophy, with late involvement of distal and bulbar muscle, gynecomastia, hyperestrogenemia and impotence. Twenty-eight members of a large family have been evaluated by clinical examination, electrophysiological studies, serum CK levels, neuropsychological evaluation, muscle and sural nerve biopsies. Using a pair of primers, amplifying the AR region containing the (CAG)n repeats and, visualisation of PCR products on ethidium bromide-stained Nu Sieve/agarose gel, we showed that all five affected males and obligate carrier females had a fragment that was about 70-80 bp larger than the normal on. In seven KD family members the PCR product was cloned and sequenced. Two young males showed an increment of the (CAG)n repeats but were still asymptomatic, even though one had high CK values, and the other showed pathologic EMG and muscle biopsy. Interestingly several female carriers exhibited slight signs of the disease and a pathological EMG., Furthermore three affected males and four female carriers had subnormal neuropsychological performances. Telethon 91-92 Financed Study.

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OLIVOPONTOCEREBELLAR ATROPHY: PHENOTYPIC VARIANT OF X-LINKED, ADULT-ONSET ADRENOLEUKODYSTROPHY. A Alfaro, M L Giros, A Barcelo, A Piqueras, V Martinez, *Valencia & Barcelona, Spain*

We report two first cousins with adult-onset adrenoleukodystrophy (ALD) who presented with impotence, bladder disturbances, intellectual decline, and difficulty in walking. A maternal uncle died at age 50 with paraplegia and dementia. one of the patients had predominant gait ataxia, dysarthria, and pyramidal signs with increased muscle stretch reflexes. The other patient had weakness, areflexia and sensory impairment in the legs. Electromyography and nerve conduction studies confirmed a severe sensorimotor demyelinating polyneuropathy. Neither of them had signs of adrenal insufficiency. CT and MRI findings were strikingly similar in both patients, with an intense bulbar, pontine and cerebellar atrophy. Extensive areas of demyelination involved chiefly the splenium of the corpus callosum. and the periventricular white matter of the occipital and temporal lobes. Very-long-chain fatty acids (VLCFA) were markedly elevated in serum, lymphocytes and cultivated fibroblasts. ALD is mostly a disease of childhood. The usual adult form, adrenomyeloneuropathy (AMN), is characterised by adrenal insufficiency and spastic paraparesis. Although there are a few reported cases of an adult-onset cerebral form of ALD, prominent cerebellar disturbances in patients with X-linked ALD seem uncommon.

53
1-H MAGNETIC RESONANCE SPECTROSCOPY OF THE GUINEA PIG OPTIC NERVE: UNDETECTABLE LEVELS OF N-ACETYLASPARTATE. M Rango, F Bamonti, F Greco, D Spagnoli, G Tomei, G Scarlato, L Zetta, *Milan, Italy*

The compound N-acetylaspartate has been proposed as a neuronal marker. N-acetylaspartylglutamate (NAAG) has been implicated in cellular communication at several levels in the visual pathways. Previous studies of the cat optic nerve by 1-H Magnetic Resonance Spectroscopy (MRS) have shown high levels of N-acetylaspartate (NAA) and of the putative neurotransmitter N-acetylaspartylglutamate (NAAG). We describe here the in vitro 1-H MRS spectrum of the guinea pig optic nerve and do not confirm

the presence of NAA. Optic nerves were removed from guinea pigs and spectra of optic nerve perchloric acid extracts were obtained by 1-H MRS (Bruker 500 MHz). Five animals were studied. Numerous low-molecular-weight compounds were identified in the spectrum, including neurotransmitters, amino acids, phospolipid precursors and other common metabolites. NAA was not present to an appreciable extent. NAAG was detected at high levels. This is in contrast to most regions of the brain where NM levels are high and NAAG levels are about 10-20% those of NAA. Our findings may be useful for the development of 1-H MRS studies based on guinea pig optic nerve experimental models.

54
ANALYSIS OF EFFICACY OF PHARMACOLOGICAL TREATMENT OF CEREBRAL OEDEMA NEUROPATHOLOGICAL EXAMINATION. K Honczarenko, T Jezewski, I Kojder, C Fryze, *Szczecin, Poland*

Cerebral oedema was induced using Clasen and Klatzo thermal method. Cerebral lesions were generated in parietal region of the brain in Wistar rats, weight 240-400 grammes, by freezing cerebral cortex. Experiment was performed on 33 rats, divided into 3 groups. Group I (10 rats) was administered 1 ml of 0.9 % NaCl IM, Group II (11 rats) was administered synthetic analogue of ACTH 3 mg/kg bw., Group III (12 rats) was administered Dexamethasone phosphate 3 mg/kg bw. Drugs were administered directly after cerebral oedema was induced, after 24 and after 48 hours. Clinical observations lasted 3 days, then rats were killed using Thiopental. Neuropathological examinations concerned the character and degree of necrosis, topography and intensity of cerebral hyperaemia Changes in the parenchyma and character of neuronal lesions were also evaluated. In all three groups we found areas of cryogenic necrosis under destroyed cortex, and adjacent necrotic area with macrophage infiltrates. In group I we observed early phase of necrosis with macrophage reaction only. In group II proliferation of capillaries was seen. In group III we observed majority of the areas where astrocytes predominance was remarkable. Hyperaemia was seen in all cerebral vessels and was most distinguished in groups II and III According to the neuropathological examination the most potent anti-oedematous effect appeared to have Dexamethasone.

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PHOTOCHEMICALLY INDUCED PERIPHERAL AND CENTRAL DEMYELINATION IN THE RAT NERVOUS SYSTEM MORPHOLOGICAL CHARACTERISTICS. J Verlooy, Jos V Reempts, B V Deuren, M Borgers *Antwerp, Belgium*

We present a simple, reliable and reproducible method for the induction of demyelination of the peripheral nerve as well as of the spinal cord in rats based on the generation of reactive oxygen species. Male Wistar rats weighing (250 g were intubated and kept under anaesthesia while a midline incision was made at the level D10-D12. The interlaminar space D12-L1 is exposed and the yellow ligament is removed. Then 0.1cc Rose Bengal (30 mg/ml) is injected in the subarachnoid space, after which an illumination of 20 minutes follows through a l.S mm optic fiber. At the end of the survival period the spinal cord and the proximal part of the spinal nerve were fixed and routinely embedded in Epon. Evaluation was performed on 2 Êm sections, stained with azure eosin. Areas of interest were selected for ultrastructural observation. Histopathological changes of the spinal nerve seem to be similar as those already described for sciatic nerve photochemical demyelination (Exp Neurol, 120, 283-290, 1993). The denudation of axons is complete at 4 days after which a recovery can occur. The dorsal fascicles of the spinal cord are lesioned: the gray matter is spared. The histological characteristics of the lesion are similar to those observed in the spinal nerve. However, a clear distinction can be made between the morphologic appearance of demyelinated dorsal fascicles (ensheated by oligodendroglial) and spinal nerves originating at the irradiated area (ensheated by individual Schwann cellls).

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A STUDY OF WILSON'S DISEASE PATIENTS FROM POLAND. JU Gajda, A Czlonkowska; *Warsaw, Poland.*

Wilson's disease (WD) is an autosomal recessive disorder of copper transport resulting in accumulation in liver and brain tissue. Since 1956 we confirmed the diagnosis of WD in 247 patients along with 70 cases of probable WD in siblings of patients who refused diagnosis or died with clinical features highly suggestive of WD. Seventy-five percent of all cases were familial, 25% sporadic. In a group with clinically and biochemically defined WD the age of diagnosis was 26.8 ± 9.27 and the age of onset of clinical symptoms was 24.8 ± 7.4 years. At the time of diagnosis in 43 cases the stage was preclinical, 14 had only signs of hepatic dysfunction and 190 suffered predominantly from neurological symptoms. The most common neurological manifestations were tremor (185 cases); dystonia was less common (27 cases). Sixty-nine patients died/ and the outcome of 16 is unknown. Of the currently surviving 158 patients 62 are presently without symptoms, 75 markedly improved, 22 worsened and 2 were unchanged. The most frequent causes of death were liver failure or gastrointestinal hemorrhage.

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ABNORMAL CEREBRAL HEMODYNAMICS IN PATIENTS WITH ECLAMPSIA, PREECLAMPSIA AND HELLP-SYNDROME. P Zunker, J Ley-Pozo, P Louwen, S Happe, HC Buschmann, A Schick, EB Ringelstein, *Munster, Germany.*

Preeclampsia and eclampsia represent different forms of pregnancy induced hypertension. The HELLP syndrome also widely overlaps with preeclampsia/eclampsia. This study was performed to evaluate haemodynamic changes in the large intracranial cerebral arteries and their temporal profiles in the above syndromes. Hypertensive disorders of pregnancy were categorised according to the American College of Obstetricians and Gynaecologists. Criteria for HELLP syndrome were total bilirubine > lmg/dl, AST > 69 U/l, LDH > 499 U/l, platelets < 100 000 cells/mm^3). The mean blood flow velocities of the middle (MCA), anterior and posterior cerebral arteries of both hemispheres were assessed repetitively by means of transcranial Doppler ultrasonography. Arterial blood flow velocities of patients with eclampsia (N=3), preeclampsia (N=5), preclampsia and HELLP syndrome (N=4), isolated HELLP syndrome (N=l), preeclampsia superimposed on chronic hypertension (N= 1) or chronic hypertension (N= 1) were elevated. In summary, in patients with pregnancy induced hypertension, MCA flow velocities were up to twice as high as in normals and depended on the arterial blood pressure. The severity of eclampsia did not influence cerebral hemodynamics. Flow changes typical for vasospasm were not detected. Hemodynamic abnormalities returned to normal within 3 weeks after dilevery. our findings support the hypothesis that the syndrome of eclampsia results from a forced vasodilatation with passive overdistension of cerebral arterioles leading to hypertension with abnormally high flow velocities in the proximal cerebral arteries. This may lead to neurological symptoms comparable to those in hypertensive encephalopathy.

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EFFECTS OF IPMUNOADSORBENT TREATMENT ON NEUROLOGICAL DISORDERS WITH POSITIVE ANTI-NUCLEAR ANTIBODIES. T Yamawaki, M Takao, N Suzuki; *Ibaraki, Japan*

Efficacy of the plasmapheresis, including immunoadsorbent treatment (IAT), has been reported in many cases of autoimmune diseases. Particularly IAT has recently become popular because it has an advantage that plasma or albumin preparation is not necessary. We investigate effects of IAT on 6 cases of neurological disorders with positive anti-nuclear antibodies (ANA), i. e., ophthalmoplegia with rheumatoid arthritis (RA), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), Guillain-Barre syndrome (GBS), polymyositis (PM), multiple sclerosis (MS) and HTLV-l associated myelopathy (HAM) IAT with IM-TR-350 or IM-PH-350 (Asahi Medical Co., Japan) was performed once or twice a week and IAT sessions were carried out totally 7 times. After IAT, the neurological symptoms and the values of ANA and immunoglobulin were evaluated. The clinical and neurological symptoms were remarkably improved in the cases of RA, GBS, PM and MS, with a marked reduction in the values of ANA. Beneficial effects we also observed in the cases of CIDP and HAM. Drastically ameliorated symptoms with concomitant marked reduction in ANA (1:160 to 1 :0) were observed in the case of the ophthalmoplegia with RA. No obvious adverse or side effects were noted in all cases. It is concluded that IAT is one of the useful tools in the treatment of neurological disorders with positive ANA.

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NOSOLOGIC CLASSIFICATION OF SNEDDON'S SYNDROME. K WeilBenborn, S Schellong, C Ehrenheim, J Wollenhaupt, C Goetz, D Lubach, *Hannover, Germany*

The combination of generalised livedo racemosa and cerebral infarction is referred to as "Sneddon's syndrome". However, ambiguity in etiology and classification confuses diagnosis and therapy. Study aim was to find out whether patients with the diagnosis of "Sneddon's syndrome" represent a homogeneous group or may be-subdivided into different disease subgroups. Patients and methods: 31 patients (30 f, 1 m; 18...74 y) presenting with livedo and stroke were examined. The following examinations were performed: serum testing for immunological and hemostaseologic parameters, echocardiography, ultrasound of cerebral and peripheral vessels, cerebral MRI and neuropsychological assessment. The clinical findings suggest a subdivision of the patients into four groups: A - 3 patients with livedo and stroke of arteriosclerotic origin; B - 7 patients with livedo, stroke and signs of an immunological systemic disease; C - 4 patients with livedo, stroke and deficiency of coagulation inhibitors; D - 17 patients with livedo and stroke without any sign of an underlying or associated disorder. Obviously, patients with the diagnosis of "Sneddon's syndrome" cannot be assigned to a distinct disease entity. With respect to etiologic and therapeutic considerations, a differentiation should be made between a "symptomatic and an "idiopathic" Sneddon's syndrome.

60
LOCALIZED BRAIN PROTON MAGNETIC RESONANCE SPECTROSCOPY IN THE NEUROLOGIC COMPLICATIONS OF AIDS. J Vion-Dury, F Nicoli, SO Confort-Gouny, CO Dhiver, S Lamoureux, AM Salvan, J-A Gastaut, J-L Gastaut, P Cozzone. *Marseille, France*

Recently, it has been proposed that proton localized Magnetic Resonance Spectroscopy of the brain was able to detect metabolic changes in brain of HIV patients showing normal MR images. We have examined 9 healthy volunteers and 44 HIV patients (16 seropositive patients, without any neurologic or neuropsychologic or psychiatric clinical signs, and 28 patients with clinical neuroAIDS). Standard spin-echo (SE) imaging was conducted on a Siemens Magnetom SP63 (1.5 T). Then, proton MR spectroscopy of the brain was performed using a SE sequence (echo time = 135 ms). The spectroscopic VOI (8 ml) was located in the parieto-occipital region of the brain, according to a multicenter trial protocol. Signals from N-Acetyl-Aspartate (NAA, neuronal marker), Choline-containing molecules (CHo) and Creatine-Phosphocreatine (PCr) have been analyzed. In neuroasymptomatic patients, the NAA/Cho ratio is significantly reduced when compared to control subjects. The same ratio is also significantly reduced in patients with atrophy and in patients with diffuse lesions. In patients who display a normal MRI, MRS is abnormal in 7% of neuroAIDS patients and in 2O% of the asymptomatic patients, therefore increasing the diagnostic sensitivity of MR examination.

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MICROANGIOPATHY OF BRAIN AND RETINA. N Vila, F Graus, T Ribalta, R Blesa, J Santamaria, *Barcelona, Spain*

An unusual microangiopathy characterised by encephalopathy, hearing loss and retinal occlusions has been described in 18 patients. All were women, and more than 50% persisted with serious neurological deficits despite immunosuppressive therapy. We present two further patients with atypical features. The first was a 29 year-old man, and the second a 37 year-old woman. Both patients presented with headache, subacute personality changes and unsteady gait. Neurological examination disclosed dementia, gait ataxia and bilateral Babinski signs. Hearing loss was not observed. Extensive laboratory work-up and four vessel angiography were nor-al. The MRI showed high signal areas in T2-weighted sequences in the white matter, and retinal infarcts with retinal arteriolar occlusions as ophthalmoscopic findings. Brain biopsy disclosed microinfarcts with important gliosis surrounding small blood vessels. Vasculitis was no observed. Both patients did not respond to treatment with prednisone and cyclophosphamide. Patient 1 progressed despite of plasmapheresis and he remains demented 8 years later. Patient 2 gradually improved with immunoglobulins (0.5 g/Kg/day, 5 days, every 2 months). A year later she is able to carry an almost normal independent life. We conclude that this syndrome can affect young men; and that high doses of endovenous immunoglobulins could be an alternative therapy in patients with neurological deterioration despite other immunosuppressive treatments.

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POST-STROKE INSOMNIA TREATED WITH CITALOPRAM. K Vestergaard, A M Drewes, G Andersen, S J Taagholt. *Aalborg, Denmark*

Sleep disorders following stroke are common, but few polysomnographic recordings (PSG) have been made. Stroke may disturb the serotonergic neurotransmission, which is important in sleep mechanisms. A 48 year old man with no previous sleep disturbances suffered a left hemispheric infarction in the internal capsule and the hypothalamus. He was not depressed but persistent complained of severe insomnia. He woke up after 3 hours and then only slept very fragmented the rest of the night. Eight months after the stroke whole night PSG were carried out before, during 2 and 4 weeks treatment with 20 mg citalopram (CipramilR), a selective serotonin reuptake inhibitor, and 4 weeks after ceased treatment. The patient kept a diary about sleeping time and sleep quality. During treatment the patient felt less tired and after 3 days, according to his diary, his insomnia had almost disappeared. PSG showed a more than 50% reduction in the total time spent in wake during treatment. REM-latency and the amount of slow wave sleep (NREM 3+4) was increased. After treatment was discontinued the patients insomnia retumed and the PSG parameters returned close to pre-treatment values. Conclusion: Sleep disorders following stroke may be treated with serotonin reuptake inhibitors, indicating that the serotonergic transmitter system is affected.

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COLLAGEN III DEFICIENCY IN PATIENTS WITH SPORADIC INTRACRANIAL ANEURYSMS. JSP van den Berg, M Limburg. *Amsterdam. The Netherlands*

The purpose of this study is to assess the possible role of a collagen type III deficiency in the pathogenesis of intracranial aneurysms (IAs). Thirty-one consecutive patients with an (un)ruptured IA were admitted to our hospital. The diagnosis was confirmed by cerebral angiography. From each patient a skin biopsy was obtained for subsequent fibroblast-culture and collagen type III determination through electrophoresis and gel-scanning. Results. In 3 (9.7%; 95% confidence limits (CL) 2.0-25.8%) a very low (< 3%) and in 7 (22.6%; 95% CL 9.6-41.1%) a lowered (3-7%) collagen type III / type I ratio was found. Conclusion: A severe deficiency of collagen type III was found in 9.7% and a moderate collagen III deficiency in 22.6% of the patients. A collagen III deficiency may play a causative role in the development of IA.

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ANAL SPHINCTER DENERVATION IN PATIENTS WITH PROGRESSIVE SUPRANUCLEAR PALSY. F Valldeoriola. J Valls-Solé, R Alvarez, MJ Marti, E Tolosa. *Barcelona. Spain.*

In a prospective study of patients with progressive supranuclear palsy (PSP), 2 out of 7 patients reported urinary and rectal dysfunction. All patients had supranuclar downgaze palsy and fulfilled all other standard criteria for the diagnosis of PSP. Those two patients did not show differences in age, initial symptoms, severity or duration of the disease when compared to the other 5 patients. We carried out an electromyographic study of the external anal sphincter with a monopolar needle electrode in all 7 patients. Among tonically activated motor units, we calculated the percentage of polyphasic potentials and their duration. Muscles of the pelvic girdle and lower extremities were also examined. A motor unit potential was considered abnormal when it contained more than 5 phases and a duration of more than 12 ms. More than 50% of abnormal potentials were found in the 2 patients with incontinence and in 2 of the 5 continent patients. Pelvic girdle muscles were normal in all patients. Signs suggestive of a plexic or radicular lesion were not detected in any patient. Denervation of the external anal sphincter muscle, which has been considered a characteristic feature of patients with multisystem atrophy, can be found also in patients with clinically defined PSP both with and without symptoms of sphincter dysfunction.

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A DOUBLE-BLIND CROSSOVER TRIAL OF L-DOPA AND PLACEBO IN IDIOPATHIC AND UREMIC RESTLESS LEGS SYNDROME. C Trenkwalder, K Stiasny, V Collado-Seidel, T Wetter, J Kazenwadel, R Kohnen, S Ramm, WH Oertel, *Munich, Germany*

Patients with idiopathic and uremic restless legs syndrome (RLS) sometimes suffer from severe insomnia and benefit from an evening dose of L-DOPA. We conducted a controlled study of 100-200mg standard L-DOPA

plus Benserazide in order to measure therapeutic effects on sleep quality and periodic limb movements (PLM) in both idiopathic and uremic RLS patients. We investigated 17 idiopathic and 14 uremic (on continuous hemodialysis) RLS patients by a 2 nights polysomnography and a 3 nights actigraphy in parallel in a placebo controlled randomised crossover trial. Patients were monitored by the latter methods and an additional sleep diary at baseline and at the end of a four weeks drug and placebo phase. On 100-200 mg L-DOPA + 25-50mg Benserazide (Madopar 125 R) as single bedtime dose RLS patients experienced subjective and polysomnographically measured improvement of total sleep time (p=0.04) and PLM reduction (p=0.01) with most improvement 2 hours after intake of L-DOPA. Actigraphy confirmed PLM reduction on two additional nights (p=0.01). These data confirm the benefit, the reliability and short-acting pharmacokinetics of a single bedtime dose of L-DOPA on sleep quality in RLS. For the first time a controlled study with L-DOPA was performed in uremic RLS patients. The recently developed actigraph reliably measures PLM during additional sleep evaluation at home.

66
TYPES OF SYMPTOMATIC ASTASIA-ABASIA. P Thajeb, Taipei, *Taiwan, ROC*

Astasia-abasia (AA) was defined as inability to stand and walk despite of a relatively normal muscle strength of the lower limbs and leg agility when lying on bed or sitting. It was most frequently caused by conversion hysteria. Rarely, astasia-abasia may occur in association with organic brain disorders. Symptomatic astasia-abasia (SAA) was coined for the latter. During a period from Jan 1990 to Dec 1993, eight patients with SAA were examined by the author. They were 6 women and 2 men with age of onset ranged from 48 years to 79 years. Two distinct types could be recognised. Type 1 SAA consisted of 2 women who presented with insidious onset of symptoms, and had long been misdiagnosed by psychiatrists as having conversion hysteria. These patients were later confirmed by CT as having huge brain tumours at the frontal lobes ("astasia-abasia of frontal lobe"). The common denominator of late signs of type 1 SAA were: dementia, akinetic mutism, sphincter disturbances, and signs of increased intra-cranial pressure (IICP). Both patients died 4 months and 1 year respectively after the diagnosis. In contrast, patients with type 2 SAA were 4 women and 2 men, who presented with acute onset of symptoms/signs of astasia-abasia, hemihypoesthesia of varying degree, asterixis, tremor, etc. All were followed up till now, and varying degree of deficit remained. We conclude that SAA differs from hysterical one in many aspects.

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ADRENOLEUKODYSTROPHY: CASE REPORT OF A FAMILY IN 4 GENERATION AND FOLLOW-UP OVER 3 YEARS OF DIETARY THERAPY. M Starck, H Albrecht, W Pollmann, N Konic, *Berg, Germany*

Adrenoleukodystrophy (ALD) is an X-linked recessive disorder characterised by adrenal insufficiency, CNS-demyelination and accumulation of very long chain fatty acids (VLCFA). We report on 4 generations of a family with 7 affected members (3 female, 4 male). All have increased VLCFAlevels. 2 of them were first diagnosed as multiple sclerosis. One symptomatic heterozygote suffers from spastic paraparesis and impairment of sensation in her legs. The other women have only slightly impaired deep sensation in their lower limbs. Neurophysiological examinations demonstrated involvement of peripheral and central nervous system in all heterozygotes, One had also a slightly increased ACTH-level. One male suffered from childhood-ALD and died 4 months after onset at the age of 10. Another developed spastic paraparesis and ataxia at the age OF 25. 11 years later he developed a rapidly progressive course and died after a series of seizures. Identical twin boys were diagnosed as Addison's disease by laboratory findings at the age of 6. Adrenoleukodystrophy (ALD) is an X-linked recessive disorder characterised by adrenal insufficiency, CNS demyelination and accumulation of very long chain fatty acids (VLCFA). The family is on a diet restricted in VLCFA with administration of Lorenzo's oil for 3 years. We observed a reduction in VLCFA-levels in all cases but neither an improvement in neurophysiological examinations nor in hormonal tests.

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KIMMERLE ANOMALY: AN ANATOMICAL VARIANT ACCOMPANIED WITH A COMPLEX OF CLINICAL SIGNS. W Split, W Sulkowski, S Kowalska, M Sawradewicz-Rybak, M Musior, *Lodz, Poland*

Kimmerle anomaly is an anatomical variant of the first cervical vertebra consisting in the presence of an osseous canal for the vertebral artery situated on the posterior arch of this vertebra. 21 patients with radiologically verified Kimmerle anomaly were examined. All of them presented with headaches, and 18 persons complained of vertigo. All the patients were subjected to tone audiometry (Madsen 08 822), ENG, studies of VEP responses and to USGD of the vertebral arteries. ENG was performed with the use of a 'TOENNIES' electronystagmograph. VEP responses were checked by stimulation of each eye by the reversible checker-board pattern with the pattern-reversal method, using a 'TOENNIES' Multiliner apparatus. USGD allowed to estimate the diameter of the blood vessels and - with the use of the Doppler method -the flow value. The studies were carried out with various positions of the head. ENG revealed changes in 17 examined patients. 9 persons showed hearing defects of perceptive type on tone audiometry. Abnormal VEP responses were noted in 12 persons. Changes of the flow in the vertebral arteries were registered in 12 examined patients, and 8 persons revealed stenosis of the lumen of one of the arteries.

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MULTIMODAL EVOKED POTENTIALS. STUDY IN MITOCHONDRIAL ENCEPHALOMYOPATHY. V Scaioli, C Antozzi, M Zeviani, S Franceschetti, G Avanzini. *Milan, Italy.*

Visual (VEPs), auditory (BAEPs) and somatosensory (SEPs) evoked potentials (EPs) were recorded in 15 patients affected by mitochondrial encephalomyopathies (ME). The patients were classified as follows: chronic progressive external ophthalmoplegia (CPEO) (group-A), 8 patients; familial CPEO (group-B), 2 patients; MELAS (group-C), 1 patient; Maternally Inherited Mitochondrial myopathy and Cardiopathy (MIMYCA, group-D), 2 patients (belonging to the same pedigree) and 2 patients with unclassified ME(group-E). VEPs were abnormal in 13/15 patients, BAEPs in 5/15 patients and SEPs in 7/15 patients. Statistical analysis revealed significant differences with respect to control group only for the VEPs. EPs were normal in MIMYCA disease, whereas the most severe abnormalities were observed in the group-E and in the MELAS patient. The patterns of abnormalities of EPs were quite a specific and did not contribute to the clinical diagnosis. However, EPs brought a significant contribution in revealing a subclinical multisystem involvement in ME, particularly of the visual pathways. In addition, the differences observed in the diagnostic categories of ME may suggest that EPs studies can contribute to the understanding of physiopathogenetic mechanisms involved in genetically related disorders.

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THE TREATMENT OF TRIGEMINAL NEURALGIA BY MICROVASCULAR DECOMPRESSION. PERIOPERATIVE NEUROPHYSIOLOGICAL EVALUATION. V Scaioli, S Brock, C Ciano, E Palazzini, G Broggi. *Milan, Italy.*

Perioperative neurophysiological evaluation (audiometry, auditory evoked potentials -BAEPs-, blink reflex, facial nerve neuronography) was performed in 47 subjects operated for microvascular decompression for trigeminal neuralgia (TN). Preoperative involvement of the auditory nerve ipsilateral to TN was demonstrated in 24/47 patients; in 5 other patients severe hypoacousia was related to remote otitis. Intraoperative BAEPs were stable in 17 patients; BAEPs changes (correlated with defined surgical manoeuvres) were moderate in 20 and severe in 5. No postoperative hearing worsening was observed in the 17 patients with stable intraoperative BAEP changes; in 6/20 patients with more pronounced BAEP changes a moderate hearing impairment was observed; the 5 severe intraoperative BAEP changes were associated with postoperative deafness. The occurrence of postoperative deficits was independent of preoperative hearing function. In 45/47 patients the treatment with drugs was discontinued without recurrence of painful symptomatology (Follow-up. 3 months - 3 years). No deficit of the V and VII cranial nerve occurred. Our data indicate a positive correlation between intraoperative BAEP changes and postoperative hearing status. Owing the high incidence of ipsilateral preoperative BAEP abnormalities (that might be relevant to the pathogenesis of TN) neurophysiological studies are mandatory for an accurate postoperative evaluation of VIII cranial nerve status.

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SARCOIDOSIS PRESENTING AS LATE-ONSET DEMENTIA. M Sanson, J Servan, Ch Duyckaerts, JY Delattre. *Paris, France.*

A 74 year old diabetic woman presented progressive dementia evolving over a period of 6 years. Clinical features included memory loss, disorien-

tation, language impairment, gaitdisturbance, urinary incontinence. Paraclinical investigations founded increased CSF protein concentration, diffuse white matter changes (leucoaraiosis) with enlarged ventricular system. At the death of the patient, clinical diagnosis was Binswanger encephalopathy. However autopsy founded enlarged mediastinal adenopathy and demonstrated cerebral sacoïdosis. Isolated progressive dementia is a very rare manifestation of sarcoidosis. To our knowledge no cases have been reported after 70 years of age. All patients reported displayed increased CSF protein. Sarcoidosis is a rare but potentially treatable cause of dementia. Diagnosis should be considered in demented patients with increased CSF protein.

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A PRELIMINARY REPORT OF TREATMENT OF HTLV-I ASSOCIATED MYELOPATHY (HAM) BY COMBINED THERAPY WITH ANTI-FREE RADICALS AND VASODILATORS. S Aoba, O Hasegawa, A Komiyama, S Yamaguchi, K Johkura. *Yokohama, Japan*

In many patients with HTLV-I associated myelopathy (HAM), the spinal cord is most severely damaged at the lower thoracic level, which corresponds to vascular watershed zone. Therefore, anticoagulants, antiplatelet agents or vasodilator agents are expected to improve signs and symptoms of HAM patients. On the other hand, there are a number of experimental studies describing post ischemic reperfusion injury induced by formation of free radicals. To improve not only the circulation failure but minimise the toxicity of free radicals in HAM, we performed combined therapy with anti-free radicals (allopurinol 300mg/day, a-tocopherol 300mg/day and ascorbic acid 600mg/day) and a vasodilator agent (dipyridamole 300mg/day) in six patients for six months. Prior to and after the trial, these patients were evaluated on the Shimabukuro score. They all responded well to this therapy. Ankle clonus was alleviated in all of 5 patients, and the impairment of deep sensation was reduced in 3 of 6 patients. However, SEP failed to show remarkable improvement after 6 months. No serious adverse effects were encountered during this trial. Results of this preliminary study suggest a favourable effect of the combined therapy with anti-free radicals and vasodilators on HAM patients.

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PARANEOPLASTIC STIFF MAN SYNDROME IN A WOMAN WITH BREAST CANCER. L Rosin, M Solimena, P De Camilli, H-M Meinck. *Heidelberg, Germany & New Haven; CT, USA*

Stiff man syndrome (SMS) is characterized by progressive rigidity and superimposed spasms. The presence of glutamic acid decarboxylase antibodies (GAD) in 60% of patients suggests an autoimmune etiology. We studied a 59-year-old woman with progressive rigidity of the shoulders, arms and back. Active and passive motion elicited severe spasms which resulted in serial rib fractures and shoulder subluxation. After onset of motor symptoms, ductal adenocarcinoma was detected. Before surgery, treatment with clonazepam (24mg/day) was rather ineffective, but she improved after surgery and prednisone treatment. CCT and MRI of brain and spinal cord, as well as laboratory analysis and cerebrospinal fluid were normal. There were no organ- or non-organ-specific nor GAD autoantibodies, but autoantibodies directed against a 128 kD protein, identified as amphiphysin, were found. Detection of autoantibodies against amphiphysin, a synaptic vesicle protein, in a patient with SMS and breast cancer establishes a new paraneoplastic syndrome. It is also another hint at the supposed autoimmune a etiology of SMS.

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SPINAL CORD ISCHEMIA RELATED TO ABDOMINAL AORTIC ANEURYSM. J Roquer, N Marti, A Cano, A Pou-Serradell, *Barcelona, Spain.*

Ischemic spinal cord lesions related to abdominal aortic aneurysm are rare. We report on 3 cases of this association with different clinical manifestations. One of them presented with three attacks of backache and reversible paraplegia mimicking transient ischemic attacks and he had a giant dissecting aortic aneurysm (from subclavian to left common iliac artery). Another patient suffered a subacute paraparesis (level T4) preceded by dorsal and abdominal pain and had an large thoraco-abdominal aortic aneurysm associated with bilateral common iliac artery aneurysms. The third experienced a sudden paraplegia (level Tll) preceded by back pain and had an large abdominal aortic aneurysm. The clinical polymorphism of these cases may be explained by the particular pathophysiology and anatomical distribution of the spinal cord arteries and also by the diversity of described ischemic mechanisms: dissection of aorta, progressive occlusion of regional radicular branches (by thrombosis or compression) and repeated embolization from the thrombus in the aneurysm to the radicular arteries arising from the region. In patients with the association of backache and/or abdominal pain preceding the development of paraparesis the diagnosis of abdominal aortic aneurysm should be considered.

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INVOLVEMENT OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEMS IN PRIMARY AND SECONDARY VASCULIDES. S Robeck, A Enqelhardt, B Neundörfer. JR Kalden, *Erlangen, Germany*

We investigated 92 consecutive patients with primary or secondary vasculitis for involvement of the peripheral and central nervous system. All patients were examined clinically, by electrophysiological methods (EEG, ENG, thermometry, vibratometry). In cases with evidence of CNS- involvement SPECT, CT and/or MRI were carried out. Peripheral neuropathies were clinically detected in 43 (47ø/0) patients, with a symmetrical pattern in 22 (24%) cases and an asymmetrical pattern in 21 (23 %). Patients with polyneuropathy were significantly older and more often had primary vasculitis. Thermometry and vibratometry were not specific, while a decreased nerve conduction velocity and a decreased amplitude were reliable measured of clinical neuropathy. 31 (36%) patients had signs attributable to CNS-involvement (10 cerebral ischemia, 9 neuropsychiatric disturbances, 2 migraine. 1 meningoencephalitis, 1 chorea, 1 myelopathy and 1 epilepsy). CSF samples were investigated in 33 cases and abnormal in 17 (51%). EEG studies showed more often diffuse (n = 31) than focal (n = 6) abnormalities. SPECT scans showed diffuse hypoperfusion in 8 cases and focal hypoperfusion in 11 cases. The MR was abnormal in 14/22 cases. Of the laboratory findings only a decreased complement correlated with CNS-involvement and positive ANCA with PNS-involvement. Compared with patients suffering from secondary vasculitis, patients with primary vasculitis were older, had a significantly higher incidence of neuropathies and a lower incidence of CNS-disturbances.

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ELBOW PROBLEMS AMONG NORWEGIAN HANDBALL PLAYERS – A NEUROLOGICAL STUDY. IR Rise, G Dhaenens, S Tyrdal, *Oslo, Norway*

Among handball players goal keepers are especially vulnerable to hyperextension trauma of the elbows. They may complain of radiating pain or numbness in the ulnar aspect of the forearm in addition to local pain. We have performed a neurological and neurophysiological study in handball players with elbow problems to see if we could detect objective signs of injury to the nervous system. Material and methods: A questionnaire was sent to all teams in the 4 top divisions. 45 % of the goal keepers and 4 % of the field players had current elbow problems. The players were included in our study if they had neurological symptoms (9) or if they were scheduled for an elbow operation (4). Neurological and neurophysiological examination were performed in the 13 players included (11 goal keepers, 2 field players). MRI of the elbows was performed in 8 of the players. Results: Five players had sensibility changes and one had a weak abd.dig.minimi muscle. Neurophysiological examination of the ulnar and median nerves showed normal distal motor and sensory latencies, F- wave latencies and nerve conduction velocity incl. fractional ulnar measurement in all the players. EMG performed in the abductor digiti minimi- and flexor carpi ulnaris muscle was also normal. Conclusion: Handball goal keepers with elbow problems suffer from symptoms suggestive of ulnar nerve affection. The radiating pain may lead to impaired performance, but permanent injury to the ulnar nerve does not seem to appear.

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CTA SELDINGER TECHNIQUE OBSOLETE. LMP Ramos, TW Polder, CAJ Broere, LJ Polman, *Utrecht, The Netherlands*

Spiral CT angiography is a new, minimally invasive technique for vascular imaging by combining two recently developed techniques: slip-ring CT scanning and computerized three dimensional- and multiplanar reconstructions. Spiral CT angiography is used to evaluate the presence of an intracranial aneurysm or to assess the relationship of the intracranial arteries to a tumor. Case reports: 1. PICA-aneurvsm. 19-years-old male.

Blanco history. Trauma and subarachnoidal bleeding. MRI: blood clot and flow phenomenon in the left vertebral artery. PICA aneurysm is not visualized. CTA: PICA aneurysm. 2. De novo aneurysm. 63-years-old male. Screening for familiar carotid aneurysms. 1980 operation for left sided cerebri media aneurysm. CTA: Axial slice at level of cerebri media trifurcation. New aneurysm medial to the previously clipped aneurysm. 3. Carotid dissection. 49-years-old female. Left hemisphere TIAs. CTA: Subtotal occlusion of the left internal carotid artery 1 cm distal to carotid bifurcation. Left carotid DSA: Mouse-tail appearance as seen in carotid dissection. Spiral CT Angiography is a fast and minimally invasive technique for evaluating the intra- and extracranial vasculature.Previously, Seldinger angiography would have been THE only method to diagnose the above mentioned disorders.

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ESTIMATING PHYSICIAN REQUIREMENTS FOR NEUROLOGIST IN ALICANTE (SPAIN). R Martin, R Gomez, M Alberdi, JM Delgado, J Matias Guiu, *Alicante; Spain*

Estimates of the number of neurologist needed in Spain have been rarely done. Applying an adjusted needbased model we have estimated a 5.3 neurologist/100.000 population rate in Alcoi. However controversy remains about the uniformity of this data. Then, we have undertaken a similar study in Alicante (sanitary area 21). Information was collected by means of questionnaire administered in face-to-face interview with general practitioner of the sanitary area. Total needs were estimated by means of the method described by the GNEMAC. The neurologist's time needed per annum for the more frequent neurological conditions were the following (hours): M.S.: 30.41; T.I.A.: 38.73; epilepsy: 166.82; P.D.: 48.73; dementia: 56.06; migraine: 511.68; polyneuropathy: 46.70; stroke: 231.27. The total neurologist's time requirements were 4046.16, that means required rate of 6.13 neurologist population. This rate, slightly higher than that from Alcoi, confirm that physician requirement for neurologist in Spain is high and next to the requirements in the United States. Consequently, we may suggest that the neurological care on The Spanish Health Service is evolving to a direct care model. These date contrast with the low number of neurologist actually employed on the Spanish Health Service .

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THE EFFECT OF THYMECTOMY ON PERIPHERAL T LYMPHOCYTE SUBPOPULATIONS IN MYASTHENIA GRAVIS: A TWELVE MONTH FOLLOW-UP. R Karabudak, E Kansu, O Saribas, T Zileli. *Ankara, Turkey.*

The influence of thymectomy on the phenotype of T lymphocyte subsets was studied by the indirect immunoluorescence technique. 10 controls and 10 myasthenic patients who had normal T cell populations before thymectomy were studied and followed-up 1, 2 - 3 and 12 months after thymectomy. Several factors which may influence T lymphocyte subsets, such as the treatment regimens, the activity of the disease were almost uniform in the patient population. The percentages of CD3(+), CD4(+), and CD8(+) cells were determined. The Mann-Whitney U Test was used to compare the preoperative results of the patients with the controls. The statistical significance of the pre and postoperative T cell subpopulation values were determined by Wilcoxon's Test. In the preoperative period, no significant difference was observed in the number of T cell populations in MG patients compared to controls. A decrease which gradually returned to normal values in the CD4 (+)/ CD8(+) ratio, reflected by the decrease in the number of CD4(+) T cells ($p<0.05$) was observed one month after thymectomy. Our data, showing a short term decrease in the CD4(+) T cells early after thymectomy may suggest that a) the effect of thymectomy on the CD8(+) T cells may not necessarily be predominant b) thymectomy m adults does not leave any permanent deficit m cell-mediated immunity.

80
A TWO-STEPS PITUITARY APOPLEXY IN RELATION TO RUNNING. F Proust, D Hannequin, P Freger, P Creissard, *Rouen, France.*

Multiple predisposing factors have been implicated in the genesis of pituitary apoplexy. One case occurring in the context of diving has been reported (Bakheit & Kennedy, 1989).We describe here a patient who presented a pituitary apoplexy in two steps following running efforts . A 47 years old man was admitted with severe headache, nausea and diplopia. The symptoms started 4 days after a 20 km running race. Interestingly, one year before he had experienced headache and a left ptosis following a similar running effort. These symptoms had regressed spontaneously over one month. In the intervening period, the patient practised jogging on distances from 6 to 8 km without ill-effect. The patient was apathetic. He had a right partial III and IV nerve palsy, and a left VI and VI nerve palsy. Visual acuity was reduced and perimetric testing disclosed bitemporal hemianopsia. The MRIscan showed an intrasellar tumor, with central iso intensity and peripheral high intensity signals. Surgical removal of a pituitary tumour was carried out through a trans-sphenoidal approach. The tumour consisted of structureless tissue due to a vascular necrosis. This report illustrates an original etiology of apoplexy pituitary and demonstrates that the potential of recurrence is an argument for the surgical management

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CONTINUOUS INTRATHECAL INFUSION WITH A DOUBLE CATHETER SYSTEM. J Proano; J Patrignani, L Redondo; J Castro, *Sevilla, Spain.*

The intrathecal administration of therapeutic drugs is carried out through ventricular or dural catheterization. A single catheter is connected to a subcutaneous reservoir. This technique involves high risk of infection of the reservoir. This risk can be lowered with a double catheter system. In the present paper we compared both techniques In four patients with amyotrophic lateral sclerosis (ALS), TRH was infused through in a single catheter placed at L4-L5 connected to an Ommaya reservoir. Six other patients ALS, were treated with a double system catheter placed L4-L5 or L3-L4 level connected to a Pudenz reservoir. The entry of drugs into CSF was demonstrated way the injection of Technetium into the reservoir. The single catheter system had to be withdrawn due to infection by Staphylococcus albus or Candida albicans, while no local infection occurred with the double catheter system. Conclusion: When a double catheter system in used for connection with valvular reservoir, the dynamic of CSF behaves as a clearing up system, avoiding the injection of the reservoir

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SPASTIC PARAPARESIS: A PREDOMINANT PHENOTYPE OF ADULT ADRENOLEUKODYSTROPHY. A Pou Serradell, A Ugarte, Ma L Giros, Ta Pampols. *Barcelona. Spain.*

Adrenoleukodystrophy (ALD) is an X-linked disorder caused by impaired capability of peroxisomes to metabolize very long chain fatty acids - (VLCFA). The variability of the presenting symptoms, neurological and endocrinological, as well as the protracted course, makes the diagnosis sometimes difficult. We describe 3 patients, 2 brothers and 1 sporadic case, with ALD. All developed progressive difficulty in walking: In case 1 spastic paraparesis (SP) appeared at 18 years of age, progressed to supraspinal involvement and lead to death a 25 years of age. In case 2 (brother of case 1)SP appeared at age 20 and, the 37 year-old patient, is handicapped in a wheelchair but he is intellectually normal. In case 3, SP was noticed several years after polyneuropathic troubles (sural nerve biopsy showing typical material inclusion in Schwann cells) once appeared, the disease progressed with supraspinal abnormalities and the patient died at age 31. The salient biochemical feature was the accumulation of VLCFA. We concluded that SP may represent, in some cases, the only phenotypical expression of ALD; it may also represent a transitional between the rapidly progressive cerebral form and the protracted adult variants of ALD. We believe that SP is not modified by the hormonal treatment of ALD.

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CLINICAL SYMPTOMS AND DIFFERENTIAL-DIAGNOSTIC DIFFICULTIES IN THE ONSET OF LYME'S NEUROBORRELIOSIS. C Sabev, S Gikova, D Zekin, N Antonova, L Georgieva, V Stanev, G Popova, S Kostadinova, M Pepeliarska -*Sofia ,Bulgaria*

28 cases of clinically and serologically verified Lyme's neuroborreliosis were analysed in a hospital set-up. Early clinical and neurological symptoms are described and compared with data from the literature. At the onset of the disease are established more than 20 early clinical symptoms involving practically all anatomic levels of the nervous system. Leading in occurrence are sensory disturbances and motor deficiencies in various degrees and topical distribution as well as disorders in coordination and cephalalgic and depressive states. Considerable polymorphism and frequent combination of early symptoms are also established. Differential-diagnostic possibilities regarding different onset neuroborreliosis syndromes are considered.

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BILATERAL FAST MRI OF THE CARPAL TUNNEL IN RHEUMATOID ARTHRITIS. C Pierre-Jerome, SI Bekkelund, G Husby, SI Mellgren. *Tromsö, Norway.*

Rheumatoid arthritis (RA) commonly affects the wrist and damage to the median nerve may occur. This study evaluated quantitatively the changes of the carpal tunnel and the median nerve. 30 patients and 44 controls were included in the study. All were women with mean age 44.6 years in the patients and 42.5 years for the controls. Bilateral fast field Echo (FFE), 3 mm thick axial slices were used. The examination time was 2 min and 50 secs. At the level of the hook of the hamate, cross-sectional area of the carpal tunnel and signal intensity of the median nerve were calculated in both groups. Mean value of the area of the carpal tunnel were 219.7 sq. mm for the patients and 221.6 in the control group (P=0.83). Mean value of the area of the median nerve was 6.3 sq. mm for the patients and 7.4 sq. mm for the controls (P=0.21). No significant difference were noted in the signal intensity of the nerve between the two groups. However, there was correlation between disease duration and reduced area of the median nerve in the patients. Incidental findings included aberrant median artery (1 case) and hypoplastic hook of the hamate (2 cases). Fast MRI has potential as an objective method for evaluating RA.

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ENTRAPMENT NEUROPATHY OF THE SUPRASCAPULAR NERVE IN VOLLEYBALL PLAYERS: DIAGNOSTIC VALUES OF ELECTRICAL AND MAGNETIC STIMULATION. G Pelliccioni, A Attaccalite, M Guidi, E Brizioli, O Scarpino. *Ancona, Italia*

A traumatic suprascapular nerve palsy is induced in volleyball players by the chronic overuse of the shoulder. The nerve lesion can be localized either at the supraspinatus notch with weakness and amyotrophy of both the supraspinatus and infraspinatus muscles, or distally at the spinoglenoid notch involving only the infraspinatus muscle. The diagnosis can be confirmed by the electromyographic examination. The conventional electroneurographic method further supports the diagnostic hypothesis, but is of limited use to the difficulty in obtaining an adequate electrical surface stimulation. In order to evaluate the usefulness of peripheral magnetic stimulation in this entrapment neuropathy, we studied five cases of volleyball players affected by symptomatic suprascapular nerve lesion at the spinoglenoid notch. Another group of twelve asymptomatic volleyball players was also examined. In the symptomatic subjects the magnetic and electrical stimulation at the Erb's point showed an increased latency of the motor response in the right affected side. The significant difference in CMAP latencies demonstrated between the two sides in the group of asymptomatic players reveals a subclinical neuropathy and allows an early identification of at risk subjects. The magnetic stimulation, due to its painless characteristic, could be preferentially used in a screening study of this sportive population.

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CEREBRAL BLOOD FLOW CHANGES FOLLOWING LONG-TERM TREATMENT WITH ACETYL-LEVOCARNITINE IN PATIENTS WITH CHRONIC CEREBROVASCULAR DISEASE. S Passero, V Caruso, N Battistini. *Siena; Italy*

In a double-blind, randomised, placebo-controlled trial we studied the effect of long-term (6 months) oral treatment with acetyl-levocarnitine (ALC) (3 g/day) on regional cerebral blood flow (rCBF) in patients with mild cognitive impairment and chronic cerebrovascular disease. rCBF was measured by the Xenon 133 inhalation method at the beginning of the study and after 3 and 6 months of treatment, and was computed as the Initial Slope Index (ISI). In the placebo group, follow-up rCBF examinations showed no significant changes of hemispheric ISI (3 months: +0.06 left, +0.39 right; 6 months: -0.7 left, -0.22 right), while in the treated group there was a significant increase in rCBF perfusion which involved almost all regions of both hemispheres. These changes were already observed at the 3 month examination and persisted to the 6 month assessment (3 months: +4.82 left, +4.71 right; 6 months: +4.07 left, +4.41 right). The widespread increase in rCBF that we observed may be due to increased metabolic demand by the nerve tissue functionally reactivated by the drug. It is well known that cerebral blood is closely correlated to the energy metabolism of nerve tissue, particularly to the activity of synapse transmission. Since ALC possesses cholinergic properties, the most plausible hypothesis may be that of an effect on synapse transmission. However, more recent findings suggest that the pharmacological properties of ALC may be related to its specific enhancement of energy metabolism at mitochondrial level.

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RETINOL BINDING PROTEIN AS A NEW BLOOD-CSF BARRIER PARAMETER FOR THE LOW MOLECULAR WEIGHT RANGE. P Oschmann, J Hägele, CR Hornig, J Lohmeyer, W Dorndorf, *Giessen, Germany*

We evaluated the retinol binding protein (RBP - M.W.: 21000 - solely extradurally produced) as a new blood-CSF barrier parameter for small proteins, e.g. determination of locally produced interleukins. The RBP was measured with a modified nephelometric method (RBP-Test, Behring; BN 100 Nephelometer) and the method was adapted to the CSF. The detection limit was 0.54 mg/l. The recovery rate in CSF was between 95.2% and 104.7% for different standard RBP concentrations diluted with CSF. The coefficient of variation was between 0.46% and 0.8% for the intra-assay precision, between 0.53% and 12.6% for the interassay precision. The concentration varied in serum between 11.7 mg/l and 153.7 mg/l (n=31) and in CSF between < 0.54 mg/l and 12.51 mg/l (n=22). The correlation coefficient between the albumin and RBP quotient for different blood-CSF barrier dysfunctions was r =0.7519 ($p < 0.0012$) (n = 15). In 18 patients with different conditions IL-6 levels (M.W.: 26.000) between 3.86 pg/ml and > 2000 pg/ml (serum) and 3 pg/ml and < 2000 pg/ml (CSF) were measured. The RBP quotient was 3.8-388.5. With a modified evaluation graph according to Reiber an intrathecal IL-6 production could be detected in 5 patients. In conclusion RBP can be used as a reliable blood-CSF barrier parameter in the low molecular weight range and may be useful for calculation of intrathecal synthesis of IL6.

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IMMUNOCYTOCHEMICAL CHARACTERISATION OF INTERCELLULAR ADHESION MOLECULES (ICAM) ON CELLS PRESENT IN THE CSF. P Oschmann, M. Heilmann, M. Kaps, W. Dorndorf, *Giessen, Germany*

The process of cell adhesion is crucial for the induction phase of immune mediated diseases. Recent studies have elucidated the upregulation of intercellular adhesion molecules (ICAM) on endothelial and lymphocytic cells in different inflammatory diseases. Therefore they might be sensitive tool for the early detection of inflammatory CNS diseases. In this study immunocytochemical method (modified APAAP) should be developed for ICAM 1- (Dianova) and - 2 (Serva) detection on CSF-cells. Different techniques of cell enrichment, slide preparation, fixatives and antibody concentrations were evaluated. The two step centrifugation and sedimentation chamber technique with added foetal calf serum and methanol-formalin-aceton as fixative preserved the ICAM-epitopes best. The coefficient of variation was 14.7% (ICAM-1) and 13.3% (ICAM-2) for the intra-assay precision regarding the detection of ICAM-1 and -2 positive lymphocytes. Morphologically mainly lymphoid cells were stained. The positivity rate varied in different inflammatory conditions for ICAM-1 between 2.6-20% (lymphocytes), and ICAM-2 between 5.8-42.6% (lymphocytes). In conclusion ICAM-1 and -2 epitopes can be reliably stained on CSF-cells. The occurrence mainly on lymphoid cells supports their possible diagnostic role as an early inflammatory marker.

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TRANSORAL INJECTIONS OF BOTULINUM TOXIN (BT) IN ADDUCTOR TYPE LARYNGEAL DYSTONIA (ATLD). A Ohly, AO Ceballos-Baumann, K Joussen, B Conrad. *Munich; Germany.*

Background: Because of variable results with EMG guided percutaneous injections into the vocalis cricoarytaenoideus muscle complex we decided to test the safety and efficacy of an alternative approach, the laryngoscopically guided transoral method. Methods: The first 18 Patients with 37 treatment sessions with a longer follow-up than 6 months were analysed. The same outpatient procedure as for collagen injections into the vocal cord was used. Results: The dose of BT was 48 (20-60) Units Dysport (R) spread over two injections per vocal cord. Patients rated the effect in 38.8% of treatment sessions as "symptom free", in 44.4% as improvement >50%, in 11.1% as improvement <50%, and in 5.5% as no improvement. The duration of benefit was 4.9 (2-8) months. Transient hypophonia and mild choking on fluid with mean duration of 38. weeks occurred in practically all patients who had meaningful symptom relief. All five patients who had previously been treated by the percutaneous approach preferred the transoral procedure. Conclusions: Laryngoscopically guided laryngeal injections of botulinum toxin are a safe and efficient alternative to the percutaneous approach. Depending on the particular expertise available it might be even easier to implement than the EMG guided percutaneous approach.

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NECK CT MORPHOMETRY IN PATIENTS WITH SLEEP APNOEA. J Obenberger, K Sonka, *Prague, Czech Republic*

Sleep apnoea syndrome (SAS) was studied in 30 patients using General Electric CT Pace plus. Mesam 4 had been used to confirm the diagnosis and to state 3 degrees of night ventilation abnormality. Slices 5mm thick with 5mm intervals between from hard palate to hyoid bone perpendicular to the longitudinal axis 8 of the pharynx 5mm slices in 5mm intervals were examined at the peak of inspiration Measurements at 4 levels (nasopharynx, velopharynx, retrobasilingually and at hyoid level) in cm2 were compared with data derived from a normal population. Measurements of the tongue were of special interest with regard to macroglossia. Frontal and sagittal reformations verified data from axial scans. Separate dynamic scanning (8 fast scans lOmm/lOmm in 40 seconds) enabled us to compare the volume of air in the measured area under conditions of single prolonged inspiration and the volume measured in sequential inspirations. Results from Mesam 4 correlated well with the degree of airway obstruction derived from CT measurements. A high correlation was found when the functionally most (3rd degree) affected was compared with those of lesser degree in functional obstruction (degrees 1+2). We have thus shown that CT may be helpful for therapeutic decisions in SAS.

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MARCHIAFAVA-BIGNAMI DISEASE: INTERHEMISPHERIC DISCONNECTION AND BALINT'S SYNDROME, SPONTANEOUS FAVOURABLE OUTCOME. F Nicoli, J Vion-Dury; B Chave, S Confort-Gouny, T Houallah, P Cozzone, J-L Gastaut. *Marseille, France*

We report a new case of Marchiafava-Bignami disease with favourable outcome. Initial neuropsychological examination showed a typical interhemispheric disconnection syndrome associated with a Balint's syndrome. This association, never described in the literature, was due to extensive demyelination of corpus callosum and parieto-occipital white-matter in both hemispheres. Despite the intensity and the diffusion of these lesions, and in the absence of any vitamine treatment, the clinical and neuroradiological (CT, MRI) improvement occurred spontaneously, early and rapidly. This course, similar to that of toxic drug withdrawal, suggested that this was not a process of vitamin deficiency and that the withdrawal of the putative toxic occurred before the genesis of irreversible white-matter lesions. Data from the literature indicate that a wide extension of corpus callosum lesions to the semi-ovale centre has a poor vital and functional prognosis. our case shows that it is not always correct and that the intralesional necrosis and cavitation is not the rule. We consider that the most reliable factor of poor prognosis seems to be an initial coma.

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ARE THERE INDICATIONS FOR A CENTRAL SYMPATHETIC ORIGIN OF THE POSTAPOPLECTIC OEDEMA OF HAND AND FOOT? B Neundoerfer, S Tex, C Seeber, T Mokrusch. *Erlangen, Germany.*

Oedema of the hand and foot is a common sign in patients suffering from stroke, but its origin is not well understood. Peripheral mechanical reasons are discussed but unproved. The present study was designed to look for possible deficits in central sympathetic pathways. 68 patients with a single unilateral ischemic stroke were investigated. Localization and area of the lesion were evaluated from CCTs. Circumference of hand and foot was measured daily. 71% of the patients showed unilateral oedema (mean difference 1.4 (0.5-2.5)cm). The maximum was on day 3 to 5, and later than 3 weeks, no oedema was observed. In 46% of the cases, sympathetic signs were observed (hyperhydrosis, hyperaemia, hypemia, hyper- and hypothermia). There was a high correlation between oedema and paresis (P=0.33), hyperreflexia (P=0.006), and pyramidal signs (P=0.001). From 43 defined cerebral CCT-regions there was a high correlation between oedema and the localization of infarction in the internal capsule (n=0.0004) with a predominance for the posterior part, while no correlation was found for parietal and occipital areas. It is concluded that postapoplectic unilateral oedema is caused by lesions of the central sympathetic pathways and not by peripheral mechanisms.

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IMPORTANCE OF THE SUSPENDED SENSORY SYNDROME (SSS) IN DIAGNOSIS OF MULTIPLE SCLEROSIS. TX Arbizu Urdiain, SM Yelamos, P Villanueva, J Ballabriga, E Basart, J Peres Serra, *Barcelona, Spain*

Patients with Multiple Sclerosis (MS) show sensory symptoms in 78,2% of cases. Suspended Sensory Syndrome (SSS) has not been recognized as clinical pattern of MS. We report 20 patients with definite MS that showed a SSS as manifestation of their illness. We prospectively studied 234 patients with Definite MS by means of the EDMUS (European Database for Multiple Sclerosis). Twenty (8,5%) patients showed at least an attack consisting of SSS. In eleven attacks the SSS was the only (or principal) neurologic abnormality. The disease began with a SSS in eight (3,5%) patients. We didn't find any patient with syrinx on MRI. Eight patients with MS and syrinx were reported in the literature, only one showed SSS. Pseudoradicular syndrome in MS has been recently reported in four patients. In our series there are five patients with this syndrome. We report a neurologic classic syndrome (SSS, often with syringomyelic dissociation) that has not been recognized to date as a clinical pattern of MS, frequently showed by our patients. MS must be included in differential diagnosis of SSS, especially in young adults. This is important today because a baseline treatment could be useful for patients diagnosed in an early stage of their illness.

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PALATAL MYOCLONUS AND AUTOANTIBODIES TO GLUTAMIC ACID DECARBOXILASE (GAD). R Nemni, S Braghi, G Comi, E Bonifacio, MG Natali-Sora, N Canal, *Milan, Italy*

Autoantibodies (Ab) directed against GAD have been reported in the serum from patients with stiff-man syndrome (SMS) and with insulin-dependent diabetes mellitus (IDDM). We report the presence of anti-GAD IgG Ab in patient with palatal myoclonus (PM) and epilepsy in the absence of SMS and IDDM. A 22-year-old woman with a 2 year history of complex partial seizures poorly controlled by the use of antiepileptic drugs, began to complain of PM. EEG showed an epileptogenic focus in the left temporal lobe. MRI of the brain was normal. The Patient's serum was positive for islet-cell and GAD Ab but was negative for other Ab. The Patient's serum strongly immunoprecipitated 35S-methionine labelled in vitro translated recombinant human GAD65. Immunoblot of human GAD65 deletion mutants showed strong reactivity against GAD fragments in which amino acids 1 to 288 were deleted, but no reactivity when the COOH terminal residues 512 to 576 were also deleted. Marked reduction in the frequency of epileptic attacks and improvement in PM occurred when a benzodiazepine was added to therapy. Tests for anti-GAD Ab may be indicated in patients with PM not associated with brain lesions.

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NONTRAUMATIC SPINAL EXTRAMEDULLARY HEMATOMA A REPORT OF TWO CASES WITH CLINICAL AND MRI CORRELATION.YN Debbink, TR Marra, *Milwaukee, Wi, USA*

Two patients with nontraumatic spinal extramedullary hematoma (SEH) are reported. One patient with a cervical lesion and unilateral myeloradiculopathy was taking 160 mg of aspirin daily; the other patient with a lumbar lesion and cauda equina syndrome was taking 5 milligrams of coumadin daily. Common presenting symptoms included intense pain with radicular radiation, followed by progressive motor, sensory and sphincter deficits. Magnetic resonance imaging verified the cervical lesion. Myelography followed by computed tomography was needed to confirm the lumbar hematoma. The former patient had a dramatic spontaneous recovery. Despite early multi-level surgical decompression and clot evacuation, the latter patient had a poor outcome. Prognosis seemed to depend on both location and size of the hematoma as well as premorbid factors such as spinal canal diameter. MRI is clearly the imaging modality of choice, allowing for confident recognition of the size, extent and pathologic substrate of the lesion. Although not emphasized in the literature, aspirin use may represent a potential risk factor for SEH.

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NORMAL PRESSURE HYDROCEPHALUS: CLINICAL FEATURES AND DIAGNOSTIC CRITERIA. N Afsar, D Ince, S Tekin, C Aykut, S Aktan. *Istanbul; Turkey.*

Normale-pressure hydrocephalus (NPH) may be cited as one of the treatable dementias, thus its early detection and treatment important. The clinical presentation may be in the form of a combination of the classical triad made up of gait disturbance, dementia and urinary incontinence. The differential diagnosis includes other treatable causes of dementia as well as lacunar state and vascular dementia. The diagnosis can be made by cranial imaging laboratory techniques, and the demonstration of cebrospinal fluid (CSF) circulation disorder by means of cisternography. As more than one

agent may be causing dementia among this population, a dilemma may arise when deciding whether or not the patients will be benefiting grom surgical intervention. In this study 8 patients presenting to the Marmara University School of Medicine Neurology Department with the clinical suspicion of NPH, were differentiated from other causes of dementia and each had a cisternography. Among those, 5 patients were found to have an impaired CSF circulation and one had aqueduct stenosis. Four out of these patients underwent a ventriculoperitoneal shunting operation and were followed-up for a maximum of 2 years. The diagnostic criteria of NPH as well as eligibility for shunting operation are discussed here.

97.
WERNICKE'S OPTIC NEUROPATHY WITH VESTIBULAR FAILURE. S Mossman, P Timmings, *Wellington, New Zealand*

Three patients with high alcohol intake and poor diet presented with a sudden onset of severe visual loss, double vision and ataxia. On examination, cognition was normal. Vestibular failure was evident on clinical examination or investigation in 2/3 patients specifically examined. Visual acuity of <l/60 in all 3 patients improved dramatically within hours of thiamine with return to near normal visual function over days (>6/9), Delayed visual evoked responses progressively decreased over 3-6 months. Two patients had serial observations of their gait. he vermal ataxia improved in one in the absence of any change in vestibular function while in the other the vermal ataxia at presentation was unchanged despite resolution of severe vestibular hypofunction. These 3 cases demonstrate (i) Sudden visual loss may be a feature of Wernicke's syndrome; rapid deterioration and rapid recovery of vision relate to thiamine metabolism while delayed VERs may reflect structural changes in myelin, as seen in a rodent model of thiamine deficiency. ii) Vestibular failure can be demonstrated at the bedside of a conscious Wernicke's patient by an impairment of the impulsive vestibular ocular reflex. This will be shown by video. (iii) The main cause of the gait ataxia in Wernicke's syndrome may be cerebellar rather than vestibular.

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CATHETER ASSOCIATED PHLEBITIS - AN EVERYDAY PROBLEM IN I.V.-THERAPY OF STROKE. T Mokrusch, S Seitz-Dertinger, W Solbach, B Neundörfer, *Erlangen, Germany*

Every third nosocomial infection in German university clinics is a catheter-associated phlebitis. In a prospective study, we investigated its possible etiology. 144 venous catheters of 88 patients were investigated. All patients suffered from ischemic stroke. Criteria of exclusion were: motor restlessness; i.v.-therapy with antibiotics, steroids or heparin; cardiac insufficiency >NYHA 3; serum creatinin level > 1.1 mg%. Standard i.v.-therapy was HES and an electrolyte solution. Vasculon 2 venous catheters were used (gauge 18, 20 and 22). Observation time was 72 hours, with clinical signs of thrombophlebitis the catheter was removed earlier. Antibiograms were performed from the catheter tip and a catheter-flush. In 62.5% of all cases, a local reaction was observed within 72 hours. predominantly with larger sizes (gauge 18 more often than gauge 22). Hypertonia, diabetes mellitus and hypercholesterolemia did not reveal as risk factors, whereas hypertriglyceridemia was highly correlated with phlebitis. In antibiograms, we found Staph. aureus, CNC, streptococci, enterobacteriaceae, without however, any statistical correlation to local symptoms. our conclusion is that the catheter associated phlebitis is of primarily irritative etiology, it is no primary infection. One of the most important clinical consequences is the use of smaller catheters.

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AUTOSOMAL DOMINANT SPASTIC PARAPLEGIA WITH ADDITIONAL UNIQUE FEATURES IN A LARGE KINDRED OF GERMAN ORIGIN. H Meierkord, A Mainz. *Berlin, Germany.*

The hereditary spastic paraplegia's (HSP) in general are divided into two groups: pure hereditary spastic paraplegia implying pyramidal signs in the lower limbs and increased tendon reflexes in the upper limbs but no other neurological features and the complicated forms which may show additional signs such as amyotrophy, extrapyramidal involvement or other features. The complicated forms are extremely rare. We describe a large kindred of 13 affected individuals in 4 generations with an autosomal dominant syndrome of complicated spastic paraparesis. Features include spastic paraparesis, hypomimia, badykinesia, rigidity, dysarthria, a complex eye movement disorder, epilepsy and incontinence. The pattern of expression varies in different family members. Extensive investigations were carried out on 4 affected members but no biochemical defect or cytogenetic abnormality was found. Linkage analysis for mapping the disease gene is currently in progress.

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ANTI-200KD NF IGM ANTIBODIES IN NEUROLOGICAL DISEASES. E Manfredini, E Nobile-Orazio, E Calabrese; S Allaria, C Mariani, G Scarlato. *Milan; Italy.*

Antibodies to the 200kD neurofilament (NF) are a normal constituent of the human antibody repertoire but were reported more frequently or at higher concentration in neurodegenerative disorders. To determine the pathogenetic relevance of this reactivity we measured anti-NF IgM in 32 patients with Alzheimer's disease (AD), 31 with motor neuron diseases (MND), 12 with other neurodegenerative disorders, 75 with neuropathy (PN) and IgM gammopathy without neuropathy, 128 with other immune diseases (OID), 25 with multiple sclerosis (MS) and 20 normal subjects. IgM reactivity with 200kd NF was tested by immunoblot after SDS-PAGE of bovine cauda at the dilution of 1:1,600 and titrated by 2-fold dilutions. Anti-NF IgM were found in 5 patients with AD (16%), 10 with MND (33%), 5 with PN and IgM gammopathy (7%), 10 with other PN (8%), 8 with MS (32%) and 14 with OID (37%). Most patients had titers up to 1:3,200, while 4 OID patients had titers of 1:12,800 up to 1:51,200 and 4 with PN and IgM gammopathy and titers of 1:25, 600 up to 1:200,000. The neuropathy in patients with high anti-NF IgM was heterogeneous and was always associated with other causes of neuropathy including cryoglobulinemia or MAG reactivity. The increased frequency of anti-NF IgM in both neurodegenerative and immune diseases and the lack of association between high anti-NF IgM and homogeneous neuropathy features cast some doubt on their pathogenetic relevance.

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EFFECT OF POSTURE ON BALANCE: THE NEUROREHABILITATIVE ROLE OF COMPUTERISED DYNAMIC POSTUROGRAPHY. M Sinaki, S Lynn, K Westerlind, *Rochester, U.S.A.*

The prevalence of falls, especially in the elderly is affected by disturbance in control of balance. Treatments or training programs to improve balance appear warranted but sensitive methods for detecting changes in balance are needed. One such technique is Computerized Dynamic Posturography (CDP). This pilot study was designed to compare balance in patients with and without kyphosis. Because the center of gravity may be closer to the limits of stability in individuals with kyphosis, they may exhibit poorer balance than individuals with normal posture. To control other variables, age-matched osteopenic women with and without kyphosis were studied. Patients included 14 females (mean ± SE age, 67.7 ± 2.4 years); 4 were kyphotic. Four trials of 6 sensory organization tests and 2 trials of 4 motor performance tests were performed. Results indicated a significant learning effect ($P < 0.01$) for all tests; scores improved 2.7% and 6.3% for the simpler and more difficult tasks, respectively. Although not always statistically different ($P = 0.02$-0.30), patients with kyphosis had poorer balance, indicated by increased sway, longer motor latency times, and balance strategy scores emphasising the hip. These women, as has been shown clinically and, as determined from CDP, might be more prone to falls. These data suggest that CDP is an effective technique to assess balance changes. The data also stress the importance of controlling for a learning effect.

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EXPRESSION OF TRANSFORMING-GROWTH-FACTOR-β1-mRNA IN CEREBROSPINAL FLUID CELLS OF PATIENTS WITH MENINGITIS. LM Ossege, B Voss, Th Wiethege, E Sindern, Jp Malin. *Bochum & Bergmannsheil, Germany*

Meningitis is an acute inflammatory disease of pia and arachnoid and the fluid in the subarachnoid space. Mostly it derives from viral or bacterial infections. It can be accompanied by complications and may lead to brain damage and death. The process of infection and cell damage evoke cellular and immunologic reactions, e.g. a high secretion of cytokines. Especially tumor-necrosis-factor-alpha (TNF◊ and interleukin-1 (IL-1) promote inflammatory reactions of subarachnoid space. On the other hand transforming-growth- factor-β1 (TGF(1) has antagonistic effects on TNF◊ and IL-1 mediated processes and leads therefore to suppression of inflam-

matory reactions. Our interest was focused on the observation of TGF(1 participation in the development of meningitis. The expression of TGF(1-mRNA in cerebrospinal fluid (CSF) cells of 10 patients with aseptic or bacterial meningitis and typical clinical symptoms was investigated by non-radioactive in situ hybridisation. A high amount of TGF(1-mRNA was detectable in the CSF cells of all cytological preparations. Neutrophilic granulocytes expressed more TGF(1 -mRNA than lymphocytes and monocytes/macrophages. Following this, TGF(1-mRNA seems to be more expressed in cases of bacterial meningitis than in viral forms. This shows, that cellular immunemediated defence reactions are activated in meningitis to suppress inflammatory processes and that the distinct cell types of CSF may participate in different ways.

103
AUTONOMIC AND SENSORY ABNORMALITIES IN ALS. D Linden, P Berlit, *Essen, Germany*

Amyotrophic lateral sclerosis (ALS) is believed to be a degenerative disorder of only motor neurones. However, recent studies indicated additional subclinical involvement of sensory pathways. Furthermore, sympathetic ganglia were sometimes abnormal on histopathological examination. We performed somatosensory evoked potentials (SEP) and sympathetic skin responses (SSR) in seven unselected patients with clinically definite ALS. One patient presented initially with hemiplegia (Mill s variant) with minor sensory disturbances (palmoplantar hypalgesia) and pathological SEP and SSR of the involved side. MRI was consistent with bilateral pyramidal tract degeneration. Sensory complaints and SEP/SSR findings improved whereas the motor disorder rapidly progressed with severe bulbar involvement. Another patient showed borderline SEP and a pathological SSR of a severely paretic leg. All other patients had abnormal SSR but normal SEP. In summary, we report the unusual presentation of a patient with remitting sensory and autonomic abnormalities in the early course of ALS However, persistent sensory abnormalities are uncommon as are pathological SEP In contrast, abnormal SSR are common, indicating concomitant degeneration of sympathetic pathways in ALS.

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ISOLATED CENTRAL NERVOUS SYSTEM VASCULITIS (ICNSV): TWO PROBABLE CASES WITH DRAMATIC IMPROVEMENT UNDER STEROID THERAPY. F Le Doze, F Chapon, V de la Sayette, S Schaeffer, M Dary, B Lechevalier, F Viader. *Caen, France*

ICNSV is responsible for a diffuse encephalopathy with seizures, focal signs and confusion leading to coma. Cerebral imaging, brain biopsy and CSF are often non diagnostic. An infection, possibly of viral origin, is the putative mechanism of this disease. We report the cases of two 51 y-o women who presented encephalopathy of rapid onset and fluctuating course over a period of several months, consisting of progressive alteration of consciousness leading to coma, seizures and non specific alterations of EEG, increased CSF protein (0,7 and 1,5 g/l), normal cerebral digital angiograms, CT scan and MRI, normal ESR and absence of antibodies against DNA, SSA and SSB soluble antigens. Case 1 was characterised by headache as first symptom, delusion, ataxia, extrapyramidal hypertonia and distal tremor. Case 2 was characterised by previous Basedow's disease and initial rapidly treated hyperthyroidism, fever, recurrent right stroke-like hemiparesis. Right prefrontal meningocerebral biopsy was normal in case 1 and showed scarce perivascular lymphocytes in case 2. Steroids at an immunosuppressive dosage resulted in a dramatic improvement within two weeks. Although patient 1 worsened after an initial rapid decrease of posology, the steroids could be progressively reduced and stopped 4 and 3 years post-onset respectively, allowing complete recovery. In our patients the clinical presentation, the recovery under steroids as well as the absence of any obvious etiology make the diagnosis of ICNSV highly probable. These cases highlight the importance of extensive etiological work-up in order to undertake rapidly cytotoxic and/or steroid therapy.

105
BRAIN STRUCTURES INVOLVED IN SOMATIC PAIN : EXPRESSION OF IMMEDIATE EARLY GENE-ENCODED PROTEINS. M Lanteri-minet, J de Pommery, J Weill-Fulazza, M Menetrey, *Paris & Nice, France.*

Evoked expression of the immediate early gene- encoded proteins (c-Fox, Fos B, Jun B, Jun D, c-Jun and Krox-24) were used to monitor sensory processing in the hindbrain of rats undergoing somatic inflammation. Experiments were performed on freely moving animals that did not experience any other constraints than those imposed by the disease itself. Local injection of chemicals were used to cause subcutaneous inflammation of the plantar foot or monoarthritis. The following results will be mainly based on c-Fos expression as this protein proved to be the most effective marker. In the caudal medulla oblongata structures involved were: caudal intermediate reticular nucleus, subnucleus reticulates dorsalis, ventrolateral reticular formation and lateral paragigantocellular nucleus. Structures involved at the ontomesencephalic junction level mostly included: superior and dorsal lateral subnuclei of he parabrachial area, nucleus cuneiform and most caudal portions of the lateral central gray. Occlusion: The structures involved only partially overlap with those implicated in anaesthesia r visceronociceptive processing (Lanteri-Minet and al., Neuroscience, 1992, 55: 737-753) thus suggesting that a certain degree of specificity could exist for some of them. Caudal medulla oblongata would be more involved in eliciting cardiovascular behaviors that pain licit while the pontomesencephalic junction would be more involved in mediating pain of inflammatory origin.

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ISOLATED OR PREDOMINANT OCULAR MOTOR NERVE PALSY SECONDARY TO BRAINTEM STROKE. LG Lazzarino, A Nicolai, A Nappo. *Gorizia & Viterbo, Italy*

Isolated ocular motor nerve palsies (OMNP) are rarely described as a consequence of strokes and are usually attributed to lesions involving the intracranial peripheral portion of the nerves. We observed 6 patients with isolated or predominant OMNP in whom CT scan and/or MRI disclosed brainstem infarcts or haemorrhages. In five patients there were various combinations of oculomotor disorders and in all cases neuroimaging revealed small infarcts or haemorrhages in the midbrain in the area of oculomotor nuclei or fascicles. In a patient with an isolated VIth nerve palsy CT scan and angiography revealed a megadolichobasilar artery and MRI disclosed a small infarct in the pontine tegmentum, probably involving the fascicles of the sixth nerve. Non ocular neurologic signs and symptoms were absent or slight in all patients and included sensory changes in one patients and a clumsy hand in two. The CT scan and MRI findings correlated with ocular signs. The patients reported confirm that isolated OMNP can arise from brainstem stroke, and indicate that brainstem strokes should be considered in the differential diagnosis of isolated OMNP and appropriate diagnostic investigations performed.

107
CHOLINERGIC NEUROTRANSMISSION ENHANCEMENT INFLUENCES BRAIN GLUCOSE KINETICS AND SYMPTOMS IN PROGRESSIVE SUPRANUCLEAR PALSY (PSP). J Blin, P Mazetti, B Mazoyer, S Ben Ayed, S Rivaud, C Malapani, B Pillon, M Vidailhet, B Dubois, C Pierrot-Deseilligny, T Chase, Y Agid; *Paris France.*

PSP, a degenerative disease with subcortical lesions and a diffuse loss of cholinergic neurones, exhibits ocular and cognitive symptoms. We evaluated the effects of physostigmine, an anticholinesterase inhibitor, on ocular movements (pursuit, saccades, antisaccades), neuropsychological performances (seven tests exploring memory, attention, frontal lobe activities) and brain glucose kinetics (using 18F-deoxyglucose and PET). Six patients were evaluated with placebo and physostigmine in blind and randomised condition using intravenous infusion and maximal rate individually determined (5 to 20 µg/kg/hr). Its effects were evaluated at steady-state while plasma cholinesterase inhibition was observed. Errors were reduced in antisaccades ($p = 0.03$) and in every neuropsychological tests recording reaction time we used ($p = 0.04$ & 0.03) as well as performances in two other tests ($p = 0.04$ & 0.02). Brain glucose metabolism was studied using brain and arterial 18F-deoxyglucose kinetic data and a three compartment model. Blood-to-brain glucose transfer showed a mean increase (p reached 0.0001 after ANOVA) in frontal cortex and thalamus from 8 to 32% of placebo values. This study suggests it is possible to enhance cholinergic neurotransmission in PSP which results in improvement of several ocular, neuropsychological and metabolic parameters.

108
NEUROLOGICAL COMPLICATIONS OF PRIMARY BILIARY CIRRHOSIS. A prospective clinical study. A Joutel, R Poupon, P Giral, MG Bousser, E Roullet, *Paris, France*

Several neurological disorders of unknown mechanism have been reported in patients with primary biliary cirrhosis (PBC), including peripheral neu-

ropathy, progressive ophthalmoplegia, transverse myelitis and multiple sclerosis (MS). However neurologic involvement in PBC has not been the subject of any systematic evaluation. The goals of this study were to estimate the frequency of neurological manifestations in PBC and to assess their relation to the Sjögren's syndrome present in up to 90 % of patients with PBC. Twenty-five patients were randomly selected from a French PBC cohort and examined by a neurologist. They were asked for neurological and sicca symptoms and a detailed history was taken. All patients were women aged 35 to 75 years (mean: 53.8). Seventeen patients (68 %) had xerostomia, xerophtalmia, or both; 14 patients (56%) had neurological symptoms or signs (sicca symptoms (SS): 12/14), and 11 had none (SS: 5/11). Eight patients, all with SS, had distal symmetric lower limb sensory symptoms and signs consistent with peripheral neuropathy; 4 other patients had isolated neurological Signs (absent tendon reflexes, distal sensory loss, ptosis) and 2 had sensory symptoms only. In addition, 2 patients without neurological manifestations had a first-degree relative with MS. In this purely clinical study we found a high prevalence of neurological manifestations in PBC, which may be related to the presence of the Sjögren's syndrome. This unsuspected finding needs further evaluation which is in progress.

109
IMPACT OF CONTINUOUS EEG MONITORING IN THE NEUROSCIENCE ICU (NICU-CEEG) ON CLINICAL DECISION MAKING. KG Jordan. *San Bernardino, USA.*

We tried to examine the impact of NICU-CEEG on patient management decisions. In the O.R. and epilepsy units, CEEG has proven beneficial, but its value in the NICU remains unestablished. Retrospective analysis of 200 patients with acute cerebral injuries consecutively monitored with NICU-CEEG. Correlation of on site and post hoc NICU-CEEG interpretation with ICU course and management decisions. Impact on decision making was defined as decisive, contributing, or none. Results: admitting diagnoses were: acute cerebral ischemia (ACI) 28 %, uncontrolled seizures (SZ) 22%, intracranial hemorrhage (ICH) 22%, metabolic coma (MC) 10%, brain tumours (BT) 8%, CNS infections (INF) 6%, and head trauma (HT) 4%. In ACI, progressive focal slow or new generalised slowing detected worsening ischemia. Resolution of focal slow occurred with or preceded clinical improvement. Asymmetrical frontal delta or regional slowing with suppressed background indicated increasing mass effect in ICH or INF. Nonconvulsive seizures (NCS) occurred in 34%. 65% of these had nonconvulsive status epilepticus (NCSE). NICU-CEEG findings influenced decisions regarding transport for CT scans, anticonvulsant therapy, and hemodynamic manipulations. Overall, clinical impact of NICU-CEEG was decisive in 51% contributing in 31%, and none in 18%. Conclusion: Systematic NICU-CEEG can detect or anticipate changes in cerebral function and significantly impacts management decisions.

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NEUROLOGIC COMPLICATIONS OF INFECTIVE ENDOCARDITIS. JM Gergaud, JP Breux, P Roblot, G Grollier, JP Neau, R Gil, B Becq Giraudon. *Poitiers, France.*

Six males and 4 females, of mean age 67.7 years, with neurologic complications (NC) (19%) among 53 cases of infective endocarditis, reported from January 1983 to December 1990, were studied retrospectively. NC were present on admission in 6 cases: 2 generalised seizures, 4 strokes, associated with 2 meningeal syndromes. Four cases of NC occurred during hospitalisation: 1 stroke with coma, 1 transient ischemic attack, 2 generalised seizures. Blood cultures were positive in 6 cases: 5 group D Streptococci (1 enterococcus, 4 S. D bovis), 1 Gram negative bacillus. Three cases with an alimentary of entry were identified for the 4 D bovis Streptococcus endocarditis. Cerebrospinal fluid was purulent in 1 patient (S. D bovis), aseptic in 1, hemorrhagic in 2, and normal in 2. Cranial computed tomography was performed in 5 cases, and revealed: absence of abnormality in 1 case, infarct in 3 cases, brain abscess in 1 case. There was no angiographic documentation to assess for mycotic intracranial aneurysm. Bidimensionnal echocardiography revealed the presence of vegetations in 8 of the 10 patients with NC, and in 19 of the 43 patients without NC (P<0,04). Antimicrobial therapy was maintained 5 to 6 weeks. Two patients underwent cardiac surgery. Two patients died of subarachnoÔd hemorrhage. Compared to the previously reported studies, where Staphylococcus was usually described, our results showed a higher frequency of D bovis Streptococcus, an older age, a higher frequency of stroke and digestive portal of entry.

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DIFFERENTIAL EFFECT OF AMANTADINE ON FATIGUE ASSOCIATED WITH SCLEROSIS, PARKINSON'S DISEASE, AND AMYOTROPHIC LATERAL SCLEROSIS. JL Dobato, Y Perez Gilabert, C De Andres, JL Munoz Blanco, D Mateo, S Gimenez-Roldan, *Madrid, Spain.*

Fatigue, a subjective feeling of declining muscular energy for prolonged motor activity disproportionate to strength, is common in a wide range of neurological disorders As amantadine may be useful in fatigue associated with multiple sclerosis (MS), we investigated whether amantadine was beneficial on fatigue associated with Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). Baseline scores in 10 MS patients complaining of fatigue on the Visual Analogue Scale (VAS) and Fatigue Severity Scale (FSS) were significantly greater ($p<0.05$) (VAS, 6.3 ± 0.7; FSS, 73.8(3.04) than in 10 PD patients (3.8 ± 0.7 and 39.72 ± 7.37, respectively) and 6 ALS patients (3.89 ± 0.8 and 47.88 ± 13.9, respectively). All 3 groups scored significantly higher when compared to 20 healthy age and sex matched controls. There were no intergroup differences when many qualitative variables of fatigue were compared except speech, which was more impaired in ALS patients. Heat exposure worsened fatigue to a similar extent in all three groups. A base-line state was established in all 3 groups on VAS and FSS scores, Beck depression inventory, an attentional task, and muscle strength to repeated ergonomic contractions. Patients were randomly allocated to receive either amantadine (200 mg/d) or placebo for a one-week period each in a double-blind cross-over design. A week of wash-out was intercalated before shifting either to placebo or to the active drug. Amantadine showed a beneficial effect on fatigue both on EM and PD ($p < 0.05$) but not in ALS patients. Amantadine had no effect when compared to placebo on all other variables in any of the 3 groups. We believe that different mechanisms may underly fatigue associated with disease of the motor neuron, basal ganglia, and demyelinating disorders.

112
WHEN DO WE MAKE AN X-RAY OF THE CERVICAL SPINE IN PATIENTS WITH BLUNT NECK AND/OR HEAD TRAUMA. J de Kruijk, A Twijnstra, J Wilmink, P Leffers, *Maastricht, The Netherlands*

The aim of this study was to investigate the usefulness of x-ray of the cervical spine in patients with blunt neck and/or head trauma. In the emergency room, many patients with blunt neck and/or head trauma are screened by radiography. We selected a group of symptoms that can be used to decide whether it is necessary to x-ray of the cervical spine. Patients presenting in the emergency room of our hospital with blunt neck and/or head trauma in 1991 were divided into risk groups presenting low, moderate and high risks of having a cervical injury. The division was based on the patients' symptoms. In each group we counted how many x-rays were made and whether cervical injuries were seen on these x-rays. We found that 57% of all x-rays were performed in the low risk group. None of these showed any cervical injuries. 41% of all x-rays were made in a technically imperfect. We conclude that x-rays of the cervical spine in trauma patients are useful in the moderate and high risk groups, but not in the low risk group.

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ANTIGANGLIOSIDE ANTIBODIES IN TOXIC OIL SYNDROME NEUROPATHY. C Iniguez, A Jimenez-Escrig, M Nocito, ML Villar, P Gonzalez-Porque, JM Gobernado. *Madrid, Spain.*

The toxic oil syndrome (TOS) is a disorder similar to the myalgia-eosinophilia syndrome that emerged in Spain in 1981 in users of rapeseed cooking oil. These patients developed an acute flu-like illness that progressed in many cases to a combination of peripheral neuropathy, interstitial pneumonitis and connective tissue alterations. At the present time some patients are under neurologic evaluation due to sequelae. The precise cause and mechanism of the peripheral nerve lesions have not been established. We evaluated antiganglioside antibodies (AGA) GM1, GD1b, GD1a, GM2, A-GM1, both IgG and IgM class in 12 patients with TOS and peripheral neuropathy; 43 blood donors and 77 patients with other neurologic diseases were used as controls. AGA were determined by ELISA. Positive samples were tested by HPLTC. In 3 (25%) patients with TOS, IgM antibodies to GD1a were detected (titers >1:400). None of the control patients had positive titers > 1:200. Low positive titers (values lower than 3 SD of the controls) were found to IgM antibodies GM1, GD1b and AGM1 in GD1a positive TOS patients. No correlation was found between clinical status and AGA. This specific AGA pattern may reflect the pathogenic mechanism of TOS neuropathy.

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RESPIRATORY ABNORMALITIES DUE TO CRANIOVERTEBRAL JUNCTION COMPRESSION HC Chandler, RS Howard, HA Crockard, NP Hirsch, F Henderson, JM Stevens. *London, UK*

Apnoea and sudden death are known to occur as a consequence of medullary compression. However lesser respiratory abnormalities may be associated with foramen magnum lesions which cause brainstem compression. The presence of nocturnal hypoventilation may indicate the potential for perioperative respiratory difficulties. Thirty eight patients with severe craniovertebral compression (12 rheumatoid, 14 congenital platybasia/ Klippel-Feil, 6 osteogenesis imperfecta, 5 tumours, 1 odontoid fracture) were studied with overnight pulse oximetry and subsequent computer analysis. Overnight baseline oxygen saturation ($Sp0^2$) and the number of dips in Sp02 lasting longer than 10 seconds were calculated per hour of recording. All patients underwent multiplanar CT/myelography or MRI scanning with an assessment of craniovertebral angles and qualitative assessment of medullary and spinal cord compression. Rheumatoid patients had the greatest respiratory abnormalities, but only when the medulla was deformed by a translocated odontoid peg. Nocturnal respiratory abnormalities were rare in patients with other lesions at the craniocervical junction. No correlation was found between the severity of the lower cranial nerve palsies and the presence of respiratory abnormalities. These studies suggest that clinically unsuspected respiratory abnormalities may occur in patients with severe medullary compression, especially when due to rheumatoid arthritis. Nocturnal oximetry may be used to detect these abnormalities, possibly identifying patients prone to postoperative respiratory complications.

115
SUDDEN DEATH IN A LATE ONSET MITOCHONDRIAL ENCEPHALOPATHY. M Guidi, T Rossi, G Pelliccioni, M Del Gobbo, M Maidani, O Scarpino. *Ancona; Italy.*

Sudden death has been occasionally described in infants affected by mitochondrial encephalomyopathy, whereas this fatal event is very rare in adults. We report the clinical history of a patients affected by diabetes mellitus from 20 years who acutely developed confusional state, cortical blindness, focal neurological deficits, cognitive impairments and myoclonic jerks, at the age of 49 years. The clinical signs and EEG characteristics pointed initially to diagnosis of Creutzfeldt Jakob disease (Heidenhain variant). The encephalic MRI was characterized by multiple cortico-subcortical lesions. A week after the hospitalisation his clinical condition improved slowly and EEG abnormalities changed in both morphology and recurrence following the positive clinical evolution. The diagnosis of MELAS was successively confirmed by high value of lactic acid rest and after exercise, by molecualr genetic study of mitochondrial DNA of muscle biopsy and by muscle and brainMRI spectroscopy. The patients was treated fot two years with antiepileptic drugs and ubidecarenone during which he did not have any relapses of stroke like episodes. Successively the patient suffered of a respiratory virus disease and died suddenly during a night, probably for an acute cardiorespiratory insufficiency. Autopsy findings did reveal the cause of death, making and acute cardiac energy crisis a likely hypothesis.

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PREDICTIVE FACTORS OF IN-HOSPITAL CENTRAL NERVOUS SYSTEM COMPLICATIONS FOLLOWING LIVER TRANSPLANTATION. F Graus, A Pujol, A Rimola, J Beltran, JC Garcia-Valdecasas, M Navasa, L Grande, J Galofre, J Visa, J Rodes, E Tolosa. *Barcelona, Spain.*

We prospectively evaluated 84 consecutive adult patients with chronic liver disease before and after liver transplantation to define the type and incidence of post-transplant neurologic complications, and to assess possible pretransplant and operative variables associated with in-hospital central nervous system (CNS) complications. There were 25 (30%) patients who presented 23 neurological complications of the central and 6 of the peripheral nervous system. Seventy percent of the complications occurred in the first month post-transplant. The most frequent CNS complications included anoxic (6 patients) and septic (5) encephalopathy, brain haemorrhage (5), and ciclosporine neurotoxicity (3). Patients who presented CNS complications had a higher mortality rate than those who did not (55% vs. 17%, p=0.002). Multiple logistic regression analysis showed abnormal pretransplant neurologic examination suggestive of chronic hepatic encephalopathy (p=0.007) and non-cholestatic liver disease (p=0.012) to be independently associated with in-hospital CNS complications. These data indicate that CNS neurological complications following liver transplant are common in patients with non-cholestatic liver disease and are associated with increased mortality. Pretransplant neurological examination is an important predictor of CNS complications that occur in the immediate post-transplant period.

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ADRENOLEUKODYSTROPHY: PHENOTYPE DISTRIBUTION IN A GROUP OF 41 SPANISH PATIENTS WITH THE PATHOGNOMONIC INCREASE OF VERY LONG CHAIN FATTY ACIDS (VLCFA). ML Giros, M Ruiz, T Pampols, *Barcelona. Spain*

During the past 5 years we have diagnosed 41 Adrenoleukodystrophy (X-ALD) hemizygotes, 40 heterozygotes and 2 affected foetuses from 33 kindreds. According to the classification in six main phenotypes proposed by H. Moser (J Inhere Metab Dis 1992; 15: 645-664), that it is based on criteria of age of onset, nature of pathology and the main site of pathology, we found the next hemizygote phenotype distribution: 27% childhood cerebral form, 2% adolescent cerebral form, 7% Adult cerebral form, 39% Adrenomyeloneuropathy,12% Addison only and 12% Asymptomatic/ Presymptomatic. An 8% of the heterozygous women above 25 years developed some clinical signs. Coexistence of different phenotypes was found in 6 families: Adult cerebral form and Addison in one, Childhood cerebral form, asymptomatic and Addison in two, Childhood cerebral form and asymptomatic in one, Adrenomyeloneuropathy and asymptomatic in one (in a 6th family, clinical data are insufficient). Three of the asymptomatic cases are above the age of presentation of index case and two of them are below. With the limitations of the low number of cases it could be remarked the relative low frequency of childhood cerebral form: 27% in comparison with the 48% of Moser experience.

118
ERYTHROCYTE BAND 3 PROTEIN IN NEUROACANTHOCYTOSIS. L Ginsberg, L Bruce, AE Harding and MJA Tanner. *London & Bristol, UK*

Defective anion transport activity of the red blood cell membrane has previously been described in patient with neuroacanthocytosis (Kay et al., Expl Clin Immunogenet 1990;7:181). A patient from a large and well-characterized neuroacanthocytosis kindred (Hardie et al., Brain 1991;114: 13, Case 4) showed a similar defect, with anion transport at 70% of normal values. However, the cDNA sequence of the erythrocyte membrane band 3 protein (the anion transporter) was normal in this patient These results suggest that abnormal erythrocyte membrane anion transport, if found consistently in neuroacanthocytosis, may be due to a regulatory defect of band 3 protein rather than a mutation in the protein-coding sequence of its gene.

119
ZIDOVUDINE AND PERIPHERAL NEUROPATHY IN AIDS. JP Lefaucheur, P Chariot, J Verroust, R Gherardi. *Creteil; France.*

Zidovudine therapy may prevent HIV encephalitis, but its influence on HIV-associated peripheral neuropathies is unknown. We tried to correlate zidovudine intake and occurrence of the different forms of peripheral neuropathy in HIV-infected patients. This retrospective study (1987-1993) included 100 HIV-infected patients with peripheral neuropathies classified as: inflammatory demyelinating neuropathy (IDP: 20), mononeuropathy multiplex (MM: 20) and distal sensory polyneuropathy (DSP: 60). Circulating CD4 cell count was correlated with total cumulative dose of zidovudine (CDZ) in the different groups. Patients with IDP had the highest CD4 cell number (210/ml $>$ 47) and low (untreated: 56%, treated: 60g $>$ 18), consistent with the occurrence of IDP at early and intermediate stages of HIV infection. Patients with DSP had low CD4 cell number (135/ml $>$ 27) and high CDZ (untreated: 19%, treated: 356g $>$ 38), consistent with the occurrence of DSP in patients with full-blown AIDS. Patients with MM had low CD4 cell number (171/ml $>$ 46), contrasting with a low CDZ (untreated: 44%, treated: 162g $>$ 45)/ (CD4 in MM vs DSP: ns, CDZ in MM vs DSP: p<0.01). Conclusion: Our results suggest that mononeuropahty multiplex occurs in HIV-infected patients who are not treated or have received a low cumulative dose of zidovudine despite advanced stage of HIV infection.

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DIFFERENTIAL PROFILE OF MIGRAINOUS PATIENTS WITH ANALGESIC INTAKE. L Galiano, I Montiel, R Martin, R Falip, J Matias-Guiu, *Alicante; Spain*

Migraine headache is a common, recurrent and often incapacitating disorder. We performed this study in order to determinate the characteristic features of migrainous patients with regular or frequent intake of ergotamine preparations and Nonsteroideal Anti- inflammatory drugs (NSAIDs) and the existence of significant differences between both groups. Patients were diagnosed of migraine according to operational criteria of IHS. 186 patients were included, 68 (36.6%) suffering from migraine without aura and 118 (63.4%) migraine with aura. 46 (24.7%) were males and 140 (75.3%) females. Mean age of the sample was 35.6 ± 12.9 years. 139 (74.7%) patients reported an intake of analgesics and 47 (25.3%) ergotamine preparations. In patients with NSAIDs intake the mean age was significantly lower than in patients with ergotamine for treatment of migraine. When clinical features of these two headache groups were examined, the duration of migraine attacks in the NSAIDs group was significantly higher (p=.0014) than in the ergotamine group, and the severity of migraine was lower (p<.05) than in this group. Among associated symptoms, nausea and vomiting were significantly less frequent (p=.024) in the NSAIDs group than in the group of patients with ergotamine intake.

121
MULTICHANNEL RECORDING AND ELECTRICAL BRAIN MAPPING OF VISUAL P-200 POTENTIAL UNDER DIFFERENT STIMULUS CONDITIONS. A. Taghavy, H. Hamer. *Erlangen, Germany*

Previous study with monochannel recording indicated that P200 represents an electrophysiological correlate of arousal/attentive behaviour within pattern flash P300 using different check-sizes of the infrequent stimuli (Taghavy and Brütting (1988) J Neurol). A very closely related, if not identical potential is observable in pattern reversal visual evoked potentials (PVEPs=P100-potential). We therefore, studied the characteristics of this potential in condition of full-field and foveal stimulation with multichannel recording being a more appropriate technique to verify the widely spread scalp recorded potentials initiated by the reticular formation. The full-field and foveal PVEPs (16x16 squares; 16 degr. of visual field; and 4x4 squares; 5 degr.of visual angel respectively; sens.=50 V; filter freq.=1-30 Hz) were derived from 16 locations on the scalp (10/20-system) against linked mastoids in 13 healthy male students (23-32y) with normal vision. The amplitudes of P200 were mapped and their latencies measured. (1) In contrast to N140 localized in the occipito-parietal region, P200 is recordable in virtually all electrodes over the scalp. (2) The amplitudes of P200 behaved similarly in both conditions in contrast to the P100-complex. (3) The latencies of this potential were shortest in frontal electrodes (e.g. F7: 191.8±9.2 ms; F8: 190.9±7.6 ms) and it spreads continously over the scalp having longest latencies in occipital leads (O1: 221.5±15.4 ms; O2: 220.4±15.3 ms). Therefore, the latencies in frontal electrodes were significantly shorter than the occipital latencies of P200 (p<0.01). P200-potential may indeed represent the arousal/attentive reaction independent of quality of stimulation within one modality.

122
ADCA TYPE I : MAPPING OF THIRD LOCUS SCA3 AND ABSENCE OF GENETYPEPHENOTYPE CORRELATION. A Benomar, G Cancel, G Stevanin, A Durr, Y Agid, A Brice. *Paris, France.*

Autosomal dominant cerebellar ataxia type I are clinically and genetically heterogeneous. Progressive cerebellar ataxia is variably associated with other signs, such as deep sensory loss, pyramidal and extrapyramidal signs, supranuclear ophthalmoplegia, sphincter disturbances, dysphagia and dementia. Their frequency increases with disease duration which explains clinical variability among patients. Two genes responsible for the disease, SCA1 on short arm of chromosome 6 and SCA2 on the long arm of chromosome 12 are already localized. We mapped third locus (spinal cerebellar ataxia 3 - SCA3) to chromosome 14q24.3-qter in one family and confirmed its location in two other families. Linkage analysis with twelve 14q microsatellite markers allowed to restrict the candidat interval to an 4cM region. other families were excluded from all three loci. Clinical features and age at onset were similar in SCA1 and SCA3 patients. We could not provide firm evidence for anticipation, which has been demonstrated in SCA1 and SCA2 kindreds, in SCA3 families. However, an earlier age at onset is observed when the disease is paternally transmitted. In conclusion, we mapped SCA3 locus to chromosome 14q in 3 French families and demonstrated further genetic heterogeneity. No clinical criteria allowed differentiation between the families studied.

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QUANTITATIVE CEREBRAL MRI IN RHEUMATOID ARTHRITIS. SI Bekkelund, C Pierre-Jerome, G Husby, SI Mellgren, *Tromsö, Norway.*

Autoimmune mechanisms are assumed to be important in the pathophysiology of rheumatoid arthritis (RA). Although rare, cerebral vasculitic infarction with clinical manifestations occurs in RA patients. To search for a possible predominance of lesions reflecting vasculitis and other abnormalities in RA, we studied 30 patients and 44 controls with MRI. Mean age was 44.6 years for the patients and 42.5 years in the control group. Nine patients (30%) had cerebral white spots compared with 15 (34%) of the controls. Mean number of white spots were 1.4 in patients and 2.3 in controls (P=0.55). Mean area of the greatest lesion in each patient was 27.4 mm^2 for the patients and 29.8 mm^2 in the control group (P=0.77). Measured on a midline sagittal slice, the mean area of corpus callosum was 752.7 mm^2 in the patients and 802.2 in the controls (P=0.11). Mean area of the medial cerebral surface was 9528.3 mm^2 in the patients compared with 9834.7 mm^2 in the controls (p=0.45). The area of the midline cerebellar configuration was 1612.0 mm^2 in the patients and 1572.3 in the control group (p=0.52). There were no significant differences in relative signal intensity of the white spots and corpus callosum between the two groups. Thus, the number and sizes of the white spots were equal in the two groups. This does not support a higher frequency of even clinically silent infarcts due to vasculitis in the RA patients. Also there was no evidence of cerebral atrophy in the RA patients compared with controls.

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PRE AND POST LIVER TRANSPLANTATION NEUROLOGICAL SCREENING IN HEPATIC FAILURE PATIENTS. A PROSPECTIVE STUDY OF 20 CASES. P Bedoucha, , C Labaune, M Lanteri-Minet, MH Mahagne, M Chatel, *Nice, France.*

The incidence of post transplantation neurological symptoms in liver failure patients and the difficulty to unravel the various pathogenic mechanisms of these symptoms led us to pursue a prospective study comparing the results of pre-transplantation nervous system screening to the post-transplantation findings. Twenty patients were included in the study, 10 were evaluated pre and post transplant. All cases presented post hepatitis sclerosis; sex ratio 2.3M/lF. The screening included: neurological examination, biological screening (liver and renal functions), neurophysiological studies (EMG, EEG, Sensory, Cochlear, visual and cognitive evoked potentials), MRI imaging. Before graft, neurological abnormalities were found in 12 patients before graft. EEG abnormalities in 9; acoustic evoked potentials in 9: visual potentials in 2; EMG in 4. MRI revealed T1 hypersignaling symetrical areas in pallidum in 17 patients, extended to the mesencephalon in 11; T2 weighted imaging revealed hyperintensity in caudate and putamen nuclei in 6 cases and in the centrum semi ovale in 2. MRI abnormalities were present in 85% of cases while neurophysiology parameters were altered in only 45% of cases. Among post transplant patients, 30% showed a decrease of the T1 abnormalities found before the transplantation; this decrease is accompanied with neurological improvement. Data will be presented showing the need of pretransplant screening including MRI imaging in the evaluation of transplantation effects.

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THE FAVORABLE EFFECT OF INJECTING PHYSIOLOGIC NaCl-SOLUTION ON NEUROLOGICAL SYMPTOMS IN PATIENTS WITH LUMBAR DISC PROLAPSES. V Desnizza, B Widjaja-Cramer, *Baden, FRG*

The compression of nerve roots by disc herniation at the lumbosacral or lumbar L4-L5 levels is one of the causes of low back pain and neurological deficit in the legs. We describe the positive results of perineural injection treatments with physiologic saline solution (0,9 per cent sodium chloride) in 3 patients with CT and MRI confirmed L4-L5 disc herniations who refused to undergo surgical intervention. The therapy was performed in 12 sessions ; 2 ml of 0,9 % NaCl-solution as injected perineurally in about 24 projection points of the nerve branches at the Ll-L5 levels. The relief of pain was seen between the 4th-6th session The beneficial re-

sponse to the injection tasted up to 3-4 years and there were no detectable changes on CI scans obtained one year after the therapy. The same favourable result of injection therapy was seen in 53 (84%) of 63 patients with neurological symptoms and independently confirmed disc prolapses. The influence of the NaCl-solution on the neurogenic inflammation and on stimulation of blood microcirculation around the nerve tissue is discussed as a possible mechanism for the efficacy of this treatment.

126
STIMULUS-SENSITIVE TRUNCAL MYOCLONUS OF PROBABLE SPINAL ORIGIN. A Schulze-Bonhage, H Kott, A Ferbert. *Kassel, Germany.*

Stimulus-sensitive myoclonus has been shown to occur with cortical and reticular brainstem origin. Here we describe a patient with probable spinal origin of truncal stimulus-sensitive myoclonus. A 49-year-old female patient had suffered from myoclonic jerks of back and abdominal muscles for eight years. Jerks would be elicited by slight touching her back and neck but not by touching the extremities. Also, lying in bed would trigger jerks often hindering the patient from falling asleep and causing arousal during the night. Over the years, the intensity of jerking gradually increased; there was slight improvement after administration of tetrazepam. Clinical examination showed regular, non-habituating evokation of jerks of truncal muscles with maximal intensity when stimuli were applied to the lower back. Electrophysiological investigation showed EMG bursts of more than 200 ms duration with minimal latencies of 20-30 ms after touching the skin with a trigger reflex hammer. Recruitment of muscles was first ipsilateral, then contralateral to the side of stimulation; latencies were longer with increasing distance from the stimulus site. MR of brain and spinal chord was normal. Somatosensory, auditory, and visual evoked potentials were of normal latency and amplitude, as were motor evoked potentials from erector spinae and extremity muscles. So far, stimulus-sensitive myoclonus has been described with stimulation and motor responses in the extremities. In this patient with truncal stimulus-sensitive myoclonic jerks, the sequence of muscle recruitment and the short latencies of motor responses after application of stimuli make a spinal origin most probable.

127
GENERALISED MYOKYMIA IN GOLD THERAPY: "CHOREE FIBRILLAIRE DE MORVAN" (MORVAN'S FIBRILLARY CHOREA) OR ISAAC'S SYNDROME (CONTINOUS MUSCLE ACTIVITY) INDUCED BY GOLD? J Marta-Moreno, C Sanz-Sebastian, LF Pascual, F Abad Alegria, F Morales. *Zaragoza, Spain*

We report a patient undergoing gold therapy (sodium aurothiomalate. 50 mg intramuscular weekly for eight weeks) who developed a complex of generalised myokymia, muscle weakness? excessive sweating, tachycardia, irritability, emotional lability, insomnia. glove and stoking burning paraesthesias and psychiatric symptoms with visual hallucinations. The clinical and electrophysiological characteristic of this entity, which consistently resolves with cessation of gold therapy, is reported. These symptoms and signs are identical to one described in the French medical literature as choree fibrillaire de Morvan. The possible relationships with the continuous muscle fiber activity syndrome (Isaac's syndrome) is discussed.

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EVALUATION OF POSTURAL, FOOD AND EXERCISE INDUCED HYPOTENSION BY NON-INVASIVE 24 HOUR AMBULATORY RECORDING IN AUTONOMIC FAILURE. M Alam, CJ Mathias, *London, UK.*

In autonomic failure (both pure PAF and Shy-Drager Syndrome SDS), a variety of events including time of day, head-up posture, food and exercise influence blood pressure. The object of our studies was to determine whether 24 hour ambulatory monitoring would detect such abnormalities. We studied 9 PAF, 9 SDS patients, 9 idiopathic Parkinson's disease (IPD), and 8 normal subjects (NS). In NS respective daytime and nighttime values were 125 ± 7/75 ± 2 and 110 ± 2/61 ± mmHg; in PAF 113 ± 4/69 ± 2 rising to 137 ± 3/79 ± 2 at night; in SDS 115 ± 8/77 ± 5 rising to 133 ± 4/87 ± 3; in IPD 119 ± 4/75 ± 2 falling to 99 ± 2/62 ± 1. In PAP and SDS postural change was greatest in the morning; 130 ± 4/77 ± 2 to90 ± 3/57 ± 3 in PAFand 116 ± 11/79 ± 7 to 103+ ± -9/78 ± 6 in SDS. After meals BP fell from 118 ± 6/73 ± 4 to 96 ± 4/59 ± 2 in PAF and 125 ± 7/84 ± 5 to 108 ± 7/70 ± 5 in SDS. After walking BP fell from 99 ± 5/61 ± 5 to 88 ± 4/55 ± 3 in PAF and 116 ± 11/79 ± 7 to 103 ± 9/74 ± 11 in SDS. Hypotension did not occur in IPD or NS. Non-invasive 24 hr ambulatory monitoring, therefore, enables assessment of postural, post-prandial and exertion induced hypotension, It emphasises the reversal of the normal circadian fall in BP at night. This technique should aid the management of hypotension in such patients even in the home situation.

129
THE SYMPATHETIC SKIN RESPONSE: LATENCY AND AMPLITUDE ASYMMETRY IN NORMAL MAN. M Kushnir, G B Groozman, AD Korczyn, *Tel Aviv, Israël.*

We tried to examine whether significant right-left asymmetry exists for the SSR. The sympathetic skin response (SSR) is a simple test for appreciation of the sympathetic limb of the autonomic nervous system, widely applied in clinical practice. However, insufficient data is available concerning. Latency and amplitude asymmetry in healthy subjects. SSR latency and amplitude were examined in both hands after stimulation of either median nerve (MN) in 40 normal subjects, and either tibial nerve (TN) in 30 normal subjects. Latencies to onset and to the negative peak, and peak to peak amplitude of the response were measured. After stimulation of left MN or left or right TN, mean SSR latency (to the negative peak) in the left hand was shorter than in the right hand (1735 ± 172 msec in left and 1805 ± 177 msec in right; 1730 ± 165 msec in left and 1783 ± 167 msec in right; 1734 ± 147 msec in left and 1786 ± 155 msec in right, following stimulation of left MN, left TN and right TN respectively, $P<0.05$). Right-left differences were (mean ± SD): left MN, 115 ± 31 msec; left TN, 104 ± 24 msec and right TN, 86 ± 38 msec. Stimulation of the right MN resulted in symmetric responses (1802 ± 190 msec in left and 1798 ± 166 msec in right). Mean SSR amplitudes have not shown asymmetries. Asymmetry of the SSR latency has to be considered for standardisation of SSR parameters.

130
THE SYMPATHETIC SKIN RESPONSE IN REFLEX SYMPATHETIC DYSTROPHY. Ve Drory, A Korczyn, *Tel Aviv, Israel.*

The reflex sympathetic dystrophy (RSD) is an uncommon condition which occurs following partial nerve injuries and is accompanied by signs of autonomic hyperactivity. Since the mechanism underlying RSD is largely unknown, it was of interest to examine the possible involvement of the sympathetic system in this disorder. The sympathetic skin response was examined simultaneously in the involved and contralateral limbs of 12 consecutive patients with RSD of an upper or lower limb. It was normal in the involved limbs of five patients, of lower amplitude than on the contralateral side in three and absent only on the involved side in four. The response abnormality did not correlate with either the stage or the duration of RSD. These abnormalities could reflect either the peripheral nerve injury underlying RSD or secondary central nervous system disturbances.

131
A PET STUDY OF REMEMBERED SACCADES IN NORMAL SUBJECTS. EPO Sullivan, IH Jenkins, DJ Brooks, L Henderson, C Kennard. *London; UK.*

We investigated the role of the frontal lobes in remembered saccades. Seven right handed male volunteers were studied using H2 15O activation positron emission tomography (PET). The saccadic task consisted of a target being flashed at one of five horizontal eccentricities (> 5 degrees). After a delay of up to 1000 milliseconds a buzzer sounded and the fixation light was extinguished to trigger a saccade to the remembered location of the target. In the rest state subjects listened to the buzzer with eyes closed. Comparison of regional cerebral flow in the two conditions showed significant activation ($p<0.001$) in the remembered saccade task, both in the frontal eye fields (FEFs) and the supplementary motor area (SMA) in the frontal lobes. The prefrontal cortex was not seen demonstrated. Other areas significantly activated included basal ganglia, midbrain, thalamus, parietal area 7, and striate and extrastriate cortex. Conclusion: 1) The preeminent role of the FEF and SMA in the production of remembered saccades compared to other frontal lobe areas has been demonstrated. 2) The presence of a cortico-striatal pathway involved in remembered saccades has been confirmed..

29 June 1994

Poster Session 5

1
NERVOUS SYSTEM INVOLMENT IN LIVER TRANSPLANTION. A SERIE OF 173 PATIENTS. P Bedoucha, C Labaune, H Guggenheim, M Lanteri-Minet, MH Mahagne, M Chatel, *Nice, France.*

From 1988 to 1993, 173 liver transplants were performed in our hospital; sex ratio was 3/1; liver failure was due to post hepatitis sclerosis in 72% of cases. Neurological symptoms were found after the transplant in 61 patients; this 35% rate of occurrence is in the range of previous results reporting a 20-40% incidence rate. All patients were under immuno-suppressive therapy, predominantly ciclosporine (150-300ng/ml), and eventually associated with steroids. Neurological symptoms were of five types: encephalopathy (58%), seizures (21%), central motor weakness (6%), peripheral nerve involvement (6%), persisting headaches (4%). No case of Central Pontine demyelination syndrome was found. Pathogenic mechanisms included metabolic disturbances (51 %; hepatic failure, renal encephalopathy, ionic imbalance, ciclosporine toxicity (19%); systemic or meningeal infections (18%) and cerebrovascular syndromes (2.3%). Neither age, sex, type of liver failure, nor the technical surgical procedure seem to play any role in the occurrence of nervous system symptoms. These results are comparable to reports by others. It is worthnoting that the occurrence of neurological symptoms does not alter the general outcome of the liver grafted patients. The etiologic screening should include EEG, CT and MRI imaging, lumbar puncture when needed. The frequency of post transplant nervous system manifestations urges us to perform identical screening prior to transplant.

2
CONTRALATERAL AND RECIPROCAL PROPRIOCEPTIVE FACILITATION AND INHIBITION OF POTENTIALS EVOKED BY TRANSCRANIAL MAGNETIC STIMULATION AND ITS POSSIBLE USE IN REHABILITATION OF HEMIPARESIS. St Baykouchev, A Struppler, N Tchalucova, J Jotova. *Plovdiv; Bulgaria.*

Ten probands been studied. Potentials evoked by MgS in left and right m.flexor digitorum longus and m.extensor carpi radialis both have been recorded by superficial electrodes. Both muscles were in a light isometric contraction, sustained /with 0,4 Nm/ by torquemotor II/ after A. Struppler/. A brisk stretch/ 1,2 Nm in 6 ms/ have been superimposed either on the right or on the left flexor, the MgS supplied with the same (A) side 50 ms after beginning of the stretch. A total of 44 muscle potentials were estimated. An averaging of 5-8 events have been done. At the stretched side, the flexor potentials were enhanced in all probands, irrespective of the coil side /e.g. MgS destination/. In the stretched extensors the rate of facilitation was respectively 8:3 and 9:2. On the side contralateral to the stretch inhibition/ or no facilitation/ was found in 8 of extensors and 6 of the flexors of the patients, when the MgS have been destined contralaterally as well, and in 6 of extensors and 5 of the flexors when the MgS was destined to their side. We conclude that the effect of stretch 50 ms before the MgS, is not only a facilitation in the stretched muscle but also an inhibition to the contralateral side and, to a less extent, to the antagonist muscles. It is a patter, of excitatory and inhibitory influence, which could be useful in enhancing the movements and its reciprocal or synergic background. This was confirmed in a few cases with postictal hemiparesis.

3
HISTOPATHOLOGIC AND IMAGING CORRELATION OF MENINGEAL ENHANCEMENT IN INTRACRANIAL HYPOTENSION. B Mokri, JE- Parisi, BW Scheithauer, DG Piepgras, M Miller. *Rochester, Minnesota, U.S.A.*

Intracranial hypotension has been recognized to cause diffuse meningeal gadolinium enhancement on MR imaging, frequently associated with presence of subdural fluid collections. Increased protein and lymphocytes may be noted in CSF analysis. The mechanisms of subdural collections, meningeal enhancement and CSF changes have remained speculative. Meningeal biopsies in 5 patients with intracranial hypotension and meningeal enhancement were analysed. On surgical inspection, the dura and leptomeninges appeared normal. The histologic findings in all cases were similar. The essentially unremarkable pia-arachnoid demonstrated only a minimal increase in collagen, with no evidence of inflammation or increased vascularity. Although the periosteal dura was preserved, the subdural zone contained a thin layer of small blood vessels and fibroblasts in an amorphous matrix, corresponding to the zone of potential subdural collection in the layer of borderline dural cells. These pathologic observations point to absence of primary meningeal pathology or inflammatory or vascular abnormalities, and suggest that pachymeningeal enhancement as well as subdural collections, likely reflect secondary reactive phenomena induced by hydrostatic CSF changes, with resultant vasodilatation, increased permeability of pachymeningeal microvasculature, and leakage of serum proteins.

4
INTERFERON B TREATMENT OF VIRAL ENCEPHALITIS. A RETROSPECTIVE STUDY. AW Kornhuber, A Köhler, PJ Hülser; J Kriebel. *Ulm, Germany.*

The efficacy of interferon β for the therapy of viral encephalitis in man, and herpes encephalitis in particular, still is not clear. The effort of a prospective double blind study would be enormous. We therefore addressed this question with a retrospective study. We included accessible cases with typical symptoms of viral encephalitis from four hospitals from 1984 to 1992. Diagnosis, symptoms, treatment, and outcome were assessed from patient records The outcome was classified with the Karnofsky scale. Sufficient data were obtained from 23 patients, 15 to 75 years. All were treated with acyclovir, seven were treated intravenously with interferon β in addition (IFN+). No significant difference between IFN+ and IFN- regarding symptoms at admission or severity Residual symptoms (RS) at all after treatment all of the IFN+ patients had RS (3 minor), 6 of the 16 IFN- patients had RS (15 minor). If we classified Karnofsky's outcome as good (80% or more), or poor (less than 80%), we found 3 poor outcomes in the IFN+ group, 4 in the IFN- group. Early treatment did not favour the outcome. Conclusion: On the basis of our data we conclude that the efficacy of interferon β may be low.

5
SNEDDON'S SYNDROME ASSOCIATED WITH HASHIMOTO'S THYROIDITIS. C Alonso-Villaverde, A Castro, L Masana., *Reus, Spain*

Sneddon's syndrome consist of ischemic cerebrovascular manifestations and generalized livedo reticularis and its etiology is uniknown. Hashimoto's tyroiditis is an autoimmune disease of thyroid gland. We report the association of this two disease. A 35-year-old woman was admitted because of grand mal seizure episode. She had history of multiple grand mal seizures. The physical examination showed a palpable goitre without nodules, livedo racemosa in trunk and extremities. Titers of free iodothyronine and free thyroxin were high, the thyroid-stimulating hormone was low. The titre of antimicrosome antibodies was 1/400 and antithyroglobulin antibodies was 1/80. She showed an increased 123 I thyroid uptake. The chest radiograph and EEG were normal. ANA, Anticardiolipin, Anti-β2-glycoprotein I antibodies and lupus anticoagulant were negative. A brain CT scan was normal but MRI revealed multiple bilateral lacunar subcortical infarction. Thyroid biopsy showed diffuse lymphoplasmic infiltration with focal oxifilic transformation and mild fibrosis. The association of Sneddon's syndrome with Hashimoto's thyroiditis favours an autoinmune origin.

6
NEUROTRICHINOSIS. A Martin Urda, J Fernandez, R Mares, L. Torre, E Mayayo, C Richart, *Tarragona, Spain.*

Neurological manifestations are exceptional in Trichinosis and few cases have been reported in recent years. A case in a 24 year-old woman with associated neurological and cardiac involvement and hypereosinophilia is presented. She started with fever, cough, dyspnea, facial oedema, cutaneous rash and myalgia. Fifteen days later she was admitted with photopsia and proximal weakness in the right arm. Subungueal splinter haemorrhages and retinal involvement were evident. Blood cell count showed hypereosinophilia (7548/mm^3) and thrombopenia (73000/mm^3). Cerebral CT scan and CSF were normal. MRI revealed multiple nodular lesions involving white matter and cortex. ECG and Echocardiogram were abnormal. Deltoid muscular biopsy confirmed the presence of encysted larvae of *T.spiralis*. Early therapy with Methylednisolone and mebendazole was

started and followed by clinical and biological improvement. Neurotrichinosis is typically associated with hypereosinophilia and cardiac involvement early in the course of the disease. Prognosis is severe. Several pathogenic mechanisms (toxaemic, allergic and larval) have been proposed . Diagnosis can be difficult in the absence of an outbreak and must be considered in patients with hypereosinophilia and neurological and cardiac involvement in order to start early treatment that can ameliorate symptoms.

7
SPINAL EPIDURAL EXTRAMEDULLARY HEMATOPOIESIS (EMH) IN THALASSEMIA: PROSPECTIVE EVALUATION OF ASYMPTOMATIC PATIENTS. A Lossos, M Gomori, E Libson, A Goldfarb, T Seigal. *Jerusalem. Israel.*

EMH is a compensatory haematopoietic mechanism complicating the chronic anaemia of haemoglobinopathies. It affects various organs and the retroperitoneal space. Thoracic epidural EMH leading to spinal cord compression is described in nearly 50 thalassemia patients. To evaluate the occurrence of subclinical spinal epidural EMH in B-thalassemia, we prospectively screened 11 randomly selected asymptomatic pts by whole spine imaging using CT/MRI. There were 8 men and 3 women ranging in age between 17-36 years. Imaging findings were correlated to disease activity. Epidural mass was detected in 5 patients (45%), causing lumbar epidural block in 2. Spinal EMH occurred only in the lumbosacral area, mostly at L5 and Sl at vertebral body level, and was associated with cortical bone disruption. Patients with epidural involvement had thalassemia major who received >13 blood transfusions/year. 5 of the other 6 pts had thalassemia intermedia receiving <11 transfusions/year. No correlation was found with other parameters of disease activity. Vertebral bone marrow haemosiderosis obscured MRI identification of EMH. In conclusion, spinal EMH is probably more common than reported in symptomatic thalassemia. It occurs at lumbar levels originating from adjacent vertebral bodies and is best evaluated by CT.

8
WHAT IS THE UTILITY OF A "WAKING ADVICE" IN PATIENTS WITH A MILD BRAIN INJURY. A de Louw, A Twijnstra, P Leffers, *Maastricht, The Netherlands*

The aim of this study was to investigate the clinical utility of and compliance with instructions given to carers of Mild Head Injury (MHI) patients to enable them to recognise an deterioration in the patients' condition ('waking advice'). Data were collected from 26 accident and emergency (A and E) departments to investigate the use and content of 'waking advice'. In a retrospective study, the records of 326 MHI patients seen at the University Hospital Maastricht were traced to explore the indication for 'waking advice'. Compliance with 'waking advice' was studied by means of an inquiry among 61 MHI patients. Only 7 of the 26 emergency departments had a written 'waking advice'. The recommended waking interval ranged from 1 to 4 hours. The 326 patients were divided into three groups. In the group with concussion, 74 per cent of the patients received 'waking advice'. In the 'no brain damage' and 'severe brain damage' groups, the percentages were 21 and 51, respectively. Compliance was highest in the group of patients who received both oral and written 'waking advice'. There is no consensus about the content of, the indication for, 'waking advice'. Compliance improved when 'waking advice' was given both orally and on paper.

9
MOVEMENT-RELATED POTENTIALS PRECEDING VOLUNTARY MOVEMENT ARE MODULATED BY THE MODE OF MOVEMENT SELECTION; P Praamstra, D Stegeman, M Horstink, A Cools. *Nijmegen, The Netherlands*

Movement-related cortical potentials were recorded in normal subjects during the performance of four different motor tasks involving joystick movements. The four tasks differed in complexity (simple vs. sequential movements) and in the mode of movement selection, i.e., whether a movement or movement sequence was made in fixed or self-determined directions. The choice of these tasks was based, firstly, on previous electrophysiological studies suggesting an effect of task-complexity on the amplitude of the Readiness Potential (RP), and, secondly, on previous PET studies showing that activity of the supplementary motor area (SMA) is especially influenced by the mode of movement selection. The results show that, for simple movements, RP amplitude is higher preceding freely selected movements than preceding movements in a fixed direction. A replication study using buttonpresses instead of joystick movements confirmed this result. The results converge with PET evidence obtained in closely similar tasks and support an SMA contribution to the generation of the RP. The results also suggest that the mode of movement selection may have a more potent influence on SMA activity than the fact whether a movement is simple vs. complex or sequential.

10
HEMIDYSTONIA-TREMOR SECONDARY TO THALAMIC CAVERNOUS ANGIOMA. E- Basart Tarrats, M Calopa, P Villanueva, S Martinez, J Ballabrina, J Peres Serra. *Barcelona, Spain.*

Cavernous angioma (CA) constitutes a significant percentage of intracranial vascular malformations. Location in the thalamus has only rarely been reported. To our knowledge, only 1 case of CA associated with movement disorder has been described: a CA involving the basal ganglia leading to focal dystonia of the hand. We present a case of hemidystonia-tremor as the only clinical manifestation of a thalamic CA. A 25-year-old, right-handed man had complained of involuntary movement affecting his left limbs since childhood. On examination he had left hemidystonia, both at rest and during voluntary movement. Dystonic posturing of the left arm was associated with an irregular postural and intention tremor. There was no paresis or sensory loss. MRI T2-weighted sequences showed a well-defined right posterior thalamic lesion with a central core of mixed-signal intensity surrounded by a rim of hypointensity characteristic of CA. Cranial angiography was normal. This case shows that hemidystonia may result from a focal thalamic lesion. A slow and irregular tremor has occasionally been found in combination with hemidystonia. As far as we know, this is the first case of thalamic CA associated with hemidystonia..

11
A CLINICAL AND GENETIC STUDY OF PARKINSON'S DISEASE (PD) IN TEN FRENCH FAMILIES. D Taussig, V Planté-Bordeneuve, M Ziegler, G Fenelon, M-H Marion, J Mallecourt, D Ranoux, G Said, *Paris, France*

The occurrence of familial PD has been discussed for years. The report of 2 large pedigrees, including autopsied cases, as well as numerous nuclear families established a genetic component to this disease. We present a clinical and genetic study of PD in 10 French families. Index cases were selected on the basis of clinically typical PD, and at least one affected relative. Eighty five individuals have been examined and collection of all available data about dead affected members, performed. In addition, a group of sporadic PD, sex and age matched, were seen. A total of 23 individuals (12 females and 11 males) were affected. Six out of the ten families were multi-generation kindreds. Neurological examination was unremarkable in all cases, except for extrapyramidal signs. The parameters studied (age at onset (OA), initial symptoms, duration of disease) were variable within and between families. By contrast, no statistical difference were found between the familial and the sporadic group. In multi-generation kindreds, anticipation was found in the 6 families, with earlier OA in children compared to their parents (mean difference 26.5±4.2 years, $p<0.001$), whereas OA within generation was identical (mean difference 6±5.2 years, $p>0.05$). The transmission is likely to be autosomal dominant, with incomplete penetrance. Thus, familial PD is clinically heterogeneous. Anticipation is found in the multi-generation kindreds and could be an interesting clue for the molecular approach of the disease.

12
ALCOHOL-RESPONSIVE MYOCLONIC DYSTONIA WITH LIGHTNING JERKS IS NOT LINKED TO THE DYT1-REGION ON CHROMOSOME 9q34. T Gasser, C Kabus, L Ozelius, R Wenzel, XO Breakefield, *Munich & Berlin, Germany; Charlestown, MA, USA*

A family with myoclonic dystonia with lightning jerks was identified. The index patient presented with bilateral, asymmetric, myoclonic jerks affecting predominantly the upper extremities, with the right side more affected than the left, and mild dystonic features (torticollis). Six definitely affected individuals have been identified. Transmission is compatible with autosomal dominant inheritance. Average age of onset of myoclonus was 12 (range 6 to 18) years. Two of the secondary cases also had mild dystonic symptoms in addition to myoclonus (torticollis and writer's cramp, re-

spectively). Blood was collected and DNA was extracted from 14 individuals, four of whom are definitely affected, two are probably, and one is possibly affected, as well as from seven unaffected family members. Genotypes were determined using simple sequence repeat polymorphisms (GTn-repeats) that span a 10 cM region on chromosome 9q34 containing the gene for early-onset generalised torsion dystonia (DYT1). The definitely affected family members did not share a common haplotype within this region, thus excluding linkage with this portion of chromosome 9. Alcohol responsive myoclonic dystonia with lightning jerks therefore is not caused by a mutation of the DYT1-gene in this family. Recently, we have identified an additional German family with myoclonic dystonia. Linkage studies will be extended to this family.

13
PATHOGENESIS OF OBSTRUCTIVE SLEEP APNEA SYNDROME; UPPER AIRWAY OBSTRUCTION AND DISORDERED CONTROL OF BREATHING. H. Boot, FGA Van Der Meché, RML Poublon, JM Bogaard, AZ Ginaï, PIM Schmitz, *Rotterdam, The Netherlands.*

Sixty patients, 53 men and 7 women, referred for excessive snoring or suspected sleep apnea syndrome were analysed by Polysomnography, Mueller Manoeuvre, Cephalometric Roentgenography and Pulmonary Function Testing, to evaluate the contribution of static and dynamic upper airway obstruction in the pathogenesis of sleep related breathing disorders and Obstructive Sleep Apnea Syndrome (OSAS). Desaturation index and Maximal desaturation were used in the analysis. Body Mass Index, increased collapsibility at the base of the tongue, increased distance between hyoid and manfibular plane, increased soft palate diameters and decreased peak inspiratory Flow, were found to be related to increased oxygen desaturation parameters. The significant obstruction parameters together could explain only 37% of the variability of maximum desaturation and 31% of the variability of desaturation index. Sixty to seventy percent of the variability in desaturation parameters may therefore be explained by multiple other mechanisms, including; oscillations within the central nervous system, deranged motoneuron activity of the upper airway and respiratory musculature, and changes in metabolic set-point increasing the loop-gain of the respiratory control system during sleep. related breathing disorders and OSAS.

14
PREVALENCE OF IDIOPATHIC FOCAL DYSTONIAS IN THE PROVINCE OF SEGOVIA; SPAIN. AP Sempere, J Duarte, F Coria, C Cabezas, LE Claveria. *Segovia, Spain*

We performed a study to investigate the prevalence of idiopathic focal dystonias in the province of Segovia with a population of 147,188 (1991 census). Segovia is a suitable place for epidemiological studies since all neurological care is provided by only one Neurology Section. Results: The crude prevalence rate for all focal dystonias was 279 per million persons (95%: 193- 364) on December 30, 1993. The prevalence rates were $163/10^6$ persons for cranial dystonia, $61/10^6$ persons for writer's cramp, $34/10^6$ persons for torticollis, and $20/10^6$ persons for spasmodic dysphonis. The sex ratio (M:F) was 1 :3 for cranial dystonia, 1: 2 for writer s cramp, 1 :4 for torticollis, 2:1 for spasmodic dysphonia, and 3:7 for all focal dystonias. The average age at onset was older for cranial dystonia and spasmodic dysphonia (58 years) than for writer's cramp (37 years) and torticollis (36 years). Conclusions: The prevalence rate for focal dystonias in Segovia is similar to the figures reported from Rochester, Minnesota. However, in our study cranial dystonia including essential blepharospasm and writer's cramp were the most common focal dystonias.

15
PARANEOPLASTIC OPSOCLONUS-MYOCLONUS SYNDROME - Two unsusual cases. J Scholz, N Nitschke, P Vieregge, B Wirk, FH Hochberg, *Lübeck, Germany & Boston, USA.*

Paraneoplastic opsoclonus-myoclonus syndrome (OMS) is a rare disorder. We present two patients. The first, a 45 year old woman, suffered from a metastatic solid, moderately differentiated ovarian carcinoma, hitherto not reported with OMS. Surgical resection, polychemotherapy and administration of benzodiazepines resulted in marked improvement. Patient 2, a 48 year old man, had small cell carcinoma of the lung. Serum and CSF reacted with a single band of relative molecular weight of 58-59 kD in immunoblots of extracts of Purkinje cells, human neuronal nuclei and a neuroblastoma cell line. OMS improved dramatically with Prosorba protein column after 5 treatment cycles. None of the patients had anti-Hu, anti-Ri or anti-Yo antibodies.

16
DOPAMINE D2-RECEPTORS AND REGIONAL CEREBRAL GLUCOSE METABOLISM IN WILSON'S DISEASE. G Schlaug, H Hefter, S Arnold, K Kessler, A Wirrwar, G Stocklin, RJ Seitz. *Düsseldorf, Jülich, Germany*

Wilson's disease (WD) is an autosomal-recessive disorder of copper metabolism affecting extracerebral and cerebral tissue. Regional cerebral glucose metabolism (rCMRGlc) and dopamine D2-receptors was measured with positron emission tomography in 15 WD-patients and related to their clinical presentation and structural abnormalities as evidenced by MRI. Improvement of neuropsychiatric dysfunction after therapeutic intervention was examined in repetitive scans. The rCMRGlc was measured with [^{18}F]-fluoro-2-D-deoxyglucose and the SCX PC4O96 PET camera according to the autoradiographic model. For measurements of the D2receptors the accumulation of the ligand [^{18}F]-fluoro-methyl-spiperone (FMSP) was recorded dynamically for 150 minutes and quantified by Patlak-graphical analysis in addition to striatal/cerebellar ratios. Neuropsychiatric impairment was scored semiquantitatively. None of the patients suffered from relevant hepatic malfunction at the time of PET scanning. The severity of neuropsychiatric impairment showed a high correlation with reduced rCMRGlc in the striatum, a week correlation with MRI abnormalities, but no correlation with striatal FMSP accumulation. The heterogeneity between striatal rCMRGlc and FMSP accumulation corresponds to the wide spectrum of clinical manifestation, underlying pathophysiology, and different stages in the recovery process. Increases of striatal rCMRGlc and even more of the striatal FMSP accumulation were associated with neurological improvement due to therapy.

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HEREDITARY ESSENTIAL TREMOR: CLINICAL AND LINKAGE ANALYSIS STUDY OF A LARGE FRENCH PEDIGREE. V Planté-Bordeneuve, A Joutel, P Labauge, E Tournier-Lasserves. *Paris, France.*

Essential tremor is the most common movement disorder. It is inherited as an autosomal dominant disorder of unknown pathogenesis in about half of the cases. We have performed a clinical study and linkage analysis of a large French caucasian pedigree, which includes 3 living generations. Forty three individuals have been studied by the same clinician. Eleven subjects (3 males and 8 females) suffer from a permanent bilateral postural tremor of the upper limbs and/or head tremor, occasionally associated with voice tremor. Mean age at onset is 51 (range 19-78 years old). Neurological examination performed in 6 affected members and in 32 clinically unaffected subjects was unremarkable, except for the tremor. In particular no dystonic posture or extrapyramidal syndrome were observed.The transmission of the disease is most likely autosomal dominant. All affected members were the offsprings of an affected parent. Penetrance is age dependent and complete above 70 years of age. Linkage analysis is currently conducted with a candidate gene approach, using Genethon microsatellites highly polymorphic markers. Two methods of analysis are used to examine the data for possible linkages including the analysis of affected members only, as well as standard lod score analysis on all subjects using various liability classes. Linkage data will be presented at the meeting.

18
PREVALENCE OF EXTRAPYRAMIDAL DISORDERS IN SANITARY AREA 2 (MADRID, SPAIN). A Luengo, J Parra, J Colas, M J Fernandez. *Madrid, Spain*

We made a two-phase epidemiological survey in a community of 119,236 inhabitants, located in the area Northeast of Madrid and including of four villages (Coslada, San Fernando de Henares, Mejorada del Campo and Velilla de San Antonio). They form a closed sanitary area completely controlled by the Public Health System. We know the age distribution of the population (National Statistic Institute, 1993). The survey was carried out during two years Prevalence day was established on July 1, 1993. We excluded people younger than 12 years (19,6%). First-phase was carried out by 55 Primary Care physicians and during 103 consecutive weeks, 1,375 patients week were screened. We used the WHO protocol (1982), and obtained a 99% sensitivity. Specificity was studied in 93 healthy relatives of the patients and was 92,7%. Second phase was performed by three neurol-

ogists in the 1.77O positive cases with stringent diagnostic criteria. We found 3O cases of Parkinson's Disease, S3 of Secondary Parkinsonism, 16 of Essential Tremor and 4 with other extrapyramidal disorders . Crude prevalence ratio was $10^7/10^5$. Age and gender prevalence ratios are also provided.

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HALLERVORDEN-SPATZ ASSOCIATED WITH GRAVES' DISEASE. FAMILY STUDY OF CYP2D6. A Luengo, J Garcia Agundez, J Parra, J Colas, E Ruiz, J Benitez. *Madrid & Badajoz. Spain.*

A 28 year old female first daughter of non consanguineous parents, was studied for a disorder lasting since 12 years and consisting of progressive dysarthric speech, orofacial dyskinesias, progressive cerebellar ataxia and minimal pyramidal signs. No mental deterioration was present. Diffuse enlargement of the thyroid gland was found. No haematological nor biochemical abnormalities were found, including copper, iron and transaminases. There was an increase of T3 plasma levels (212 ng/dl) with low TSH levels (0.15 μu/ml). MRI showed a marked bilateral pallidal hypointensity peripheral and central hyperintensity in T2WI, the characteristic "eye of the tiger sign" of Hallervorden-Spatz disease. Diagnosis of Graves-Basedow disease was made based on endocrinologic and gammagraphic studies. In patients with Parkinson's Disease, it has been demonstrated larger frequency of the wt/CYP2D6B genotype, related to alterations in debrisoquine metabolism has been reported. We present a new case of this rare disorder presenting in association with Graves-Basedow disease, a feature previously described; a family study of CYP2D6 showed no mutation for this allele in the four members of the family.

20
IN VITRO AND IN VIVO MODULATION OF CCK-8 ON D2 RECEPTORS IN RAT BRAIN. XM Li, PB Hedlund, K Fuxe. *Stockholm, Sweden.*

Quantitative receptor autoradiographical experiments were performed to investigate the in vitro and in vivo effects of cholecystokinin octapeptide (CCK-8) on D_2 receptors in rat brain. In vitro studies showed that 1 nM CCK8 significantly increased the KD values of the D_2 agonist [3H]N-propylnorapomorphine (NPA) binding sites within the rostral part of the caudate-putamen (CPu) and the caudal part of the nucleus accumbens (Acb) by 64% and 148%, respectively. CCK8 at 1 nM significantly decreased the IC50 values of DA for the D2 antagonist [125I]iodosulpride binding sites within the rostral (by 46% and 57%, respectively) and the caudal (by 56% and 75%, respectively) parts of the CPu and Acb. 30 min after an intracerebroventricular injection of 1 nmol/rat CCK8, the K_D value of [^{3}H]NPA binding sites within the caudal part of the forebrain, and the IC_{50} value of DA for the [^{125}I]iodosulpride binding sites within the caudal part of the Acb were significantly increased by 160% and decreased by 77%, respectively. These results demonstrate that CCK8 regulates the D_2 receptors more potently in the caudal parts of the CPu and Acb where CCK co-exists with DA in the DA neurons, providing strong evidence supporting our hypothesis of CCK/D_2 receptor interactions in the brain.

21
A THERAPEUTIC TRIAL OF FLUMAZENIL IN HEMIBALLISMUS. J Kulisevsky, A Avila, ML Berthier. *Barcelona . Spain.*

Gabaergic action in CNS can be modulated by drugs acting on specific recognition sites that allosterically modulate GABA-A receptors and by endogenous substances which binds to the benzodiazepine/beta-carboline recognition sites. Alterations of GABA/benzodiazepine receptor complexes were detected in Huntington's disease patients, notably, chorea shares common mechanisms with hemiballismus. Amelioration of chorea with antagonists of the benzodiazepine ligands of the GABA/benzodiazepine receptor complex was not tested. After informed consent, three patients with vascular hemiballismus agreed to receive flumazenil (lmg intravenous) or placebo in a double-bind, randomized, crossed study. Ballismus was rated with a five degree scale at base-line, 5, lO, 20, 30, and 60' after placebo or flumazenil. No significant clinical changes were seen in the three patients with either flumazenilor placebo. Two patients were unable to distinguish between them, and the other(case 2)complained of a mild feeling of anxiety after flumazenil, a known occasional effect of the drug, which may has been provoked the mild deterioration observed. Although abnormalities of gabaergic transmission were implicated, the ineffectiveness of flumazenil at the dose used suggests that interactions at the level of GABA/benzodiazepine receptor complex are not an important factor in the pathogenesis of chorea/ballismus.

22
LONG TERM FOLLOW-UP OF PREFRONTAL LEUCOTOMY IN TOURETTE'S DISORDER. J Kulisevsky, ML Berthier, A Avila. *Barcelona. Spain.*

The usefulness of neurosurgery for the treatment of severe Tourette's disorder(TD) has been recently emphasized. Due to the difficulty in performing prospective studies, updated evaluations of single cases can help to estimate its therapeutic role. A 69 year-old man with a severe TD underwent a bilateral prefrontal leucotomy at age 29 to alleviate coprolalia, copropraxia and obsessive-compulsive disorder (OCD). No improvement was observed during the following five years. Simple and complex tics and associated behavioural abnormalities gradually disappeared thereafter without medical treatment. However, they recurred at age 67. At age 69, CT scan showed bilateral low-density areas involving the anterior-inferior centrum semiovale (similar to that of recently published cases of bilateral anterior stereotactic cingulotomy in TD); SPECT showed lack of perfusion on the anterior centrum semiovale bilaterally as well as marked hypoperfusion in the surrounding mesial and dorsolateral frontal regions; and neuropsychological examination showed a severe and selective impairment on tests susceptible to frontal lobe dysfunction. TD patients candidate to neurosurgery should be fully informed about the risks of postoperative frontal functional and cognitive deficits which, as in the present case, can persist as long as 40 years after surgery.

23
HEMIBALLISM, HEMICHOREA AFTER HEMORRAGIC STRIATO-CAPSULAR INFARCTION. J-M Gerard, J Cambier, C Caucheteur, L Divano, *Mons, Belgium*

The clinical and neuroradiological features of a patient With haemorrhagic striato-capsular infarct and contralateral hemiballism-hemichorea is described and shown on videotape. A 92 years old diabetic woman presented with an acute movement disorder involving the right upper and lower limbs. Cerebral computed tomography and nuclear magnetic resonance showed a large recent haemorrhagic infarct in the left lenticubstriate arterial territory. Echodoppler study of the heart and carotid arteries were normal. The patient made a nearly complete recovery in a few weeks. The most common clinical presentation of striato-capsular infarction is a motor stroke affecting mainly the upper limb. Abnormal movements during the acute phase of the infarction are rarely described; to our knowledge hemiballism, hemichorea was observed only in one patient. In this case the haemorragic component of the lesion was also striking.

24
PSYCHOGENIC TREMORS: DIAGNOSIS AND OUTCOME. G Deuschl, B Köster, C Scheidt, CH Lücking, *Freiburg, Germany.*

Compared to the early years of our century, psychogenic tremor became a rare disease. 19 cases were collected from the files of our movement disorder unit and followed for a mean period of 44 months. (range 4-118). A small porportion of these patients (4/19) had stance tremors of varying intensity almost never being subject to diagnostic difficulties. The major diagnostic problems was found in the legs and upper extremity tremors. On examination, among other criteria varying tremor frequencies were seen clinically and electropyographically during distraction. All the patients exhibited a co-contraction of the muscles that could be perceived by the examiner during passive movements of the shaking extremity confirmed by polymyographic recordings. We consider this to be the most important clinicla test separating psychogenic tremors from all other tremors. Most of the patienst retired due to their tremors but tremor persisted even after retirement. A favourable outcome was only seen in a few young patients treated with psychotherapy. We conclude that psychogenic tremors can be diagnosed by means of clinical test only and that the clinical course is nowadays mostly unfavourable.

25
EFFECTIVENESS OF FLUOXETINE IN FAMILIAL KINESIGENIC CHOREODYSTONIA: A DOUBLE BLIND, PLACEBO CONTROLLED, REPRODUCED STUDY. D Mateo, JL Dobato, MA Mena, S Gimenez-Roldan. *Madrid, Spain.*

We report a 21-year-old man and his mother who since adolescence had experienced daily episodes of choreodystonic posturing of the limbs.

Many of the episodes could be witnessed, EEG recorded and videotaped in the younger patient. They were usually triggered by sudden, brisk, volitional movements, often heralded by a feeling of muscular tension and paresthesiae in one foot, ending either in an abortive episode (AE) or in an attack of PKC prolonged for 15-20 seconds. Numerous investigations, including repeated EEG recordings, calcium, phosphorus and PTH serum levels, CSF analysis and MRI were all normal. Fluoxetine, a potent, highly selective inhibitor of 5HT uptake, and placebo were given to the younger patient each over a three-week period. The number of PKC episodes during fluoxetine administration decreased from 6.12 ± 1.18 to 0.1 ± 0.1 while the AE decreased from 2.85 ± 0.50 per day to none ($P < 0.001$, t test for paired samples). There were no changes in Reisberg Anxiety Scale though the Beck Depression Inventory score dropped from 22 to 5 while under fluoxetine. 5HIIA CSF concentration were decreased at baseline and further dropped to 7 ng/ml while under the active drug. The clinical improvement under fluoxetine was maintained during a long-term open-label phase. Six months later, a further change to placebo was followed by a significant, prompt relapse both in the daily number of PKC and AE . We conclude that basal CSF 5-HIIA levels are decreased in familial kinesigenic choreodystonia. As happens in depressed patients, fluoxetine further decreases 5-HIIA levels in CSF while bringing about a dramatic reduction in the number of both choreodystonic and abortive episodes. This suggest that abnormalities in 5HT pathways are presynaptically involved in familial kinesigenic choreodystonia.

26
PAROXYSMAL DYSTONIA CAUSED BY AN INTERNAL CAPSULE INFARCTION. F Chedru, P Oubary; P Rondot, *Meaux & Paris, France.*

Three weeks after a stroke - resulting in a mild right-sided hemiparesis - a 42 y.o. woman developed tonic spasms on the paretic side. These consisted of brief (1 - 3 minutes), painful, and tight contracture of distal musculature of the right limbs leading to a stereotyped posture: wrist extended, fingers flexed, thumb strongly opposed and (when the lower limb was involved) foot in adduction and hyperextension. Often preceded by homolateral paresthesiae, the spasms recurred from 5 to 40 times a day, occasionnally elicited by voluntary movements, stress or hyperventilation. EEG performed during and between the attacks remained normal. After 6 weeks , the tonic spasms spontaneously resolved . MRI scan showed a discrete lacunar infarct in the posterior limb of the left internal capsule. With the exception of a paper by Merchuut and Brumcick (Stroke, 17, 1986,1319-21), similar paroxysmal dystonic movements, well known in multiple sclerosis, had not been reported up to now in stroke. The authors discuss the pathophysiology of the phenomenon and its apparent rarity in cerebral infarctions.

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HEMIBALLISMUS INITIATED BY LEVO-DOPA TREATMENT IN A PATIENT WITH PARKINSON'S DISEASE AND SPASTIC HEMIPARESIS. CN Anagnostou, CP Panagopoulos, DE Ziogas. *Volos, Greece.*

We present the case of a 67 year old man with an onset of Parkinson's disease lasting since 15 years. During the last 10 years, he has been on Levodopa treatment which recently has produced the "on-off" phenomenon. Four years ago, an haemorrhage in the left subcortical region left him resulted in a right-sided spastic hemiparesis. Computerized Tomography and Magnetic Resonance Tomography demonstrated a medium sized lesion occupying mainly the left posterior thalamic and subthalamic regions, partially affecting the posterior limb of the ipsilateral internal capsule and the globus pallidus. During the course of his recovery from the haemorrhage, he developed involuntary movements of hemiballismus type on the hemiparetic side of his body. Involuntary movements fluctuated and increased in intensity during the "on" period of the L-Dopa effect and their complete disappearance during the "off" period. The damage to the subthalamic nuclear connections caused by the hemorrhagic lesions the primary aetiological mechanism of the hemiballismus. This effect of L-Dopa on the damaged pallido-subthalamic-pallidal neuronal system, could contribute to a better understanding of the anatomical and pathophysiological dopaminergic pathways in the basal ganglia region.

28
CORTICAL MAPPING OF NEUROFIBRILLARY DEGENERATION IN PROGRESSIVE SUPRANUCLEAR PALSY EVIDENCE FOR A STRONG INVOLVEMENT. P Vermersch, Y Robitaille, D Gauvreau, A Destée, H Petit, A.Delacourte. *Lille, France.*

A study was performed to quantify and map the neurodegenerating process in cortical and subcortical brain areas from 3 cases of progressive supranuclear palsy (PSP). Our approach was based on a western blot analysis of pathological Tau proteins, which are the basic components of neurofibrillary lesions. We found that: (i) the abnormal Tau proteins can be detected in all cortical areas, sometimes in larger amounts than in some subcortical areas, except in one case where some posterior cortical areas were spared; (ii) these abnormal Tau proteins consist of a doublet called Tau 64 and 69, except for the entorhinal cortex where we detected, as for Alzheimer brains, the triplet of Tau proteins called Tau 55, 64 and 69; (iii) the amounts of abnormal Tau proteins were higher in some neocortical regions, especially in the frontal lobe, as compared with the hippocampal formation. Our results show that the neocortical pathology in PSP, as revealed by the presence of pathological proteins, is more extensive than previously thought so far. Our biochemical approach clearly differentiates between two types of neurofibrillary pathology, the Alzheimer type with a triplet of abnormal Tau proteins and the PSP type with a characteristic doublet.

29
EFFECTS OF ANIRACETAM ON CLINICAL PATTERN AND CEREBRAL BLOOD FLOW OF OLD PATIENTS WITH DEGENERATIVE DEMENTIA (SDAT). M Rizzo, U Ficola, P Marozzi, F Piccoli, *Palermo, Italy*

Aniracetam (1-anysoyl-2-pyrrolidinone) a new molecule which shows an ability to increase the long-term potentiation of synaptic transmission in animal hippocampus, causes a dose dependent reduction of calcium uptake and a significant increase of cerebral blood flow, has demonstrated clear cognitive - enhancing activity in behavioural animal models and in human clinical studies. Furthermore, the clinical efficacy of the molecule has been demonstrated on elderly patients with senile dementia of the Alzheimer's type as well as on patients with senile cognitive decline. Aniracetam effect on patients showing mild to moderate degenerative dementia and on functional end metabolic activity (SPET), was investigated. The treatment was carried out with 1500 mg/die of aniracetam or placebo. Cross-over began at the end of the second month of treatment. Full treatment period ended at the fourth month. Clinical, neuropsychological and SPET evaluation was carried out at baseline at the second month and at the end of treatment. Results are in accordance with previous clinical observations.

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LEUKOARAIOSIS IN THE SENILE DEMENTIA OF ALZHEIMER'S TYPE (SDAT). M Janelidze, R Shakarishvili, T Gagoshidze, T Vashadze, A Tsiskaridze. *Tbilisi, Georgia*

Brain white matter damage, visualised as leukoaraiosis on CT and as white matter hyper intensity (WMH) on MRI can be seen in vascular dementia, SDAT, and elderly healthy volunteers. In patients with SDAT its presence corresponds from 19% to 35% according to different authors. 44 patients with probable SDAT were included in our study. Diagnosis of SDAT was affirmed by NINCDS-ADRDA criteria. 13 of them (29%) had WHM on MRI. Patients mental state was evaluated by MMSE, the Blessed dementia scale and a neuropsychological test battery. Our analyses revealed that: 1) duration of illness at the moment of investigation was longer in patients with WHM than without; 2) severity of dementia evaluated by these scales was greeter in patients with WMH than in patients without; and 3) this difference was demonstrated especially by decline of attention, concentration, abstract thinking and conceptual reasoning in this subgroup of patients. The patients looked apathetic, uninitiative, while differences in respect to verbal ability comprehension and visuospatial skills between these two groups were minimal. According to our data we can consider that in patients with SDAT clinical signs of white matter damage appears in the advanced stage of disease. White matter damage worsens cognitive capabilities of the brain and reveals frontal lobe dysfunction symptoms, indicating the spread of pathology in cortico-subcortical pathways.

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EARLY CLINICAL MANIFESTATIONS OF SUBCORTICAL ARTERIOSCLEROTIC DEMENTIA (SAD). R Shakarishvili, A Tsiskaridze, M Djannelidze, T Gagoshidze, T Vashadze, *Tbilisi, Georgia.*

Vascular dementia has two clinical varieties: cortical atherosclerotic dementia and subcortical arteriosclerotic dementia which itself includes two

clinical entities; status lacunaris and Binswanger's subcortical arteriosclerotic encephalopathy (BSAREV). We observed 48 patients with SAD. The patients were selected according to the Hachinski ischaemic scale and diagnostic criteria for vascular dementia. Relatively the patient were divided in three groups; 1) pure status lacunaris (15 patients, where MRI revealed only multiple lacunes); 2) pure BSARFN (12 patients where MRI showed only periventricular white matter hyperintensity (WMH), and 3) a mixed group (21 patients where lacunes and WHM coexist).Presence of dementia and its severity were determined by MMSE and the Blessed dementia rating scale. Comparison of clinical and anamnestic data revealed that in the first group clinical manifestations of lacunar syndromes preceded decline of cognitive capabilities in 11 patients, while in other 4 mnesic disability was the first symptom of the disease onset. In the second group in 11 cases mnesic disturbances were one of the first disease manifestations. In 17 patients of the third group changes in cognitive sphere were preceded by clinical manifestation of lacunar syndromes. In 39,6%, development of SAD was not preceded by lacunar syndromes. It seems to be explicable in the cases of BSAREN caused by diffuse white matter damage (leukoencephalopathy). In the cases of lacunar infarcts development of dementia might be caused both by the quantity of lacunes and their localization.

32
COMPARATIVE STUDY OF THE APROSODIA IN ALZHEIMER'S DISEASE AND MULTI-INFARCT DEMENTIA. JM Perez Trullen, PJ Modrego Pardo, C Iniguez, ML Vazquez-Andre. *Zaragoza, Spain*

Prosody has been regarded as the third element of language. Aprosody is related to lesions of right hemisphere in cerebrovascular diseases, Alzheimer s disease, Parkinson s disease and depression. The purpose of this study is to evaluate comparatively the existence of aprosody in Alzheimer's disease and in multi-infarct dementia. Fifteen patients with Alzheimer s disease and 14 with multi-infarct dementia were included in a prospective study. All were evaluated from a neuropsychological viewpoint using the: MiniMental, Blessed Scale, Clinical Dementia Rating and Ischemic Scale. Aprosodia was evaluated according the criteria of Monrad-Krohn. The average age of patients with Alzheimer s disease was 67 (range:55-80) years and 69 (range:50-83) years for patients with multi-infarct dementia. Intrinsic aprosody was observed in 11 (73%) of Alzheimer subjects in comparison with none of patients with multi-infarct dementia (X^2, $P<0.001$). Emotional aprosodia was observed in 11 patients with Alzheimer s disease and in 2 of multi-infarct dementias (X^2, $P<0.01$). Intellectual aprosody was observed in 13 patients in both groups. Inarticulated aprosody was found in 14 (93%) of Alzheimer patients in comparison with 10 (71%) of patients with multi-infarct dementia. We conclude that aprosody is more frequent and severe in Alzheimer's disease than in multi-infarct dementia.

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MEDIAL TEMPORAL LOBE ATROPHY MEASURED BY CT IN EARLY STAGE OF ALZHEIMER'S DISEASE. F Pasquier, L Bail; L Naccache, F Lebert, JL Gauvrit, JP Pruvo, H Petit, *Lille, France*

Medial temporal lobe (MTL) atrophy determined by temporal-lobe oriented computed tomography (CT) 1 year before death is strongly associated with Alzheimer's disease (AD) diagnosed histopathologically. The aim of this study was to find out if MTL atrophy could be detected in patient at early stage of AD and if this atrophy was specific of AD. CT procedure described by Jobst et al (1992) was performed in 91 subjects aged 48-71 consecutively recruited in a Memory Disorders Unit: 19 probable AD, 15 possible AD (NINCDS-ADRDA), 37 patients with miscellaneous memory disorders, 7 anxious/depressed (DSMIII-R) with normal performance on memory tests, and 13 controls. There was no overlap between distribution of the measurements in probable AD (6 of them having a Mini Mental Scale score > 24) and anxious/depressed and controls who did not differ from each other. The cut-off was 11 mm. Measurement distribution was bimodal in possible AD and miscellaneous memory disorders. MTL atrophy was observed in some but not all Lewy's body diseases, alcoholic Korsakoff syndromes, frontal lobe type dementias with global temporal lobe atrophy. This study confirms the presence of MTL atrophy measured by temporal-oriented CT in early probable AD.

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RISK FACTORS AND CLINICAL FEATURES OF VASCULAR DEMENTIA. V Parlato, S Carlomagno, M Panisset, A Santoro, A Lavarone A, F Boller, V Bonavita. *Naples, Italy.*

In order to determine the risk factors and clinical features of vascular dementia (VaD) (Roman et al.,1983) we studied 1 59 patients hospitalized at the Institute of Neurological Sciences of Naples suffering from cerebrovascular disease (CVD). 102 patients met criteria for VaD, where 57 resulted as CVD non demented patients. We evaluated informations from medical history, ECG, biochemical examinations and vascular risk factors (hypertension, cardiac diseases, diabetes, hypercholesterolemia and smoke abuse). Age, sex, educational level and time after onset of the disease did not differentiate the two groups. A chi-square comparison did not show significative differences between demented and non demented patients for all risk factors. Clinical evaluation was based on the occurrence of neurological signs (classified as prefrontal, subcortical, parietal and diffuse, according to Wallin et al., 1991) The occurrence of prefrontal, subcortical, extrapiramidal signs and Epstein reflex was significantly higher in VaD patients. These last findings suggest that involvement of prefrontal and subcortical structures is related to the clinical expression of dementia in CVD. Furthermore our data support the hypothesis that standard evaluation of risk factors is not suitable to identify specific risk factors for vascular dementia.

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CLINICAL DETERMINANTS OF DEMENTIA IN STROKE PATIENTS. A Padovani, V Di Piero, M Giannini, E. Zanette, S Di Cesare, M Altieri, GL Lenzi. *Roma, Italy*

The risk factors for dementia after stroke are incompletely understood. We investigated the clinical features associated with dementia in a sample of stroke patients. A consecutive series of 178 stroke patients were studied. A comprehensive clinical and laboratory evaluation, including neck vessel ultrasound, CT scan and/or MRI study, and a comprehensive neuropsychological battery, was performed. Diagnosis of dementia was carried out according to DSM-III-R criteria and requiring impairment of memory and of at least other two cogntive domains. Fifty-three subjects (30%) fulfilled the criteria for dementia. By a univariate regression model, dementia was significantly associated with age, history of prior strokes, number of stroke events and carotid pathology. Extrapyramidal signs, motor impersistence, and personality changes were significantly related with dementia. Stroke features associated with dementia included multi-infarct or multi-lacunar state, subcortical atrophy, and leukoaraiosis severity. Stepwise regression analysis demonstrated that carotid pathology, subcortical atrophy, number of lacunae, number of infarct, and leukoaraiosis were independently related with dementia. Conclusions. Our results suggest that dementia in stroke patients is a multi-factorial disease depending on site and number of stroke lesions with additional contribution of carotid pathology, leukoaraiosis and subcortical atrophy.

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CSF AND SERUM METABOLIC PROFILE OF PATIENTS WITH HUNTINGTON'S CHOREA: A STUDY BY HIGH RESOLUTION PROTON NMR SPECTROSCOPY AND HPLC. F Nicoli, J Vion-Dury, JM Maloteaux, C Delwaide, S Confort-Gouny, M Sciaky, PJ Cozzone. *Marseille, France. Bruxelles, Belgium.*

We studied both CSF and serum of 11 patients suffering from Huntington's disease (HD) and 12 control subjects by combining high resolution proton NMR spectroscopy and HPLC. NMR spectroscopy analysis of the CSF shows a significant increase (6O%) in pyruvate concentration in HD patients. No unexpected molecules were detected. Glutamate, glutamine, aspartate, proline and GABA levels were found unchanged in the CSF of HD patients, using HPLC analysis. Conversely, a significant increase (30%) in the CSF level of glycine was detected. These observations are in agreement with the metabolic hypothesis of HD pathophysiology. In addition, the protocol combining NMR spectroscopy and HPLC provides a straightforward evaluation of brain metabolic status and blood-brain-barrier function.

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RESYMPTOMATIC COGNITIVE CHANGE IN A INDIVIDUAL WITH FAMILIAL ALZHEIMER'S DISEASE: A NEUROPSYCHOLOGICAL AND PET STUDY. SK Newman, AM Kennedy, RSJ Frackowiack, EK Warrington, MN Rossor. *London, UK*

In order to determine the earliest clinical features of autosomal dominant Familial Alzheimer's disease (FAD) we have studied an at risk individual

from a histopathologically confirmed early onset pedigree. This presymptomatic individual was studied over a two year period on three occasions. On each occasion the Mini Mental State Examination (MMSE) was recorded and a comprehensive neuropsychological assessment was made. In addition at the time of the third assessment Positron emission tomography (PET) was performed, using 18 Fluorodeoxyglucose in order to calculate cerebral glucose metabolism. This case sought medical attention for memory difficulties 26 months after the first assessment. At the time of the third assessment she was still able to score 29 out of 30 on the MMSE. The first neuropsychological assessment revealed a moderately selective verbal memory deficit in the context of mild generalised intellectual impairment. Subsequently a progressive deterioration of visual memory and a relatively mild decline of perceptual and spatial skills was observed. Language and literacy skills however remained comparatively intact. The PET scan showed a global reduction in cerebral glucose metabolism which was most prominent in the parieto temporal cortex bilaterally. Conclusion: This study describes the presymptomatic and metabolic features of an individual who subsequently developed FAD.

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CASE-CONTROL STUDY OF SERUM ALUMINIUM IN LATE ONSET PROBABLE ALZHEIMER'S DISEASE. Pablo Martinez-Lage, J. Manuel Martinez Lage, JosÇ M. Manubens,Francisco Lacruz, Rosa Larumbe, Javier Muruzabal. *Pamplona, Spain.*

Backround: The possibility of a causal link between Al and Azheimer's disease (AD) must be kep open in spite of the ambiguity surrounding this question (S.L. Rifat, 1994) Among the possibilitie of studying the relations ship between AI and AD (exosure in driking water, presence in neuritic plaque cores, concentration en CSF, test of deferoxamine, etc.) serum Al levels -which reflect environmental individual exposure- could fit very well for a case-control study, a measure of association seldom designed before. Methods: We selected 47 AD patients and 47 controls matched by age, race, sex and residency. All of them were subjects of a representative sample of Pamplona's population older than 70 involved in an epidemiological study on prevalence and incidence of dementing brain disease in old age. The diagnosis of AD was first assessed by CAMDEX instrument criteria and afterwards evaluated neurologically ful filling the NINCDS-ADRDA criteria for AD. Graphite-furnace atomic absorption spectrophotometria was used to determine serum Al levels in patients and controls. Calcium and iron status were also studied. Results: No significant differences were observed between AD patients and controls for serum Al levels (mean 4.02 ± 1.22 ng/nl and 3.88 ± 1.56 respectively) or for the other studied parameters. Serum Al values were similar to those previously reported. Conclusions: Serum Al level is neither a risk factor for AD nor a help to address the environmental Al questions or to solve the uncertainty about its neuropathological evidence Study supported by Fundacion Ramon Areces, Madrid.

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EEG COHERENCE IN ALZHEIMER'S DISEASE (AD). T Locatelli, M Cursi, M Mauri, D Liberati, G Comi, C Fornada, N Canal. *Milan, Italy*

Cognitive dysfunction in Alzheimer's disease (AD) has been supposed to be the result not only of neuronal death but also of the lose of afferent and efferent cortical connections (Morrison 1986). EEG coherence looks at the synchronisation of different cortical regions and gives information about functional connections among cortical areas. We studied EEG coherence (C), using an AR model, in order to evaluate changes of brain connectivity in 10 probable AD patients (NINCDS-ADRDA criteria). We found a significant alpha C decrease in 6 patients, more evident between nearest electrodes and a significant delta C increase in 2 of these 6 patients between frontal and posterior electrodes. The AD group showed a significant decrease of alpha band C, particularly in temporo-parietal areas, more marked in patients with severe different pathophysiological changes: the alpha C decrease could be due to cortico-cortical connections, while the delta C increase could be related to the influence of subcortical cholinergic structures on cortical electrical activity.

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CSF COPPER IN ALZHEIMER'S DISEASE. LM Iriarte, M Lopez, A Grilo, D Jimenez, M Repeto, *Sevilla, Spain.*

Relatively little information is available on concentrations of metals in CSF of patients with dementia. The purpose of this paper is to present our results for the CSF concentration of the metals Cu, Zn, Al, Ca, Mg, Mn and Cd in patients suffering From Alzheimer's Disease, compared with other dementing disorders and controls. CSF samples were taken from healthy controls and 42 demented patients: 28 AD 10 Vascular dementia and 4 Parkinson's disease. The CSF concentration of metals were measured using atomic absorption spectrophotometry. The results obtained were as follows: Cu was significantly lower in AD patients than in controls. There were no relationships of CSF metals to age or degree of cognitive impairment. Our findings are consistent with Plantin's findings of low values for Cu concentration in brains from AD patients. The significance of low CSF Cu in AD is not clear.

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A MOVEMENT ASSESSMENT BATTERY DIFFERENTIATES AUTISM FROM CATATONIA WITH MUTISM, JR Brasic, JY Barnett, BB Sheitman, JG Young, *New York City, USA.*

Utilising a Movement Assessment Battery (Barnet et al. (in press) Int J Neurosci), a neurologist (JRB) rated in vivo 2 unmedicated male subjects, a 6-year-old with autistic disorder (A) and an 8-year-old with schizophrenia, catatonic type (C) (Diagnostic and statistical manual of mental disorders, third edition, revised. American Psychiatric Association, Washington, D.C. 1987).A was rated once; C was rated 6 times approximately monthly. On the objective subscale of the Hillside Akathisia Scale (Fleischhacker et al. (1989) Psychopharmacol Bull 25:222-226), the mean scores were A, 19, and C, 7 ± 4. On the Timed Stereotypes Rating Scale (Campbell M (1985) Psychopharmacol Bull 21:1082), the mean scores were A, 101, and C, 60±32.The mean scores on the Clinical Global Impression Scale for Attention Deficit Disorder were A, 2, and C, 0.8 ± 0.45, and on the Clinical Global Impression Scale for Obsessive Compulsive Disorder were A, 3, and C, 1.6±1.95 (Leckman JF et al. (1988) Clinical assessment of tic disorder severity. In: Cohen DJ et al. (eds) Tourette's Syndrome and tic disorders. John Wiley & Sons, New York, pp 55-78).The marked differences in scores between A and C indicate that the systematic assessment of movement disorders assists in the difficult differential diagnosis of severe neuropsychiatric disorders.

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CHANGES IN T-LYMPHOCYTE SUBSETS AND LYMPHOKINE SECRETION IN ALZHEIMER'S DISEASE: CORRELATION WITH DISEASE STAGE. M Huberman, F Shalit, C Brodie, E Kott, B Sredni. *Kfar-Saba and Ramat Gan, Israel*

In the present study we investigated changes in T-lymphocyte function and T cell subsets in Alzheimer's Disease (AD), as correlated with severity of the dementia. Mononuclear cells (MNC) were obtained from AD patients divided into mild and moderately-severe groups and from age-matched controls. T-lymphocyte markers (CD4, CD8, HLA-DR) were determined using flow cytometry quantitative analysis. Lymphokine secretion (IL-2, IL-6, IFN) was assessed using ELISA kits. In the mild stage of the disease we observed a slight increase in the HLA-DR+ marker, but no changes in the CD4 and CD8 subsets. In contrast, a significant increase in IL-6 production from PHA-stimulated MNC from mild AD patients was observed as compared to controls. In the moderately-severe stage we observed a significant increase in the HLA-DR+ and CD4+ markers, a slight decrease in the CD8+, as well as elevated mitogen-induced levels of IL-2, γIFN and IL-6 secretion. Marked changes in immunological parameters in the moderately-severe group support the hypothesis of a peripheral immune reaction in AD which may be correlated with the clinical stage of the disease.

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CONSCIOUS AND UNCONSCIOUS PERCEPTION OF SOUNDS IN A PATIENT WITH CORTICAL DEAFNESS A PET STUDY. A Engelien *(Aachen,Germany; London,UK),* D Silbersweig *(London UK; New York, USA),* E Stern *(London,UK; New York, USA);* W Huber *(Aachen;Germany)* C Frith *(London,UK),* R Frackowiak *(London,UK)*

SB, a by now 24-year-old patient, suffered from two consecutive strokes in 1990 and 1991. Both strokes occurred in the territory of the middle cerebral artery with large perisylvian lesions on both sides, completely destroying the primary auditory cortex of either hemisphere. Behaviourally, he was able to detect the onset and the end of sounds only when selectively paying attention to auditory stimuli. We used $H_2{}^{15}O$ Positron Emission Tomography to demonstrate the brain correlates of the conscious perception

of the presence of sounds when he was attentive, as opposed to non- attentive acoustic stimulation. The latter condition , compared with rest, shows only a minor cortical activation in the superior right parietal cortex. Comparison of the activations in the attentive and the non-attentive state demonstrated bilaterally massive prefrontal superior, parietal and middle temporal activations around the lesions. Our preliminary conclusion is that residual hearing in cortical deafness is possible only by bilateral activation of attentional networks.

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NATRIURETIC PEPTIDES IN DEMENTIA. F Miralles, MD Albadalejo, M Antem, I Pastor, R Martin, J Matias-Guiu. *Alicante, Spain*

Natriuretic peptides are a family composed of three homologue polypeptidic hormones called Atrial Natriuretic Peptide (ANP), Brain Natriuretic Peptide (BNP) and Type-C Natriurctic Peptide (CNP). These peptides have been widely described in the CNS, with a unique and different distribution in every case. This fact, along with their role as neurotransmitters of other hormones, may consider them as biologic markers in those diseases of the CNS with hormonal changes, such as Alzheimer's disease. We have determined the plasma levels of ANP and BNP in a control group of 72 subjects, 37 men and 35 women, with a mean of 69,7 years of age (S.D. 8,4; range 48-92 years), and a group of 37 patients, 13 men and 24 women, with a mean of 69,3 years of age (S.D. 9,6; range 51-87 years). 28 of these patients had dementia (15 degenerative dementia and 13 non-degenerative dementia) and 8 suffered from Parkinson's disease. ANP and BNP were determined by a competitive radioimnmunoassay (RIA) with double antibody. The plasma levels of ANP and BNP were significantly correlated both in the control group and in the patients' group (r=0,51483 and r=0,59131, respectively). We found a significant decrease of BNP in the total group of patients, as well as in every subgroup. The differences found for plasmatic BNP indicate that this peptide may act as an non specific marker neuronal damage, altering its levels in all the processes which involve both damage and degeneration different cerebral areas.

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EVALUATION OF THYROID FUNCTION IN AGING AND RELATION WITH DEMENTIA. F Miralles, M Antem, I Pastor, MA Estelles, R Martin, J Matias Guiu. *Alicante; Spain*

Different studies have suggested that a relation between thyroid function and dementia may exist. However no conclusive data appears in the literature. We have studied the thyroid function in a group of 105 subjects older than sixty years who were living in a geriatric home and we have only excluded ! the persons who have an endocrine disease. We have evaluated, the thyroid stimulating hormone levels (TSH), the free fraction of thyroid hormones and the Sex-hormone binding globulin (SHBG), at the beginning of the study and at the end of a two-years follow up study. Mini-Mental State Examination (<23) and Blessed test (>9), were used to separate demented patients. TSH and SHBG was determined by a fluoroimmunoassay (DELFIA, Dissociation Enhanced Lanthanide Fluoro Immuno assay), in solid phase. FT4 (free thyroxine) and FT3 (free triiodotyronine) was determined by radioimmunoassay (RIA) (Coat-a-Count Free T3 and Free T4). No changes were found in demented patients in levels of TSH, FT3 y FT4, neither at the beginning nor after two-years period. However, the values of SHBG in the demented patients were significantly increased after the two-year period (p=0,038) in comparison with the levels found in non demented patients. In conclusion we found an increase of SHBG as an association factor to dementia development in geriatric patients, which seems not to be related with thyroid function.

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TEMPORAL PATTERN OF COGNITIVE DECLINE AND INCONTINENCE IS DIFFERENT IN ALZHEIMER'S DISEASE, DIFFUSE LEWY BODY.DISEASE AND MIXED DEMENTIA. T Del Ser, H Severo Ochoa, D Munoz, V Hachinski, *Leganes, Madrid & London, Ontario, Canada.*

In 50 demented patients (DSM-III-R criteria), longitudinally assessed with the "Extended Dementia Scale" (EDS), the date of onset of bladder incontinence was recorded. The pathological postmortem diagnosis was Alzheimer's disease (AD) in 22 cases, diffuse Lewy body disease (DLBD) in 9 cases, AD + DLBD in 10 cases and AD + vascular lesions (AD+VL) in 9 cases. At the onset of bladder incontinence only 4 AD cases (18%) but 7 DLBD cases (77%), 8 AD+DLBD cases (80%) and 7 AD+VL cases (77%) scored more than 20 in the EDS (X2=18.01; d.f.:3; p<0.001). The mean score of the EDS was 17 (SD 36.8) in AD cases, 113.4 (SD 73.8) in DLBD cases, 71 (SD 55.8) in AD+DLBD cases and 77.3 (SD 66.9) in AD+VL cases (ANOVA d.f.: 3; F: 7.81; p<0.001). We conclude that the temporal pattern of mental deterioration and incontinence is different in AD, DLBD and mixed dementia. Loss of continence is associated with severe cognitive decline in AD but bladder incontinence usually precedes mental failure in cases with cortical Lewy bodies or vascular lesions.

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POSATIRELIN EFFECT ON PATIENTS WITH SENILE DEMENTIA OF ALZHEIMER TYPE (SDAT):A DOUBLE-BLIND MULTICENTRE TRIAL VS ASCORBIC ACID AND CITICOLINE. D Cucinotta, U Senin, R Girardello, G Crepaldi, *Bologna, Perugia, Milan, Padova, Italy*

Posatirelin or L-pyro-2-aminoadipyl-L-leucil-prolinamide is a synthetic neuropeptide that? in animals, has showed a strong activity on memory and learning, on recovery from consciousness impairment, and a peculiar "in vitro" neurotrophic activity and has confirmed its efficacy in clinical studies, improving consciousness impairment due to vascular dementia. In present study, patients with probable SDAT (DSM-III-R-criteria) underwent a 15-day run-in with placebo, followed by either 90-day treatment with 10 mg Posatirelin daily, or 500 mg Citicoline daily, or 100 mg Ascorbic Acid daily by i.m. A 30-day follow-up was carried out with oral placebo. 194 patients (Posatirelin=63; Citicoline=63; Ascorbic Acid=68) completed the study. The sample size was calculated by choosing GBS as target variable, while Index of Mental Decline (IMD), Rey Memory Test, Greene Scale, Toulouse-Piéron Attention Test and Raven Progressive Matrices were selected as secondary variables. Statistical analysis of GBS showed a significant efficacy of Posatirelin on intellective, motor and emotional functions and on many symptoms. Analogous results were obtained by IMD, were apathy, affective disturbances and inter-personal relationship were positively influenced. The activity of Posatirelin persisted during follow-up period, pointing out a carry-over effect. No changes in haematochemical and hormonal parameters, nor alterations of arterial blood pressure or heart rate were observed in patients treated in this study.

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BETA AMYLOID AND TAU IN THE CSF OF PATIENTS WITH AGE-ASSOCIATED MEMORY IMPAIRMENT. F Croria, I Rubio, J Duarte, AP Sempere, DB schens, C Vigo-Pelfrey, *Segovia, Spain & San Francisco, CA, USA*

Age associated memory impairment (MMI) is a heterogeneous clinical condition characterised by forgetfulness of recent events. Patients with MMI can be classified into three evolutive groups: I) patients who developed dementia of the Alzheimer type; II) patients with a psychoaffective disorder, responsive to antidepressants; and III.) patients with a fluctuating memory disturbance, who may develop a mild vascular type dementia. To test the differential diagnostic value of putative biological markers of Alzheimer's disease (AD), the CSF levels of amyloid and tau proteins were measured by ELISA in patients with MMI, patients with dementia of Alzheimer type (DAT), and controls with no organic neurological disease. We found that: I) the levels of CSF-tau in pg/ml were significantly higher in DAT patients (172±85) than in controls (1 13±44), and MMI (114±59); 2) there were no significant differences in the CSF-tau levels among the three evolutive groups of MMI patients; 2) group I and group III showed CSF-tau levels significantly higher than group II. These preliminary results suggest that: 1) The CSF levels of tau protein distinguished patients with DAT from controls with a sensitivity of 5O% and a specificity of 86%; 2) The levels of CSF-tau can predict outcome in some patients with MMI. Longitudinal studies and clinicopathological correlations are in progress to know the specificity and sensitivity of this method in the early diagnosis of AD.

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AGE-ASSOCIATED MEMORY IMPAIRMENT AND CEREBRAL AMYLOID ANGIOPATHY F Coria, I Rubio, MA Garcia, J Duarte, AP SempereE, LE Claveria, MP Ortega, *Segovia Spain*

Age-associated memory impairment (AAMI) refers to memory disturbances of the elderly, currently attributed to brain senescence. Patients with AAMI can be classified in three evolutive groups: I) patients who de-

veloped dementia of the Alzheimer type; II) patients with a psychoaffective disorder responsive to antidepressant drugs; and III) patients with a fluctuating memory disturbance, who may develop a mild dementing state with clinical and neuroimaging features of vascular or mixed dementia. We report on pathological findings in one case from group I and two cases from group III. Brains sections were labelled with antibodies for -amyloid, purified neurofibrillary tangles and ubiquitin. The patient from group I had abundant plaques and tangles, confirming the clinical diagnosis of Alzheimer's disease. Group III patients showed multiple small lacunar infarcts and leukoaraiosis, numerous ,13-amyloid plaques, and a few neurofibrillary tangles in the hippocampal region. In addition, there were numerous ~-amyloid deposits in cortical and leptomeningeal blood vessels. We conclude that: 1) MMI may represent an early clinical stage of Alzheimer's disease and sporadic cerebral amyloid angiopathy, thus expanding the clinical spectrum of β amyloidosis; 2) Widespread amyloid deposition in corticomenigeal blood vessels may induce ischaemic changes in distant periventricular white matter, leading to cognitive syndromes micmicking MMI, vascular or mixed dementia.

50
LIPID PEROXIDATION INDUCES PLATELET ABNORMALITY IN ALZHEIMER'S DISEASE AND IN AGEING. E Calabrese, C Mariani, L Bet, L Bava, E Magni, G Scarlato, *Milan & Brescia, Italy.*

Different changes of cell membrane composition and structure have been found in autopsy brain tissue of neurologically normal elderly people and patients with Alzheimer's disease (AD). These may result from the injurious effect from the lipid peroxidation and from the injurious effect of cytoplasmic free radicals action. The same basal levels of malondialdehyde (MDA), an intermediate of the lipid peroxidation process, were previously found in different brain regions of AD patients and controls. However, under stimulation, MDA synthesis was significantly higher in AD brain than in controls. AD is associated with alterations in cells, as platelet membrane fluidity changes. To examine a possible correlation between peripheral abnormalities and autocatalytic oxidation of lipids we investigated the levels of basal and stimulated lipid peroxidation in platelets of AD patients and controls by measuring MDA formation. Basal MDA levels were not different among AD and age-matched controls. However, the increment between basal and stimulated MDA levels were strongly correlated with age: healthy volunteers between the ages of 19 and 25 years showed lower MDA levels (97%), whereas control group between the ages of 60 and 82 years showed higher MDA levels (307.15%). AD patients presented synthesis rate 155% MDA. Our results seem to support the hypothesis of a platelets involvement correlated to lipid peroxidation in ageing. A decrease of antioxidant enzyme activities (Cu/Zn Superoxide Dismutase, Glutathione Peroxidase and Catalase) related with age has already been reported in blood. The intermediate MDA levels found in AD patients could be explained by an increased activity of these enzymes in platelets, as previously demonstrated in erythrocytes.

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INCIDENCE OF DEMENTIA AFTER FIRST STROKE: 3-YEAR FOLLOW UP. BD Aronovich, TA Treves, NM Bornstein, AD Korczyn, *Tel Aviv, Israel.*

We tried to determine the incidence of dementia after first-ever ischemic stroke. Temporal relationship between occurrence of stroke an development of dementia is an important clue for a vascular etiology of dementia. therefore, it is important determine at which rate dementia develops following stroke. Methods: In a prospective study, we followed 158 consecutive patients who had first ever ischemic stroke in 1988 and 1989, but were not demented at that time. Survival analysis (Kaplan-Meier) was performed for a follow-up period of 3 years, wherein the end-point was development of dementia (DSM-III-R criteria). Results: The cumulative incidence of dementia in these patients was 30% within 1 year and 35% within 2 years. Subsequently, only few additional cases of dementia developed. Absence of risk factors for vascular disease was highly protective against the development or dementia. Conclusions: Dementia after first-ever ischemic stroke is mire common that expected an manifests within the first year after -vascular event..

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SAFETY OF ANTICOAGULATION IN ACUTE STROKE (AS). N Van Blercom, S Blecic, Ph Violon, J Hildebrand. *Bruxelles, Belgique*

Anticoagulation is recommended to prevent early recurrence of cardioembolic stroke but its use is temperated by fear of complications. The aim of this study was to evaluate the safety of heparin in AS presumably due to cardioembolism and in stroke in evolution. On 472 consecutive patients admitted in the Stroke Unit of the neurological department between April 1992 and September 1993, 241 were treated within 13.3± 8 hours following stroke onset by continuous infusion of Heparin 30.000U/day for 10 days. 162 had a presumed cardioembolic stroke (CES) and 79 a stroke in evolution (SIE). All patients had brain CT before treatment and 10±4 days after or earlier in case of neurological deterioration. Hemorrhage on CT and untractable hypertension were the only exclusion criteria. Treatment related complications occurred in 21 patients (8.7%) There were only 3 haemorrhagic transformations (2CES,lSIE), 7 gut bleeding,6 epistaxis 4 multiple ecchymoses and 1 fall in platelet count. No death was attributed to heparin. In conclusion, this study demonstrates the safety of early anticoagulation during the first 10 days after acute ischemic stroke.

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TRIFLUSAL AND PREVENTION OF CEREBROVASCULAR ATTACKS: DOUBLE-BLIND CLINICAL STUDY VS ASA. S Smirne, L Ferini-Strambi, D Cucinotta, M Zamboni, L Ambrosoli, A Poli, *Milan, Bologna, Italy*

Triflusal, 2-acetoxy-4-trifluoromethylbenzoic acid, is an antiaggregant drug that inhibits platelet cyclooxygenase and cAMP-phosphodiesterase. A parallel group design randomized, double-blind, double-dummy, negative trial, Triflusal versus acetylsalicylic Acid (ASA), in the prevention of cerebrovascular attacks was performed. 183 patients, 106 males and 77 females, aged from 45 to 80 years (mean 66.1 ± 9.3 SD) with recent reversible ischemic attacks (RLA) were enrolled: 90 patients were treated with Triflusal 600 mg/day and 93 with ASA 300 mg/day. Prevention of RIA, stroke and vascular death were end-point criteria. The "per protocol" efficacy primary analysis showed in Triflusal group (no. of patients= 81) no recurrent episode in 75 patients (92.6%) and the occurrence in 6 patients (7.4%). In the ASA group (no. of patients= 84) no ischemic episode was recorded in 79 cases (94%), cerebrovascular events occurred in 5 patients (6%). The chi-square analysis showed homogeneity distribution of success and failures by treatment (chi-square= 0.004; P= 0.95): the statistical power was 100%. Other examinations, as efficacy secondary variables (echotomography and duplex-sonography of extracranic cerebral vessels) were performed before and at the end of treatment. The intention to treat safety analysis showed that 13% of patients in Triflusal group and 16% of patients in ASA group complained gastroenteric disturbances. 18 patients out of 183 (9.8%), 10% in Triflusal group and 9.7% in ASA group, dropped out during the trial for reasons other than end-point.

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HEPARIN THERAPY IN ACUTE STROKE - RISK OF HEMORRHAGIC COMPLICATIONS J Kuehnen, C Tilgner, M Daffertshofer, A Schwartz, *Mannheim, Germany*

Hemorrhagic transformation and parenchymatous hematoma are well known complications in cerebral ischemia especially after emboligenic stroke. To determine whether heparin therapy for secondary prevention of ischemia increases the risk of secondary hemorrhagic complications, we studied 224 patients (128 males, 96 females) with different stroke types. 67 patients were treated with an effective intravenous heparin anticoagulation (PTT between 1.5 - 2.5 ×), 146 patients with low dose heparin administration (PTT normal), and 11 patients without any anticoagulation. CT scans were obtained at the onset of stroke and in follow-up studies. Only 1 /67 patients with an effective heparin dosis developed a computertomographic proven hemorrhagic transformation and 2/67 a parenchymatous hematoma. Under low dose heparin 5/146 cases were associated with hemorrhagic transformation and 2/146 with a hematoma. 3 treated patients worsened. In 212 patients (93.4%) we saw no hemorrhagic complications including 9 cases without any anticoagulative drug, however 26 patients developed a neurological deterioration, which is definitely less than reported in the literature even in the natural history of cerebral ischemia. Conclusions: From our data we could not determine an additional risk for spontaneous hemorrhagic transformation or parenchymatous hematoma with effective heparin therapy for secondary prevention after ischemic stroke of any origin.

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IDENTIFICATION OF VASCULAR PATHOLOGY IN ACUTE ISCHAEMIC STROKE USING TRANSCRANIAL COLOUR-CODED

REAL-TIME SONOGRAPHY. PJ Martin, ME Gaunt, RJ Abbott, IF Pye, AR Naylor, *Leicester, UK*

Strategies for vessel recanalisation in acute stroke rely on rapid patient selection We used transcranial colour coded sonography (TCCS) plus extracranial carotid colour duplex to assess the cerebral circulation in 48 patients (28 males; median age 72 years) with acute stroke to identify those with major vessel occlusion. The clinical stroke syndrome was classified as total (TACI) (n=23) or partial (PACI) (n=20) anterior circulation infarction, posterior (POCI) (n=2) or lacunar (LACI) (n=3) infarction. Haemorrhage was excluded by CT/MRI TACI. 7 patients had ipsilateral internal carotid artery (ICA) occlusion and 8 patients had middle cerebral artery (MCA) occlusion In 6 patients, symptomatic MCA mean velocity was reduced (median; 18 cm/s versus 49 cm/s contralaterally; P<0 05) PACI: 2 patients had ICA occlusion and both had interhemispheric collateral flow via the anterior communicating artery All patients had MCA mainstem patency Overall, ipsilateral MCA mean velocities were reduced (median; 45 cm/s versus 50 cm/s contralaterally; P<0 05). In POCI and LACI, no abnormalities were detected in the anterior or vertebrobasilar circulations. TCCS and extracranial colour duplex enable non-invasive imaging of the cerebral circulation and rapid identification of major vessel occlusion in acute ischaemic stroke. The haemodynamic information may complement the anatomical information of CT/MRI in selecting patients for active intervention.

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ACETAZOLAMIDE INDUCED CHANGES OF CEREBRAL BLOOD FLOW ASSESSED BY TRANSCRANIAL DOPPLER ULTRASOUND. M Muller, M Raltzig, K Schimrigk, *Homburg, Germany*

In 32 healthy volunteers [16 males, 17 females, mean age±standard deviation 44±16 years] we studied by transcranial doppler ultrasound acetazolamide [ACET; 1 gr. iv.] induced changes of the mean blood velocity [MBV] and the pulsatility index [PI] in the middle [MCA; n=53], anterior [ACA; n=44] and posterior cerebral [PCA; n=35] artery and in0 the basilar artery [BA; n=22) recorded 15--20 minutes after injection. In all arteries the ACET induced relative increase of the MBV ex- pressed as percentage of the flow velocity at rest estimating the vasomotor reactivity (VMR)] ranged from 42±20% to 51±25% accompanied by a significant decrease [t-test: p< 0.001] of the PI ranging from 11±13 to -.16 ±13. Both the VMR and the decrease of the PI did not significantly differ between the 4 arteries. The ACA/MCA and the PCA/BA-ratios did not change after ACET. The VMR increase in the MCA and ACA correlated significantly with one another [p< 0.01, r=.3771]. We conclude that the VMR, and hence the increase of the cerebral blood flow, does not differ regionally after a vasodilatory stimulus.

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ASSOCIATED MOVEMENTS IN STROKE PATIENTS AND NORMAL CONTROLS. M Krams, B Moering, M Rijntjes, J Faiss, HC Diener, C Weiller. *Essen, Germany*

We studied the incidence of associated movements in stroke patients and normals. Methods/Results: 1. Of 110 non-plegic stroke patients who performed a finger-opposition-task (OT) with both their affected and unaffected hand, 30 % with a right and 25 % with a left hemiparesis showed distinct associated movements (AM) in the unaffected hand when performing OT with their paretic hand, whereas only 14 % (13 %) showed AM in the paretic hand, while finger-opposing with their unaffected hand. 2. In an age-matched control group of 130 controls, 8 % showed AM in either hand while performing OT. When normals were asked to perform a more difficult task (alternate simultaneous flexion of two fingers at the time), 35 % showed AM with no significant difference between right and left hand. 3. Of 20 professional string players, no one showed AM while performing OT and the more difficult simultaneous flexion task Conclusions: AM may be an expression of the cognitive modelling of finger movements, occurring dependent on the relative difficulty of movement planning. We hypothesise that the higher incidence of AM in stroke patients while moving their paretic hand may reflect a take-over of movement planning by the unaffected hemisphere. This is supported by PET-activation data looking at functional reorganisation after stroke.

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CEREBRAL SINUS THROMBOSIS PRESENTING AS INTERHEMISPHERIC BLEEDING. B Yaqub, SM Al Deeb, A Daif, H Sharif, *Riyadh, Kingdom of Saudi Arabia*

Out of 31 patients presenting with cerebral sinus thrombosis, 6 presented with headache, impairment of consciousness with or without papilloedema, and without lateralising neurological findings. Initial CT brain scan without contrast showed a high density lesion in the interhemispheric space mimicking interhemispheric bleeding, brain oedema and small or normal ventricle size. Two were interpreted as normal while subarachnoid haemorrhage was suspected in the others. Arteriography showed cerebral sinus thrombosis. Two of the 6 were anticoagulated, while the others were treated with supportive therapy alone. Five patients died, including those who were anticoagulated. Comparing this group with the remaining 25 patients, they had a much worse prognosis as 3 out of the 25 patients died. In conclusion, cerebral sinus thrombosis presenting as interhemispheric bleeding seems to have a poor prognosis.

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THE BLOOD PRESSURE, HEART RATE AND GLYCEMIA CHANGES IN EXPERIMENTAL BRAIN ISCHEMIA. J Tatay; E Diez-Tejedor; F Caroeller; A Frank; J Roda. *Madrid, Spain.*

Autonomic and metabolic changes have been described during brain ischemia. Those are not evidenced when it is global. We have studied some manifestations and their modifications during both global (GTBI) and focal (FTBI) transitory brain ischemia. Twenty one Wistar rats were subjected to GTBI, and 11 to FTBI during 2O minutes, followed by reperfussion. Mean blood pressure (MBP), heart rate (HR), glycemia before, during and after brain ischemia were registered. The pH, pO_2, and pCO_2 were maintained constant using intravenous buffered solutions. Significant differences were found: During GTBI the BP rose (99±3 to 125±3 mmHg; P=0.0001) and returned to normal in the postischemia period. However, HR decreased after ischaemia since reperfusion in both; GTBI (276±3 to 255±5 b/m; P=0.0001),and FTBI (389±9 to 359±13 b/m; P=0.01). hyperglycemia was present from beginning of ischemia in both groups: GTBI (111±7 to 141±8 g/dl; P=0.006) and FTBI (109±9 to 132±10 mg/dl; P<0.02). We conclude that GTBI and FTBI could produce some autonomic changes: MBP (only in GTBI) and HR as well as hyperglycemia. These effects might play a role in the pathophysiology of brain ischemia.

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FOCAL CEREBRAL ISCHEMIA IN THE RAT; A STEREOLOGICAL MORPHOMETRIC STUDY. F Carceller, JM Roda, E Diez-Tejedor, C Avendano. *Madrid, Spain.*

The quantification of experimental cerebral infarction has been carried out by a wide variety of methods, yielding results which, quite often, are conflicting or difficult to compare. In the present study we have undertaken to provide reliable quantitative estimates of the cerebral cortical infarction, applying an unbiased stereological method to a well controlled model of cerebral ischemia in 12 Long Evans rats. Results from this and other studies from other groups, indicate that estimates of infarct size based on direct volume measurements of infarcted tissue have a large variance, a part of which is due to the accompanying brain oedema. For this reason, the volume ratio between the spared cortex of the right infarcted hemisphere and the total cortex of the left noninfarcted hemisphere would be the best index to detect differences in the amount of cortex that was damaged by the infarct, regardless of the intensity of the accompanying, oedema. The validation of the method enables us, moreover, to predict the sample size needed to detect differences between control and treated rats in therapeutic trials, for any expected level of therapeutic efficacy.

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A PROSPECTIVE STUDY: CEREBROVASCULAR DESEASES (CVD) AND RISK FACTORS IN NOVOSIBIRSK AMONG MEN AND WOMEN AGED 25-64. T Vinogradova, V Feigin, A Tarasov. *Novosibirsk, Russia*

A prospective population studies of prevalence and risk factors of CVD among men and women aged 25-64 are very important for prevention and treatment of CVD. In 1985-1986 and 1988-1989 some screening examinations in three Novosibirsk districts of representative population sample aged 25-65 have been carried out. Results: age-adjusted prevalence of stroke was 11,0 cases per 1000 men and 10,5 cases per 1000 women aged 25-64 years. The frequency of arterial hypertension among studied population was 31,0% in men and 31,3% in women, smoking - 56.4% and 4.4%, dislipidemiae - 8,4% and 12,8%, ischemic heart disease - 11,5% and

14,0%, and overweight - 18,7% and 41,1%, respectively. The most important diet stroke risk factors were high calory food, high conception of carbohydrates and low consumption of vitamin anti oxidants.

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SEIZURES AT THE ONSET OF SUBARACHNOID HEMORRHAGE. AN Pinto, P Canhao, JM Ferro, *Lisboa, Portugal.*

We tried to identify the prevalence, associated findings and influence on prognosis of seizures occuring at the onset of subarachnoid hemorrhage (SAH). Prospective data collection of all SAH admissions (n=283) during a 5 year period were studied. Sixteen patients (5,7%) had seizures at the onset of SAH. None had previous history of seizures. One was alcoholic. None had metabolic imbalance. Severity (Hunt grade), amount of CSF blood (Fisher grades) identification and location of the aneurysms were similar in SAH with and without early seizures. Hemiparesis was more frequent in SAH with early seizures (31 vs 9%; difference=22%; CI=46-0,3%). None had recurrent seizures while in hospital. Early seizures carried an increased risk of rebleeding (OR = 9.1; CI = 27.3) and of death or severe disability (OR = 3.8; CI = 1 1-1 .4). Conclusions: damage to the motor cortex is one of the factors involved in the genesis of early seizures following SAH. These seizures are associated with an higher risk of rehemorrhage, severe disability and death.

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CEREBRAL INFARCTION AND HABITUAL SNORING J-Ph Neau, P Ingrand, J Pacquereau, J-C Meurice, AM Tantot, R Gil. *Poitiers, France*

Snoring has recently been as a ischaemic strokes. We studied 120 patients (95 males, 25 females) aged 40-75 years admitted to the University Hospital of Poitiers. Cerebral infarction was confirmed by a neurologist and by CT scan and/or MRI. 120 age-matched controls (±4 years) were sampled. The cohabiting relatives of patients and controls were interviewed using the same standardised questionnaire about smoking, sleeping (snoring, apnoeas and excessive daytime sleepiness) and drinking habits. We determined the occurrence of habitual risk factors. The time of stroke onset was noted. ECG, carotid doppler ultrasounds, TD echocardiography, and 24 hour ECG Holter were systematically performed to determine the possible mechanism of the ischaemic stroke. Arterial hypertension (HTA) ($p<0.001$), smoking ($p<0.001$), cardiac arrhythmia ($p<0.001$), coronary heart disease ($p=0.05$) and hypercholesterolaemia ($p=0.007$) were significantly related with brain infarction whereas arteritis, diabetes, alcoholism, obesity and valvulopathy were not. Habitual snoring (always or almost always) was a significant risk factor ($p < 0.01$). After adjustment for HTA, habitual snoring remained significantly related to ischaemic stroke ($p=0.04$). Habitual snoring was strongly related to cerebral infarct in patients with HTA ($p=0.008$) while no significant association was found in patients without HTA ($p=0.62$). The suspicion by the partner of apneas during sleep was also correlated with stroke ($p<0.01$). Finally, we do not find any association between habitual snoring and sleep-related stroke, and between snoring and mechanisms of ischaemic strokes.

64
THE ROLE OF AUTOIMMUNITY IN VASCULAR DEMENTIA. S Tekin, C Aykut, S Aktan. *Istanbul; Turkey.*

The role of vascular endothelial cell (VEC) specific antibodies in the etiopathogenesis of vascualr dementia are investigated in this study. It is now known that immunologic mechinisms have a role in the initiation of atherosclerotic process. No antibodies against VEC specific antigenic systems has been demonstrated in small vessel (lacunar) infarcts. Autoantibodies has been detected in 80% of multi-infarct dementia but VEC specific antibodies have not been studied yet.We studied VEC specific antibodies in 17 patients with the diagnosis of vascular dementia according of Minimental Score, Hachinsky Ischemia Scale and Chui's Criteria; in 17 nondemented patients with small vessel infarcts and in 16 healthy, nondemented control group patients by using Teraski microtoxicity technic. All three groups were correlated according to known vascular risk factors.Myocardial infarction and hyperlipidemia were more prevalent in vascular dementia than in other groups ($p<0.05$). VEC specific antibodies were positive in 94% demented patients whereas no antibodies were detected in small vessel infarcts or control group.There results may suggest the existence of an immunologic mechanism in the etiopathogenesis of vascular dementia differing from small vessel infarcts. This mechanism may also explain why all small vessel infarcts do not present as dementia.

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HYPOTHERMIA AND CEREBROLYSIN PREVENT ISCHEMIC BRAIN DAMAGE BY DELAYED DEVELOPMENT OF CYTOTOXIC BRAIN ISCHEMIA. M Schwab, R Bauer, U Zwiener, *Jena, Germany*

Moderate reduction of cerebral blood flow (CBF) far above the threshold of infarction can cause delayed neuronal cell death as well. Hypothermia prevents irreversible brain damage and disruption of the blood brain barrier, too, but there is no direct evidence that mild hypothermia reduced a cytotoxic brain edema CERE, a brain tissue hydrolysate containing a mixture of 85% free amino acids and 15% small pep tides (MW<10000) reduced the mortality rate after permanent bilateral common carotid artery ligation (PBCAL from 31.7% to 16.7%. Control and CERE treated adult Wistar rats with body temperatures of 35°C or 37° were subjected to PBCAL for 6h. PBCAL led to a short strong CBF reduction and was restored on a reduced level of about 50-80% within a few minutes. CBF was restored at a higher level in hypothermic, and eve more in CERE treated, animals ($p<0.05$). In ECoG, power ratio, and the relative spectral power in $\alpha + \beta$ and showed a significant correlation to the changed CBF values only during the time of stronger CB reduction ($p<0.05$). Protective effects of hypothermia and CERE were shown ($p<0.05$). There was no sign of disruption of the blood brain barrier in all animals after 6h. Nevertheless, the water contents in the frontoparietal cortex and in the hippocampus were significantly higher in ischemic animals with 37°C body temperature than in non ischemic ones ($p<0.05$). Increase of brain water content was significantly lower in hypothermic and still clearer in CERE treated animals ($p<0.05$). Thus, cytotoxic brain edema began to develop 6h after onset of even moderate CBF reduction. Mild hypothermia and more pronounced CERE diminished CBF reduction and delayed development of cytotoxic brain edema.

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CEREBRAL ARTERY DISSECTION: AN IMPORTANT CAUSE OF STROKE IN THE YOUNG. M AL Deeb, B Yaqub, T J TJan, M Aabed. *Riyadh, Kingdom of Saudi Arabia.*

Five young patients (22-35 years old), 4 males and 1 female, presented with symptoms due to cerebral vessel dissection. In 2 patients who presented with hemiplegia, CT and MRI revealed infarction in the anterior choroidal artery territory. Arteriography showed internal carotid artery dissection extending to the anterior choroidal artery. No risk factors were observed. One male was blind since childhood and had continuous rotating movements of the neck. The other, a young female, had collapsed while performing Arabic dancing with forceful flexion and neck rotation. Two male patients presented with coma and ophthalmoplegia due to a top of basilar artery syndrome, shown by CT and MRI. Arteriography showed dissection in the vertebral artery (there was also asymptomatic dissection in the internal carotid artery in one). No risk factors were found. One male patient presented with the clinical features and imaging findings of lateral medullary syndrome. Arteriography showed dissection of the vertebral artery involving the posterior inferior cerebellar artery. All were treated with a low dose of aspirin 300 mg daily. One died, 4 recovered with a mild to moderate deficit but were able to return to work. Spontaneous cerebral vessel dissection, though uncommon, should be seriously considered as an aetiological factor in strokes in the young.

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MIDDLE CEREBRAL ARTERY INFARCTIONS: STUDY OF FACTORS IN 440 PATIENTS. S Berges, T Moulin, T Crepin-Leblond, D Chavot, F Cattin, MH Snidaro, JL Chopard, L Rumbach. *Besançon, France*

There is little data on the natural course of MCA infarcts in large populations with ischemic stroke. This is an important consideration in therapeutic trials. Using the Besançon Stroke Registry, we selected 440 consecutive patients (pts) from amongst 1050, admitted within 24 hours after a first stroke. Inclusion criteria were: clinical presentation with MCA ischemia, at least 1 CT scan (one initial and 84% had a control with a supratentorial infarct). Medical history (onset, course), clinical features, etiology, CT patterns, Ranking scale (RS) at 1 month and biological variables were collected. We have used univariate and multivariate analysis. There were 235 males, 205 females and median age 70.6 y (18 to 96). 74% of pts were admitted under 12 hours (mean 8.1 h). Infarcts were located in the following territories: total MCA in 94 pts, superficial MCA (superior or inferior) in 193 pts, deep MCA in 19 pts, multiple MCA in 17 pts or other territories (borderzone MCA 28, ACA 5, ACP 11, AchA 3). In all pts, out-

come was: RS (1-3) 46%, RS (4-5) 30% and death 24%; in total MCA infarct: RS (1-3) 5%, RS (4-5) 35% and death 60%. The predictive variables for outcome were: infarct location, clinical presentation (Orgogozo scale), early course (at day2), biological values (initial TA, glycemia, fibrin, hematocrit) and CT findings (early CT signs of ischemia, mass effect). Selecting 3 variables (Orgogozo scale, early CT signs of ischemia, clinical course at day2), a predictive model of death can be proposed: Our findings suggest that it is possible to predict, using simple data, the outcome for patients in the early stages of MCA ischemia.

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MOLECULAR AND CELLULAR PATHOLOGY OF SPORADIC CEREBRAL ANGIOPATHY. I Rubio, MA Garcia, MP Ortega, F Coria. *Segovia, Spain*

Sporadic cerebral amyloid angiopathy (SCM) is characterized by recurrent lobar haemorrhages and widespread amyloid deposits in corticomeningeal blood vessels. We studied six autopsied cases by biochemical, genetic, and immunohistochemical methods. We found that: 1) Amyloid extraction from leptomeningeal vessels showed that vascular amyloid in all cases is formed by aggregates of Alzheimer , <-amyloid protein; 2) Molecular analysis of exons 16 and 17 of the , <-amyloid precursor protein gene from two cases disclosed no mutations. 3) Microscopic examination of brain sections demonstrated widespread vascular amyloid deposits, and a variable number of neuritic. plaques in all cases. 4) Vascular amyloid deposits were associated with a progressive degeneration of smooth muscle cells, but not endothelial cells. Amyloid-infiltrated and non-infiltrated vessels also showed prominent ubiquitin immunoreactivity. 5) Amyloid-infiltrated vessels were often surrounded by hypertrophied astrocytes and reactive microglia. We conclude that: 1) SCM is a <-amyloid disorder. 2) SCM and familial cerebral amyloid angiopathies are etiologically heterogeneous; 3) SCM is characterized by increased ubiquitin production in vascular cells, a progressive degeneration of smooth muscle cells, and a limited glial reaction. These pathological features are relevant in understanding the mechanisms underlying haemorrhagic and ischemic stroke in this condition.

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PRIMARY INTRACEREBRAL HEMORRHAGE CLINICOANATOMIC OF 17 AUTOPSIED CASES. APou Serradell, J Roquer, C Oliveras Ley, F Alameda, S Alfonso. *Barcelona, Spain*

The aim of this report is to analyse the main clinical and neuropathological features leading to a fatal outcome of Primary Intracerebral Hemorrhage (PIH). 362 patients were admitted in our Service with PIH in the past 9 years (1984-1993). 103 (28%) of them died. Post mortem studies were done in 30 of such cases:Among them we excluded those having traumatic antecedents,anticoagulant therapy, a recognized cause of intracerebral bleeding and those with suspected etiology of death other than PIH. 17 cases were choosen and 19 items were considered in each one. Risk factors were only present in 12 cases, high blood pressure being the most frequent. Localisation were lobar (L) in 7, capsulo thalamic or basal ganglia (BG) in 9 and multiple in 1, size were superior to 4.5 cm in 15, midline structures were displaced in 16, rupture of hematoma into the ventricular system or subarachnoidal space occurred more often than expected by neuroimaging studies. The nature of the vascular lesions was segmental lipohyalinosis in 10, disseminated intravascular coagulation in 1, amyloid angiopathy in 1, unknown in 5. Tentorial herniation was present in 6 and secondary arteriolar and venous hemorrhage of the midbrain in 3. 10 other clinical items were considered. We conclude that the main cause of death in PIH is the expanding effect of the bleedinq mass and its incapacity to become stabilized.

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THE CORRELATION OF CAROTID ARTERY PLAQUE MORPHOLOGY WITH RISK FACTORS. S Podobnik-Sarkanji, V Demarin, T Rundek, *Zagreb, Croatia*

A group of 83 patients with symptomatic and asymptomatic carotid atherosclerotic lesions were analyzed. The morphology of carotid plaques were determined using Color Doppler Flow Imaging, Acuson 128 XP. The plaques were described as: soft; fibrous, heterogeneous; calcified; intra plaque hemorrhage. For each patient putative other risk factors were collected. The values of cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, apoprotein A and apoprotein B were deter milled by laboratory tests. The morphology of carotid artery plaques were analyzed with respect to the risk factors. More heterogeneous plaques were found in males ($p<0.05$). The hypertensive group had a greater number of soft and calcified plaques ($p<0.05$). In the group with low level of physical activity and alcoholics significantly more soft plaques were found ($p<0.0001$). In the group with diabetes significantly more soft and heterogeneous plaques were found ($p<Q.000l$). In the group with low level of HDL-cholesterol significantly more heterogeneous plaques were founs found ($p<0.000l$). In the group hypertension, diabetes and alcohol consumption the evidence of intraplaque hemorrhage was found. In cases of soft plaques the most common risk factors are elevated cholesterol, low level HDL-cholesterol, cigarette smoking; in cases of heterogeneous plaques the most common risk factor is low HDL-cholesterol ($p<0.05$); in cases of fibrous plaques the most common risk factors are elevated cholesterol and cigarette smoking; in cases of calcified plaques the presence of cigarette smoking, hypertension, elevated cholesterol and low HDL-cholesterol are equally important; in cases of hemorrhage into the plaque the most important factor is hypertension ($pc0.05$).

71
ISCHEMIC STROKE IN YOUNG ADULTS. J Pniewski, H Kwiecinski, A Torbicki, J Mieszkowski, *Warsaw, Poland*

We examined 57 patients aged 18-45 years (mean 37) with the diagnosis of ischemic stroke (n=46) or TIA (n=11) by means of CT, transoesophageal echocardiography, Doppler ultrasonography, and angiography in order to establish the cause of ischemic event. In 16 (28%) patients the pathology (occlusion or stenosis) within carotid arteries, which could be responsible for ischemic event, was shown. That group was classified as stroke of vascular origin. In 5 (9%) patients the abnormalities within the heart (mitral stenosis, bacterial endocarditis and acute myocardial infarction) were found. This group, in whom no evidence for vascular pathology was found, was classified as cardioembolic stroke. In 14 (25%) patients mitral valve prolaps (MVP) and in 13 (23%) patent foramen ovale (PFO) were found. In 23 (4O%) patients PFO or MVP was the only detectable abnormality and they were classified as having possible cardioembolic stroke. In 13 (23%) patients no abnormalities that could be responsible for ischemic event were detected and they were diagnosed as stroke of undetermined origin. We have shown in this study, that potential cardiac sources of ischemic stroke are detectable in 5O% of patients. our data confirm, that cardiogenic embolism is one of the most important mechanisms of stroke in young adults.

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SPONTANEOUS DISSECTION OF THE VERTEBRAL ARTERY. Plaza, E Diez-Tejedor, J Munoz, A Frank, P Barreiro, *Madrid, Spain*

Spontaneous vertebral artery (VA) dissection is an infrequent cause of vertebrobasilar schaemic stroke in children and middle-age adults. The diagnosis of VA dissection is based n the accurate identification of clinical features and angiografic signs dissection. We describe ix cases of vertebrobasilar and cerebellar ischaemic stroke with spontaneous dissection of A. In all patients a CT-Brain Scan, MR and angiography were performed, they were man, to range-age from 9 to 44. In only one case the localization was intracranial. In 5 was unilateral. There was previous arteriopathy in 5 of the whole series (and dysplasia.). The clinical features was, basically, neck pain and brainstem or manifestations. We conclude that the spontaneous VA dissection should be considered in the differential diagnosis of the vertebrobasilar young patient strokes. The angiography is indicated to confirm the diagnosis of dissecting aneurusm. This cases support the theory that an underlying arteriopathy can be an important predisposing factor to arterial dissection in young patients.

73
CBE IN TIAS AND UCIS: EFFECTS OF BLOOD VISCOSITY, BLOOD PRESSURE AND AGING. V Petrunjashev, I Velcheva, D Hadjiev, S Yancheva, *Sofia, Bulgaria.*

The study was carried out in 62 patients with TIAs and 97 patients with unilateral cerebral infarctions (UCI). Doppler sonography (4MHz) of the main neck arteries and SPECT with 133Xe inhalation were used for assessment of CBF. The effects of some blood viscosity parameters (hematocrit, fibrinogen and plasma viscosity) and also of mean arterial blood

pressure (MABP) and aging on the CBF were estimated. Decrease of the neurosonographic velocity parameters and reduction of rCBF in the temporal fronto-temporal and temporo-occipital areas were established and they were more pronounced in the patients with UCI. No significant differences between the hemorheological, MABP and age values in both patients' groups could be disclosed. Multiple regression analysis revealed a leading role of aging and hematocrit for the decrease of the neurosonographic velocity parameters in TIAs, and for reduction of mHBF and rCBF in patients with UCI. The significance of the influence of blood viscosity, blood pressure and age factor on CBF in patients with cerebrovascular disease is discussed.

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ASSESSMENT AND CONTROL OF CAROTID-CAVERNOUS FISTULAS WITH CT, AGR AND TDS. L Petrov, S Karakaneva, A Petkov, E Nikolov, *Sofia , Bulgaria.*

The findings of CT, angiography, and transcranial doppler sonography(TDS) of five patients with trauma carotid-cavernous fistulas are compared. In the diagnosis the CT scan is of limited use. It demonstrates the ipsilateral or bilateral dilatation of the sinus cavernous, and superior ophthalmic vein, and proptosis. Angiography, especially with digital subtraction, is the method of choice for a clear definition of the anatomy of the fistulas. There has been used various approaches to evaluate tolerance to carotid occlusion. The findings of serial TDS of all patients are correlate with the findings on CT and Angiography. The changes in the ophthalmic veins with arterialistion and reversal of their flow is detected by TDS. the Doppler signals are characterised by high mean and end-diastolic flow velocities, low pulsatility, and bruits were observed. The use of various compression tests allows evaluation of the collateral capacity of the circle of Wills. TDS is the ideal noninva- sieve, reprolucible and reliable method for postoperative control.

75
VISUAL REACTIVITY; A NEW DIAGNOSTIC APPROACH TO FUNCTIONAL DEFICIT IN POSTERIOR INFARCTION. L Niehaus, *Berlin, Germany.*

Aim of this TCD-study was to demonstrate the influence of posterior infarction on visual reactivity (VR). Methods and Material: We developed a standardised method of measuring flow parameter changes in the PCA (P2) during intermittent photic stimulation at a frequency of lO Hz. VR was accessed by mean blood flow velocity changes (ΔMBFV) in TCD. The Lateralization-Index (LI) was definedaccording to ΔMBFV of each side. LI = (Δ MBFVright - ΔMBFVleft)×l00/ (ΔMBFVright + ΔMBFVleft) IS patients (aged 42 to 82 years) with posterior infarction were studied. 13 patients with ischemic lesions in the region supplied by PCA showed territorial infarction in either CCT or MRI. Six patients were examined within the first ten days after infarction (group A) andfourteen (group B) at least 3O days after onset. Five patients could be studied at both times. Results: All patients in group A demonstrated marked impairment of VR on the affected side and pathological LI. Four patients with embolic infarction showed significantly higher MBFV on the affected side. In these subjects MBFV and VR improved to almost normal value over time. In 12 patients of group B MBFV upon stimulation increased significantly at both sides. In two patients, however, lack of increase suggested occlusion of P2. LI always indicated side of infarction. Conclusion: We conclude that higher MBFV and marked impairment of VR on the affected side indicate hyperperfusion after rapid recanalisation with a disturbance of vasomotor reactivity. The little impairment on VR after thirty days may demonstrate rapid normalisation of vasoreactivity in posterior infarction. By this dynamic examination method a new approach to pathophysiology of infarction may be achieved.

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MECHANISMS OF HEMIATAXIA IN THALAMIC LESIONS (DEJERINE-ROUSSY SYNDROME). T Maeda, K.Nagata, Y.Satoh, Y.Hirata, *Akita, Japan*

To investigate the relationship between crossed cerebellar diaschisis (CCD) and hemiataxia in patients with. thalamic lesions. Three right-handed patients with thalamic lesions (1 hemorrhage and infarctions) presented with hemiataxia in the contralateral upper and lower extremities, through all phases of the disease. Cerebral blood flow (CBF), oxygen metabolism (CMR02) and/or glucose metabolism (CMRglu) were measured quantitatively by positron emission tomography (PET) in the acute and chronic phases .The patient's PET results were assessed by comparison with PET data from normal age-matched controls. In the affected thalamus and ipsilateral frontal cortex, CBF, CMR02, and CMRglu were all reduced compared to controls. However, metabolic activity was preserved in both cerebellar hemispheres, and CCD was not observed in any patient. Hemiataxia associated with thalamic lesions does not appear to be due to involvement of the cerebellar hemispheres.

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SHORT-TERM PROGNOSIS OF PATIENTS WITH ACUTE ISCHEMIC STROKE AND NON-VALVULAR ATRIAL FIBRILLATION. ML Sacchetti, D Toni, M Fiorelli, C Gori,C Argentino, *Rome, Italy*

In a continous series of 427 patients with acute ischemic stroke we compared the 15 day clinical outcome of 87 cases affected by non valvular atrial fibrillation (AF) wen respect to the 340 non-AF stokes. The capability of CT images (performed in 420 cases within 10±4 hrs of onset) in predicting clinical outcome, was also investigated. A good prognosis was defined by a CNS score higher than 6.5. Deceased cases as well as cases with a CNS score <6.5 were considered as having had a poor outcome. Baseline characteristics and clinical outcome of selected cases are given in Table 1. The short- term prognosis of AF patients was significantly worse than that of non-AF cases, in terms both of self-sufficiency and death rate (P<O.OOl). The major cause of death was cerebral herniation (n=15/23 vs 27/43) (p=n.s.).Early CT images well correlated with clinical outcome (p<.OO1). Although AF patients showed an higher frequency of early positive CT signs, the result did not reach statistical significance. AF cases presented significantly larger early CT lesions than non-AF patients (P<0.005). Furthermore, a significantly difference was found in the ability of early positive CT signs to predict the poor prognosis in patients with AF with respect to non-AF I cases (P<0.OO l)(Table 2). Our data support the hypothesis that AF is liable to worsen the spontaneous evolution of stroke over the acute phase. In the context of selection of patients to be enrolled in acute ischemic stroke clinical trials as well as in the evaluation of drug efficacy, AF cases should be evaluated separately. Early CT images may help in the selection of cases with a worse prognosis.

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CEREBRAL ISCHEMIA DUE TO SACCULAR CEREBRAL ANEURYSM. WARNING SIGN PRIOR TO SUBARACHNOID HEMORRHAGE? Ph Lyrer, EW Radu, O Gratzl, *Basel, Switzerland*

Ischemic events due to emboli from a saccular aneurysm have rarely been mentioned. We present four patients, who suffered from cerebral ischemia and saccular cerebral aneurysm The history, the clinical signs, CT and angiography strongly suggested emboli from a thrombus within the aneurysm being the cause of the events One patient developed a major subarachnoid hemorrhage one day after ischemic symptoms One patient suffered from focal subarachnoid hemorrhage. In two patients there was no bleeding when diagnosis was made. In one of these patients histologic examination confirmed the presence of a clot within the aneurysm. The pathogenetic mechanisms of ischemia in patients with cerebral aneurysm and ischemic events as warning signs of subarachnoid hemorrhage are discussed in details.

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SMALL INFARCTS IN THE CENTRUM OVALE: STUDY OF THEIR PREDISPOSING FACTORS. D Leys, F Mounier-Vehier, Ph Rondepierre, X Leclerc, O Godefroy, MJr Marchau, Ph Scheltens, JP Pruvo. *Lille, France; Amsterdam, The Netherlands.*

The aim of this study was to investigate whether most small (<l5mm) subcortical infarcts (SSI) located in the centrum ovale (CO) are lacunes. We conducted this study in 255 consecutive patients with a first-ever ischaemic stroke. Fifty seven patients had CO-SSI. Patients with CO-SSI were more likely to have silent infarcts (95% CI.OR: 5.2-20.1), lacunar syndromes (95% CI.OR: 5.5-55.1), arterial hypertension (95% CI.OR: 1.5-5.4), leukoaraiosis (95% CI.OR: 2.3-8.1) and basal ganglia -SSI (95% CI.OR: 1.4-6.4) and less likely to be males (95% CI.OR: 0.3-0.9) and to have a non-lacunar syndrome (95% CI.OR: 0.010.07). The logistic regression analysis showed 4 independent factors of CO-SSI: silent infarcts (p=O.OOl), diabetes mellitus (p=0.0198), arterial hypertension (p=0.0252)

and leukoaraiosis scores (p=O.OOl). The presumed cause of stroke was "large-vessel atherosclerosis" in 7 patients and "cardioembolism" in 16. Patients with CO-SSI are likely to have risk factors for small-vessel occlusion, but other mechanisms account for one third of them.

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CEREBRAL VENOUS THROMBOSIS: STUDY OF CAUSES AND PROGNOSIS IN 18 CONSECUTIVE PATIENTS (1990-1993). PH Rondepierre, M Hamon, F Mounier-Vehier, X Leclerc, E Janssens, D Leys. *Lille, France.*

The management of patients with presumed cerebral venous thrombosis (CVT) has been recently modified by (i) the introduction of cerebral magnetic resonance imaging (MRI) and (ii) evidence (in 1991) that heparin decreases mortality and morbidity. No large consecutive series of patients with CVT has been reported since then. The aim of our study was to determine the role of clinical data in the diagnosis delay and in the ask of early death. Clinical and radiological data and outcome were studied in an homogenous sense of 18 patients with CVT consecutively included in this study over a 2-year period (1991-1993). All patients were treated by heparin at the acute stage. In 9 patients, the diagnosis was established with certainty within 10 days after onset: in this group, the onset was sudden and no patient died at the acute stage. In the 9 remaining cases, the onset was insidious with progressive headache; the diagnosis was established more than 10 days after onset and 2 patients died at the acute stage. This study suggests that the prognosis in CVT mainly depends on the delay in diagnosis and treatment. MRI is necessary in emergency in patients with symptoms presumably due to CVT.

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EARLY PREDICTORS OF DEATH AND DISABILITY AFTER ACUTE CEREBRAL ISCHAEMIA. H Henon, D Leys, O Godefroy, X Leclerc, F Mounier-Vehier, Ph Rondepierre, C Lucas, JP Pruvo. *Lille, France.*

Therapeutic trials are currently running to improve outcome in ischaemic stroke. The aim of our study was to determine early predictors of death and disability within 24 hours after stroke onset.152 consecutive patients with ischaemic stroke were evaluated within 24 hours of onset. We determined the 8-day mortality rate and the 3-month functional outcome by means of the Glasgow Outcome Scale (GOS). Clinical and CT variables were collected within 24 hours of onset and were tested in a multivariate statistical model. The 8 day mortality rate depended on the level of consciousness at admission. Death or dependency at month-3 (GOS 3-5) depended on the level of consciousness, severity of the clinical deficit, history of stroke and age. This risk was only of 10 % (95% CI: 2-18%) in patients < 70 years with an Orgogozo's score ≥ 60, normal consciousness and no previous stroke. Active and placebo groups should be balanced for the initial level of consciousness, seventy of the clinical deficits, history of stroke and age. Treatments which are potentially active but also dangerous, such as fibrinolytic drugs, should not be used in patients who have predictors of good outcome.

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SILENT INFARCTS IN PATIENTS WITH ISCHEMIC STROKE ARE RELATED TO AGE AND SIZE OF THE LEFT ATRIUM. F Mounier-Vehier, D Leys, PH Rondepierre, O Godefroy, JP Pruvo. *Lille, France.*

The aim of this study was to determine risk factors for silent infarcts in stroke patients. We conducted the study in 595 consecutive patients with stroke or transient ischemic attacks. Silent infarcts were defined as asymptomatic infarcts detected on CT scans performed within 24 hours of onset, in patients without a of history of stroke and unrelated to the symptoms and signs of the index stroke. We compared patients with silent infarcts with the remainder for cerebrovascular risk factors and presumed mechanism of stroke. One hundred and sixteen patients had at least 1 silent infarct; 141 silent infarcts and 265 symptomatic infarcts were subcortical infarcts ≤15 mm. Univariate analysis showed that patients with silent infarcts were more likely to be older than 65 years (99% CI.OR: 1.11-3.49), to have left atrial enlargement on echocardiography (99% CI.OR: 1.02-26.70) and leukoaraiosis (99% CI.OR: 1.39-4.21). Discriminant analysis found 2 independent factors: left atrial enlargement (P=0.007) and age> 65 (P=0.03). Age and left atrial enlargement are the 2 main factors associated with the presence of silent infarcts in patients with ischemic stroke or transient ischemic attacks.

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STROKE PATTERNS IN PATIENTS WITH INTERNAL CAROTID ARTERY OCCLUSION. F Mounier-Vehier, JP Pruvo, D Leys. *Lille, France.*

Stroke patterns in patients with total occlusion of the internal carotid artery (ICA) of presumed atherosclerotic origin, and no other potential cause, remain unknown. The aim of our study was to determine the pattern of stroke in such patients. Of 1,000 consecutive patients admitted for an acute ischemic event over a 4-year period and surviving more than 10 days, 42 (31 males and 11 females, mean-aged 63.2 years) had a unilateral total occlusion of the ICA of presumed atherosclerotic origin and no other potential cause of stroke. They had 2 CT scans, doppler ultrasonography and B-mode echotomography of the cervical arteries or angiography and transthoracic echocardiography. Locations of infarcts were compared between both hemispheres. We found ipsilateral infarcts in 34 patients (81%; 99%CI: 65-97%) and contralateral infarcts in 14 patients (33%; 99%CI: 15-52%). Infarcts ipsilateral to the ICA occlusion were more likely to be cortical (OR: 8.50; 99% CI.OR: 2.26-31.98) or subcortical ≥ 15 mm (OR: 8.84; 99% CI.OR: 1.53-51.03). The prevalence of subcortical infarcts <15mm did not differ between hemispheres. This study suggests that (i) infarcts ipsilateral to an ICA occlusion are likely to be cortical or subcortical >15mm, (ii) subcortical infarcts <15mm in such patients may be coincidental.

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SPONTANEOUS CERVICAL EPIDURAL HEMATOMAS MIMICKING SPINAL CORD TRANSIENT ISCHEMIA. P Le Coz, F Woimant, M Haguenau, *Paris, France.*

Spontaneous cervical epidural hematoma is an uncommon event that initially produces a permanent neurological deficit unless there is early surgical decompression. Spinal epidural hematomas are well-recognized by CT scan and especially by sagittal MRI of the spine. However spontaneous recovery remains exceptional. We describe 2 patients? a 24 year old man and a 79 year-old woman with no previous history of trauma who were admitted in emergency for a sudden weakness of limbs? respectively a tetraplegia and a right hemiplegia. Both patients complained of inaugural and acute neck pain. No cortical or brainstem dysfunction were observed. Brain CT scan was normal. In both patients? motor deficit completely resolved in few hours and MRI of the spine showed on T1 a signal isointense extending from C3 to C6 consistent with an hematoma. Laboratory data and angiography were normal. Neck pain lasted about a week. Follow up MRI was normal one month later. Conclusion: Epidural hematoma revealed by transient neurological manifestations is exceptional. However, it must be considered in the differential diagnosis of other acute painful vascular conditions like symptomatic vertebral dissection to avoid inappropriate anti coagulation.

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CIRCADIAN RHYTHMICITY AND DIURNAL ACTIVITY IN ONSET OF INTRACEREBRAL HEMORRHAGE. H Kuçukoglu, S Baybas, A Dervis, B Yalçiner, N Yilmaz, M Ozturk, B Arpaci.. *Istanbul; Turkey.*

Hundred forty four acute stroke diagnosed as spontaneous intracerebral hemorrhage, were investigated, prospectively for circadian rhythmicity and diurnal activity during the onset of the stroke. Forty mine percent were male, and the mean age was 62.9 years. The occurrence of stroke was more between midnight and 6 am, increased abruptly around 6 am, and remained high until midnight (p 0.001). Ninety two percent were awake at stroke onset; 45.5% were at rest, 44.7% had normal activity, 9.8% occurred during exertion (p 0.001). Eight percent took place during sleep (p 0.001). We conclude that hemorrhagic stroke occurs during days hours, when the patient is awake. In addition, exertion has not been observed to be an important risk factor. Our results could help to understand the basic physiological mechanisms of the intracerebral hemorrhage, and thereby aid to in their prevention.

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SERUM LEVELS OF NITRATES IN FOCAL CEREBRAL ISCHEMIA. JA Molina, FJ Jimenez-Jimenez, JA Navarro, E Ruiz, J Arenas, A Perez-Sempere, JA Egido, C Soriano-Soriano, L Ayuso-Peralta, P Fernandez-Calle. *Madrid, Alcala de Henares & Segovia, Spain*

To ascertain the possible role of nitric oxide (NO) as a risk factor for cerebral ischemia, we studied the serum levels of nitrate (oxidation product that provides an indirect estimation of NO), in 49 patients between the 3rd and 7th days after a cerebral ischaemic event (TIAs, RIND and cerebral infarction) and: in 65 matched-controls. Nitrates were measured in serum by a' kinetic method in which nitrate is reduced to nitrite (Greiss ' reaction) by copper-coated cadmium granules. The serum levels of nitrate did not differ significantly between patients with cerebral ischaemia patient and control groups (42 . 6±3 . 34 and 44.8±2.67 μmol/L, respectively). They were not influenced by age, blood pressure, or smoking and alcohol-drinking habits. These results suggest that serum levels of nitrate are apparently unrelated to the risk for cerebral ischaemia.

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CEREBRAL VENOUS AND ARTERIAL THROMBOSIS IN ACUTE ULCERATIVE COLITIS. J-Ph Neau, P Beau, J-M Gergaud, C Coudero, C Agbo, R Gil. *Poitiers, France*

Cerebral venous and arterial thrombosis are infrequent, but well-described extraintestinal complications of ulcerative colitis (UC). We report two cases. Case 1. A 33 year-old man, diagnosed with UC 7 years ago by colonoscopic examination and biopsies, had an acute relapse of UC which was treated with prednisolone and mezalazine. A few days later he developed headaches and generalised tonic clonic seizures. Neurological examination was normal. CT scan showed the "empty delta sign" and cerebral angiography demonstrated venous thrombosis of the superior sagittal sinus and right parietal veins. A coagulation profile gave normal results. Anticoagulation treatment was started and stopped 3 months later. Case 2. A 34 year-old woman developed diarrhoea, weight loss and abdominal pain. Colonoscopy confirmed pancolitis and biopsies revealed a histologic picture consistent with acute UC. Oral mesalazine and prednisolone were started. Two days later she developed an acute right hemiparesis with aphasia. The platelet count was 748.000/mm3. CT scan showed a left middle cerebral territory infarction and cerebral angiography an occlusion of the left MCA. Despite the anticoagulation, the severe hemiplegia with aphasia has persisted. Thromboembolic disease has been reported in 1.3-7.1% of cases of inflammatory bowel disease. 16 cases of cerebral venous thrombosis and 13 cases of cerebral arterial thrombosis in patients with UC were described. Cerebral complication is related to exacerbation of colitis in 90% of patients. The outcome is poor. The treatment remains difficult and controversial. The mechanism of cerebral thrombogenesis is unclear but a hypercoagulable state in those with active UC may be postulated.

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CRONIC ATRIAL FIBRILLATION IN PATIENTS WITH ASYMPTOMATIC CEREBRAL INFARCTION. I Vecchio, C Tornali, A Nicoletti, L Rampello, G Pennisi, R Raffaele. *Catania, Italy.*

In only the past decade has it become clear that atrial fibrillation (A.F.) is marker of increased risk for stroke. Several recent epidemiologic and clinical studies have confirmed this association. In addition to these clinical strokes, A.F. has been associated with subclinical "silent" strokes. Our study confirms the importance of A.F. associated with cerebral embolism. A retrospective analysis of 28 patients with atrial fibrillation presenting with symptoms of cerebral embolism between 1990 and 1993 was performed. Five patients had computed tomographic evidence of previous, clinically silent cerebral infarction. In a control group of 48 patients (study prospectively) in sinus rhythm symptoms of cerebral ischemia, six had computed tomographic evidence of previous, clinically silent cerebral infarction. In those patients with A.F. all infarcts were peripheral and consistent with embolism, while in two of six patients in sinus rhythm the asymptomatic infarcts were lacunes. The purpose of our study was to assess the prevalence of previous asymptomatic cerebral infarction in patients with A.F. at the time of their initial symptomatic cerebral ischemic event.

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TC-99M HMPAO SPECT IN ACUTE ISCHEMIC INFARCTION, EXPRESSING DEFICITS AS MILLILITER ZEROPERFUSION: PRELIMINARY RESULTS. RA Dierckx, A Dobbeleir, BA Pickut, E Timmermans, W Deberdt, J Vandevivere, PP de Deyn. *Ghent, Belgium*

In 27 patients (mean age 68.8 years) we compared the relative contribution of perfusion SPECT and CT-scan in acute ischemic infarction. Also, we examined the correlation of SPECT lesions with clinical evaluation at onset. SPECT was performed using a 3-headed SPECT system equipped with lead fanbeam collimators. Acquisition was started 20 minutes after intravenous injection of 25 mCi Tc-99m HMPAO. SPECT deficits were expressed as milliliter zeroperfusion, being a virtual parameter simultaneously accounting for extent and degree of hypoperfusion. This method provides a workable, accurate virtual parameter, with the assumption that the contralateral brain region remains uninvolved. Interobserver reproducibility in 12 SPECT studies with lesions varying between 6 and 369 cc showed a correlation coefficient r=0.99. Whereas mean delay since the onset of symptomatology was approximately 7 hours for both SPECT and CTscan, SPECT showed lesions concordant with the neurological clinic in 100% and CT-scan in 48%. Moreover, we found a statistically significant correlation ($P<0.01$) when comparing size of SPECT lesions during the acute stage with Orgogozo Scale score obtained on admission. In conclusion, perfusion SPECT expressing deficits as millilitre zeroperfusion deserves consideration as sensitive functional baseline in treatment strategies for acute ischemic infarction.

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PRECIPITATING FACTORS IN ADULT SUDDEN DEATH CAUSED BY STROKE. Y Hirata,Y Satoh, K Nagata, T Maeda, *Akita, Japan*

This study was designed to elucidate the precipitating factors in adult sudden death (intrinsic death) due to cerebrovascular disease (stroke) within 24 hours of onset. Fifty-three adults (44 men, 9 women, under age 60), victims of sudden death caused by stroke (33 brain hemorrhage, 19 subarachnoid hemorrhage, 1 brain infarction) were studied. Precipitating situations and risk factors of stroke were investigated. Sudden death occurred most frequently during work (15.1%). Other situations, in order of decreasing frequency, were; while asleep (13.2%), during defecation (13.2%), during sport (7.5%), drinking alcohol (7.5%), bathing (5.7%), and while house keeping (3.8%). Other instances in which sudden death occurred were; during sexual intercourse, while commuting, while shifting house, on the telephone, and while giving a speech. Cases in which the exact circumstances were undetermined, were relatively frequent (13.2%). Hypertension was the most common stroke risk factor (93%). Conclusion: The results suggest that sudden death by stroke can occur during stressful situations, and that hypertension is a high risk factor in sudden death.

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STROKE PATTERNS IN PATIENTS WITH ISCHEMIC STROKE OF UNKNOWN CAUSE AND ATRIAL SEPTAL ANEURYSMS.CH Lucas, D Leys, F Mounier-Vehier, H Henon, JP Pruvo. *Lille, France.*

It has been suggested that, in patients with atrial septal aneurysms (ASA), brain infarcts occur more frequently in the vertebrobasilar territory. The aim of our study was to compare the location of infarcts between: (i) 26 patients with an ASA and no other potential cause of stroke, (ii) 76 patients with a definite cardioembolic stroke (TOAST criteria) and no ASA, and (iii) 64 patients with definite large-vessel arteriosclerosis (TOAST criteria) and no ASA. Infarcts were less likely to be cortical ($P=0.0052$) in the ASA group than in the large-vessel atherosclerosis group but their location did not differ from that of the cardioembolic group. The prevalence of vertebrobasilar infarcts did not differ between groups. This study does not support the hypothesis that, in patients with ASA, brain infarcts occur more frequently in the vertebrobasilar territory.

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THROMBOSED GIANT ANEURYSM: ARARE CAUSE OF CEREBRAL INFARCTION. M Gomez, J Aguirre, A Berenguer, C Duran, J Parrilla, F Gonzalez, *Badajoz, Spain.*

Giant intracranial aneurysms are defined as those over 25mm in diameter. They represent approximately 2.5-5% of all intracranial aneurysms. There are 3 distinct locations: the supraclinoid portion of the internal carotid artery (45-55% in recent series); the peripheral intracranial arteries: middle cerebral artery (10-15%) and anterior cerebral artery (4-10%) and the posterior circulation (approx. 25%). The symptoms are related to their location and size. Symptoms of mass lesion occur in more than 50% of patients and subarachnoid hemorrhage in less than 30%. Other symptoms include: transient ischemic attacks due to embolism from a partial thrombosed aneurysm, evidence of intracranial pressure, headache and seizures. Here we present the case of a 60 year old man who suddenly developed aphasia and right hemiplegia. CT scan showed an image suggesting a thrombosed giant aneurysm at the Sylvian region and also a hypodensity lesion corresponding to the left middle cerebral artery (MCA) distribution.

MRI confirmed CT images and the anterograde propagation of the thrombus through the MCA. Cerebral angiography showed the complete thrombosis of the left MCA at M1 segment. Both, the complete thrombosis of a giant aneurysm and its anterograde or retrograde propagation is extremely rare. There are only 3 cases reported in the literature of cerebral infarction as a consequence of this mechanism.

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POSITIONAL CEREBRAL ISCHEMIA. A Gironell, A Rey, JL Marti-Vilalta, *Barcelona, Spain*

We present a very unusual case of an ischaemic stroke in which a transient increase in focal deficits was related to orthostatic hypotension. A 67 years old female presented with an ischaemic stroke of the left middle cerebral artery. She had previous hypertension and was taking correct antihypertensive therapy. On admission, clear fluctuations in symptomatology were noted depending on the patient's position related to orthostatic hypotension. This syndrome disappeared when antihypertensive therapy was withdrawn. Dynamic magnetic resonance angiography revealed an occlusion of the left carotid artery, a severe stenosis of the right carotid artery and retrograde flow in both ophthalmic arteries. Our case report shows positional cerebral ischaemia syndrome as a symptom of large vessel occlusion, and indicates the need for caution and supervision in initial postural changes in acute ischaemic stroke patients. Great care should be taken with antihypertensive therapy in these patients.
January 4, 1994

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SILENT INFARCTS AND COGNITIVE IMPAIRMENT. A Frank, I Plaza, M Alonso de Lecinana, J Munoz, P Barreiro, E Diez-Tejedor. *Madrid; Spain.*

It seems possible that silent brain infarcts (SBI) may influence the occurrence of cognitive impairment, although this has not been yet proven. In order to investigate this question we have analysed the presence of SBI in a group of demented patients. Fifty three patients with dementia, 30 of Alzheimer type (ATD) and 23 of vascular type (VD), similar by evolution and age (mean age (SD = 70±6 years) were studied. Mental status, severity of dementia, vascular risk factors and history of previous stroke were analysed and the number, the localization and the volume of brain infarcts were studied by TC scan. To define the existence of SBI in each case, a clinical-radiological correlation was established and the results were statistically analysed. The incidence of SBI was higher in VD (n=10, 43%) than in ATD (n=7, 23%). SBI were localised preferentially in posterior parietal (ATD) and temporal (VD) lobes. There were no differences in severity of dementia nor in existence of vascular risk factors between the two groups. Presence of SBI could be useful to discriminate between VD and ATD, but it does not seem to exert any influence in the severity of the cognitive impairment. Nevertheless, more studies should be done to confirm these findings.

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METABOLIC LONGITUDINAL CHANGES DETECTED BY PROTON MAGNETIC RESONANCE IN ISCHEMIC STROKE. F Federico, C Conte, IL Simone, P Giannini, M Liguori, V Lucivero, E Picciola, C Tortorella. *Bari; Italy.*

Proton magnetic resonance spectroscopy (H-MRS) is a non invasive technique which has proved to be useful for monitoring a number of metabolites in the brain , including N-acetyl-aspartate (NAA), creatine-phosphocreatine (Cr-Pcr), compounds containing choline (Cho) and Lactate (Lac), in patients (pts) with brain ischemia. Combined Magnetic Resonance Imaging (MRI) and H-MRS investigations were performed with a whole-body 1,5 T. iron -shielded system (Magnetom Siemens), using a Spin Echo (TE: 135 ms) sequence to acquire localized spectra from image-guided volumes of interest (from 8 to 16 ml). We examined 12 pts within 96 hours after acute cerebral infarction, and a follow up study on day 7 to 60 after stroke was performed on these patients. An analysis of our findings indicates that NAA is reduced (to 56% of contralateral) in the infarcted area more than other metabolites during the early phases of ischemia; in 5 pts serial examinations show a further but slight decrease of NAA. Lac is detected in all pts in the acute stage of ischemic lesions and in 4 pts at follow up. Our results suggest that high early lactate signal and a marked decrease of NAA implies a large stroke and a poor prognosis.

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MULTIFOCAL HEMORRHAGIC STROKE IN ECLAMPSIA AND PREECLAMPSIA. F Drislane; A Ming Wang, *Royal Oaks, MI, & Boston, MA, USA*

Preeclampsia and eclampsia have often been associated with transient cortical blindness and with bi-occipital CT scan hypodensities or multifocal increased T2 signal abnormalities on MRI. The symptoms and radiological findings are usually reversible and the prognosis good. Petechial haemorrhages have been described pathologically. We reviewed the clinical and radiological findings in 4 patients with eclampsia or Pre-eclampsia who had cerebral haemorrhages found acutely on CT scans. All had multifocal haemorrhages, usually bilaterally and often in posterior areas. Two had haemorrhages discovered after earlier normal scans. One patient died and the others had prolonged or permanent neurologic residua including visuospatial and other cognitive deficits. We conclude that eclamptic and pre-eclamptic patients with sudden neurologic symptoms do not always have benign reversible abnormalities but may have multifocal haemorrhages with long-term neurologic complications. The affected areas are most often posterior, and haemorrhages may follow the more benign findings.

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RELATIONSHIP BETWEEN HEMOGLOBIN CONCENTRATION AND ISCHAEMIC STROKE. R. Di Mascio, R Marchioli, F Vitullo, A Di Pasquale, L Sciulli,V Kramer, G Tognoni, *Chieti, Italy*

The hypothesis that high normal haemoglobin levels are associated with an increased risk of cerebral infarction does not have a consistent evidence. We examined this relationship using data from a hospital-based case-control study conducted in Abruzzo, southern Italy, between April 1990 and March 1992. The analyses were performed on 143 patients with diagnosis of first ischaemic stroke confirmed by tomography computerised scan (age 30-69 years) and 143 matched controls by sex and age with acute diseases not related to known or potential bleeding conditions. Hemoglobin, measured at admission, was higher in cases (mean: 14.2 g/L, SD 1.6 g/L) than in controls (mean: 13.7 g/L, SD 1.6 g/L) ($p < 0.05$). Compared with subjects with haemoglobin levels less than 13 g/L (reference category), the relative risks (RR) of ischaemic stroke, after adjustment for sex and age, were 1.8 (95% CI: 0.8-3.9) for the 13-13.9 g/L quartile, 2.2 (95% CI: 1.1-4.6) for the 14-14.9 g/L quartile, and 3.0 (95% CI: 1.4-6.3) for the 15+ g/L quartile. Estimates adjusted by sex, age and cigarette smoking were 1.6, 2.3, and 2.8 respectively. After allowance for sex, age, cigarette smoking, hypertension, diabetes, cholesterol levels and other covariates, the estimated RR were 1.9 (95% CI: 0.8-4.9), 2.8 (95% CI: 1.2-6.5), and 3.2 (95% CI: 1.4-7.4) for the related categories (X^2 for linear trend: 7.27, $P< 0.01$). No statistically significant effect modification was observed by strata of sex, age, hypertension, smoking and other variables. Further investigations are needed to ascertain if haemoglobin may have a causal role in cerebral infarction.

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CARBON 11-METHIONINE AND FLUORINE-18-FLUORODEOXY-GLUCOSE PET STUDY IN BRAIN HEMATOMA S Dethy, S Goldman, S Blecic, A Luxen, M Levivier, J. Hildebrand, *Brussels, Belgium.*

Three patients were examined by means of positron emission tomography (PET) with L-methyl-^{11}C- Methionine (11C-methionine) and 2-^{18}F-fluoro-2-deoxy-D-glucose (FDG), 20 to 32 days after the occurrence of non tumoral brain hematomas. PET revealed high uptake of ^{11}C-methionine in the area surrounding the hematoma in all three patients. In two patients, discrete spots of moderate uptake of FDG were found at the periphery of a hypometabolic area. PET studies were repeated in two patients 76 or 103 days after the bleeding and showed a dramatic decrease in ^{11}C-methionine uptake around the hematoma. The spots of FDG uptake had disappeared on the repeated late scans. We hypothesise that the subacute gliotic reaction surrounding brain hematomas is responsible for increased uptake of ^{11}C-methionine and the presence of spots of FDG uptake. PET studies with ^{11}C-methionine and FDG, performed 20 to 32 days after the onset, are not helpful in the differentiation between neoplastic and non neoplastic origins of an intra-cerebral hemorrhage since tracer uptake at the periphery of the lesion may be increased in both. At a later time, PET with both tracers may be helpful in making this distinction.

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TC-99M HMPAO SPECT IMAGING IN SPONTANEOUS THALAMIC HEMORRHAGE. A del Olmo, A Alfaro, E Caballero, R Sanchez, *Valencia, Spain*

We prospectively studied a series of 25 patients, 14 males and 5 females, aged 49 to 88 years (mean 70,9), in order to analyse the patterns of regional cerebral blood flow (CBF) impairment and their relations to other prognostic factors and outcome in thalamic hemorrhage (TH). Symmetrical regions of interest (ROIs) were selected on transverse slices of 12,8 mm thickness. Left to right hemispheric differences of isotopic activity were degree 0 to 3 in a semiquantitative fashion. only differences greater than 10% (maximum observed in a control group) were considered significant. only 3 (12%) patients died, but 18 (72%) remained with a variable grade of disability. outcome was significantly related (p<0,05) to the level of consciousness, volume of hematoma, ventricular index and maximum cortical homolateral cerebral diaschisis, but not to contralateral cerebellar or cerebral diaschisis. Homolateral cerebral diaschisis was related to ventricular index but not to the time of evolution and volume of hematoma. Measurement of regional CBF with Tc-99m HmPAO SPECT may be useful to predict outcome in patients with TH.

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CEREBELLAR JUNCTIONAL INFARCTS MAY BE ASSOCIATED WITH CARDIOEMBOLIC SOURCE OF STROKE. I Degaey, F Mounier-Vehier, X Leclerc, D Leys, *Lille, France.*

It has been suggested that most junctional cerebellar infarcts are due to large-artery diseases involving vertebral or basilar arteries. In order to the hypothesis that cardioembolism may also be associated with junctional cerebellar infarcts we studied risk factors and presumed mechanism of stroke (TOAST criteria) in 14 consecutive patients (9 males, 5 females; 29-84 years) with a total of 20 junctional cerebellar infarcts (Amarenco's criteria) on cerebral magnetic resonance imaging or CT- scans. Results: the presumed cause of stroke was "cardioembolism" in 5 patients: 3 with atrial fibrillation, 1 with left ventricular akinesia, 1 with valvular prothesis, 1 with cardiogenic shock), dissection of the vertebral artery in 3 patients. Six patients had a negative diagnostic work-up. Conclusion: this study suggests that cardioembolism may be a more frequent than previously suggested in patients with junctional cerebellar infarcts.

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TREATMENT OF BASILAR ARTERY THROMBOSIS: A CONTROVERSIAL ISSUE. SFTM de Bruijn, M Limburg , I Tchaoussoglou, *Amsterdam, The Netherlands*

We performed a postal questionnaire among all Dutch clinical neurologists to investigate therapeutic controversies in basilar artery thrombosis. We addressed 320 neurologists. The questions were: 1. What is your current treatment in case of a basilar artery thrombosis? 2. What kind of treatment would you prefer to investigate in a randomised therapeutic trial? 3. Do you think placebo is justified? RESULTS. The response rate was 56% (180/320). Anticoagulants were preferred by 56.2%, 'wait and see' was the main policy for 18.7% (chi^2, p=0.0000006). Only 1.7% considered thrombolytics to be an option. A future trial should investigate thrombolysis followed by anticoagulants versus only anticoagulants according to 32.3%. Thrombolysis/ anticoagulants versus placebo was the design of first choice for 29.4% (chi^2, p=0.08). 47.5% feels placebo treatment is allowed; 42.5% mentioned this to be unacceptable (chi^2, p=0.55). Conclusion: treatment of basilar artery thrombosis is variable and controversial, although anticoagulants form the therapy of first choice for the majority.

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SPONTANEOUS HEMORRHAGIC INFARCTION: INCIDENCE, PREDICTORS AND CLINICAL EVOLUTION. D Toni, M Fiorelli, S Bastianello, ML Sacchetti, C Pozzilli, C Argentino, *Rome, Italy*

In a continuous series of 150 patients hospitalised and submitted to a baseline CT scan within 5 hours of their first ever ischemic supratentorial stroke, we investigated incidence and predictors of the subsequent hemorrhagic infarction (HI), as identified by either repeat CT or autopsy performed within 7±2 days of onset, and its influence on the 30-day clinical outcome. Sixty-five patients (43%) developed HI. At hospital admission, patients with subsequent Hl had a mean Canadian Neurological Scale (CNS) score of 5.1 ± 0.2 as compared to 5.9±0.2 of non Hl patients (P< 0.01), whereas no significant differences were found as to demographic characteristics and past medical history. HI and non HI patients received similar therapies, including i.v. and oral anticoagulants. Baseline CT showed early hypo density (EH) in 61 (94%) of the patients with subsequent HI and the hyper dense middle cerebral artery sign (HMCAS) in 31 (48%) of them, as opposed respectively to l 8 (21 %) and 9 (11 %) of the non HI subjects (P 0<.00001). A multiple regression analysis showed that Hl did not influence the 30 day clinical outcome (P=0.6), as opposed to EH (P<O.OOl), baseline CNS (P<0.05) and age (P<0.001). These data suggest that spontaneous hemorrhagic transformation is a frequent occurrence in ischemic stroke and that it does not influence clinical outcome.

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RISK AND PROGNOSTIC FACTORS IN LACUNAR INFARCTION. A Cervello, A Alfaro, *Valencia, Spain*

The nosological individuality of lacunar infarction (LI) has been questioned in recent years on the assumption that LI may be only small deep infarcts with the same etiologic and pathogenetic determinants as cortical infarcts (CI). We studied a series of 170 consecutive patients with CT verified LI. Lacunes were considered small if < 5 mm and large if > 5 mm. A scale of 8 grades was established combining the number and size of LI. outcome was graded according to the abilities in daily living. A significant proportion of patients with IL < 5 mm were diabetic (p=0.002), consumed alcohol or tobacco (p=0.038) and had high values of mean corpuscular volume (MCV, p=0.009) and erythrocythemia (p=0.031). The factors most strongly related to large IL (> 5 mm) were age and past stroke The best predictors of outcome were age (p=0.003), EEG abnormalities (p=0.003), and the size of lacunes on CT (p=0.001). Patients with LI seem to comprise an heterogeneous population of at least two groups. It is probable that, as foretold by CM Fisher, only deep inverts < 5 mm in diameter deserve the name of LI.

104
SILENT CEREBRAL INFARCTION IN PATIENTS WITH BILATERAL INTERNAL CAROTID ARTERY OCCLUSION (BCAO). N Catala, G Rancurel, F Koskas, E Kieffer. *Paris, France*

Silent cerebral infarction (SCI) has been linked with severe involvement of the carotid arteries (Norris and Zhu, Stroke 1992; 23: 483-485). We had the opportunity to study 19 patients presenting an angiographically-proven BCAO. All these patients underwent cerebral CT, cerebral arteriography, neuropsychological testing and Xe133 rCBF study at rest and after IV acetazolamide. We disclosed an old infarct on CT without any relevant clinical symptoms in 5 among 19 patients (26%). These 5 patients presented 7 foci of SCI. The infarct was probably due to a hemodynamical cause in 5 among 7 affecting the centrum semiovale in the subcortical territory of the superficial middle cerebral artery (MCA) in 3 cases, the junction between MCA and posterior cerebral artery in 1, and the junction between MCA and anterior cerebral artery in 1. The parietal cortex in the distribution of the MCA was involved in the 2 other infarcts. rCBF was normal at rest in all our patients. Acetazolamide reactivity was normal in 2 and impaired in 3. Neuropsychological deficits were evidenced in 4 patients. Our study showed that SCI is a common feature associated with BCAO justifying a systematic CT or MRI study in the investigations proposed for such patients

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SPONTANEOUS SUBARACHNOID HAEMORRHAGE, A CLINICAL-EPIDEMIOLOGIC STUDY. E Botia; J Vivancos; T Leon; T Segura; C Ramo; F Lopez. *Madrid, Spain.*

We studied clinical and epidemiological features of this disease, and evaluated prognostic factors for the development of major clinical problems. This is an observational study from an historic cohort. A hundred and eighty patients with spontaneous subarachnoid haemorrhage (SAH) confirmed by CT and/or lumbar puncture were included since January 1986. Age, sex, stroke risk factors, neurological status at admission (Hunt-Hess, Glasgow y WFNS scales) clinical features, amount of bleeding, (Hijdra et al. scale) angiographic findings, major complications or deaths frequency, treatment, and three and six month clinical status, were recorded. We present several descriptive parameters. Whole incidence was similar in both sexes and was greater in fourth and fifth decades of life, without a seasonal predominance. Throbbing headache, vegetative, and conscience disturbances were usually the first symptoms. A characteristic clinical picture and a very good prognosis was observed in idiopathic SAH. The best markers for poor outcome were: age >5O year old, high values in the above quoted scales, arterial hypertension, development of major systemic

or neurological complications, amount of bleeding measured by Hijdra et al. scale. We think the letter is an easy to reproduce and accurate method to predict outcome.

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The TEL-AVIV STROKE REGISTRY: 3286 PATIENTS. NM Bornstein, BD Aronovich, VG Karepov, AJ Gur, AD Korczyn, *Tel Aviv, Israël*

We tried to evaluate the role of various risk factors, and management of big cohort of patients with acute stroke. Israîl is a country with a heterogeneous population, of which a significant proportion was born abroad. The people differ in their genetic background, early environment, diet and other habits. Since May 1988 we have conducted a prospective hospital-based stroke registry using systematic computer coding of data. 3286 consecutive patients with stroke were admitted until November 1993 Results: Mean age was 72±7.4 years; 57.9 males. (64% patients were Ashkenazi and (35.8%) Sephardi. Cerebral infarctions were diagnosed in 80.9%, primary intracerebral haemorrhages in 8.4% and transient ischemic attacks in 10.8%. Past medical history of hypertension was in 50.9% of the patients, followed by diabetes mellitus, 24.3% ischemic heart disease, 28.1%, smoking 12.8%, atrial fibrillation 12.9% peripheral vascular disease 8.6% and hyperlipidemia 8.2%. Conclusions: This registry allows to study the natural history and clinical manifestations of stroke in different ethnic groups.

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STUDY OF LIPOPROTEINa (LPa) AND CAROTID STENOSIS IN STROKE, B Berlanga, V Gracia, C Fiol, F Rubio, *Barcelone, Spain.*

Lipoprotein(a), c-LDL, c-HDL, total cholesterol, other known risk factors and the degree of carotid stenosis were evaluated in 46 ischemic stroke patients, and in 46 age-matched control group. In stroke patients Lp(a) mean and median values were higher (32.49 mg/dl and 21. 80 mg/dl, respectively) than in the control group (21.55 and 14.95 mg/dl). We also observed higher mean values in cholesterol and lipoproteins in patients than in controls: total cholesterol 6 mg/dl (p=O.OOO), c-LDL 4.14 mg/dl (p= O.OOO) and c-HDL/TC coefficient 0.19 mg/dl (p=0.026). Hypertension (p=O.OOO) and smoking (p=O.OOO) were the first risk factors in patients, followed by hyperlipidemia. During the acute phase of stroke (two weeks), total cholesterol, c-HDL and c-LDL levels diminished, while Lp(a) and triglycerides parameters ascended. In addition, we observed significant cervical carotid stenosis in moderate degree (30-69%) correlated with Lp(a) 21.55 mg/dl. In conclusion: the present study emphasises the role of Lp(a) as an independent and mayor risk factor for carotid ischemic stroke.

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LIPID PEROXIDATION AND GLUTATHIONE IN CEREBRAL ISCHEMIA REPERFUSION INJURY. C Aykut, S Aktan, H Kurtel, U Ozkutlu and B Yegen. *Istanbul; Turkey.*

Oxygen free radicals are important factors in neuronal injury during cerebral ischemia and following reperfusion. Oxygen radical-mediated lipid peroxidation damages the membranes and increases the vascular permeability. Glutathione is an important endogenous antioxidant and protects the neuron by limiting the lipid peroxidation following ischemia and reperfusion. In this study, we investigated the role of oxygen free radicals in early reperfusion time intervals by using forebrain ischemia-reperfusion model in rats. After the animals were subjected to 10 min of ischemia by bilateral common carotid arteries reversible occulsion and stimultaneously hypotension, at 4 and 60 min of reperfusion, we determined thiobarbituric acid-reactive material (TBAR, an indicator of lipid peroxidation) and glutathione released upon reduction of protein glutathione miwed disulfides. Sham operations were performed for each corresponding group (n=8). While lipid peroxidation began to occur following 60 min of reperfusion (p<0.05), glutathione was depleted in early reperfusion(p<0.005). At 60 min of reperfusion, glutathione level was slightly increased but still being under the control group (p<0.05). At the beginning of ischemia-reperfusion injury, endogenous glutathione stores were consumed and lipid peroxidation was limited but by 60 min of reperfusion, intracellular antioxidant mechanisms were not sufficient in prevention of oxidative injury so lipid peroxidation was markedly elevated.

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PREVIOUS INFECTIONS AS AN IMPORTANT RISK FACTOR FOR CEREBROVASCULAR ISCHEMIA. AJ Grau, F Buggle, S Heindle, C Steichen-Wiehn,T Banerjee, M Maiwald, H Becher, W Hacke, *Heidelberg, Germany*

In a case-control study we investigated 197 patients with acute ischaemic stroke or TIA between 18 and 80 years and 197 controls matched for sex, age and area of residence in order to determine if recent infections are a risk factor for cerebrovascular ischaemia. In the week before ictus or examination, 38 patients (19,3%) but only 10 controls (5,1%) suffered from infections (relative risk 4.5, 95% confidence interval 2,1-9,7, p<0.001). During the 2 to 4 preceeding weeks, infections were not found significantly more often among patients than controls. Among these 38 patients, respiratory tract infections (n=23) and infections of bacterial origin (n=20) dominated. Infections were of similar importance in men and women (relative risk 4.60 and 4.33, respectively). Significant associations of infections and cerebrovascular ischaemia were found for the age groups 51-60 and 61-70 years, but not in younger patients a patients between 71 and 80 years. Infections remained a significant risk factor when hypertension, diabetes mellitus, smoking and hyper-cholesterolemia were included as covariates in a logistic model. Recent infections may be a hitherto underestimated risk factor or trigger mechanism for cerebrovascular ischaemia.

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SYNCOPE BY UNUSUAL "STEAL SYNDROME": BY-PASS FROM VERTEBRAL ARTERY TO INTERNAL CAROTID ARTERY WITH PERSISTENT EMBRYONIC PROATLANTAL ARTERY. J Aguirre, M Gomez, W Villafana, F Medina, A Berenguer, F Gonzalez, *Badajoz. Spain.*

Persistent embryonic anastomoses between internal carotid artery (ICA) and vertebro basilar system are very rare (0.8%). Proatlantal artery connects the vertebral with carotid system through the occipital artery. This artery, via retrograde perfusion, preserve the flow of the ICA. A few reported cases of persistent proatlantal artery have been associated with hypoplasia or aplasia of the vertebral arteries. The direction of the flow is usually to the vertebral system so patients may have symptoms due to ischemia of the carotid system. Common carotid artery atherosclerosis associated with persistent proatlantal artery is also uncommon. Here we present an exceptional case of syncopes due to a vertebro basilar to carotid system steal effect caused by atherosclerotic disease of both common carotids. CT scan showed an ischemic lesion in parieto-occipital territory. Duplex ultrasound demonstrated occlusion of left common carotid artery and a critical stenosis of right common carotid artery. Cerebral angiography showed the complete obstruction of left common carotid followed by a flow at the carotid bulb coming from the left vertebral artery. Stenosis >70% of the right common carotid was also seen. Surgical treatment bypassing right subclavian-to-carotid artery was performed in this patient obtaining hemodynamic and clinical relief

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IRON RELATED DAMAGE IN ACUTE ISCHEMIC STROKE. A Davalos, JM Fernandez-Real, W Ricart, S Soler, E. Planas, A Molins and D. Genis. *Girona, Spain*

The clinical role of ferrous-iron mediated free radical mechanisms has not been settled in acute stroke. We evaluated the influence of iron stores, measured as serum ferritin, on the outcome of acute cerebral infarction. Admission and fasting glycemia, glycated haemoglobin, serum cortisol, serum ferritin and 24-hour urine free cortisol levels were measured within the first 24 hours in 67 patients admitted by an acute ischemic stroke. On day 30th, 33 had good outcome (Canadian Scale Score >7) and 34 poor outcome (death or CSS <7). Fasting glycemia (P=0.001), serum cortisol (P<0.001), and urine free cortisol (P=0.001), but not admission glycemia and glycated haemoglobin, had higher levels in patients with poor outcome. Serum ferritin values were greater in the poor outcome group (218 ±156 ,ug/L vs 133±125 ug/L, P=0.004), and a linear correlation between the ferritin values and the degree of worsening Or improvement of the CSS on y 30th was found (P=0.002). Serum cortisol (OR 5.5, 95%CI 1.6-18.4) and serum ferritin (OR 4.4, 95% CI 1.2-11.1) were independently related with poor outcome in a logistic regression analysis. High serum ferritin within the first 24 hours after acute ischemic stroke was related to a poor prognosis, independently of the stress response. More research is needed to determine the origin of this increased serum ferritin, and the therapeutic implications.

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MULTIPLE SCLEROSIS AND BIPOLAR AFFECTIVE DISORDER HLA CLASS I AND II ANTIGENS AND MRI. E Iceman, Z Gulay, I Do-

ganer, B Tekinsoy, G Damlacik, G Badlan, B Genc, K Yulug, *Izmir, Turkey*

Both multiple (MS) sclerosis and bipolar affective disorder (BAD) are commonly seen in some families and there a is higher concordance rate for these diseases in monozygotic twins than dizygotic ones. Genetic factors seemed important in these relapsing-remitting . Sometimes mood abnormalities could be the first clinical imbecile manifestation in MS and discrete hyperintense subcortical abnormalities on MRI have been reported in BAD. The frequent association of BAD and MS raises important etiologic and clinical considerations. In this study MRI, HLA Class I and class II antigens were studied in 25 patients with BAD according to DSM III criteria and in 100 MS patients. Fifty healthy subjects were chosen as a control group. Only one of the patients with BAD had neurologic signs. In the BAD group MRI revealed undefined bright focus (UBF) in 10 patients (40 %), atrophy in 9 patients (36 %) and heterotopia in 1 patient (4 %). The frequency of HLA B8, HLA B7, HLA-B24 increased in patients with BAD. Increase of HLA-A1, HLA- B8, HLA-DR2 frequency was found in MS group. The frequency of HLA-B8 in both groups increased, and there was inverse correlation in HLA-A2. On the basis of the case reported and the evidence of published studies, our results suggest that there may be a real association of BAD with MS. BAD may be an initial symptom of MS, preceding other neurologic symptoms by several years and due to the anatomical site at the demyelinating rocs. Alternatively there may be a shared genetic predisposition to BAD and MS.

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THE RELATIONSHIP BETWEEN COGNITIVE DISTURBANCES AND SPECT, MRI ABNORMALITIES IN MULTIPLE SCLEROSIS. E Ideman, H Dural, F Idiman, K Kutlul, G Damalik, Y Baklan, B Metin, E Tekinsoy, O Obuz, *Izmir, Turkey*

It has been known FOR a long time the patients with multiple sclerosis show disturbances of higher cognitive functions. Cognitive decline is more frequent at me more advanced stages of the disease and in chronic progressive MS. The aim of this study was to examine the regional distribution of 99 m Tc HMPAO in the brain, the extent of cerebral lesions by MRI and the relationship between neuropsychological findings and abnormalities on MRI and SPECT. In twenty patients with MS neuropsychological disturbances using neuropsychological tests including eight items were studied. Then in all of them MRI and SPECT were done. Cognitive functions were impaired in 18 patients (90 %), MRI and SPECT abnormalities were found in 19 and 17 patients respectively. SPECT showed bilaterally significant hypo perfusion in 7 patients and unilateral hypoperfusion particularly in left temporo-parietal region of 7 patients. In the other 3 patients right temporo-parietal hypoperfusion was demonstrated. A relationship was found between severe cognitive disturbances and left temporo-parietal hypo perfusion or whole brain hypoperfusion on SPECT and left parieto-temporal lesions on MRI. This study underlines the practical utility of SPECT and MRI in the investigation of cognitive dysfunction in MS.

114
IMMUNE CHANGES IN MULTIPLE SCLEROSIS PATIENTS TREATED WITH AZATHIOPRINE.P de Castro, M Carreno, I Iriarte, M L Subira. *Pamplona Spain*

Benefit from azathioprine (AZT) treatment in multiple sclerosis is controversial. The aim of this study was to describe immunological changes in patients treated with azatioprine and to correlate these changes with clinical evolution. We studied 40 patients (29 women, 11 men) with clinically diagnosed MS. The patients were treated with azathioprine for 6-9 months, 100-150 mg a day. Immunological status was evaluated using a test of cellular immunity (with quantification of CD19, CD3, CD4, CD4+CD45, CD4+CD29, CD25, CD8PE, CD8F+HLAIIP+, CD8+CDIIbF+, CD8+ CDIIbF- and response to mitogens). Age was 41,2±9,8 years; disease duration was 9,81±8,6 years. Correlation with clinical data was calculated using nonparametric distributions techniques. Immunostimulation was observed in 48% of patients before starting the study. Lymphopenia and decrease in helper CD4 cells were observed as the most frequent effects of azathioprine. Immunostimulation were demonstrated in more than 40% of patients in the end of study. 18% of patients passed from normal immunity to immunostimulation during the treatment with AZT. Tendency to stabilization of the disease was observed without any relation with immunological changes. Conclusions: Lymphopenia and decrease of helper CD4 cells were the most frequent effects of treatment with azathioprine. Usual doses of azathioprine are not effective to produce immunosuppression in all patients.

115
EFFECTS OF INTRAVENOUS METHYLPREDNISOLONE ON LYMPHOCYTE DISTRIBUTION AND FUNCTION IN PATIENTS WITH MULTIPLE SCLEROSIS. AD Crockar, M Treacy, AG Droogan, TA McNell, SA Hawkins, Belfast, *Northern Ireland*

Intravenous methylprednisolone (IVMP) is the most effective known treatment for relapses of Multiple Sclerosis (MS) but the mechanism is unclear. Ten patients in relapse of clinically definite MS were treated with a 5 day course of IVMP (500 mg daily). Circulating lymphocyte subpopulations and determination of mitogen-induced γ interferon (γ-IFN) production, were performed immediately prior to initiation of therapy (Day 1), during therapy (24 hours after first dose, Day 2) and at 24 hours and 1 week post therapy (Days 6 & 12 respectively). Significant reductions in CD3+, CD4+, CD8+, CD4CD45RA+ and CD4CD45RO+ subpopulations were noted within 24 hours of initiation of therapy. These changes had returned to normal by Day 6 and remained normal on Day 12. Despite the reduction in total T cell numbers during treatment the γδT cell subpopulation was not significantly altered. HLA-DR expression on B cells and monocytes declined transiently on Day 2 to approximately 50% of pretherapy levels. δ-IFN production was significantly reduced ($p<0.05$) during therapy, but had returned to pre-treatment levels by Day 6 {Day 1:2148 ± 656 IU/ml; Day 2:1068 ± 470 IU/ml; Day 6:2424 ± 1158 IU/ml; Day 12:1940 ± 978 IU/ml} Decreased γ-IFN production may play a role in the rapid onset of improvement that occurs following IVMP therapy.

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CONTROLED STUDY OF BIOFEEDBACK EFFICACY FOR HEADACHE IN CHILDREN. L Grazzi, G Bussone, *Milan, Italy*

Tension type headache is a common clinical picture in children and Biofeedback (BFB) is considered a good treatment for it. A placebo effect has been hypothesised responsible of the clinical improvement, although the long-lasting follow-up period induce to think to a real efficacy of this approach. We compared clinical results (expressed by Pain Total Index-PTI) obtained in 2 groups of children suffering from episodic tension type headache: group A was treated by 10 sessions of Electromyographic-BFB; Group B was not given instructions for relaxation and only basal EMG levels were recorded for 10 sessions. Follow-up sessions were fixed for both groups 1 month, 3, 6, 12 months after the end of the treatment. A significant clinical improvement after treatment was observed in both groups; at the last follow-up, 12 months after the end of treatment, PTI decreased significantly in group A, not in group B. (Group A:$p<0.01$;0.001; Group B: $p<0.001$; ns).No changes in muscular tension values were observed. A significant clinical improvement after treatment was observed in both groups; the improvement continues to increase only in group A until 12 months after: probably because these patients learned really the relaxation practice. This result seems to confirm BFB as an optimum approach for tension type headache in children.

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SUBCLINICAL ANTERIOR HORN CELL INVOLVMENT IN JUVENILE MYOCLONIC EPILEPSY. C Ertekin, N Ediboglu, H Bilgin, S Ertas. *Bornova-Izmir, Turkey.*

An electromyographic finding of subclinical anterior horn cell involvement of spinal cord was found in g patients with Juvenile Myoclonic epilepsy (JME). Quantitative interference pattern analysis of EMG recorded from the Anterior Tibial muscle showed that the ratio (Amplitude: Turn/Turn:Sec) was significantly increased in 25 patients with JME (12 female, 13 male), and 12 patients with lower motor neuron disorders compared with those of 22 normal subjects and 15 patients having frequent generalised tonic- clonic seizures. It is suggested that subclinical anterior horn involvement detected only by the EMG techniques can be related to a genetically determined component of JME.

118
LARGE FOCAL TUMOR LIKE DEMYELINATING LESIONS OF THE BRAIN IN CHILDHOOD M Eraksoy, H Ozcan, *Istanbul, Turkey*

Demyelinating lesions may resemble primary or metastatic brain tumors on CT or MRI, and even be mistaken for neoplasm on biopsy. We present four children in whom an incorrect diagnosis of CNS neoplasm and abscesses made on the basis of radiological appearance (3) and biopsy (1). The ages of patients were 4,12,14,14 years at the onset of their symptoms. Two patients had acute transverse myelitis some years ago, the other patient developed additional lesion and neurologic signs 6 months later and one had monophasic course. All four improved significantly after corticosteroid therapy. Follow-up periods of the patients were ranging from 1 year to 3 years. This report highlights the critical importance of accurate clinical, radiological, pathological diagnosis and therapy of large demyelinating lesions with mass effect in childhood.

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STRESS HORMONES AND ERYTHROPOIETIN INCREASED VALUES ARE ARGUMENTS FOR CENTRAL APNEAS AND AGONY IN THE SUDDEN INFANT DEATH SYNDROME. A Coquerel, V Le Cam-Duchez, J-P Goument, F Pfaff, C Basset, J Tayot. *Rouen, France*

The Sudden Infant Death Syndrome (SIDS) remains unexplained in 40-70 % autopsied cases. To determine whether the unexpected death is instantaneous or after a more or less duration of agony we assayed stress hormones [i.e. ACTH, Beta-Endorphin (BE) and Cortisol (COR) in blood (cardiac puncture) and in CSF], and blood Erythropoietin (EPO), a sensible hypoxic marker, increased in case of sleep apnea. Since EPO values are related to age, sex, and Hemoglobin A & F contents, we established normal values of EPO in healthy 0-24 months old infants (Le Cam-Duchez et al., 1994) and compared them to SIDS ones. SIDS Blood and CSF samples (n=59) were obtained at hospital admission, in a 3-24 hours postmortem delay (PMD). ACTH excepted, PMD did not influence stress hormone or EPO levels. We conclude that stress hormones from central and adrenal origines are increased in almost all SIDS. Among various parameters which could induce a central suffering, hypoxia related to apneas seems frequent since EPO is often increased after death. Whether EPO release is due to a profound agonic apnea or to frequent sleep apneas, during previous weeks, remains to determine. We proposed to test newborns with EPO and COR in case of increased risks for SIDS or after a life threatening event.

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MITOCHONDRIAL DNA DELETION IN A PATIENT WITH MELAS AND FANCONI SYNDROME. Y Campos T Garcia-Silva, A Cabello, J Arenas. *Madrid., Spain*

We found .1 large mtDNA deletion (about 5 Kb long) in a patient with proximal tubulopathy and MELAS syndrome. The proband, a 5 year-old girl, was normal at birth. At age 2 years, she presented with hypoglycaemia, seizures and left hemiplegia. CT and MRI scan were consistent with cerebral infarction . Four months later, she was lethargic and had hypoglycaemia, lactic acidosis and generalised renal Fanconi's syndrome. Physical showed mild delay, muscle atrophy and failure to thrive. Ophthalmoscopic examination was normal. Muscle biopsy showed ragged-red fibres (RRF) and Cox negative fibres. Respiratory chain enzymes in muscle homogenate were normal. She did not harbour the point mutation at bp 3243 of the $tRNA^{Leu(UUP)}$ gene of mtDNA. Although mtDNA deletions are almost invariably associated with Kearns-Sayre (KSS) syndrome and sporadic progressive external opIthalmoplegia (PEO) plus RRF, our data show that some patients with a clinical picture other than KSS or PEO can harbour mtDNA deletions. However, our patient was only 5 years old and may develop the clinical characteristics of KSS later.

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MOLECULAR ANALYSIS OF SPINAL MUSCULAR ATROPHY IN SPANISH FAMILIES. E Bussaglia, E Tizzano, J Colomer, M Baiget, *Barcelona, Spain.*

Three different forms of childhood spinal muscular atrophy (SMA) have been clinically defined on the basis of severity and age of onset: acute form (type I), intermediate SMA (type II) and the chronic form (type III). The gene causative of this autosomal recessive disease has been mapped to chromosome 5q13, and a wide range of biallelic and multiallelic close markers flanking the gene have been described. We have studied 47 families with at least one affected member with SMA using a combination of 11 flanking markers. Prenatal diagnosis was asked in 7 occasions (one couple two times), 5 with the acute form and two with the intermediate form. The results suggested, with an accuracy higher than 99%, that 2 foetus were affected, 4 were carriers and one was non-affected. 21 siblings of the affected members with a prior probability of being carriers of 66%, were analyzed in order to determine a higher risk or a lower risk of being carriers. At present, molecular analysis by flanking polymorphic markers represents a reliable and accurate method of analysis in SMA families. The cloning and identification of the causative gene will allow direct studies of the genotype and prenatal diagnosis in families at risk

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THE PIRIFORMIS MUSCLE SYNDROME: A RARE CAUSE OF ACQUIRED SCIATIC PARALYSIS IN CHILDREN. O Boespflug-Tanguy, P Gimbergues, D Campagne, C Bommelaer, B Delaguillaume, A Tanguy, *Clermont-Ferrand, France*

The piriformis muscle syndrome results from an entrapment of the sciatic nerve by the piriformis muscle under which it emerges after passing trough the greater sciatic foramen. We report the case of a nine years old boy refered for a slow, progressive varus deformity of the right foot. At neurological examination, weakness and amyotropy following a L5-S1 distribution were observed and ectrophysiological studies were compatible with compression of the proximal part of the sciatic nerve.CT scan and MRI of the sacro-lumbar/gluteal region demonstrated an homogeneous hypertrophy of the right piriformis muscle without abnormal signal even after gadolinium injection. Surgical exploration confirmed the narrow exit for the sciatic nerve under the piriformis muscle.This muscle was transected and its deep portion partially resected to obtain a complete freedom of the nerve. 6 months after surgery, partial clinical recovery of the foot function has been observed.Histological examination of the resected muscle failed to reveal any tumoral, infectious or hemorragic lesions bu histoenzymology studies showed irregular size of muscle fibers with type I predominance.

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CT-SCAN IN CHILDREN WITH INBORN NEURODEGENERATIVE DISORDERS. S Assami, H Ramtami, M Tazir, M Ait-Kaci-Ahmed. *Algiers, Algeria*

We report 34 children with metabolic diseases : 20 children had sphingolipidoses, 3 mucopolysaccharidoses, 1 adrenoleukodystrophy and 10 had ceroid-lipofuscinosis. Diagnosis in all patients was established by biochemical or histological means. CT was performed in every patient. In 7 children with late infantile ceroid-lipofuscinosis CT showed cerebellar atrophy with concomitant cerebral atrophy and enlargement of the ventricles. In patients with other metabolic diseases, the main finding is more or less symmetrical low density in the white matter. Some localisations of this hypodensity are constant suggesting the diagnosis in metachromatic leucodystrophy (MLD). Cerebral atrophy seems to be important at the final stage of late infantile MLD.

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APHASIA SCREENING IN DEMENTIA: THE ZARAGOZA APHASIC SCORE. Pascual LF,Fernandez T,Hortells M, Sanz C, Morales F, *Zaragoza Spain*

Clinical diagnosis of aphasia can be problematic in patients with dementia and language dysfunction The Zaragoza Aphasic Score has been specifically designed for aphasia screening in dementia. It evaluates oral language in 4 categories: Naming (a wrist watch, its watch strap and its clasp; the elbow; the shoulder; a buttonhole); Word list generation (animals); Narrative Language : (tell me three things that a good housewife should do) and Paraphasia. Application begins with visuoverbal naming: any failure is considered as anomia; on the contrary, a flawless performance in naming has a 98% negative predictive valuefor aphasia in our patient group). If anomia is present, the Zaragoza Score gives 1 point if Word list generation is ≤ 3; 1 point if Narrative Language is ≤ 1; 1 or 2 points for isolate or clear paraphasia. The cutoff for Aphasia (derived from Vascular aphasia patients) is ≥ 2. Confronted with the gold standard (diagnosis by a neurologist) in a group of 106 patients with cognitive, dementia and vascular and degenerative aphasia there are 31 true positives, 70 true negatives,1 false negative and 4 false positives. This brief Scale can be an useful aid for aphasia screening in dementia

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EFFECTIVE TREATMENT OF POST-STROKE DEPRESSION WITH THE SELECTIVE SEROTONIN REUPTAKE INHIBITOR, CITALOPRAM. G Andersen, K Vestergaard, L Lauritzen, *Aalbotg, Denmark*

Background and purpose: The aim of the study was to investigate the efficacy and safety of the selective serotonin reuptake inhibitor citalopram in treating post-stroke depression, available treatments being poorly tolerated. A 6-week double-blind placebo-controlled trial was undertaken. Diagnosis and outcome were using the Hamilton Depression Scale, and unwanted effects were measured using the UKU effect rating scale. Sixty-six consecutive depressed patients from an unselected population of 285 patients aged 25-80 years entered the trial 2-52 weeks post-stroke. They were assigned to equally treatment and placebo groups. The initial level of depression was comparable in the two groups, baseline Hamilton Depression score being 19.4 and 18.9, respectively. Demographic parameters also comparable in the two groups. Significantly greater improvement was seen in patients treated with citalopram (10-40 mg/day) r 3 and 6 weeks, both when including all patients (intention-to-treat analysis, $p<0.05$) and when patients who dropped out during the first 3 weeks (efficacy analysis, $p<0.005$). Half of the 28 who entered the trial 2-6 weeks post-stroke recovered within a month, independent of the given. This indicates a high degree of spontaneous recovery in the early phase after stroke. In , placebo recovery was infrequent in patients who became depressed 7 weeks or more post-stroke. serious side effects related to the treatment were detected, those present being mild and usually onclusions: The trial demonstrates that the selective serotonin reuptake inhibitor citalopram offers an post-stroke depression.

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A POST-ENCEPHALITIC EXTRAPYRAMIDAL SYNDROME WITH DOPA-RESPONSIVE DYSKINESIAS. F Picard, C Marescaux, F Sellal, M Collard, *Strasbourg, Franc)*

We report the case of a 39 year-old man presenting simultaneously akinesia and abnormal movements which have both been completely suppressed by dopatherapy. This extrapyramidal syndrom occurred after a long period of lethargy due to an encephalitis at the age of 5, which evoked a sporadic form of Von Economo encephalitis. Akinesia, rigidity and resting tremor were progressively associated with abnormal movements. Dyskinesias included cervical and orofacial dystonia with oculogyric crises, and slow, stereotyped, rhythmic and purposeful movements of the upper limbs. Akinesia and, paradoxically, all abnormal movements disappeared with dopatherapy at age 24. Currently, akinesia and abnormal movements reappear if L-dopa is withdrawn. Neither CT scan, nor MRI of the brain, nor PET using 18F-FDG visualise any lesion. PET using 18F-Dopa shows bilateral symmetrical lesioning of dopaminergic pathways, restricted to pathways projecting to the posterior putamen (as in Parkinson's disease). Thus, association of an akinesia with involuntary abnormal movements might be a result of a limited lesion involving only one of the two nigrostriatal dopaminergic pathways.

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STIFF-PERSON SYNDROME CAUSED BY ANTERIOR PITUITARY HORMONE DEFICIENCY. A Papadimitriou, T Avramidis, E Alexiou, T Anastopoulos, *Athens, Greece*

Stiff-person syndrome is a rare disorder characterised by persistent rigidity and painful spasms of axial and limb muscles. Few cases are associated with diabetes, thyrotoxicosis and only one case with ACTH, Growth hormone and prolactin deficiency has been reported. We report a case with clinical features of stiff-person syndrome and multiple anterior pituitary insufficiency. A woman 51y/o was admitted in our Department in Feb 1992 because of 2 year progressive painful rigidity-spasticity of and lower limb muscles with characteristic lordotic stature and gait. EMG showed continuous normal motor unit discharges at rest bilaterally in poses, agonists and antagonists of lower limbs which subsided slightly in a fully relaxed position. Complete work-up including X-ray, haematology and rheumatologic tests were normal. A slight disproportion observed in the level of TSH compared with T3 and T4 values urged us to proceed to further hormone determinations that confirmed complete pituitary insufficiency, T3:1,3 nmoles/lt, T4:69nmoles/lt, TSH:2,6miu/ml LH:1,9Omiu/ml F.S.H:14,2miu/ml GH:O,O5miu/ml, cortisol:1,3 μg/ml. After a three month treatment with hydrocortisone and thyrohormone rigidity disappeared and patient recovered completely. Conclusion: Every case of stiff-person syndrome should have thorough hormone determinations in order to exclude pituitary insufficiency.

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SPINAL CORD ISCHEMIA RELATED TO ABDOMINAL AORTIC ANEURYSM. J Roquer, N Marti, A Cano, A Pou-Serradell, *Barcelona, Spain.*

Ischemic spinal cord lesions related to abdominal aortic aneurysm are rare. We report on 3 cases of this association with different clinical manifestations. One of them presented with three attacks of backache and reversible paraplegia mimicking transient ischemic attacks and he had a giant dissecting aortic aneurysm (from subclavian to left common iliac artery). Another patient suffered a subacute paraparesis (level T4) preceded by dorsal and abdominal pain and had an large thoraco-abdominal aortic aneurysm associated with bilateral common iliac artery aneurysms. The third experienced a sudden paraplegia (level Tll) preceded by back pain and had an large abdominal aortic aneurysm. The clinical polymorphism of these cases may be explained by the particular pathophysiology and anatomical distribution of the spinal cord arteries and also by the diversity of described ischemic mechanisms: dissection of aorta, progressive occlusion of regional radicular branches (by thrombosis or compression) and repeated embolization from the thrombus in the aneurysm to the radicular arteries arising from the region. In patients with the association of backache and/or abdominal pain preceding the development of paraparesis the diagnosis of abdominal aortic aneurysm should be considered.

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AUTONOMIC FUNCTION IN MYOTONIC DYSTROPHY. D Frongillo, FA Delfino, M Cannata, L Calo, R Vichi, G Antonini V Fragola, D Cannata. *Rome, Italy.*

To assess autonomic function (AF) in patients (pts) with myotonic dystrophy (MD) standard cardiovascular tests (CT) and autoregressive power spectral analysis (PSA) of heart rate (HR), at rest (r) and after 60° passive head up tilt (u), were performed in 28 pts (19 men and 9 women, mean age. 36.8 ± 10.2 years) with MD and in 40 normal controls (ctr) matched for sex and age. Blood pressure (BP) and HR were continuously monitored by Finapres and single lead electrocardiography. Although no abnormalities existed in the response pattern to CT in pts with MD, a trend towards lower values was found for the Valsalva ratio, HR variation on standing and diastolic BP rise with handgrip in pts respect to ctr. Instead, pts and ctr did not differ significantly with regard to PSA of HR (pts: low frequency (LF)r=52±23 nu; high frequency (HF)r=34±23 nu; LFr/HFr= 3±1,8; LFu=73±22 nu; HFu=15±10 nu; LFu/HFu=9±7; ctr: LFr=60±30 nu; HFr=27±11 nu; LFr/HFr=2,5±1,5; LFu=75±11 nu; HFu=14±8 nu; LFu/HFu=8,7±5,5). Our data suggest that AF is normal in pts with MD. The lower values of CT in our pts with respect to ctr could be explained by reduced muscle function in this neuromuscular disease. PSA of HR should be considered a more reliable test in investigating AF in pts with neuromuscular impairment.

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AUTONOMIC DYSFUNCTION IN PATIENTS WITH SYNCOPE. R Martin, M Salas, C Ruiz, I Montiel, J Matias-Guiu, *Alicante; Spain*

Though orthostatic hypotension is common in patients with syncope, data on the whole autonomic function of these patients are scarce. We have tested the autonomic performance of 188 patients with syncope [77 males; 111 females; mean age: 43(20.5] and compared the results with that of 170 health controls [66 males; 104 females; mean age: 45(15.7]. Heart rate response to Valsalva manoeuvre, deep breathing and standing, and blood pressure (BP) response to standing, handgrip and cold pressure test (CPT) were investigated. Patients have a lower response of heart rate to Valsalva manoevre, deep breathing and standing than controls [mean Valsalva ratio: 1.08 (95% confidential interval (CI): 1.06, 1.10) vs 1.20 (CI: 1.17, 1.24), p:0.0000; mean expiratory-inspiratory difference: 12.37 (CI: 11.2, 13.6) vs 18.94 (CI: 16.2, 21.7), p:0.000; mean 30:15 index: j 1.15(CI: 0.84, 1.47) vs 1.2(CI: 1.17, 1.25), p:0.000]. The fall of BP to standing was higher in patients than in controls [mean fall: -7.14 (CI:-8.86, -5.42) mmHg vs -1.38 mmHg (CI:-3.2, -0.43), p:0.000], and the response of BP to handgrip was lower in patients than in controls [mean rise: 14.49 mmHg (CI: 12.86, 16.12) vs 16.88 mmHg (CI: 15.47, 18.3), p:0.001]. There was no signifi-

cant differences in CPT. These data suggest that patients with syncope have a autonomic hypofunction with an imbalance between parasympathetic and sympathetic function.

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PHARYNGO LARYNGEAL ELECTROMYOGRAPHY IN SWALLOWING DISORDERS. A Feve, B Angelard, J Lacau St Guily. *Paris. France*

Swallowing is a complex phenomenon, which involves neurological reflexes and voluntary control. Swallowing disorders can be due to a central dysfunction in extrapyramidal or cerebrovascular diseases, or to peripheral neurogenic abnormalities. Local abnormalities involve loss of contraction or relaxation of the superior oesophageal sphincter (SOS). Endoscopic electromyography (EEMG) permits the assessment of contraction and motility of every segment of the pharyngo oesophageal tract. A circular bipolar electrode is located on the endocavitar probe. EEMG is recorded simultaneously against the posterior pharyngeal wall, the SOS (cricopharyngeal muscle), and the striated musculature of the proximal oesophagus. In neurogenic disease, EMG reveals fasciculations, low-amplitude action potentials, and absence of basal tone. In muscle disease (polymyositis, inclusion myositis), lower recruitment during swallowing and a lower basal tone have been demonstrated. Central disorders are associated with irregularities in the sequence of contractions. A longer swallowing reaction time has been demonstrated in Parkinson's disease. The first voluntary stage of swallow, associated with contraction of the pharyngeal musculature can disappear in stroke patients. In swallowing disorders of the elderly, a loss of relaxation of the SOS can be shown, and is in keeping with the results of radio cinema. Surgical myotony is thus indicated. Pharyngo oesophageal surface electromyography, combined with clinical neuro-ENT investigations is a new, painless way of assessing swallowing.

Symposium 4
New Therapies in Neurology

Chairmen: AK Asbury; FGI Jennekens

NEUROPROTECTION. PR Bar, *Utrecht, the Netherlands*

The nervous system functions optimally when it is physically untouched, when it is provided with fuel and oxygen and waste products are removed via an intact blood circulation, distribution of ions inside and outside cells is controlled, when the natural defence systems operate and when a delicate balance between trophic factors derived from supporting and target-cells is achieved. any change in these working conditions may lead dysfunction and damage, ranging from small, almost imperceptable changes which can be corrected for by the nervous system's plasticity, to serious and irreversible loss of function. Certain processes and metabolites are thought to play a role in nervous system damage, seemingly irrespective of the primary cause. Thus, at the end of a schort (acute trauma, ischaemia) or long period (degenerative diseases) in which the balance is disrupted, a common final pathway seems to be followed, leading to cell death. In the final stage calcium, the cell's main regulatory ion, is often no longer under its normal tight control but is involved in several destructive pathways. Free radicals are thought to be involved in tissue damage in a large number of disorders. For example during in ischaemia, sustained, uncontrolled, transmitter release (mainly glutamate) leads to acute calcium overload and the formation of free radicals. The effect of chronic exposure to marginally élévated calcium levels may also be detrimental and could play a role in degenerative descorders or ageing. Also, a decrease in one of the elements of free radicals. For example the genetic link between familial ALS and a mutation in the superoxide dismutase gene (SOD, on chromosome 21) has led to the suggestion that such exposure may eventually ead to generation of vulnerable neuronal subpopulations (motor neurons).
Neuroprotection may occur through prevention of direct actions of calcium or radical, or, upstream, by suppressing their production or release. In fact, the higher up in any cascade one can interrupt a damaging chain reaction, the more efficacious treatment may be expected to he. For example in ischaemia, damage can be prevented by blocking glutamate (NMDA) receptors or voltage operated channels, through which calcium ions enter the neurons, or by buffering intracellular calcium. Blocking AMPA receptors, which prevents depolarization of neurons (a condition for NMDA activation), may result in a more effective reduction of calcium entry, namely by blocking calcium entry through NMDA channels and voltage-operated channels at the same time. While it has been though that radical scavengers such as the 21-aminosteroids, which are potent antioxidants, protect neurons during ischaemia/reperfusion directly, it has become clear that their primary effect may be on the microvasculature in the affected brain area. Due to their highly lipophilic nature these substances may not even migrate past the endothelial cell membrane and exert their effects partly through changes in membrane fluidity.
Trophic factors may provide neuroprotection via general increase in cell metabolism or via a boost in the resistance through the activation of a more specific defense strategy, e.g involving an increase in the activity of enzymes involved in radical defence or stabilization of intracellular calcium levels. For both options experimental proof exists. In order to understand, and possibly exploit, there effects of growth factors for clinical use, analysis of their cellular mechanism of action is of great importance. A survey of approaches to neuroprotection will be presented, which will incorporate recently developed drugs and strategies.

GROWTH FACTORS. M Sendtner, *Martinsried, Germany*

The survival an functional maintenance of spinal motoneurons, both during the period of developmental cell death and in adulthood, have been shown to be dependent on trophic factors. In vitro experiments have previously been used to identify several survival factors for motoneurons, including ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), members of the neurotrophin, fibroblast growth factor (FGF) and insulin-like growth factor (IGF) gene families. Some of these factors have also been shown to be active in vivo, either on chick motoneurons during embryonic development or on lesioned facial motoneurons. Lesion of the facial nerve in newborn rats leads to the degeneration of more than 75% of the corresponding motoneuron cell bodies in the facial nucleus, local application do CNTF, brain-derived neurotrophic factor (BDNF), IGF-I;LIF but not basic fibroblast growth factor (FGF-2) an fibroblast growth factor-5 (FGF-5), can significantly prevent cell death of these motoneurons. The responsiveness of motoneurons to multiple factors in vitro and in vivo suggests that motoneuron survival an function arc regulated by co-ordinated actions of members of different gene families.
To study the individual physiological roles of neurotrophic factors in motoneurons, we have established transgenic mice where the genes for CTNF an other neurotrophic factors have been disrupted. In CNTF deficient mice, progressive postnatal motoneuron degeneration can be observed, indicating that this factor is necessary for the maintenance of postnatal motoneuron survival, and that deficiency of CNTF in such mice cannot be fully compensated by other neurotrophic factors. Pharmacological use of these factors, as studied by daily subcutaneous infection of CTNF an BDNF en *pmn* (progressive motoneuronopathy) mice, does not lead to significant functional improvement and rescue of degenerating motoneurons, whereas continuous supply of CNTF by intraperitoneal injection of CTNF secreting D3 cells markedly improves motoneuron survival an function. This could be due the short half-life of CTNF in the circulation. In adult rats, intravenously injected radioiodinated CTNF is rapidly removed from the blood with an initial plasma half-life of 2.9 minutes. Most of the injected CTNF is bound to the liver, liver cells express specific binding proteins for CNTF, and the incorporation and degradation of intravenously injected CTNF by the liver may occur after association of CTNF with the soluble CNTFR in the circulation. Probably as a consequence of its binding to hepatocytes, CTNF induces acute-phase responses in liver. Our results indicate that the potential therapeutic use of these factors in human motoneuron disease depends on the identification of optimal means of administration and a better understanding how these factors interact physiologically in regulating motoneuron function and survival.

RECEPTOR-DIRECTED THERAPY: THE MODEL OF MIGRAINE, Peter J. Goadsby, *Sydney, Australia*

Neurology as a specialty has never lacked precision in the localisation of lesions, if they were present, nor in care in the description of a clinical syndrome. Two aspects of modern neuroscience have transformed, neurology, as a specialty, by adding pathophysiological understanding to clinical conditions and in many cases adding to therapies. No other neurological condition has benefited more from the application of modern neuroscience than headache, and it is in the therapy of migraine that a receptor-based approach has been very successful. Beginning with the finding that serotonin (5-HT), a ubiquitous naturally occurring amine, could alleviate an acute attack of migraine) the definition of the multiplicity of serotonin receptors has provided neurological patients with options previously not even considered. The field began to expand in the direction of 5-HT after it was shown that an intravenous infusion of the amine would relieve headache. Unfortunately the relief of headache was associated with dread-

ful flushing and diarrhoea and was not practical. Research has been directed at determining if the receptor involved in the alleviation of the pain could be disassociated from the other effects. When this field was being developed there were two clear receptor sub-types, D and M and an atypical group. The combination of excellent chemistry, almost intuitive pharmacology and more recently careful molecular biology has resulted in the classification in Tablel and 2. It is within the multiplicity of 5-HT1-like receptors that an important receptor for migraine therapy was identified. The 5HT 1D-like receptor has emerged as a useful target in migraine therapy. The pharmacology of this receptor has emerged in parallel with the development and understanding of the drug sumatriptan, which was developed specifically to target this site. Sumatriptan was designed to act as 5-HT had done in the early sixties, i.e. alleviate migraine, but to lose by modification and chemical alterations the unwanted side effects of 5-HT. The modification of the 5-HT molecule resulted in a compound that acted at a few receptor subtypes, initially thought to be the 5-HT-lA and D subtypes with a sub-classification of the 5-HT-lD receptor coming later. In this respect the pharmacology of the ergot-derived compounds has been of considerable interest since their actions in migraine, long known and often exploited, may also be explained by their 5-HT-lD agonist properties. The result of all these pharmacological developments has been the addition to clinical neurology of a potent effective treatment for the acute attack of migraine in the form of sumatriptan.

Table 1: Modified Classification of serotonin receptors

Receptor	Second messenger	Antagonist	Function
S-HT_1-like	J,AC		(see Table 2)
5-HT_2	↑PI turn-over	methysergide pizotifen cyproheptadine	Contraction of smooth muscle CNS excitation
		subtypes	IC, 2, 2F
5-HT_3	K+	ondansetron granisetron	membrane depolarization
5-HT_4	↑AC	ICS205930	stimulates some cholinergic GI contraction
		GR113808	striato-nigral system
5-HT_5	?	-	A and B classes
5-HT_6	?	-	Single type
5-HT_7	↑AC	-	role in circadian rhythms

Abbreviations: AC, adenylate cyclase; PI, phosphoinositide.

The classification and understanding of 5-HT receptors has also impinged, though less profoundly, upon migraine prophylaxis. Most of the migraine prophylactics share in common some effects at S-HT2 receptor, with antagonist properties being highlighted in contrast to the agonist effect that is required at the 5-HT-1 receptor for the acute attack. This, however, clearly does not account for the actions of all drugs, such as valproate, and without a model for the initiation of the migraine attack it is difficult to exploit this knowledge immediately. There is cause for considerable optimism, however, since some better definition of receptor sub-types using molecular techniques may further point to directions for prophylactic therapy.

Table 2: Classification of serotonin (5-HT) sub-class I receptors

Subtype	Second messenger	Agonist	Function
lA	↓AC	8-OH-DPAT dihydroergotaunine	hypotension behavioural (satiety)
lB	↓AC	CP-93,129	central autoreceptor (rat)
lDα	↓AC	sumatriptan dihydroergotaunine CP122,288	Trigeminal neuronal receptor
lDβ	↓AC	sumatriptan dihydroergotamine	Craniovascular receptor
lE	↓AC	-	?
lF	↓AC	-	?

Note: AC, adenylate cyclase; 8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino)tetralin (this compound is used in the laboratory for pharmacological purposes and has no current clinical uses).

Unfortunately, the 5-HT-1 like agonists strategy is very useful for many patients but it is not perfect. Some patients experience side effects, although they are usually mild and transient, so that the original intention to eliminate unwanted 5-HT effects remains to be achieved completely. Furthermore, not all patients with migraine respond to this approach so that some part of the puzzle remains to be defined. Moreover, the 5-HT-lD receptor exists as both a vascular receptor (β subtype) and a neuronal receptor (α subtype). Activation of the 5-$HT_{1D\beta}$ results in c-AMP mediated vasoconstriction whereas the $5HT_{1D\alpha}$ receptor activation acts on the trigeminal nerve as a presynaptic inhibitory system turning off firing both in the periphery and in the trigeminal nucleus caudalis. All these observations only add more questions but they are optimistic; can a better drug be designed, can the receptor target be more closely defined, are other 5-HT receptors involved in some or all patients? As we enter the last part of this millenium neurology is entering a golden era of therapeutics which will combine an understanding of disease pathophysiology with improved treatments with the end result being a very much improved quality of life for patients afflicted by the conditions that we manage.

NEURAL TRANSPLANTATION. NP Quin, *London, UK*

The prospect of transplantation of functioning tissue or cells into the brains of individuals with neurological disease is one of the most challenging and exciting prospects in clinical neuroscience. There are good (and also bad) reasons why Parkinson's disease (PD) was chosen as an initial test-bed for trials of this potential therapy. Thus: the disease is common, yet 25% of cases are misdiagnosed; animal models exist but are imperfect; the principal pathological lesion is in substantia nigra, but there are more widespread histological and neurochemical deficits; cells can be implanted into stratum, but are there divorced from afferents in midbrain; levodopa treatment shows that major functional benefit is possible, but vastly magnifies its variability; Finally, PD is a progressive disease whose cause is unknown, so that whatever killed the patient's nigral cells originally might also kill the graft. Adrenal autografts were not successful, and animal experimental work strongly favours the use of embryonic or foetal ventral mesencephalic tissue. However, the use of such tissue derived from humans introduces new ethical considerations.

More than 200 patients with parkinsonism worldwide have so far received human foetal nigral grafts, but definitive results have been published for only a minority. Details of the procedure have differed widely between groups and patients: embryonic/foetal age; number of mesencephalic grafted; cell suspensions versus solid tissue pieces; open versus stereotactic surgery; graft placement in caudate versus putamen versus both; unilateral versus bilateral; immunosuppression versus no immunosuppression. Some recipients have had pre- and post-operatory others only post-operatory and others no, PET scans. Finally, and most importantly, the thoroughness with which baseline and post-operative assessments have been repeatedly conducted, and the degree to which antiparkinsonian drug treatment has been kept constant or changed, has varied greatly.

Critical assessment of published reports indicates conclusive evidence for graft survival and major clinical benefit related to the graft in only a handful of patients. Nevertheless, this justifies cautious optimism about the potential of neural grafting as a partial treatment for selected individuals with PD. Other patients may well have benefited, but conclusive published evidence is lacking, whilst in yet others the graft has not worked. Differences in the above variables presumably account for these discordant clinical results, and need careful analysis to determine optimal graft conditions.

If neural grafting can be reliably and reproducibly shown to work in Parkinson's disease, then this would lead to similar approaches in other neurodegenerative conditions, such as striatal grafting in Huntington's disease and nigral and striatal grafting in multiple system atrophy, as well as trials of grafting in sites and diseases not involving basal ganglia.

Symposium 5
Functional Brain Mapping

Chairmen: RSJ Frackowiak, O Paulson

FUNCTIONAL MAPPING OF THE BRAIN WITH MAGNETIC RESONANCE IMAGING D.G. Gadian, *London, UK*

Magnetic brain completely . Functional neuroimaging with magnetic resonance (functional MRI) relies on the detection of changes in local haemodynamics that are associated with cerebral activation. The initial func-

tional MRI studies of the human visual cortex Involved the administration of the paramagnetic contrast agent Gd-DTPA to act as a marker of cerebral blood volume. This approach to activation studies was rapidly superseded by an alternative MRI approach which had the major advantage that no extrinsic contrast agent was used. This latter approach exploits the fact that on deoxygenation of haemoglobin, the electron spin of the haem Fe2+ changes from a diamagnetic state to a paramagnetic state. The magnetic susceptibility effects associated with this paramagnetism cause signal attenuation in T2-weighted images. In practice, T2*-weighted images show increases in signal intensity in activated regions of the brain. This is consistent with findings from positron emission tomography studies which have shown that during cerebral activity there is an increase in local blood flow with relatively little change in oxygen consumption, so that the venous blood should become more oxygenated on activation.
Activation studies of the primary visual and motor cortices provide an appropriate means of establishing and validating this new method of functional neuroimaging, partly because these systems are relatively well characterized, and also because the haemodynamic changes (and hence signal intensity changes) in these areas are likely to be considerably greater than those associated with higher cognitive functions. One of the main requirements is to establish the extent to which such higher functions are accessible to investigation by functional MRI. Initial studies, for example observations using word generation or mental imagery, appear encouraging, but a great deal more work needs to be carried out in order to establish the sensitivity of functional MRI to the wide range of cognitive tasks that are of interest to the neuroscience community.
In addition to the neuroscientific applications of functional MRI, there is also scope for clinical applications, for example in presurgical mapping of primary cortical areas, and in the investigation of epilepsy.
Technical points that need to be considered include the possible contributions of additional contrast mechanisms, the effects of motion and of large draining vessels, the sensitivity to small activations, and choice of methods for image analysis. Meanwhile, on the basis of results emerging from an increasing number of centres, it seems likely that functional MRI will lead to major advances in our understanding of normal brain function and of brain dysfunction in disease.

FUNCTIONAL MAPPING OF THE SOMATOSENSORY SYSTEM IN MAN. PE Roland, *Stockholm, Sweden*

Studies of the human brain with 133Xe-intracarotid technique and positron emission tomographic (PET) techniques have shown that man has at least seven somatosensory areas: the primary somatosensory area SI in the post central gyrus, the secondary somatosensory areas SII, the supplementary sensory area SS in the anterior precuneus, the cortex lining the postcentral sulcus, the anterior part of the superior parietal lobule/, the cortex lining the anterior part of the intraparietal sulcus, and the cortex in the parietai opercuium and relroinsular corlex. These areas seem to have different roles in the representation of kinesthesia, vibration, pain, tactile surfaces and curvature .

THE HUMAN MOTOR SYSTEM STUDIED WITH-POSITRON-EMISSION-TOMOGRAPHY. Rudiger J. Seitz, *Düsseldorf, Germany*

The cerebral structures controlling limb movements in man can be studied simultaneously within the entire brain by measurements of the regional cerebral blood flow (rCBF) with positron emission tomography (PET). Based on evidence from animal experiments, rCBF is an indicator for energy consumption of active synapses. Results of PET activation studies are usually obtained by pixel-by-pixel statistics across subjects after spatial image standardization. Our laboratory developed algorithms for response identification and intermodal PET/MR image alignment that allow the analysis of activation studies in individual subjects.
Functional PET measurements were validated by demonstrating that limb movements induced significant rCBF increases in a somatotopical distribution along the precentral gyrus. Individual PET image analysis revealed that these areas of rCBF increase were localized in the anterior wall and the depth of the central sulcus and that movement rate was tightly related to the rCBF increase. In addition, these studies suggested a representation of motor functions, both in a hierarchy of distinct areas and as distributed connectionistic processing. Specifically, it was demonstrated that voluntary simple, sequential, complex and trajectorial movements significantly activated different parts of the premotor and frontomesial cortex. However, as evident from individual image analysis the frontomesial activations differed considerably among different subjects due to inter-subject variability of brain anatomy and task performance.
Evidence for plastic changes of cortical representations was obtained from experiments on human motor learning. During motor skill acquisition significant rCBF changes were also observed in parietal cortical areas/ probably related to on-line error analysis during somatosensory or visual guidance of movements. Notably, rCBF changes could clearly be identified in subcortical structures such as the basal ganglia and cerebellum during different types of skill learning. Evidence will be presented suggesting that these subcortical activations did not represent a general phenomenon of motor activity but appeared to be related to specific aspects of movement dynamics.
In hemiparetic cortical, striatocapsular and thalamocapsular stroke the extent of the remote metabolic disturbances induced by the lesions was comparable among these patients, but varied in location due to the different sites of the structural lesions. Reduction of maximal grip force and impaired individual finger movements correlated with the degree of damage to the corticospinal tract. In patients who had recovered from hemiplegia finger movements of the affected hand consistently induced maximal rCBF increases in the contralateral primary sensorimotor cortex. Individual rCBF image analysis in patients with striatocapsular infarction indicated that additional activations in premotor areas ipsilateral to the stroke lesion and in primary and premotor areas contralateral to the stroke lesion were determined by the site of damage of the internal capsule. However, deficient activation patterns compared to healthy subjects during tactile exploration were related to persistent impairments of somatosensory information processing. It is concluded that restitution of motor function after stroke appeared to result from substitution by closely related cortical areas occurring more readily than compensation of associated cognitive impairments .

FUNCTIONAL MAPPING OF THE VISUAL SYSTEM. Richard SJ Frackowiak, *London, UK*

Clinical neurologists have a long tradition of inferring function from the minute observation of disturbed behaviour and correlations of such clinical findings with descriptions of the extent of anatomical brain damage. Advances in basic animal neurophysiology and anatomy have enlarged that perspective in recent years. The advent of non-invasive imaging and monitoring techniques applicable to the human brain in life have indicated a way forward for the direct investigation of the functional organisation of the human brain in a more accurate, sensitive and controlled fashion than previously possible. The theme of this presentation is to describe experiments that have aimed to investigate the human visual system with such modern/non-invasive techniques.
Regional perfusion in the striate cortex is dependent on the presentation rate of a flashing visual stimulus. A similar result has been obtained recently with fMRI by Belliveau and colleagues. Use of an optimised flash stimulus, with presentation of the visual stimulus in one or other hemifield at various eccentricities/ has permitted a mapping of the retinotopic representation f visual space in the striate cortex, and calculation of the magnification factor. Colour vision has been studied in subjects whilst they viewed an abstract collage rendered in different colours or in shades of grey and significant activation was found in the caudal part of the *fusiform gyrus*. Visual motion can be localised to two areas lying in the right and left hemisphere over the convexity of the brain at the junction of the occipital and temporal lobes just above the intercommissural plane. This region is clearly quite different from that demonstrated with the colour experiment. Damage to these areas results in achromatopsia or akinetopsia respectively.
Visual integration has been studied with the use of visual illusions, notably form-from-motion and motion-from-form to investigate the inter relationships of different specialised cortical visual areas in the generations of these unusual percepts. There have also been studies in patients to assess mechanisms of residual and recovered function. A patient with akinetopsia and grossly disturbed visual motion perception has been imaged. Another patient with a hemianopia and calcarine destruction who has some residual motion perception has been studied to assess the relevance of anatomical pathways other than the geniculo-calcarine in human vision.

Oral Session 29 - Neuro-Oncology (1)

1
PREOPERATIVE AND POSTOPERATIVE FOLLOW-UP OF BRAIN TUMOURS: TRANSCRANIAL DUPLEX SONOGRAPHY AND COMPUTED TOMOGRAPHY FINDINGS. G Becker, A Krone, K Schmidt, E Hofmann, U Bogdahn. *Wurzburg, Germany.*

To determine the sensitivity of transcranial duplex sonography (TDS) in identification of residual tumour and tumour recurrence, 20 patients with high-grade glioma were submitted to pre- and early postoperative CT (first postoperative day) and TDS (7th postoperative day) examinations. Follow-up examinations were performed after a time interval of 6-12 weeks. A total of 98 TDS and 85 CT scans were performed. Eight of the 20 patients had intraoperative, sonography-guided, histological evaluation of the resection site. In 1 9 of the 20 patients early postoperative TDS examinations revealed hyperechogenic areas at the resection margin. In accordance with histolological findings these hyperechogenic areas indicated residual tumour. In comparison, early postoperative CT illustrated contrast enhancement at the resection site in only 1 2 of the 20 patients. Although CT displayed no contrast enhancement at the resection line, TDS and histological findings demonstrated residual tumour in 7 of the remaining 8 patients. In 4 patients tumour re growth was identified 1-5 month earlier by TDS than by CT. The sensitivity of TDS in detection of residual tumour and tumour regrowth seemed to be superior to CT. TDS may specify and complement diagnostic information's obtained by conventional neuroimaging modalities in the perioperative diagnostic workup of brain tumours.

2
EXPRESSION OF WILD-TYPE P53 AFTER GENE TRANSFER WITH A DEFECTIVE HERPES VIRAL VECTOR RESULTS IN DOWN-REGULATION OF MUTANT P53 EXPRESSION AND UP-REGULATION OF mdm-2. MR Rosenfeld, P Meneses, MG Kaplitt, J Dalmau, J Posner,C Cordon-Cardon; *New york, USA*

The objective of this study was to determine the effect of the in vitro transfer of the wild-type p53 tumour suppressor gene to a primary human brain tumour that expressed mutant p53. Wild-type p53 cDNA was subcloned into a defective herpes simplex virus (HSV) and a stock of defective HSV vector carrying the p53 gene (dvCMV-p53) was obtained. The medulloblastoma cell line, DAOY was found to express a mutant form of p53 by immunohistochemisty and sequence analysis. DAOY cells were infected with dvCMV-p53 or a control virus and then analysed for the presence of wild-type p53 mRNA and protein by the reverse transcription-polymerase chain reaction, Western blotting, and immunohistochemistry. Infected cells were also studied for changes in mdm-2 expression by immunohistochemistry. Infection of DAOY cells with dvCMV-p53 resulted in the overexpression of wild-type p53 protein. The novel expression of wild-type p53 resulted in the inhibition of expression of the endogenous mutant p53. Over-expression of wild-type p53 also resulted in the up-regulation of mdm-2 expression. Further studies are in progress to determine if gene transfer of wild-type p53 results in apoptosis or cell cycle arrest.

3
RESTRICTION OF SCH MUTATIONS TO TUMORS PREDISPOSED BY NEUROFIBROMATOSIS 2. K Hoang-Xuan, P Merel, M Sanson, F Vega, JY Delattre, M Poisson, I Nishisho, JP Moisan, C Theillet, O Delattre, G Thomas. *Paris, France*

Recurrent deletions of chromosome 22 are observed in a variety of human cancers, suggesting that this chromosome segment encodes one or more tumor suppressor genes. We have recently isolated on chromosome 22 the SCH gene, the constitutional mutations of which are responsible for Neurofibromatosis 2 (NF2), an inherited disease predisposing to nervous system tumours, mainly schwannomas and meningiomas. Demonstration in these latter tumours of concomitant loss of chromosome 22 and SCH somatic mutations indicates that this gene acts as a tumour suppressor gene. In this study, we have looked for the prevalence of mutations in the 16 coding exons of SCH in 56 schwannomas, 56 meningiomas, 73 gliomas, 14 ependymomas, 15 neuroblastomas, 6 medulloblastomas, 30 pheochromocytomas, 15 colon carcinomas and 15 breast cancers, using the DGGE technique. In contrast to schwannomas and meningiomas where somatic mutations were identified in approximately 30)% of cases, no mutation was observed in the other tumour types, although recurrent chromosome 22 deletions were observed in these tumours. These results suggest that: 1) the occurrence of SCH mutations may be restricted to schwannomas and meningiomas. 2) frequent loss of chromosome 22 in other tumours may be associated with the inactivation of a tumour suppressor gene distinct from SCH.

4
DEXAMETHASONE-STIMULATED TUMOR NECROSIS FACTOR-PRODUCTION GENE TRANSFECTED GLIOBLASTOMA CELLS. Jiahong Zhu, R Retska, F Weber, W Walther, M Brock, *Berlin, Germany*

The ability to transfer and express recombinant genes within brain tumours provides a potent source of therapeutic proteins that are synthesised locally. In order to make a glioblastoma able to produce tumour necrosis factor α (TNFα), we introduced a TNFα gene into a rat glioblastoma cell line F98 by cationic liposome-mediated gene transfection. A plasmid containing a TNFα gene under the control of MMTV(mouse mammary tumor virus) 5´ long terminal repeat sequence (LTR) and used this LTR as its promoter, and a NeoR gene by a tk promoter was transfected into F98 cells with cationic liposomes DC-chol or Lipofectin. The transfected cells were selected for G418R, cloned, and, subsequently, assayed for TNF oc activity in the culture supernatant. Lipofectin transfected cell clones produced between 800 pg/ml and 2.0 ng/ml TNFα. DC-chol transfected cells produced about 15 ng/ml. The control F98 cells did not produce detectable amounts of TNFα. Since MMTV promoter is a well characterised target of transcriptional regulation by steroid hormones and allows glucocorticoids to positively regulate expression of a gene, we examined the stimulating efficiency of dexamethasone on expression of TNFα. After dexamethasone stimulation (10 6), about 8-fold more TNFα was produced in lipofectin transfected cells. The stimulation exerted by dexamethasone was more efficient in a DC-chol transfected clone, yielding up to 1 7-fold increase of production of TNFα. The mechanism by which dexamethasone acts on MMTV promotor is that the MMTV promoter contains a "glucocorticoid response element"(GRE) and a specific binding site for glucocorticoid receptor is present in the region of GRE.

5
NOVEL EXPRESSION OF IMMUNOREACTIVE HUD (PARANEOPLASTIC ENCEPHALOMYELITIS) ANTIGEN IN NON-NEURAL MAMMALIAN CELLS USING A DETECTIVE HERPES VIRAL (HSV) VECTOR. J Dalmau, MG Kaplitt, P Meneses, J B Posner, MR Rosenfeld; *New York, USA*

HuD, a neuron-specific RNA binding protein, is the target of anti-Hu associated paraneoplastic encephalomyelitis (PEM) and sensory neuronopathy (PSN) in patients with small cell lung cancer. The exact role of HuD in neurons and in the pathogenesis of the paraneoplastic disorder is unknown. The objective of this study was to develop a system that will allow for the in vivo expression of paraneoplastic antigens. HuD cDNA was inserted into a defective HSV vector (dvHuD) and viral vector stocks were obtained. Generation of dvHuD was confirmed by Southern blot. Expression of HuD protein was determined by Western blot analysis and immunohistochemistry. Infection of HuD-negative mammalian cell lines with dvHuD resulted in the synthesis of immunoreactive HuD protein. Injection of dvHuD into rat liver in vivo resulted in HuD expression in this non-neuronal tissue. The "de novo" expression of HuD was identified in the nuclei of the cells, suggesting that although HuD is neuron specific, it may interact with non-neuron specific nuclear localizing ligands. Studies with sense and antisense constructs to determine the biological role of the HuD antigen and to develop an animal model of PEM/PSN are in progress.

6
UPTAKE OF FE-52 TRANSFERRIN IN HUMAN BRAIN TUMORS: A PET STUDY. U Roelcke, K von Ammon, EW Radu, R Pellikka, KL Leenders. *Villigen, Zurich & Basel, Switzerland*

In vitro, the number of transferrin receptor positive cells in gliomas is increased according to tumor malignancy. This study was performed to assess in vivo brain tumor uptake of transferrin using positron emission tomography and the tracer [52Fe] which after injection binds to plasma transferrin. 21 patients were studied (6 AC=astrocytoma, 10 GBM= glioblastoma, 5 MEN=meningioma). Tracer uptake was quantitated by multiple time graphical plotting (ki=tracer uptake) and a non-linear least square algorithm to obtain Kl (tracer influx), k2 (efflux) and k3 (specific binding). Plasma radioactivity was found in the 80kD (transferrin) fraction. Tracer uptake (Ki mean+/-SD [E5/min]) was slow but increased in GBM (13.0+/-4.5) and MEN (32.1+/-16.4) compared to AC (2.58+/ 0.8) and normal brain (2.2+/-0.8) and was correlated with Kl ($p<0.01$). Tumor k3 could be derived only in one meningioma. Conclusion: In vivo, iron-transferrin uptake in gliomas seems not to reflect specific receptor binding in tumors but transport of macromolecules across the blood-brain barrier. This may have implications for the estimation of drug (e.g. transferrin-toxin conjugates) delivery into tumors after systemic administration.

7
AUTOANTIBODIES TO CNS PROTEINS IN CEREBRAL METASTASIS AND PARANEOPLASTIC SYNDROMES. R Kaiser, R Kaufmann, M Czygan, CH Lucking. *Freiburg, Germany.*

We investigated the diagnostic significance of antibodies to central nervous system (CNS) proteins in patients with carcinomas and neurological syndromes Methods: 22 patients with paraneoplastic syndromes of the CNS [PS], 15 with meningeal carcinomatosis or cerebral metastasis (MC) and 48 controls with other neurologic diseases (OND) were investigated by western blotting for IgG-, IgM- and IgA-antibodies to proteins eluted from human cerebral cortex and cerebellum concentrations of immunoglobulins in CSF and serum samples were adjusted to be equal. Results: 18/22 patients with PS, 9/15 with MC and 8/48 of controls revealed IgG-, IgM-, and/or IgA autoantibodies in CSF and/or serum to any CNS proteins IgG-autoantibodies in CSF and/or serum were detected in 10 patients with PS (45 %) and in two patients each with MC (13 %) and OND (4 %) In 8/10 patients with PS, IgG-antibodies were specific for Hu- and Yo-antigens In some patients with PS, IgG-, IgM-, and IgA-autoantibodies to other CNS antigens were detected, too Intrathecal synthesis of IgG-autoantibodies, assessed from the single or darker staining of antibody bands in CSF, was demonstrated in 8/10 patients with PS. Conclusion: Besides Hu- and Yo-antibodies further autoantibodies might be relevant in paraneoplastic syndromes. The significance of IgM- and IgA-autoantibodies remains to be determined.

3
CLINICAL, ELECTRODIAGNOSTIC (EMG) AND MAGNETIC RESONANCE IMAGING (MRI) CHARACTERISTICS OF RADIATION INDUCED BRACHIAL PLEXOPATHY (RBP). NK Olsen, P Pfeiffer, N Egund, SM Bentzen, L Johannsen, K Mondrup, C Rose, *Odense, Denmark*

To characterise RBP, we performed a thorough neurological follow-up examination in 207 recurrence-free breast cancer patients treated according to the Danish DBCG 77 and 82 protocols. DBCG 77: 79 patients received 36.60 Gray (Gy) in 12 fractions, twice a week. Additionally, 48 of the patients received chemotherapy. Median follow-up 60 months. DBCG 82: 128 patients received 50.00 Gy in 25 fractions, five times weekly. Additionally, 82 of the patients received chemotherapy. Median follow-up 50 months. Results: Symptoms and signs were similar in both groups. However, in DBCG 77, disabling and mild RBP was found in 19 and 16%, respectively, as compared to DBCG 82 where the corresponding figures were 5 and 9%, respectively (p=0.001). RBP was more frequent in younger patients (p=0.001) and patients receiving chemotherapy (p=0.01). Multivariate logistic regression showed that RBP strongly depended on age and dose per fraction. Neurophysiological investigation in 46 patients showed chronic partial Denervation. MRI showed disintegration of the normal anatomy with shrinking of the brachial plexus branches in 6 out of 10 patients with clinical RBP. Histological evaluation showed diminished number of sensory nerve fibres. Conclusion: Large dose per fraction and young age predispose to brachial plexus lesions.

Oral Session 30 - Neuro-Oncology (2)

1
IDENTIFICATION OF AN APC GENE MUTATION IN A FAMILIAL ADENOMATOUS POLYPOSIS COLI ASSOCIATED WITH CEREBRAL TUMOR. MJM Dupuis, C Walon, D Boucquey, K Harmant-Van Rijckevorsel, N Lannoy, Ch Verellen-Dunoulin. *Ottignies, Brussels, Belgium*

The association of polyposis coli and malignant CNS tumours I has been linked to a recessive disease (Turcot's syndrome). Some CNS tumours, especially medulloblastoma, have also been reported in hereditary dominant Familial Adenomatous Polyposis (FAP). Different mutations have been observed in the APC gene of FAP, which has been located on chromosome 5q21-22. Turcot's syndrome has been reported not to be allelic to FAP. We report a case of adult medulloblastoma in FAP. Patient affected by polyposis in the family included mother, sister, and 2 out of 3 daughters of the propositus. Genetic studies in the family support linkage to FAP gene. The mutation is identified as a four bases deletion (GGTGCT replace by CT) in the exon 15 at the 1365 codon of APC gene. The correlation between specific genetic APC mutations to specific clinical symptoms like CNS tumours are in progress.

2
CIRCULATING ANTINEURONAL ANTIBODIES IN LUNG AND OVARIAN CANCER. U Liszka, M Drlicek, G Cavaletti, B Casati, C Kolig, U Zifko, G Bogliun, L Marzorati, W. Grisold, *Vienna Austria and Milan, Italy*

The central and peripheral nervous system may be affected by paraneoplastic neurologic syndromes. In some of them a correlation with auto antibodies has been described, in others, the pathogenesis is still obscure. Sera of clinically examined patients with lung cancer (LC) and ovarian cancer (OC) and non neoplastic controls were screened for the presence of circulating antineuronal antibodies (CANA) by immunofluorescence. Results were confirmed by immunoblotting. In 27 of 81 small cell LC patients and 4 of 103 OC patients CANA could be found in titers ranging from 1:400 up to 1:102400. All CANA in small cell LC were of the anrti - Hu - type. In OC only CANA of the anti - Yo - type were detected. In none of the non small cell LC or the healthy controls CANA were found. 27 anti - Hu and 3 anti - You antibodies were discovered. However, only in 2 anti - Hu - positive LC patients a paraneoplastic neurologic phenomenon, in both a subacute sensory neuronopathy was found. This results indicate, that CANA are found more frequently in cancer patients than paraneoplastic neurologic phenomenon's and thus are not strictly correlated.

4
DIBROMODULCITOL (DBD) AND BCNU INCREASE SURVIVAL IN ADULTS WITH MALIGNANT GLIOMAS (MG).The EORTC Brain Tumour Group presented by J. Hildebrand, *Bruxelles, Belgium.*

The usefulness of adjuvant chemotherapy in MG of the adult remaining controversial; the most encouraging results being a 15% increase of survivors at 18 and 24 months, we prospectively tested in a multicenter essay the effectiveness of an adjuvant chemotherapy combining DBD and a nitrosourea in MG (Afra et al. Neuro-oncology, 1986;4:65-70). We thus treated with a combination of DBD and BCNU adults with newly diagnosed supratentorial MG. Of the 269 patients enroled 255 were eligible. Following operation, all patients were treated by radiation therapy (RT): median dose 60 Gy in 30 fractions. After randomization, patients of the chemotherapy arm received during RT 6 weekly courses of DBD 700 mg/msq given 3 hours before irradiation, and during the first year following RT 1 to 9 courses (median 4) of DBD 1000 mg/msq on day 1 plus BCNU 150 mg/msq on day 2. Compared to controls, patients treated with DBD + BCNU survived 13 versus 10 months ($p = 0.044$), and had a longer time to progression 8.1 versus 6.7 months ($p = 0.003$). In addition, the percentage of patients alive at 18 and 24 months was respectively 34% and 21% as compared to 21% and 12% in the control group. No death was attributed to chemotherapy. Conclusion: The combination of DBD + BCNU is an effective and well tolerated adjuvant therapy in MG. Studies aiming to determine the optimal posology are warranted.

5
TREATMENT OF OLIGODENDROGLIAL TUMORS WITH PCV (CCNU, Procarbazine and Vincristine) CHEMOTHERAPY. R.Soffietti, A Chio, C Mocellini, R Ruda, MC Vigliani, D Schiffer, R Sciolla, D Seliak, *Torino, Italy*

Recent studies have suggested a peculiar chemosensitivity of anaplastic oligodendrogliomas and oligoastrocytomas. To better define the response of oligodendroglial tumors to systemic chemotherapy a phase II study was in 1991 including patients with biopsy proven tumors recurrent after surgery and/or radiotherapy. The PCV regimen (CCNU, Procarbazine and Vincristine) was employed every 8 wks for 1 year. Seventeen patients are evaluable. We observed: a complete response (disappearance of tumor on CT) at 35 and 46 months in 2/17 patients (12%); a partial response (> 50% reduction in tumor area on CT) lasting 11-26 months in 8/17 (45%); a stable disease lasting 10-12 months in 6/17 (35%); a progressive disease in 1/17 (8%). "Responders" displayed improvement in seizures and neurological deficit. Hematological toxicity was observed in 4 patients. Conclusions: Response to PCV occurs both in pure oligodendrogliomas and in oligoastrocytomas, independently from the pretreatment with radiotherapy.

6
NF2 GENE ACTS AS A TUMOR SUPPRESSOR, IN SPORADIC MENINGIOMAS AND SCHAWANNOMAS. M Sanson, P Merel, K Hoang-Xuang, G Rouleau, G. Thomas. *Paris, France*

Neurofibromatosis type 2 (NF2) is an autosomal dominant disease which predisposes to the development of schwannomas, meningiomas and ependymomas. The NF2 gene has been located on chromosome 22 and these tumors display frequent chromosome 22 allelic loss. Using positional cloning we have isolated the NF2 gene, which encodes a product called Schwannomin. Sequence analysis showed significant homology to membrane organising proteins. such as moesin, ezrin and and predicts that this gene acts at the interface between the membrane and the cytoskeleton. Using pulsed field electrophoresis we identified large deletions in 5 patients. More subtle alterations have been identified with the DGGE technique (denaturing gel gradient electrophoresis) DNA from lymphocytes of 90 NF2 patients, and DNA from 30 schwannomas, 38 meningiomas, 10 ependymomas were investigated for mutations in the 16 coding exons. Thirty-six mutations have been identified. All but one resulted in a truncated, presumably inactive protein. In 8 tumors complete loss of function of the Schwannomin could be demonstrated since all displayed loss of the non mutated chromosome 22. Germinal deletions in NF2 patients and evidence for complete inactivation in sporadic meningiomas and neurinomas provide strong evidence that the NF2 gene acts as a tumor suppressor.

7
PARANEOPLASTIC CEREBELLAR GENERATION AND SMALL-CELL LUNG CANCER : CLINICAL AND IMMUNOLOGICAL FEATURES. F Valldeoriola, JA Villanueva, X Montalban, A Arboix, C Leno, JY Delattre, F Graus. *Barcelona, Madrid, Santander, Spain, Paris, france.*

We compared the clinical and immunological features of 8 patients with paraneoplastic cerebellar degeneration (PCD) and small- cell lung cancer (PCD- SCLC) with those of 14 patients with PCD and anti- Yo antibodies (PCD- YO).PCD was defined pathologically (3/8 patients) or on the basis of a cerebellar syndrome associated with SCLC, without clinical or laboratory evidence of any other disease that explain the cerebellar dysfunction. Autoantibodies were evaluated by immunohistochemistry and immunoblot. Clinical features were similar in both groups; 75% of PCD-SCLC and 86% of PCD- YO patients presented with a pancerebellar syndrome, and only 10 involvement % of patients in both groups had neurological symptoms other than these due to cerebellar. PCD- SCLC patients tended to have a less severe outcome; 38% PCD- SCLC but only 7% PCD-YO patients remained ambulatory at last followup. Five PCD- SCLC patients did not present any antineuronal antibody. Two patients had low titres of anti- Hu antibodies, similar to those found in 16% of patients with SCLC alone. One patient presented a cytoplasmic anti- Purkinje- cell antibody different from anti- Yo. Although the neurological syndrome is similar in PCD- SCLC and PCD- YO, PCD- SCLC patients seem to have a less severe evolution. Unlike paraneoplastic encephalomyelitis or sensory neuronopathy, PCD- SCLC iS not associated with anti- Hu antibodies.

Oral Session 31 - Mouvement Disorders (1)

1
SOME CLINICAL FEATURES DIFFERENTIATE MULTIPLE SYSTEM ATROPHY FROM PARKINSON'S DISEASE, BUT NOT FROM STEELE-RICHARDSON-OLSZEWSKI'S SYNDROME. C Colosimo, A Albanese, AJ Hughes, V de Bruin, AJ Lees, *London, UK*

Among all the consecutive cases of pathologically confirmed multiple system atrophy (MSA) collected in eight years at the Parkinson's disease Society Brain Bank sixteen, which had presented with a pure parkinsonian syndrome, were selected. Clinical findings of these cases, who presented only with parkinsonian signs but no other neurological abnormalities during the first three years from disease onset, were retrospectively studied. Only clinical features which were always available on patients records were analysed. Features which were analysed included: rapidity of disease progression, symmetrical onset of symptoms, absence of tremor at initial presentation, response to levodopa and the associated presence of autonomic dysfunction. Fourteen out of sixteen cases also were studied with a brain CT scan. The frequency of the selected items in MSA was compared to that of 20 pathologically confirmed cases of Parkinson's disease (PD) and of 16 pathologically confirmed cases of Steele-Richardson-Olszewski's syndrome (PSP). It was found that a probability scale based on the five items selected discriminated MSA with a pure parkinsonian presentation from PD, but not from PSP. Patients affected by PSP, however, commonly presented with additional clinical signs (supranuclear gaze palsy, axial dystonia, cognitive impairment) which helped to differentiate MSA from PSP.

2
MOVEMENT RELATED POTENTIA!S IN PATIENTS WITH INVOLUNTARY MOVEMENTS. JW Kowalski, *Warsaw, Poland.*

Averaged movement related potentials (MRP) were studied in patients with sudden motor acts of various origins. Scalp recorded premovement potentials related to involuntary jerks, tics, clonic spasms and spasmodic rotations in patients with: subacute sclerosing panencephalitis (SSPE), Gilles de la Tourette syndrome, hemifacial spasm and spasmodic torticollis were compared to MRP occurring in the same patients voluntary imitating their stereotyped symptoms. Self initiated, voluntary movements were always preceded by negative readiness potential (Bereitschaftspotential). They appeared about 1.4 sec prior to the onset of the EMG activity in patients mimicking relatively less abrupt movements (e.g. spasmodic) and about 700 ms if brisk jerks or spasm were imitated. Bereitschaftspotentials to involuntary movements were present only in one patient with spasmodic torticollis probably due to learned habit to restrain pathological turn of the head. In patient with SSPE jerk-locked, triphasic discharge started 28O ms before the EMG trigger. The value of MRP and limitation of this method in differential diagnosis of organic and functional stereotypical movements are discussed.

3
HAS SPINOCEREBELLAR ATAXIA TYPE 2 (SCA2) A DISTINCT. PHENOTYPE? GENETIC AND CLINICAL STUDY OF AN ITALIAN FAMILY. A Filla, G De Michele, S Banfi, L Santoro, A Perretti, F Cavalcanti, L Pianese, I Castaldo, F Barbieri, G Campanella, S Cocozza, *Napoli, Italy*

The gene of spinocerebellar ataxia type 2 (SCA2) has been mapped to chromosome 12q23-24.1 in a large Cuban kindred. Using D12S79 and D12S105 we performed linkage analysis in nine individuals including six affected members of a four generation family in which SCA1 had been excluded by direct mutation analysis. We obtained a lod score = 2.37 at theta = 0.00 for the compound haplotype. Age of onset ranged from 17 to 60 years with earlier onset in the last generation. The clinical picture appeared homogeneous showing cerebellar ataxia, slow saccades, supranuclear ophthalmoparesis, absence of corticospinal signs, and constant peripheral neuropathy. This study suggests differences between SCA2 and SCA1 phenotypes.

4
FUNCTIONAL AND MORPHOLOGICAL PROTECTION AGAINST RAT QUINOLINIC ACID MODEL OF HUNTINGTON'S DISEASE BY MK801 AND CGP40116. F Block, M Schwarz, *Aachen, Germany*

The rat quinolinic acid (QA) model of Huntington's disease is characterized by degeneration of striatal projection neurons and deficits in spatial learning (1). Systemic application of the NMDA antagonists MK801 (4 mg/kg) and CGP4O116 (40 mg/kg) was performed before stereotaxic, intrastriatal injection of QA (24O nmol). Spatial learning was tested in the water maze two weeks later. Both substances significantly decreased the increase in escape latency in the water maze which was induced by striatal QA lesion itself. Histological examination revealed that the striatal QA lesion was markedly reduced by MK8O1 and CGP4O116. The present results suggest that NMDA antagonists provide functional and morphological protection against rat quinolinic acid model of Huntington's disease. on the basis of these findings NMDA antagonists should be tested in clinical trials with Huntington's disease patients.

5
THE BEHAVIOURAL AND MOTOR CONSEQUENCES OF FOCAL BASAL GANGLIA LESIONS IN MAN. KP Bhatia, CD Mardsen, *London, UK*

Behavioural and movement disorders were analysed in 24() patients described in the literature with lesions affecting the caudate nucleus, putamen and the globus pallidus (lentiform nucleus). Reports were classified into small or isolated lesions involving one nucleus alone and large lesions with additional involvement of the adjacent internal capsule and/ or periventricular white matter. Among these, dystonia was the most frequent movement disorder recorded (36%); chorea (8%) and parkinsonism (6%) or dystonia- parkinsonism 3%) were uncommon. The commonest behavioural disturbance was the syndrome of abulia (1 disinhibition was rare (4%). Lesions of the caudate nucleus rarely caused motor disorders but were more likely to cause behavioural problems. Chorea has been described in only 6% of those with caudate lesions, and dystonia in only 9%,. The most significant behavioural disturbance described in 28%, of those with caudate lesions was the syndrome of abulia. Lesions of the lentiform nuclei rarely caused abulia (10%) but commonly caused dystonia; (49%), particularly when the putamen was involved (63%). Bilateral lesions of the lentiform nuclei, either of the globus pallidus or of the putamen, caused parkinsonism (19%) or dystonia- parkinsonism (6%) infrequently. The prominence of habulia with caudate lesions emphasises the complex cognitive role of this structure. The frequent occurrence of dystonia and, less commonly, parkinsonism with lentiform lesions emphasise the motor roles of putamen and globus pallidus.

6
SLEEP DISTURBANCE IN STEELE-RICHARDSON-OLSZEWSKI SYNDROME (SROS). VS de Bruin; C Machedo, RS Howard, NP Hirsch, AJ Lees. *London, U.K*

Sleep disturbance is an important cause of morbidity in SROS but the frequency and character of sleep abnormalities and the incidence of nocturnal respiratory insufficiency remains uncertain. A prospective study of 11 patients with SROS and age matched control subjects was undertaken using clinical assessments, a structured sleep questionnaire, spirometry, static mouth occlusion pressures and nocturnal oximetry. The mean age of the SROS patients was 63.2 (52-70) yrs and mean disease duration was 4.0 (2-6) yrs. There was moderate to severe motor disability in 9 and mild to moderate dementia in 8. In the patients with SROS the following abnormalities contributed to sleep disturbances significantly more frequent than in normal controls; depression, dysphagia, frequent nocturnal awakenings (usually associated with urinary frequency), immobility in bed, difficulty with transfers, impaired dressing and feeding. There was profound impairment of voluntary and possibly limbic respiratory control whilst automatic control was well maintained. Nocturnal respiratory abnormalities were not present even in the most severely disabled. In SROS sleep abnormalities are common and relate to the cognitive, pseudobulbar and extrapyramidal disturbances rather than any central sleep or respiratory abnormalities.

7
NEW THERAPEUTIC ALTERNATIVES FOR ESSENTIAL TREMOR: ALPRAZOLAM AND ACETAZOLAMIDE (A PLACEBO CONTROLLED, DOUBLE-BLIND STUDY). D Ince, N Afsar, S Tekin and S Aktan. *Istanbul; Turkey.*

In the treatment of essential tremor (ET), propranolol and primidone are widely used agents and both are 50 - 70 % effective. Since these drugs might cause serious side effects especially in elderly, physicians have gone toward new alternative agents in this disorder. In this study, we discussed the usage of alprazolam, a minimally sedating triazole analogue of benzodiazepine class and acetazolamide, a carbonic anhydrase inhibitor. We firstly answered the question of if alprazolam and acetazolamide were superior to placebo. Furthermore, we compared these two drugs with primidone that has definitely proved to be effective in ET. This was a double-blind, placebo-controlled, cross-over study including twenty-two ET patients. Every week, patients were evaluated according to some standard scale consisting of handwriting, feeling difficulty, response to therapy and change in social activity. Results comparing baseline and end-of treatment measures were analysed non-parametrically by multiple comparisons and "Kruskall Wallis test". We reported the superiority of alprazolam to placebo in reducing tremor severity ($p<0.05$) and found no significant statistical difference in reducing the severity between alprazolam and primidone. However, acetazolamide had no superiority to placebo in this aspect.

Oral Session 32 - Movement Disorders (2)

1
EVIDENCE FOR A UNIFYING PATTERN IN DYSTONIA: INAPPROPRIATE OVERACTIVITY OF FRONTAL ACCESSORY AREAS IN ACQUIRED HEMIDYSTONIA (AHD) AND IDIOPATHIC TORSION DYSTONIA (ITD). AO Ceballos-Baumann. D. Ceballos-Baumann, R.E. Passingham, RSJ Frackowiak CD Marsden, DBJ Brooks, *London, UK*

We tried to compare changes in regional cerebral blood flow (rCBF) associated with movement in AHD secondary to thalamic or basal ganglia lesions with ITD. Based on primate experiments dysfunction of the basal ganglia-thalamo-cortical loop is now thought to underlie the excessive motor activity in chorea and dystonia. We postulated that inappropriate disinhibition of accessory frontal areas would be common to dystonia of varying aetiology. rCBF was measured with positron emission tomography in 6 patients with ITD, 5 patients with AHD and 6 controls at rest, during performance of paced, freely selected, joy stick movements. The differences in activation compared to rest are reported at omnibus $p<0.001$. s: During movement there was excessive activation of premotor, anterior cingulate and dorsolateral prefrontal cortex in the ITD and AHD group compared to the control group. In addition, the AHD patients showed excessive activation of primary motor cortex and parietal association areas, insula, and ipsilateral cerebellum. ITD patients inappropriately activated contralateral striatum, rostral SMA, Brodmann Area 8 and showed impaired activation of caudal SMA. Conclusion: Overactivity of the basal ganglia-thalamo-cortical loop leading to disinhibition of motor accessory areas is associated with both idiopathic and acquired dystonia.

2
PROTON MAGNETIC RESONANCE SPECTROSCOPY (MRS) IN MULTIPLE SYSTEM ATROPHY AND IDIOPATHIC PARKINSON'S DISEASE.CA Davie, GK Wennlng, N Quinn, WI McDonald, CD Marsden, DH Miller. *London, UK*

Multiple system atrophy (MSA) is a degenerative disease of the central nervous system. Clinically MSA may be confused with idiopathic Parkinson's disease (IPD) though the two conditions are quite distinct pathologically and prognostically. We have carried out proton spectroscopy MRS centred on the lentiform nucleus in 8 patients with the predominantly striatonigral variant of MSA, 9 patients with IPD and 8 age matched healthy controls. Spectra were collected using a STEAM sequence at an echo time of 270ms. The MSA group had significantly lower NAA/creatine ratios (mean 1.28±0.3) compared with controls (1.8±0.12, $p=0.001$). In contrast the IPD group showed normal NAA/creatine ratios (1.79±0.337, $p>0.5$). The NAA/creatine ratio was significantly reduced in 7 MSA patients and only 1 IPD patient. In addition the Choline/creatine ratio was significantly reduced in the MSA group (1.025±0.11) compared to controls (1.22±0.19, $p<0.01$). The choline/creatine ratio showed no significant reduction in the IPD group (1.15, $p<0.5$). The reduction of the NAA/creatine ratio in the MSA group probably reflects neuronal loss, occurring predominantly in the putamen. The decreased choline/creatine ratio in the MSA group suggests a reduction in membrane turnover. Proton MRS is a useful, non-invasive technique to differentiate MSA from IPD.

3
A LINKAGE STUDY OF HEREDITARY ESSENTIAL TREMOR. TT Warner, L Williams, PC Bain, MB Davis, D Conway AE Harding, *London, UK*

Essential tremor (ET) is characterised by a bilateral upper limb tremor that is present on maintaining a posture and during action; it is often familial, exhibiting autosomal dominant inheritance with variable expression. The cause of ET is unknown and autopsy studies have failed to identify a consistent underlying pathological substrate. We report the progressive linkage study of six families with ET, containing 30 affected individuals. The families have been studied with 140 highly polymorphic (CA)n microsatellite markers spanning the autosomes, using the facilities at Genethon, France. Current analysis of the data has excluded a putative ET gene from approximately 15% of the human genome.

4
REMEMBERED SACCADES WITH VARIABLE DELAY IN PARKINSON'S DISEASE. S.Shaunak, E O'Sullivan, T Crawford, M Lawden, S Blunt, L Henderson, C Kennard, *London,UK.*

Animal studies have suggested a role for dorsolateral prefrontal cortex in oculomotor spatial working memory (SWM), and this area is known to receive a dopaminergic input. Previous clinical studies of Parkinson's disease using a task requiring SWM, the remembered saccade paradigm, have failed to demonstrate an impairment in final eye position (FEP), although there was hypometria of the primary saccade. One reason for the failure to show an effect on FEP may be that the delay period, 500 milliseconds, was too short. Therefore, in this study delay periods of up to 5 seconds were used. Eye movements in 10 patients with mild to moderate Parkinson's disease and 9 age matched controls were recorded using an infra-red system; none of the patients was receiving dopaminergic medication. Reflexive saccades and remembered saccades at five delays ranging from 1-5000milliseconds were recorded. Reflexive saccades were unimpaired in patients as compared to controls. Although remembered saccades were significantly hypometric in PD subjects at all delays (gain: PD 0. 61±0.28,control 0.92 ± 0.28,P <0.01), FEP was accurate in both groups, and was not influenced by increasing delay (FEP :PD 0.93 ± 0.22, control 1.05 ± 0.17). These results suggest that oculomotor SWM is intact in PD subjects even at delays of 5 seconds.

5
COMBINED RESTING POSTURAL INTENTION ACTION TREMOR OF HANDS: ANOTHER VARIANCE OF ESSENTIAL TREMOR (ET)
A Rapoport, I.Sarova-Pinchas, *Holon, Israel.*

We report on two male patients, aged 62 and 72, with a long history of hand tremor, for 26 and 13 years, respectively, when first seen by us. Both had hand tremor at rest, with maintaining posture, and during the whole range of the finger to nose test (kinetic or intentional). It was also present when holding objects, writing, shaving, and eating (action). The tremor was so intense in amplitude that these had to be fed, and they used a signature stamp, because their signatures were unrecognisable. The first patient had a positive family history of tremor, and the second did not. Both had other body segments involved. Their tremograms showed a 4.0-5.0 Hertz frequency, and both patients were video taped for clinical evaluation and documentation. Neither responded to drug therapy given as monotherapy or in combination with any of the following medications: propanolol, primidone, alprazolam, clonazepam or neptazane. In conclusion, we suggest these cases represent another ET variant or the "malignant end-stage" spontaneous evolution of hand ET.

6
IS BOTULINUM TOXIN USEFUL IN HAND DYSTONIA ? D Zegers de Beyl, N Mavroudakis, *Bruxelles, Belgique.*

Thirty seven consecutive patients with hand and arm dystonia (31 men, 16 women mean age : 43.4 years) were seen over 4 years. Mean duration of symptoms was 5.9 years and the dystonia was localised (< 3 fingers) in 46%. History of trauma of the affected arm was obtained in 2.7% and a family history of dystonia in 16%. In 24 patients visual analysis of the dystonic posture allowed a rational selection of muscles to be injected with botulinum toxin. only patients with 2 3 injections are presented. In patients with localised hand dystonia functional improvement was obtained in 54% and subjective improvement in 85% ; with non-localised dystonia the results were 33% functional improvement and 50% of subjective improvement. Improvement lasted between 6-24 weeks and transient functionally disabling weakness occurred after 37% of injections. Botulinum toxin appears to be a reasonable treatment for patients with localised hand dystonia, whereas results are poor in non-localised forms.

Oral Session 33 - Multiple Sclerosis (5)

1
THE MITOCHONDRIAL DNA MUTATIONS ASSOCIATED WITH LEBER'S HEREDITARY OPTIC NEUROPATHY IN MULTIPLE SCLEROSIS. Ch Confavreux, S Blanc, C Godinot, T Moreau, G Lenoir. *Lyon, France.*

Leber's hereditary optic neuropathy (LHON) affects young males and causes severe and persistent visual loss. Mitochondrial DNA (mtDNA) mutations have been described in LHON patients, specially a point mutation at position 11778. Recently, a multiple sclerosis (MS)-like phenotype on clinical, CSF and MRI grounds has been demonstrated in females from LHON families with the 11778 mtDNA mutation. Are the LHON mtDNA mutations susceptibility genetic factors in MS ? We selected from the LYON-MS database cases with clinically definite or laboratory supported definite MS according to Poser's criteria. mt DNA was analysed in: - MS patients with optic neuritis onset (n = 19) -MS patients with a family history (n = 9) - LHON patients (n = 3) - unaffected relatives (n = 3) of a LHON patient. 4 mtDNA mutations were studied: 11778, 3460. 15257, 4216. The LHON patients and the tested relatives had the 11778 mt DNA mutation. In contrast, the LHON mtDNA mutations were not found in all MS cases. We conclude that a role for LHON mt DNA mutations in MS susceptibility is unlikely.

2
INCREASED SPECIFICITY OF MRI IN THE EARLY DIAGNOSIS OF MS. F Barkhof, MW Tas, MAA van Walderveen, OR Hommes, CH Polman, J Valk. Amsterdam, *Nijmegen, The Netherlands.*

Most studies show a high sensitivity of MRI in the diagnosis of MS, but a rather low specificity. We have attempted to improve the specificity of MRI. Patients (n=57) with monophasic neurological symptoms suggestive of MS were studied prospectively with MRI shortly after onset of symptoms (mean interval 5 weeks). Lumbar puncture was performed in 34 patients. Clinically definite MS was diagnosed when new symptoms in other parts of the CNS occurred (mean follow up 13 months). So far, MS has developed in 17 patients (35%). Other diagnoses were made in 9 patients, while 31 patients remain without a diagnosis. CSF examination had a sensitivity of 69% and a specificity of 38%. When 4 or more MRI lesions were required (Paty criteria), the sensitivity was 94% and specificity 55%; with 9 or more lesions these percentages were 88 and 75 respectively. Gadolinium enhancement increased specificity to 80%, although sensitivity dropped to 55 % . The presence of an infratentorial lesion (Fazekas) had a sensitivity of 82% and a specificity of 80%. This prospective study shows that the specificity of MRI can be markedly increased by requiring either 9 instead of 4 lesions, an enhancing lesion, or an infratentorial lesion.

3
MONOCYTES REALASE PROINFLAMMATORY CYTOKINES IN RESPONSE TO MYELIN BASIC PROTEIN. PL Baron, C Constantin, E Scarpini, MA Cassatella, G Scarlato, *Milan & Verona, Italy*

Immune-mediated demyelination is thought to result from aberrant immune responses to myelin antigens and seems to be co-ordinated by cytokines. Thus, regulation of cytokine production may be relevant to the pathogenesis of inflammatory demyelinating disorders. We investigated the capability of myelin basic protein (MBP) to induce cytokine release and to activate respiratory burst by human cultured monocytes. When phagocytic cells were incubated with optimal doses of MBP, Northern blot and specific immunoassays demonstrated mRNA accumulation and release of TNF, IL-1β, IL-6, IL-8 but not of IL-12. Treatment of phagocytic cells with albumin or with galactocerebroside (galC) did not trigger production of the above cytokines. The use of a specific monoclonal antibody to TNF also demonstrated that MBP, through the induced release of TNF, potentiated monocyte respiratory burst capability. Finally, the effect of MBP on TNF, IL-1β, IL-6 and IL-8 production was abolished by dexamethasone. These findings may be useful for planning therapeutic interventions aimed at preventing the amplification of myelin damage mediated by the cytokine network.

4
RELATIONSHIP OF OBJECTIVE AND SELF-REPORT MEASURES OF MEMORY IN MULTIPLE SCLEROSIS. DW Langdon, AJ Thompson. *London, UK*

To investigate which variables influence the report of memory dysfunction by MS patients and their carers, we studied a series of 38 patients with MS and their carers, with a mean age of 40.6 years (range 21 to 63) and including 22 women. The median EDSS score was 7.75 (range 5.0 to 9.0) and the mean duration of disease was 11.8 years (range 2 months to 28 years). The patients completed an extensive battery of psychometric scales. Both patients and carers rated patients everyday memory function on the Self-report Memory Questionnaire. The patients cognitive profile

was in line with previous findings. Multiple regression analyses revealed that patient group's self-report of memory function was not related to scores on tests of memory function, however it was related to the patients reported levels of anxiety and irritability, assessed on the Spielberger scales. In contrast, carer report of patient memory function was related to patients memory function. hut not to patients emotional status. Conclusions: The report of memory dysfunction by patients with MS may be influenced by variables other than formal psychometric test competence. In contrast, carer report of patients memory function more accurately reflects underlying cognitive dysfunction.

5
PROTON MAGNETIC RESONANCE SPECTROSCOPY (MRS) STUDY OF CEREBELLAR DYSFUNCTION IN MULTIPLE SCLEROSIS. CA Davie, GJ Barker, S Webb, WI McDonald, DH Miller. *London, UK.*

The mechanisms producing permanent disability in Multiple Sclerosis (MS) are poorly understood. An important factor may be the development of axonal loss within MS lesions. To address this issue Proton magnetic resonance spectroscopy (MRS) localised to the cerebellum was performed on 8 MS patients with marked cerebellar involvement, 5 MS patients with little or no cerebellar deficit and 8 healthy controls. The groups were matched for age and disease duration. All groups underwent imaging to assess atrophy and lesion load in the posterior fossa. In the clinically affected MS group, there was a very marked reduction in the mean N-acetylaspartate (NAA)/creatine ratio (0.8±0.14, $p<0.001$) compared to cerebellar white matter from controls (1.25±0.19). The MS patients with no cerebellar deficit had a normal mean NAA/creatine ratio from cerebellar white matter (1.18±0.15, $p<0.6$) compared to controls. The choline/creatine ratio showed no significant change in either MS group. NAA is an amino acid, which in adults, is almost exclusively confined to neurones and their processes. The significant reduction of the NAA/creatine ratio in the clinically affected group strongly suggests that axonal loss plays an important role in the development of disability in MS.

6
THE MYELIN BASIC PROTEIN (MBP) GENE IS NOT A MAJOR SUSCEPTIBILITY LOCUS FOR PATIENTS WITH MULTIPLE SCLEROSIS IN ITALY. M Eoli, M Pandolfo, P Gasparini, C Milanese, A Salmaggi, A Zeviani, *Milan, Italy*

Several epidemiological observations suggest that genetic factor may influence susceptibility to Multiple Sclerosis (MS) according to a polygenic mode of inheritance. Allelic association studies and linkage analysis in families with incrased incidence of MS have been used to identify the major susceptibility loci. To date, these include the HLA system and the T cell receptor a and ∞ chains. The MBP gene has been proposed as a candidate locus as well, because; i) autoimmunity to MBP could play a role in the pathogenesis of MS; ii) genetic linkage between MS and a polymorphism close to MBP gene has recently been reported in a selected Finnish population. To evaluate a possible role of MBP as a major determinant in MS susceptibility in a Caucasian population, we selected 54 Italian MS patients, 55 healthy controls and 18 families with two or more first degree relatives affected by MS. R polymorphic (TGGA)n repeat from the 5′ region of MBP gene was amplified from genomic DNA. After separation by polyacrylamide gel electrophoresis, fine alleles were detected. The distribution of alleles did not differ between healthy and MS affected individuals. Linkage analysis was performed on the 18 families, assuming a dominant or a recessive mode of inheritance with varying penetrance. Strongly negative Lod scores were obtained with each of the above models. Heterogeneity was evaluated using the HOMOG program, but no significant evidence favouring linkage for a subset of families was found. We conclude that MBP can be excluded as a major MS determining locus in our family set.

7
A PROSPECTIVE STUDY OF THE EFFECTIVENESS OF NEUROHABILITATION IN MULTIPLE SCLEROSIS. D Kidd, AJ Thompson, *London, UK*

Whilst inpatient rehabilitation may improve both disability and handicap in patients with multiple sclerosis (MS), the duration of benefit is uncertain. To address this, a prospective study incorporating outcome measures was carried out. 47 patients (5 relapsing/remitting, 42 progressive) with definite MS undergoing 2 - 3 week rehabilitation programme were studied. Patients were assessed by a single observer on admission, discharge and after an interval of three months using Kurtzke's Expanded Disability Status Scale (EDSS), the Functional Independence Measure (FIM) and the Environmental Status Scale (ESS) The mean FIM and ESS improved from 62 and 19 on admission to 72 and 17 respectively at discharge. 90% and 47% of patients improved on the FIM and ESS respectively during their stay. 44 patients were re-examined after three months; 62% had maintained or increased their functional abilities. The mean FIM and ESS was 70 and 17 respectively. 19 patients showed some neurological deterioration, of whom 10 suffered relapse; only 2 showed deterioration on the EDSS. The mean change in FIM and ESS in those who had deteriorated was -6.2 and -0.4 respectively, and 0.2 and 1.0 in those who were unchanged. summary, whilst a third of patients had further clinical activity resulting in a deterioration in disability, and handicap, function was maintained in the majority of patients three months after discharge.

Oral Session 34 - Multiple Sclerosis (6)

1
A SERIAL MRI STUDY OF THE BRAIN AND SPINAL CORD IN PROGRESSIVE MULTIPLE SCLEROSIS. D Kidd, AJ Thompson, BE Kendall, DH Miller, WI McDonald, *London, UK*

The pathogenesis of locomotor disability in multiple sclerosis is uncertain, and cannot be explained by disease activity on brain MR scans. In order to test the hypothesis that it is due to the development of new lesions within the spinal cord, a serial MRI study was performed. 19 patients (10 primary progressive, 9 secondary progressive) underwent monthly brain and spinal cord MRI before and after gadolinium for 12 months. Active MRI lesions were defined as new, enlarging or newly enhancing lesions. The mean EDSS initially was 4.9 and 5 4 in primary progressive and secondary progressive groups respectively, and 6.1 and 6.2 after 12 months. In the secondary progressive group there were 5 relapses 4 patients. In total 110 active brain lesions developed in the secondary progressive group, and 19 in the primary progressive group. In the spinal cord there were 3 new lesions in each group, only one of which enhanced. We conclude that in progressive multiple sclerosis: (i) MRI activity is much less frequent in the cord than in the brain, (ii) clinical deterioration frequently occurs in the absence of the development of new cord lesions, (iii) the mechanisms of progressive disability remain uncertain.

2
LONG-TERM BRAIN MRI FOLLOW UP OF PATIENTS WITH MONOPHASIC ISOLATED OPTIC NEURITIS. V Martinelli, M Filippi, M Rodegher, S Mammi, A Campi, A Poggi, G. Comi, *Milan, Italy.*

Brain MRI abnormalities at presentation with isolated optic neuritis (ON) is the best predictor of subsequent development of multiple sclerosis. In this study a brain MRI long-term follow up of patients with ON who do not develop further neurological disturbances was performed to evaluate the frequency of a subclinical evolution. Nineteen patients with monosymptomatic ON were studied. Unenhanced brain MRIs were obtained at presentation and after a mean follow-up of 42.3 months (range=24-72 months). Brain MRI abnormalities at presentation were graded according to number and size. At follow up, the number of new, enlarging, reduced or disappeared lesions were counted. Brain MRI at presentation was abnormal in 9 patients (47%). In all these patients an increase of lesion load was observed during follow up, while only 1/10 patient with normal MRI at presentation developed multiple lesions ($p<0.001$). The increase in lesion load was equally distributed in periventricular and other- regions of the 9 patients with abnormal MRI at presentation. These patients had a total of 65 new, 5 enlarging and 4 disappearing lesions. Our data suggest that patients with monosymptomatic ON and brain MRI abnormalities at presentation have a subclinical disease activity despite the absence of new clinical relapses.

3
INTERACTIONS OF INFLAMMATORY FACTORS WITH THE EXTRACELLULAR MATRIX: POSSIBLE ROLE OF THE TARGET ORGAN IN RELAPSES OF MULTIPLE SCLEROSIS AND OTHER

AUTOIMMUNE DISEASES. A Miller, L Cahalon, R Hershkoviz, N Lahat, D Wallach, O Lider, *Haifa & Rehovot, Israel.*

To determine the molecular basis of the ECM- TNFα interactions, and the biological significance of the binding as well as the release of Tumour Necrosis Factor-α (TNFα) from its storage in the ECM. Background: Recent works suggest that the cytokine (TNFα) could contribute to the pathogenesis of several human neurological diseases, including Multiple Sclerosis and AIDS dementia. Despite growing evidences that the extracellular matrix (ECM) can bind growth and inflammatory factors, the interactions of TNFα with the ECM have not been clarified. Methods: ECM was prepared from bovine corneal endothelial cells. Binding of 12sI- TNFα to ECM and its release were probed by radio-labelling assays. Extraction of TNFα from the ECM was studied using various proteolytic enzymes, Heparinase and soluble TNFa receptors. Results: TNFα binds avidly and specifically to ECM and particularly to its proteoglycan component. Binding to ECM did not inactivate TNFα, but rather demonstrated differential modulating effects on various activities including cytotoxicity, cell adhesion, regulation of cytokines secretion or expression of adhesion molecules and MHC gene products. These effects were further enhanced when TNFα was released from the ECM. Conclusions: The secretion of cytokines in the process of the inflammation does not necessarily terminate with their enzymatic degradation. The extraction of inflammatory factors from their storage sites in the ECM by soluble products of activated immune cells, may represent a potential mechanism for the elicitation of relapsing inflammatory processes.

4
INTRATHECAL IGM ANTI-MBP LEVELS AND PROGNOSIS IN MULTIPLE SCLEROSIS. P Annunziata, T Martino, D Maimone, GC Guazzi, *Siena, Italy.*

To date, there is a lack of data on the antigenic characterisation of the primary humoral immune response in multiple sclerosis (MS) and its possible role in the disease progression and prognosis. To investigate this question, we assayed, by ELISA, total IgM levels in the paired serum and cerebrospinal fluid (CSF) and IgM anti human myelin basic protein (MBP) in the CSF from 62 patients with relapsing-remitting MS. We also searched for association of IgM anti-MBP with disability status (assessed by the EDSS) and disease progression rate (assessed by the Progression Index). Elevated CSF IgM anti-MBP (above the mean + 2SD of IgM anti-MBP levels in the patients with normal total IgM) were detected in 16/62 patients. There was correlation of CSF IgM anti-MBP with IgM index ($r = 0.90$; $P < 0.001$) but not with CSF/serum albumin. 19% of the patients with high IgM anti-MBP levels showed a low disability status (EDSS < 2.0) compared with 32% of the patients with normal levels (n.s.). 25% of the patients with increased intrathecal IgM anti-MBP response showed a low disease progression rate (Progression Index < 0.2) compared to 5% of the patients with normal response ($P < 0.01$). These findings demonstrate, in a subgroup of MS patients, an increased intrathecal IgM anti-MBP response, correlating with low disease progression rate.

5
RATIONALE FOR THE USE OF INTERLEUKIN-10 (IL-10) TO SUPPRESS MULTIPLE SCLEROSIS (MS) EXACERBATIONS. AM Porrini, L Dell'Arciprete, D Gambi, *Chieti, Italy*

The immune system is abnormal in MS and cytokines are thought to participate in the inflammation, demyelination and intrathecal IgG synthesis seen in the disease. Peripheral blood mononuclear cells (PBMC) are activated and spontaneously secrete pro-inflammatory cytokines (IL-1β, TNFα, IL-6, and IFNγ), particularly during the exacerbations of disease. Cytokine secretion is inhibited by IL-10, a monokine described as cytokine synthesis inhibitory factor. Viral illnesses induce production of interferons (IFNs) and exacerbations of MS are provoked by treatment with IFNg. It is likely that MS attacks, seen during viral infections, are mediated by high levels of IFNs. In order to investigate if the increased secretion of cytokines present in MS is related to abnormalities of inhibitory activity of IL-10 on cytokine synthesis we have studied the effects of exogenous IL-10 on TNFa and IL-6 secretion by PBMC of 10 MS patients and 10 healthy control subjects (NL). PBMC were incubated with LPS (500 ng/ml), IFNg (100U/ml), LPS+IFNγ to induce cytokine secretion. Recombinant human IL-IO was used at concentration of 100U/ml to inhibit cytokine production. Supernatants were collected after 24-hours of incubation and TNFa and IL-6 levels were measured by bioassay. IL-10 inhibited LPS-, IFNγ- and LPS+IFNg- induced TNFα and IL-6 secretion in MS patients and NL. No signiiicant differences were found between MS patients and NL. Our results show that IL-l0 acts as inhibitor of pro-inflammatory cytokine secretion also in MS. The effects of IL-10 might be used to suppress MS exacerbations induced by viral illnesses.

6
A CROSSOVER TRIAL OF INTRAVENOUS IMMUNOGLOBULIN VS METYLPREDNISOLONE IN MULTIPLE SCLEROSIS. PM Rothwell, RRC Stewart, RE Cull. *Edinburgh, UK.*

We performed a randomised, double-blind, crossover design clinical trial of intravenous human immonoglobulin (IVIgG) versus intravenous methylprednisolone (MP) in 10 patients following exacerbations of relapsing-remitting or progressive multiple sclerosis (MS). treatments, consisting of 5 days of 0.4g/kg/day IVIgG and 5 days of 500mg/day IV MP, were given 6 months apart. Patients were assessed before each treatment and 1 week, month, and 3 months thereafter. the Kurtzke expanded disability status score (EDSS) and the number of relapses since the start of the treatment were recorded. Nine patients completed both treatments. One patient left the trial after the first treatment. No serious side-effects occurred with either treatment. there were 5 relapses in 4 patients during the 3 months following the 9 MP treatments compared to 2 relapses in 2 patients during the 3 months following the 10 IVIgG treatments. the EDDS improved by 1.0 in 1 patient and worsened by 0.5 in 3 patients 3 months after MP treatment, and worsened by 0.5 in 2 patients 3 months after IVIgG treatment. It is concluded that IVIgG can be given safely to patients with MS. No conclusions can be drawn about the efficacy of IVIgG as a treatment in MS because of the small size and short duration of the trial, but the trend towards a reduced relapse rate following IVIgG is in keeping with a previous report, and merits further study.

Oral Session 35 - Cerebrovascular Disorders (5)

1
PIRACETAM AS AN ADD-ON TREATMENT TO INTENSIVE SPEECH THERAPY FOR APHASIA. W Huber, K Willmes, K Poeck. *Aachen, Germany*

Sixty-six patients with chronic aphasia (mean duration: 11 months) of cerebrovascular origin, were included in a double-blind, parallel-group study, comparing piracetam 4.8 g/d to placebo. During 6 weeks this medical treatment was combined with an intensive speech therapy program in the aphasia ward of the neurologic department of the RWTH-Aachen-Hospital. 50 patients could be analysed for efficacy. Outcome was measured by the Aachen Aphasia Test (AAT). At baseline both treatment groups were comparable for their age as well as for the severity and distribution of their AAT-scores. The statistical tests were stratified over the type of aphasia at baseline. Analysis of variance has shown a significant difference in favour of the piracetam group for the 'profile height', a weighted sum score of the different subtests of the AAT. While all subtests improved more under piracetam treatment than under placebo, the specific differences for the subtests 'written language' and 'token test' reached respectively significance and trend level. In general patients improved twice as much under piracetam as under placebo, while receiving the same intensive speech therapy.

2
CEREBRAL EMBOLUS MONITORING WITH DOPPLER. D Russell, SK Braekken, R Brucher, J Svennevig, *Oslo, Norway*

We have shown in an experimental animal model that Doppler ultrasound may be used to detect arterial emboli composed of materials that are often involved in cerebral emboli (Stroke 1991; 22: 253). Furthermore, that the intensity of the Doppler signal caused by arterial emboli depends on embolus type and size (Recent Advances in Neurosonology 1992: 57). A transcranial Doppler monitoring system has now been developed which automatically detects and counts emboli entering the middle cerebral

artery (EME). This method may differentiate emboli from artefacts and emboli composed of solid elements from gaseous emboli. We have applied this method in the clinical situation and our experience suggests that transcranial Doppler may now be used to automatically detect cerebral emboli in the following situations: 1. During invasive cardiovascular surgery such as cardiopulmonary bypass and carotid endarterectomy, 2. In patients with frequent cerebral TIAs to determine if they are due to hemodynamic or thromboembolic events and 3. In patients with a potential embolic source in the heart or carotid artery.

3
EVALUATION OF INTRACRANIAL COLLATERAL PATHWAYS BY TRANSCRANIAL DOPPLER ULTRASOUND IN PATIENTS WITH INTERNAL CAROTID ARTERY OCCLUSION: A COMPARATIVE STUDY WITH CEREBRAL ANGIOGRAPHY. M Muller, M Hermesl, H Bruckmann, K Schimrigk.

To minimize the risk of cerebral angiography in patients with internal carotid artery occlusions (ICA- O) we compared the evaluation of intracranial collateral pathways by transcranial doppler ultrasound (TCD) to cerebral angiography in 43 consecutive patients (30 males, 10 females, mean age 55±9 years) with a total of 44 ICA- Os. By TCD, a patent anterior communicating artery (ACoA) was assumed by a reverse blood flow in the ipsilateral anterior cerebral artery or by a prompt fall of blood flow in the ipsilateral middle cerebral artery after compression of the nonoccluded contralateral carotid artery (NCCA). A basilar artery (BA) collateral supply was assumed by a) a BA blood velocity of more than 73 cm/sec, b) a marked increase of BA blood velocity after compression of the NCCA; and c) a significantly increased blood velocity in the ipsilateral posterior cerebral artery. TCD classified correctly the collateral supply via the ACoA in 42 of 43 instances and via the BA in 37 of 40 cases (chi^2: $p< 0.0001$) showing for the evaluation of both pathways a sensivity of at least 87% and a specifity of 95%. TCD is a reliable tool for evaluating the collateral supply in patients with ICA occlusions and should precede cerebral angiogaphy for selection of patients needing angiography.

4
WHY DO HYPERTENSIVE PATIENTS HAVE DIFFERENT CAUSES AND TYPES OF STROKE ? IL Henriques, J Bogousslavsky, G van Melle, *Lausanne, Switzerland.*

Hypertension (HT) is a recognised risk factor for stroke. However, it is not well established why patients with HT have different stroke types and causes. The possible role of coexisting factors was studied in 1057 patients with hypertension and first stroke admitted to a population-based primary care center. We used logistic regression analysis (multivariate, polichotomous) and the Lausanne Stroke Registry definition of cerebral hemorrhage (CH), cerebral infarct (CI), lacunar infarct (LI), cardioembolism (CE) and large artery disease (LAD). CH was not more common (111/ 1057, 10.5%) than in the total population of the registry (213/2145, 10%). CI was associated with age over the median (69), diabetes, smoking (SMO), family history of cardiovascular disease, hypercholesterolemia, and TIA. LI represented 36% of CI, LAD 21% and CE 14.5%. LAD was associated with SMO (Odds ratio: 2.14; 95% confidence interval: 1.55-2.95) and TIA (1.96; 1.39-2.75); CE was associated with age > 69 (2.13; 1.47-3.09). In the presence of age > 69, SMO and TIA the proportion of LAD doubled (44%). When TIA and SMO were present, there was an increase in the proportion of CE (22%) when age was > 69, and in the proportion of LI (49%) when age was < 70. The interaction between HT, TIA, age over the median, and SMO may explain in art why patients with HT and stroke are more likely to have a CH, LI, CE, or LAD

5
SPONTANEOUS INTRACRANIAL HYPOTENSION COMPLICATED BY SUBDURAL HEMATOMA. F Landgraf, M Verin, A Biraben, G Edan, *Rennes, France*

We report the history of a previously healthy 50 year old man with spontaneous intracranial hypotension complicated by a bilateral subdural hematoma requiring emergency evacuation. The initial clinical presentation was postural headache worsened in the upright position, in association with bilateral cackler symptoms. CSF analysis showed a lymphocytic pleocytosis and raised CSF protein, and there was meningeal enhancement on gadolinium- MRI. Per operative biopsy showed a non- specific inflammation of the dura. Isotopic cisternography showed no evidence of CSF leak. A recurrence of headache four weeks after surgery was successfully treated with an epidural blood patch.

6
ARE CEREBRAL EMBOLI DETECTED BY TRANSCRANIAL DOPPLER A PREDICTOR FOR STROKE RISK IN PATIENTS WITH HEART VALVE PROSTHESIS? U Sliwka, RR Diehl, B Meyer, F Schondube, J Noth,. *Aachen, Germany*

Patients after valve prosthesis implantation have a higher risk for suffering strokes. Cerebral emboli give a typical signal in the transcranial Doppler spectral curves. We examinated the frequency of emboli in the middle cerebral artery with TCD over 15 minutes. A total of 135 patients were examined in the acute phase after valve implantation as well six and 12 months after the operation. The data were correlated with neurological deficits, valve types and hematological parameters. Eight percent of our patients suffered from a neurological deficite after valve implantation. These symptomatic patients had a significant ($p = 0.019$) higher emboli rate (10.9 emboli) than the asymptomatic ones (4.5 emboli). Six months later, there was no significant decrease in emboli rate, although the prothrombin time was significantly lower ($p = 0.015$). Also one year after surgery, there was no correlation between prothrombin time, valve type and emboli rate. However, symptomatic patients still presented with more emboli than asymptomatic ones. Conclusions: Emboli rate as measured by TCD signifies a risk for strokes in patients with heart valve prosthesis. No correlation between emboli rate, prothrombin time and valve type could be detected.

7
ANTERIOR CHOROIDAL ARTERY TERRITORY INFARCTS: STUDY OF PRESUMED MECHANISMS. D Leys, F Mounier-Vehier, I Lavenu, Ph Rondepierre, JP Pruvo, *Lille, France.*

It has been suggested that most anterior choroidal artery (AChA) territory infarcts are due to small-vessel occlusion, although they have also been reported in patients with internal carotid artery (ICA) stenosis or atrial fibrillation. The aim of this study was to determine the presumed mechanism of AChA territory infarcts. Sixteen consecutive patients (8 males, 8 females; 17-89 years) with an AChA territory infarct on a cerebral magnetic resonance imaging scan (Damasio's criteria), underwent doppler ultrasonography and echotomography of cervical arteries and bidimensional transthoracic echocardiography. Ten patients underwent an angiography. The presumed cause of stroke (TOAST criteria) was "definite cardioembolism" in 4 patients (atrial fibrillation in 2; paradoxical embolism in 1; left ventricular akinesia in 1), "definite large-vessel atherosclerosis" in 2, "dissection of the ICA" in 2 and "definite small-vessel occlusion" in 1. Seven patients had a negative diagnostic work-up and 6 had no risk factors for small-vessel occlusion. The AChA was not patent on angiography in 4 patients and 1 had 2 arterial cut-off in other cerebral arteries. These findings suggest that AChA territory infarcts are rarely related to small-vessel occlusion and therefore require a complete diagnostic work-up.

Oral Session 36 - Cerbrovascular Disorders 6

1
HOLTER-ECG OF PATIENTS WITH TIA/ISCHEMIC STROKE. CR Hornig, C Lammers, B Waldecker, W Haberbosch. *Giessen, Germany.*

Three hundred consecutive patients with a TIA or ischemic stroke were prospectively examined by CT (99.7 %), duplex sonography (97.7 %), routine ECG (98.7 %), Holter-ECG (87 %), and echocardiography (89 %; TEE, 61.3 %). 48 patients (16 %) were found to have nonrheumatic atrial fibrillation. Whereas 38 patients with NVAF could be identified by medical history or routine ECG, AF of 10 patients was intermittent and detected only by Holter-ECG. Associated cardiac disorders of the 10 patients with intermittent AF were mitral valve regurgitation (5), remote myocardial infarction (2), left atrial thrombus, nonischemic cardiomyopathy, left ventricular aneurysm, and aortic valve stenosis (1 each). In 4 cases intermittent AI was the only cardiological abnormality. Four patients had a concomitant atherosclerosis of the symptomatic neck artery, 3 multiple

lacunes in CT indicating small vessel disease. Cardiogenic brain embolism was assumed as quite definite in 3 patients. To identify these 3 patients, Holter-ECG examination of all patients with a normal duplex sonography of the symptomatic neck artery and no atrial fibrillation in routine ECG would have been necessary (169 patients in this series). In conclusion a few patients with cardiogenic brain embolism can only be identified widespread use of Holter-ECG with an identification rate of about 1:50.

2
DUTCH EUROPEAN SINUS THROMBOSIS (CVST) TRIAL: CLINICAL FEATURES OF THE FIRST 10 PATIENTS. SFTM de Bruijn, J Stam, *Amsterdam, The Netherlands*

In this double-blinded multi-centre trial patients with CVST (confirmed by angiography or MRI/MRA) are randomised to treatment with high dose LMW-heparin or placebo. Clinical features before randomisation of the first 10 patients are presented. The sex-ratio (male:female) was 1:9. The mean age was 39.5 yrs (range 27-69). The average duration of symptoms was 9.8 days (range 3-20). All patients presented with recent headache, 9 severe. 5 patients had seizures, 1 TIA-like episodes. Other clinical signs were papilloedema (3), dysphasia (4), and paresis (6). 5 patients had cerebral haemorrhage (CT scan), in 2 cases combined with infarcts. The mean Glasgow Coma Score (EMV, 14 point-scale) was 12.4 (range 8-14). Cerebral haemorrhage was associated with a lower EMV score (11.2 versus 13.6 respectively, Mann-Whitney test, P = 0.047). *Conclusion:* These prospective data illustrate the variable clinical picture of cerebral venous thrombosis. There was a high incidence of cerebral haemorrhage, associated with a lower EMV-score.

3
LEG WEAKNESS DUE TO STROKE. R Schneider, JC Gautier, *Aachen Germany; Paris, France*

Among 1575 patients with an acute stroke, 63 (4%) were found to have leg-predominant weakness. 1) The cerebral lesions were situated in 12 cases in the anterior cerebral artery (ACA) territory including 1 patient with a thrombosis of the sagittal sinus. 2) Lesions restricted to the rear portion of the medial part of the precentral gyrus caused a contralateral predominantly distal leg weakness. The weakness was severe with little improvement. 3) Lesions involving the medial part of the premotor cortex, the supplementary motor area and the rear portion of the medial part of the precentral gyrus caused a contralateral, severe leg-predominant hemiplegia, distally predominant and a less severe proximal weakness of the arm. Recovery was much better for the arm than for the leg. 4) Lesions affecting the medial part of the premotor cortex, the supplementary motor area and sparing the precentral gyrus caused a contralateral hemiparesis predominating on the leg but predominating proximally on both leg and arm. Recovery was good for leg and arm.

4
THE CLINICAL PRESENTATION OF ARTERIOVENOUS MALFORMATIONS (AVM) TP Berlit, B Fauser, C Klotzsch, RR Diehl, HC Nahser, D Kuhne, *Essen, Germany*

We studied 79 patients with arteriovenous malformations (AVM) by means of ultrasound methods, MRI, CCT and angiography. Mean follow up was 18,5 months. AVM were localised in the left (n = 43; 54.4 %), right hemisphere (n = 31; 39.2 %) or midline (n = 5; 6.6 %). Common feeders were branches of ICA (n = 24), MCA (n = 13) or of the posterior circulation (n = 18). There were 45 males and 34 females (mean age 37.6 years). Presenting symptoms were seizures (n = 32, 40.5 %), haemorrhages (n = 19; 24.1 % - ICH n = 11; SAH n = 8) and headaches (n = 8; migraine n = 4). Steal syndromes were encountered in 8 patients (10.1 %). During follow up, 24 patients (30.4 %) bled and 39 (49.4 %) suffered from seizures. Therapy consisted of variable combinations of embolization (n = 47; 59.5 %), operation (n = 5; 6.3 %) and radiosurgery (n = 7; 8.9 %). Eleven patients (13.9 %) were not treated. None of the treated patients rebled; only 2 patients had recurring seizures. With a combined therapeutic approach, clinical improvement was achieved in the majority of patients. Angiographical complete occlusion of AVM was seen in 23.5 % after a mean follow up of 18.5 months.

5
CAUSES OF CEREBRAL INFARCTION IN YOUNG PATIENTS. G Geraud, A Danielli, V Larrue, A Bes . *Toulouse, France.*

Using strict diagnostic criteria, we have retrospectively studied the causes of cerebral infarction in a series of 141 patients (86 men and 55 women), aged from 17 years to 45 years, and consecutively admitted to our department from 1986 to 1993. A cerebral angiography was performed in 120 (85 %) patients. Among the patients who had no angiography 17 had an obvious cardiac cause of cerebral infarction. The main cause of cerebral infarction was dissection of cervicocephalic arteries (25%), followed by classical emboligenic cardiopathies (15.5 %), atherosclerosis (8.5 %), other vasculopathies (7.8 %), hematogenous disorders (2.8 %) and migrainous infarction (1 patient). The cause remained uncertain or undetermined in 56 cases (40 %). There were more uncertain or undetermined causes in younger subjects. The diagnostic contribution of some investigations (continuous ECG monitoring, Protein C, Protein S and antithrombin III dosages) was very low, even when performed in selected cases. We identified 4 cases of unilateral isolated stenosis of the supraclinoid internal carotid artery. All cases were women, aged from 17 to 25 (mean = 22). Three had been taking oral contraceptives (OC) and to were moderate smokers. MRI demonstrated a thin, annular, hyperintense signal of the arterial wall at the level of the stenosis on T1 weighted sequences in all cases most probably related to low flow. Antiethinylestradiol antibodies were found in the 3 OC users. One of these also had antiphospholipid antibodies. Although the nature of the arterial lesion cannot be inferred from our data, the selective occurrence of the disorder in young women is noteworthy and the possible role of dysimmune phenomena into its pathogenesis should be further evaluated.

6
TC- 99M HMPAO SPECT IN ACUTE ISCHEMIC INFARCTION, EXPRESSING DEFICITS AS MILITER ZEROPERFUSION : PRELIMINARY RESULTS. RA Dierckx, A Dobbeleir, BA Pickut, E Timmerman; W Deberdt, J Vandevivere, PP De Deyn.

In 27 patients (mean age 68.8 years) we compared the relative contribution of perfusion SPECT and CT- scan in acute ischemic infarction. Also, we examined the correlation of SPECT lesions with clinical evaluation at onset. SPECT was performed using a three- headed SPECT system equipped with lead fanbeam collimators. Acquisition was started 20 minutes after intravenous injection of 25 mCi Tc- 99m HMPAO. SPECT deficits were expressed as milliliter zeroperfusion, being a virtual parameter simultaneously accounting for extent and degrees of hypoperfusion. This method provides a workable, accurate virtual parameter, with the assumption that the contralateral brain region remains uninvolved. Interobserver reproducibility in 12 SPECT studies with lesions varying between 6 and 369 cc showed a correlation coefficient of r = 0.99. While mean delay since the onset of symptomatology was approximately 7 hours for both SPECT and CT- scan, SPECT showed lesions concordant with the clinical Examination in 100 % and CT- scan findings in 48 %. Moreover, we found a statistically significant correlation ($p < 0.01$) when comparing size of SPECT lesions during the acute stage with Orgogozo Scale score obtained on admission. In conclusion, perfusion SPECT expressing deficits as milliliter zeroperfusion deserves consideration as a sensitive functional baseline in treatment strategies for acute ischemic infarction

Oral Session 37 - Peripheral Neuropathy (4) - Hereditary Neuropathies

1
A LARGE KINDRED OF AUTOSOMAL RECESSIVE MOTOR AND SENDORY HYPERMYELINATING NEUROPATHY: CLINICAL, NEUROPHYSIOLOGIC AND NEUROPATHOLOGIC FEATURES. F Bono, AC Bruni, P Valalentino, MP Montesi, G, Talerico, M. Zappia, M. Sabatelli, A. Quattrone, *Catanrazo, Italy*

A large Italian kindred of hereditary motor and sensory hypermyelinating neuropathy including more than 1990 persons and 10 patients is described. We examined six patients on clinical, electrophysiological and neuropathological grounds. The onset of the disease was early in childhood (2 years) with distal and proximal weakness (myopathic-like appearance). 3 patients (aged 20-32 years old) were on wheelchair with marked limb deformities. NCV was severely reduced (10-15 m/sec) or impossible to evaluate in older subjects. Interpeak I-III BAEPs latencies were abnormally delayed in all the patients; Sural nerve biopsy revealed highly unusual

myelin abnormalities characterised by complex redundant loops and folds of the myelin sheath. These findings suggest that this family was affected by autosomal recessive motor and sensory neuropathy, a new variant of HMSN characterised by excessive myelin outfoldings.

2
DELETION OF CHROMOSOME 17P11.2.P12 IN ITALIAN FAMILIES WITH HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES (HNPP). D. Pareyson, D.Lorenzetti, A Sghirlanzoni, V.Scaioli, B Castellotti, S. DiDonato, M.Pandolfo, JR Lupski. *Milan, Italy; Houston, Texas, USA.*

HNPP is an autosomal dominant disorder characterised by recurrent transitory mononeuropathies. Its molecular basis has been identified as a submicroscopic deletion on chromosome 17pll.2-pl2 involving the same region that is duplicated in Charcot-Marie-Tooth disease type lA (CMTlA). Subjects from 9 HNPP families were clinically, electrophysiologically, and morphologically (6 families) evaluated. Families were then typed with the polymorphic (CA)n repeats RMl l-GT and KA52Fl-GT within the CMTlA/HNPP duplication/deletion region. Allele segregation of RMl l-GT and KA52Fl-GT markers demonstrated absence of transmission from affected parents to affected siblings in four families. A 1.8 kb *Eco* RI fragment, which identifies two homologous sequences (CMTlA-REP) flanking the CMTlA/HNPP duplication/deletion monomer, was hybridized to *Eco* RI digested DNA from affected and unaffected subjects from HNPP families. A reduced hybridization intensity of a 6.0 kb fragment mapping to the distal CMTlA-REP sequence was detected in all affected individuals tested. Our data confirm the association of HNPP with a chromosome 17p deletion. and lend further support to its causative role in this disorder.

3
HEREDITARY MOTOR AND SENSORY NEUROPATHY WITH CALF HYPERTROPHY IS ASSOCIATED with 17p11.2 DUPLICATION. A Uncini, A Di Muzio, D Gambi, M Sabatelli, N Archidiacono, R Antonacci, R Marzella, M Rocchi - *Chieti, Roma & Bari, Italy*

Demyelinating hereditary motor and sensory neuropathy (HMSN I) is characterised by progressive weakness and atrophy of leg muscles. Six patients belonging to 3 generations are presented: calf hypertrophy (6 of 6), foot drop or difficult heel walking- (4 of 6), pes cavus (3 of 6), absent or depressed tendon jerks in the lower limbs (4 of 6) and mild distal sensory loss (3 of 6). Motor conduction velocities ranged from 20 to 40 m/sec. Sural nerve biopsy showed loss of large myelinated fibers, numerous onion bulbs and segmental demyelination and remyelination. Muscular CT scans, histologic and morphometric findings of the gastrocnemius muscle revealed true muscular hypertrophy. Southern blot and fluorescence in situ hybridisation documented the duplication of the entire 17p11.2 segment associated with classical HMSN IA. The pathogenesis of muscle hypertrophy in our cases is unclear. Chronic leg muscle weakness and long-standing partial denervation might cause calf enlargement by a combination of compensatory "work-induced" and stretch-induced" fiber hypertrophy. Alternatively the fact that all the affected family members presented calf hypertrophy might suggest the action of a genetic factor associated with the duplication at 17p11.2.

4
LIVER TRANSPLANTATION IN FAMILIAL AMYLOID POLYNEUROPATHY RELATED TO ABNORMAL TRANSTHYRETINE (TTR). D Adams, D Samuel, C Goulon-Goeau, PP Costa PP, AE Harding, H Bismuth, G Said, *Paris, France; London, UK & Porto, Portugal*

Familial amyloid polyneuropathies related to abnormal TTR (FAR TTR) are severe neuropathies with a fatal course in a mean interval of 10 years after the first symptoms. Liver transplantation has recently been proposed as a treatment of FAP because the liver is the main source of TTR. The aim of this study was to evaluate the efficacy of liver transplantation in patients with FAPTTR . Evaluation of the neuropathy was 1) Clinical: including a question nary, the recording of extension of superficial sensory loss, motor testing, cardiovascular autonomic tests; 2) Electrophysiological with measure of SNAPs, CMAPs' amplitudes and NCV, 3) Histopathological with quantification of nerve fibers density after nerve biopsy, 4) Biological with measure of serological abnormal TTR. These evaluations were done before liver transplantation and had to be repeated except the nerve biopsy every 6 months after the liver transplantation. Six (6 /9) patients enrolled in this study were of Portuguese origin, 8 /9 had a met 30 TTR gene mutation. The mean interval between the first symptoms and liver transplantation was 4 years. For the first six patients, a dramatic reduction of abnormal serum TTR level was observed within days after liver transplantation. The first post transplantation results will be available at the time of the meeting.

5
EXCLUSION OF CHARCOT-MARIE-TOOTH TYPE 2 TO CHROMOSOME LP IN SEVEN PEDIGREES. .De Jongh P, Lofgren A, Timmerman V, Vance JM, Van Broeckhoven C, Martin J-J. *Antwerpen, Belgium & Durham, USA.*

In seven families with autosomal dominant hereditary motor and sensory neuropathy type II (HMSN type II) or CMT2, we identified 39 patients. Diagnosis was based on the typical clinical presentation and normal or slightly reduced motor and sensory nerve conduction. Distal spinal muscular atrophy was excluded by the presence of unequivocal sensory abnormalities on clinical examination or neurophysiological testing. In one family a cyclic neutropenia co-segregated with the CMT trait. All families had an early age at onset with a mean of less than 15 years. Linkage analysis with markers of the distal part of chromosome lp. (DlS244, DlS16O, DlS228, DlS170) excluded the previously reported locus in this region as the cause of CMT2 in each of these families. Negative lod scores were obtained in an analysis including both affected and unaffected individuals and in a calculation with only patients included.

6
A FAMILY WITH HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES AND NO DELETION AT CHROMOSOME 17D11. 2. F Palau, A Cruz Martinez, S Bort, J Arpa. *Valencia, Madrid, Spain.*

Hereditary neuropathy with liability to pressure palsies (HLPP) is an autosomal dominant disorder associated with increased susceptibility of peripheral nerves to mechanical compression resulting in transient palsies and focal demyelinating neuropathy. Recently, a 1,500 Kb deletion on chromosome 17p11.2 (locus CMT1A/HNPP) has been associated with HLPP. We present a 4 generations family segregating HLPP with no deletion at CMT1A/HLPP locus on chromosome 17p11.2. Fifteen members including 6 affected individuals were available for genetic studies. Molecular analysis with marker loci D17S122, D17S125, and D17S61, showed evidence of 2 distinct haplotypes in every patient, which suggested that a deletion was not responsible. Further linkage analysis at CMT1A/HNPP locus was carried out. A maxlod value of 1.8 at zero of recombination fraction was obtained. As a result, linkage to CMT1A/HLPP locus is suggested in this family. Clinical and electrophysiological findings did not show differences from other HLPP families with a deletion at the CMT1A/HNPP locus. We conclude that HLPP shows genetic heterogeneity as do other hereditary motor and sensory neuropathies.

7
AUTOSOMAL RECESSIVE SENSORY NEUROPATHY WITH SPASTIC PARAPLEGIA. PK Thomas, P Misra, RHM King, K Badhia, M Anderson, A Caballo, J Vichez, *London UK, Valencia, Spain*

A separate variety of hereditary sensory neuropathy is recognizable in which a disorder of autosomal recessive inheritance begins in childhood with progressive distal sensory loss involving all modalities and affecting the lower limbs to a greater extent than the upper. This results in a mutilating acropathy. There is an accompanying spastic paraplegia. Five patients with this combination have been investigated, comprising two sibling pairs both with normal but consanguinous parents and a sporadic case with normal unrelated parents. Spontaneous pain was a feature in two cases, which occurred in crises' lasting several days in one. Nerve conduction studies indicated an axonopathy and nerve biopsy showed loss of myelinated nerve fibres of all diameters and a less prominent loss of unmyelinated axons. There have been previous reports of a similar disorder with autosomal dominant inheritance, but only a single report with possible autosomal recessive inheritance.

Oral Session 38 - Peripheral Neuropathy (5)

1
DYSREGULATION OF HUMAN PNS MYELIN PROTEIN EXPRESSION IN NEUROPATHIES ASSOCIATED WITH ANTI-MAG ANTI-

BODIES. JM Gabriel, B Erne, GC Miescher, J Ulrich, A Vital, C Vital, A Steck, *Basel, Switzerland, & Bordeaux, France*

Most patients with demyelinating paraproteinaemic polyneuropathy (PPN) have monoclonal IgM autoantibodies (M-IgM) that react with the L2/HNK-1 determinant of MAG and PO. Clinical and experimental studies have suggested a causal role of these anti-MAG antibodies for the development of the neuropathy. The purpose of the present study is to analyse whether chronic exposure of anti-MAG M-IgM may alter the expression of HNK-1 bearing myelin proteins such as MAG, PO or PMP22. Preliminary results of immunohistological analysis of sural nerve biopsies from patients with PPN and anti-MAG gammopathy were obtained by using anti-myelin mAbs: 1) expression of the myelin proteins MBP, MAG and Po and the glycolipid GalC seems to be decreased in a comparable amount to the myelin loss; 2) however expression levels of PO, MBP and GalC seem unchanged in the remaining myelin sheaths. 3) In contrast, MAG expression is down-regulated in a large proportion of the remaining myelin sheaths; 4) but GFAP protein expression appears to be upregulated in these patients. In conclusion, circulating anti-MAG M IgM in the serum of PPN patients may deregulate the expression of MAG itself as well as some L2/HNK-1 negative proteins.

2
ANTIBODIES TO NEURAL ANTIGENS IN MOTOR NEURON DISEASE AND MOTOR NEUROPATHY. R. Nemni, M Corbo, S Previtali, A Quattrini, R Fazio, N Canal. *Milan, Italy*

Antibodies (Ab) to glycoconjugates (GC) and to neural antigens (NA) may be involved in the pathogenesis of some degenerative diseases of the motor system. We analysed sera for these Ab from 37 patients (Pts) affected by Motor Neuron Disease (MND) and from 21 Pts affected by Motor Neuropathy (MN), as well as control sera from 37 age-matched normal subjects and from 28 Pts with sensory neuronopathy. Sera were tested against GC by ELISA, against NA by immunoblotting, and against bovine spinal cord (BSC) by indirect immunofluorescence (IF). We found high titers of Ab to GC in only 5 Pts with MN. Sera from 12 Pts (7 MND and 5 MN) reacted to NA of different molecular weights. By IF on BSC sections we found a strong IgM reactivity to gray matter in 6 Pts (2 MND and 4 MN). The IgG from 11 Pts (5 MND and 6 MN) strongly reacted with the cell body and the axon of the motor neurons, and more weakly with the grey matter. High titer Ab to GC are present in only some Pts with MN but Ab to other NA are present in a high percentage of Pts with either MND or MN. Immunosuppressive treatment was beneficial only in of 7 MND Pts but in 10 of 12 MN Pts with high titer serum Ab to NA.

3
DETECTION OF ZINC FINGER PROTEINS DIFFERENTIALLY EXPRESSED DURING NORMAL DEVELOPMENT OF SCIATIC NERVE IN RODENTS (MICE, RATS) AND IN THE TREMBLER MOUSE. K Petry, I Labatut, S Hilmi; E Ellie, *Bordeaux, France*

The differentiation and development of eucaryotic cells is organised in a precise temporal and spatial fashion. The mechanisms involved are regulated by transcriptional factors with the ability to recognise and to bind to DNA sequences. One class of such DNA binding proteins is the "zinc finger" which has a common structure in a variety of nucleic acid binding proteins. In order to study the expression of such zinc fingers we prepared monoclonal antibodies (MABs) against zinc finger peptides of the yeast transcription factor ADR1. We tested the MABs against mutants of the ADR1 zinc finger which lost their DNA binding activity. Using this approach we obtained MABs that react with structures common to the wild type zinc finger and the mutants. These MABs recognise also zinc finger proteins of other cell systems, thus they represent a new tool to study the differential expression of zinc finger transcription factors in eucaryotic organisms. We show data of zinc finger proteins that are differentially expressed during the development of rat sciatic nerve. We compared the expression of these proteins in nerve extracts from normal and Trembler mice, and observed that the adult Trembler mouse expresses the same zinc finger proteins as young immature normal animals. These observations are discussed in the context of the pathological findings in Charcot-Marie-Tooth disease.

4
PERIPHERAL NERVE INVESTIGATION IN RESTLESS LEGS SYNDROME. S Iannaccone, L Ferrini-Strambi, M Zucconl, R.Nemni, P Marchettini, A.Quattrini, S.Palazzi, S.Smirne. *Milan, Italy* .

Restless legs syndrome (RLS) may be symptomatic of some neuropathies but in many patients no etiological factors can be identified and the syndrome is defined as idiopathic. The diagnosis of idiopathic RLS is possible if the presence of peripheral neuropathy is excluded by the history and clinical examination of the patients. Epidemiological study are lacking but the current clinical opinion is that symptomatic RLS is less frequent than idiopathic. We studied 42 consecutive RLS pts (24 M and 18 F, mean age 56.8±11.6). All the subjects underwent neurological examination, haematological screening for peripheral neuropathy, polysomnography, nerve conduction studies and muscle needle examination . On the basis of clinical and peripheral neurophysiological studies 25 pts of the 42 underwent sural nerve biopsy with computer-assisted morphometric analysis of myelinated fibers. Peripheral nerve involvement was found in 31 pts (74%) and it was associated with lumbosacral plexus lesions in 5, uraemia in 2, carcinoma in 2, anaemia in 2, diabetes mellitus in 2, cryoglobulinemia in 1 and without other causes of neuropathy in 17. The pathological evaluation of sural nerve pointed out that chronic axonal involvement is the mechanism of nerve damage. In conclusion it is our opinion that patients with RLS should be subjected to peripheral nerve investigations to better classify the idiopathic and symptomatic syndromes.

5
LIPOCORTIN-1 EXPRESSION IN THE SCIATIC NERVE OF LEWIS RATS WITH EXPERIMENTAL AUTOIMMUNE NEURITIS. R Gold, M Oehlschlager, RB Pepinsky, KV Toyka, HP Hartung. *Wurzburg, Germany & Cambridge, USA*

Lipocortin-1 is a calcium-binding protein induced by corticosteroids, and may mediate part of their anti-inflammatory effects. In this study we have characterised the cellular distribution of lipocortin-1 immunoreactivity and the level of expression in adoptive-transfer experimental autoimmune neuritis (AT-EAN). AT-EAN was induced by intravenous injection of P2-specific T-cells. Sciatic nerves were dissected at the peak of disease in dose-response studies or at days 4,7,14 or 21 in time-kinetic experiments. We characterised cellular infiltrates in serial sections using monoclonal antibodies specific for α/β T-cells, panel of macrophage markers, for lipocortin-1 and the polyclonal sera from rabbit no 842 recognising human and rat lipocortin-1. In parallel, we quantified lipocortin-1 in tissue extracts by a sandwich-ELISA. Only weak immunoreactivity was found in nerves of control animals injected with non-pathogenic T-cells. Lipocortin-1 levels increased from 0.33 ± 0.08 μg/mg protein in controls to a maximum of 0.71 ± 0.23 μg/mg protein at the peak of disease and remained elevated until day 21. The majority of lymphocytes and macrophages in the lesions were positive, and a very heavily stained cell type showed a distribution and morphology similar to ED-2 positive macrophages. Increased lipocortin-1 expression in sciatic nerve may contribute to the termination of the autoimmune response and facilitate recovery.

6
PERIPHERAL NEUROPATHY ASSOCIATED WITH PRIMARY SJOGREN'S SYNDROME. F Gemignani, A Marbini, G Pavesi, S Di Vittorio, P Manganelli, D Mancia. *Parma, Italy.*

Peripheral neuropathy is a known manifestation of Sjögren's syndrome, usually ascribed vasculitis. However its prevalence, the spectrum of peripheral nerve involvement and the pathogenic factors have not been defined. We evaluated the occurrence of peripheral neuropathy in 46 consecutive patients with primary Sjögren's syndrome, according to the Copenhagen criteria. Ten patients (21.7%) showed clinical and electrophysiological signs of peripheral neuropathy, consisting in distal symmetrical polyneuropathy in 7, sensory neuronopathy in 2, and mononeuropathy multiplex in 1 patient. Polyneuropathy was mainly sensory in 5 patients, and mainly autonomic in 2. Peripheral neuropathy was the presenting manifestation in 5 patients (10.9%). We found no significant differences in clinical and laboratory variables between patients with peripheral neuropathy and non-neuropathic patients, but segregating patients with distal symmetrical polyneuropathy, onset after 50 years was significantly more common in this group (6 of 7) than in non-neuropathic patients (14 of 36; p=0.028). Neurophysiological study showed predominantly axonopathic findings, confirmed by nerve biopsy in 7 cases. Necrotizing vasculitis was not found. Conclusions: We found a prevalence of 21.7% of peripheral neuropathy in primary Sjögren's syndrome, mainly in form of mild polyneuropathy, which seems favoured by ageing, whereas vasculitic neuropathy seems uncommon, contrary to previous reports.

Oral Session 39 - Higher Functions Disorders

1
MRI CORRELATIONS BETWEEN ATROPHY OF THE CORPUS CALLOSUM AND WHITE MATTER HYPERINTENSITIES IN ALZHEIMER'S DISEASE. P Vermersh, J Roche, M Hamon, JP Pruvo, AM Durocher, Ph Dewailly, H Petit. *Lille, France.*

Patients with late onset Alzheimer's disease (AD) have more white matter changes on MRI than controls. The height of the corpus callosum (CC) is related to white matter changes. We tested the hypothesis that: (i) AD patients might have atrophy of the CC, (ii) this atrophy might be correlated to white matter hyperintensities (WMH). We thus compared the CC areas and the WMH on MRI from 15 AD patients and 15 controls. The WMH were scored according to the Scheltens' rating scale. We found a significant reduction of the CC area in AD compared with agematched controls. We demonstrated that atrophy of the CC depends mainly on the diagnosis of senile dementia of the Alzheimer type and at a lower degree on a diagnosis of presenile AD but neither on age nor on ventricle enlargement. We demonstrated a significant negative correlation between WMH scores and CC areas in AD patients. Conclusion: This result suggests that beside the greater severity of white matter involvement in late onset AD, atrophy of the CC may also be present.

2
MOTOR AREA IN MAN IN THE CAUDAL DORSAL BANK OF THE CINGULATE SULCUS. C Dettmers, G Fink, R Lemon, K Stephan, D Passingham, RSJ Frackowiack, *London UK*

We performed positron emission tomography (PET) studies in six normal right handed male volunteers (age 30 ± 3) in order to investigate the relationship between cortical activation as measured by regional cerebral blood flow and force, and to determine, which structures of the central motor system show direct tuning to force. Twelve scans were collected in each volunteer using H215O and a slow bolus administration technique. Volunteers were requested to repetitively press a Morse-key-like device with their right index finger for two minutes while lying in a supine position in the PET camera. Scans were collected twice at each of 5 different levels of exerted force and in a resting state. Group analysis revealed two regions with high correlation between local blood flow and different degrees of force: one was located in the central area of the left lateral surface (primary sensory and motor cortex) stretching from the index finger to the shoulder representation. The other was situated on the left mesial wall of the brain caudal to the anterior commissure (AC) and dorsal to the cingulate sulcus encompassing the posterior part of the supplementary motor cortex (SMA). Scans from different subjects were also co-registered with individual magnetic resonance images in order to identify more precisely the individual locations of activated areas. Activated areas on the mesial surface consisted of three distinct regions: A caudal part of the mesial area in the dorsal bank of the cingulate sulcus; a second mesial area was more rostrally located in the cingulate sulcus and a third area extended anteriorly to the dorsal part of area 6 close to the midline. The "force-paradigm" we used activates three distinct areas of the posterior SMA. It demonstrates that the caudal and rostral dorsal bank of the cingulate sulcus constitute a part of the motor system and are closely related to the execution of movement.

3
ALTERATION OF COGNITIVE SKILLS IN PATIENTS WITH FOCAL LESIONS THE CEREBELLUM. C Khati, B Pillon, B Deweer, C Malapani, N Malichard, B Dubois, G Rancurel. *Paris France.*

Six patients with focal lesions restricted to the cerebellum, of (vascular ischemic, n=4; surgical n=2) were analyzed. No extracerebellar lesion was demonstrated on MRI. All patients were submitted to extensive psychological testing including: 1) global efficiency 2) explicit memory and procedural learning (mirror reading, serial reaction time task, rotor pursuit) 3) executive functions: verbal fluency, Wisconsin CST, frontal behaviour, graphic series from which a frontal score was derived, and Delis sorting test 4) time estimation abilities with visual and auditory stimuli 5) mood and behavioural disorders. Preliminary results showed (a) normal global efficiency; (b) mild executive dysfunction without frontal behaviours, (c) decreased performance in explicit memory tests that seems to correlate with the dysexecutive syndrome; (d) impairment of both motor and non-motor procedural learning; (e) time estimation deficit; (f) absence of significant affective or behavioural disturbance. In conclusion, the results indicate that lesions of the cerebellum do not induce profound cognitive or memory dysfunction but rather specific impairments, mainly for executive functions and cognitive skills. These features remind the cognitive syndrome observed after basal ganglia lesions.

4
SOMATOSENSORY DISCRIMINATION: DEFICIENT CEREBRAL ACTIVATION PATTERNS AFTER STROKE RECOVERY. B Weder, U Knorr, Y Huang, RJ Seitz. *St Gallen, Switzerland; Dusseldorf, Germany.*

Cerebral activation induced by unilateral tactile discrimination of macrogeometric objects was identified in positron emission tomography images of regional cerebral blood flow in 6 patients who had recovered from a subcortical hemiplegic stroke. The significant activation areas were localised in highresolution magnetic resonance images and the pattern in the individual patients compared to those in 6 healthy volunteers. Primary sensorimotor cortex, supplementary motor area, superior parietal lobule contralateral to the moving hand, and premotor cortex on both sides were regularly activated in normals. In contrast, the patients showed consistent activation only in the primary sensorimotor cortex. Areas of activation in parietal association, premotor and midfrontal cortical areas could also be detected in individual patients but varied considerably among them, being far less consistently activated than in healthy subjects. This coincided with a significantly slowed discrimination rate. In patients with a lesion of the corticospinal tract there was evidence from the PET data for reorganisation of motor pathways both on the side of infarction and in the contralateral hemisphere. These results corresponded to the clinical observation that the patients had regained their capacity to move the fingers of the affected hand but remained impaired in the cognitive aspects of somatosensory information processing.

5
BETA-AMYLOID PEPTIDE INDUCED PRODUCTION OF FREE RADICALS AND NEUROTOXICITY; A PROPOSED MECHANISM FOR ALZHEIMER'S NEUROPATHOLOGY. JM Carney, DA Butterfield. *Lexington KY, U.S.A*

There is a growing consensus that oxidation plays a key role in the etiology of age-related neurodegenerative diseases. We have previously reported that there is a significant increase in brain protein oxidation in the process of normal ageing. Alzheimer's disease (AD) is an age associated progressive neurodegenerative disease. There is a growing consensus that free radicals are a major factor in AD. Incubation of b-APs (1-40 and 25-35) each demonstrate the generation of free radicals using both Electron Spin Resonance Spectroscopy (ESR) and the formation of dihydroxybenzoic acid from salicylate. bAP (25-35) generated carbon centred and oxyradicals within 3 min of solubilization. Glutamine synthetase, creatine kinase and citrate synthetase demonstrated dose-related decreases in activity: the IC50 for each was 250, 200 and 350 Um, respectively. Incubation of neocortical synaptosomes with 350 Um bAP (25-35) inactivated the intramembraneous lipid spin-label 12-nitroxyl stearate by 70% within 10 min of incubation. These data support the hypothesis that the abnormal processing fragments of the amyloid precursor protein can initiate a free-radical cascade that could result in neurodegeneration and the accumulation of amyloid deposits in selected regions of the brain.

6
CORTICAL REORGANIZATION FOLLOWING EXTREMITY AMPUTATION. ML Peris, C Peiro, A Pascual-Leone Pascual, A Pascual-Leone *Valencia, Spain.*

Ramachandran et al. (1992) described 2 subjects who following upper limb amputation reported phantom sensations evoked from the proximal stump and ipsilateral face. These findings document massive reorganisation of the contralateral sensory cortex following amputation. We present a patient whose findings raise the possibility of additional transhemispheric plasticity. This otherwise healthy 55 year old man had a traumatic, above the elbow amputation of his right arm 48 years ago. Sensory stimuli applied to the proximal stump and ipsilateral lower face, evoked modality specific, somatotopically organised phantom sensations. Sensory stimuli applied to digits 1, 2, and 5 of the left hand evoked phantom sensations in

the corresponding digits. Spontaneously the subject reported phantom movement sensations of individual fingers when moving his left hand. Active or passive movements of the left index or little finger evoked phantom movement sensations of the corresponding fingers. These sensations were direction specific, present with flexion-extension but absent with abduction-adduction. Focal transcranial magnetic stimulation evoked phantom sensations from the contralateral and the ipsilateral cortex. Cerebral magnetic resonance imaging was normal. Long time after amputation massive changes of the sensorimotor system may affect not only the contralateral cortex but also the bihemispheric projections.

7
THE ROLE OF THE RIGHT HEMISPHERE IN LANGUAGE: A POSITRON EMISSION TOMOGRAPHY STUDY. G Bottini, *London, UK*

There is some evidence that the right hemisphere induces an impairment in the interpretation of figurative aspects of language such as metaphors. However it is not clear whether the right hemisphere has a specific role in such aspects of speech. We investigated cerebral activity of six normal volunteers using positron emission tomography (PET) to explore the hypothesis that the right hemisphere has a specific role in the interpretation of figurative aspects of language such as metaphors. We also mapped the anatomical structures involved in sentence comprehension. During regional cerebral blood flow (rCBF) measurement subjects were asked to perform three different linguistic tasks: comprehension of metaphorical sentences, comprehension of non metaphorical sentences and a lexical-decision task. rCBF measurements were obtained with a CTI 953B PET scanner. A bolus of H^215O was infused as a tracer. Statistical analysis of the rCBF brain images, after transformation into a standard stereotactic anatomical space, was performed on a pixel by pixel basis, by statistical parametric mapping (SPM). We found that comprehension of metaphors and non metaphorical sentences compared with lexical decision was associated with a significant pattern of activation in a number of anatomical structures in the left hemisphere. In addition comprehension of metaphors activated sites in the right hemisphere.

Oral Session 40 - Higher Functions Disorders (2)

1
EUROPEAN PENTOXIFYLLINE MULTI-INFARCT DEMENTIA TRIAL. THE EPMID STUDY. V Folnegovic-Smalc, S Knezevic, R Bokonjic, V Demarin, B Ersmark, M Gonzalez Torres, B Guiraud-Chaumeil, K Haugaard, A Jovicic, Lang Chr, Z Levic, C Martinez Parra, J Patrignani Ochoa, O Titlbach, C Wikkelso of the European Study Group

Two hundred and eighty-nine patients were enrolled in ten European countries according to the DSM III-R criteria for MID. Fourteen core centers contributed to the protocol analysis. All patients had a Hachinski score of at least 7, Mini Mental state examination of 10-25 and a CT compatible with the diagnosis of MID and with at least one ischaemic lesion. Twenty patients dropped out before the first efficacy assessment. 122 pentoxifylline patients and 117 patients on placebo completed the trial. Both groups were fully comparable regarding their demographic and disease characteristics at the beginning of the trial. The Gottfries-Brane-Steen (GBS) scale was the primary efficacy measure. The overall score improved by 0.7 points in the placebo group and by 3.5 points in the pentoxifylline group ($p = 0.028$). The intellectual function subgroups improved by 0.4 in the placebo-treated patients and by 1.6 in the pentoxifylline group ($p = 0.013$). The total score of the SCAG showed an improvement of 4.2 points in the pentoxifylline group and 2.6 in the placebo group ($p = 0.025$). The cognitive function score improved by 1.7 on trial medication and 0.5 on placebo ($p = 0.005$). The global ratings of relatives resulted in a significant difference after 3 and 6 months ($p=0.050$ after 3 months, $p = 0.023$ after 6 months). Safety data were monitored continuously. There were no significant differences between the two groups. The authors conclude that the European Pentoxifylline Multicentre Trial on MID has clearly demonstrated the clinical efficacy of pentoxifylline in the long-term treatment (9 months) of patients with multi-infarct dementia.

2
DOES COGNITIVE IMPAIRMENT CORRELATE WITH HIPPOCAMPAL AND AMYGDALOID ATROPHY IN HERPES VIRUS (HSV) ENCEPHALITIS ? D Caparros-Lefevre, M Cabaret, B Debachy, F Lebert, M Steinling, A Verier, JP Pruvo, H Petit, *Lille, France*

As few cases of proven HSV encephalitis have been described in the past, long term cognitive sequelae have rarely been evaluated in a series of patients. In 9 patients with typical clinical and MRI signs, HSV encephalitis was proven by positive HSV Polymerase Chain Reaction and early treated with acyclovir. The average age was 49 years. Cognitive sequelae were studied during the acute stage and one year later. This included language, memory and behavioural evaluation. Metabolic study (SPECT) and MRI were performed one ear after encephalitis. Volumetric measurements of hippocampal, amygdaloid formations and lesions were obtained with MRI coronal sections. There was a predominant involvement of one temporal lobe. Lesions were associated with Unilateral atrophy of the amygdaloid corpus and hippocampus in most cases. SPECT results confirmed temporal lobe involvement with assymmetry. Memory and language deficits were moderate and were improved one year later. Behaviour disorders were usually predominant with long term sequelae, with marked increase of affective and emotional reactions. These troubles occurred in patients with unilateral right or left amygdaloid corpus atrophy. Unilateral temporal involvement in HSV encephalitis seemed to be responsible for mild memory impairment. Behavioural disorders could be related to amygdaloid formation lesion.

3
SUBCORTICAL NEGLECT IS ASSOCIATED WITH PARIETAL BUT NOT WITH FRONTAL HYPOPERFUSION. JM Ferro, G Cantinho, AI Santos, F Godinho. *Lisboa, Portugal.*

We tried to evaluate the role of cortical hypoperfusion in the production of neglect after right hemispheric (RH) subcortical strokes. Eighteen RH striatocapsular strokes were studied with CT/MR, SPECT and a comprehensive neglect testing battery 2 to 8 weeks post-onset. In the (99m)Tc-HMPAO SPECT study a semiquantitative assessment of regional cerebral blood flow was performed by means of a relative perfusion index between the two hemispheres. Squared regions of interest, 4x4 pixel, were placed in the anterior, medial and posterior cortical areas of the brain cortex in four consecutive transaxial slices, excluding cerebellum. Three index values for each of the four slices were calculated by the ratio between symmetrical count values. Only 4 subject displayed any signs of neglect. All had parietal hypoperfusion. Three other patients showed dorsolateral frontal hypoperfusion but no neglect. Conclusion: neglect following striato-capsular RH lesions is associated with right parietal diaschisis. This study supports the crucial role of the right parietal cortex in hemispatial attention.

4
THE DECISION PROCESSES ARE IMPAIRED IN PATIENTS WITH FRONTAL LOBE LESION. O Godefroy, D Leys, M Rousseaux. *Lille, France*

Patients with lesion of the prefrontal cortex are impaired in complex tasks. Despite the requirement that these complex tasks require multiple decisions, the patients ability to process the decision itself has not been evaluated. We evaluated the efficiency of the decision process using the Relative Judgment Theory. Eight patients with frontal lesions were matched according to age and education, to 6 patients with posterior lesions and 7 controls. The ability to process decisions was investigated using binary choice reaction time (RT) tests with variable stimulus presentation probabilities. Choice performances were analysed using the Relative Judgment Theory. Both patient groups exhibited longer RT (P:0.0001) whereas the error rate was higher in the frontal group (P:0.006). The decrease in stimulus probability led to an increase in RT (P:0.0001) and error rate (P:0.0001) in the 3 groups. The Relative Judgement Theory analysis revealed that poor performances of the frontal group were due to a decrease in response threshold associated with a lower change in the criteria as a function of stimulus probability. Patients with lesions of the prefrontal cortex are impaired in binary choice RT tests. This impairment of the decision process might be due to a decrease in response threshold combined with the inability to use advanced information.

5
THE P.A.S.A.T. IN THE ASSESSMENT OF ATTENTION AND INFORMATION PROCESSING IN SUBCORTICAL DISEASES. J Bagunya, T Roig, A Ensenyat, M Juncadella, O Santiag. *Barcelona, Spain.*

Attentional and length of information processing disorders are frequently present in frontal and subcortical pathology. Several authors have reported the use of PASAT (Paced Auditory Serial Addition Test) in the daily clinical practice for the assessment of cognitive disorders in head injury and multiple sclerosis patients. Thirty patients with a definitive diagnosis of multiple sclerosis (MS) and equal number of head injury patients, schizophrenics and controls (cord injury patients) were administered an extensive neuropsychological battery. Speed of information processing was evaluated with a reduced version of PASAT (PASAT-G). The three groups showed mean scores significantly lower than control group in the first series (.05). In the second series the mean scores were even lowest (.01) compared to normals. There are not significant differences between means of all groups in the last series. Conclusions: The PASAT-G has proven to be a useful instrument for measuring cognitive deficits associated with head injury, MS and schizophrenics. It requires minimal materials, it takes short time to administer and it may be worth considering the addition of PASAT-G to the assessment battery of other types of neurological disorders characterised by cognitive slowing like subcortical pathology and schizophrenia alike.

6
DOPAMINE AGONIST AND FREE-RADICALS SCAVENGER ACTIVITIES OF DIHYDROERGOKRYPTINE IN DEMENTIA OF ALZHEIMER TYPE (DAT): MULTICENTRE, LONG-TERM DOUBLE-BLIND CLINICAL STUDY VS PLACEBO. L Frattola, H Trabucchi, D Cucinotta, D De Leo, R Girardello. *Padua & Milan, Italy*

DAV.I.D.E. (DAVERIUM Italian Dementia Evaluation) is a long-term project consisting of a 2-year multicenter study vs placebo on the safety and efficacy of dihydroergokryptine mesylate in patients with DAT according to DSM-III criteria. The study consists of 1-month run-in with placebo, followed by a 12-month double-blind treatment with dihydroergokryptine 40 mg/day or placebo and by a final 12-month treatment with dihydroergokryptine 40 mg/day keeping blindness condition. We report the interim analysis of the data from 205 subjects, aged 63-83 years, who completed 12 months of treatment: 102 patients were treated with dihydroergokryptine and 103 with placebo. The sample size was calculated by choosing GBS as target variable, while IMD, MDB and MMSE were selected as secondary variables. The tests were administered before the treatment period and every 3 months afterwards. Statistical analysis of GBS showed a significantly higher frequency of therapeutic successes (total score increase ~30% vs baseline) in the treated group, while multivariate analysis showed a significant difference between treatments in GBS scale, no covariates regression, no treatment by centre interaction. The univariate analysis of GBS clusters confirmed significant difference between treatments in intellective functions and in common symptoms of dementia. In MDB, word fluency, short and long-term memory improved in dihydroergokryptine group. Safety was good: mild side effects were observed in a low percentage of both the groups.

Oral Session 41 - General Neurology (2)

1
CONGESTIVE MYELOPATHY DUE TO SPINAL DURAL ARTERIOVENOUS FISTULA (SDAVF): CLINICAL FINDINGS & DIAGNOSIS. HC Hansen, Ch Koch, H Zeumer , K Kunze ; *Hamburg, FRG*

The clinical signs and symptoms of spinal dural arteriovenous fistula (SDAVF, also known as varicosis spinalis Foix-Alajouanine) may be highly misleading and be mostly not suggestive of vascular medullary disease. In contrast neuroradiology shows a relatively uniform pattern of central medullary oedema on MRI and perimedullary varicosis on MRI or myelography. During the last 4 years, SDAVF was verified by angiography in 15 male and 4 female patients (median age 59 years) after a median interval of 18 months from the onset of symptoms. In 13 cases a spinal space occupying lesion was suspected on admission, 6 cases had been regarded as polyneuropathic syndromes. At the time of diagnosis, only 7 patients were able to walk without support. All patients had motor deficits (N=1 9) accompanied by genitourinary dysfunction (N=15) and sensory deficits (N=17) of transverse, segmental or acrodistal distribution. Pain irradiating to both thighs or paresthesia in the legs were reported in 12 patients but none of the patients presented with pain only. Patients with spastic paraparesis indicating a spinal cord lesion usually received MRI early, however the central oedema was often misinterpreted as a glioma. The majority of our patients presented clinically with peripheral motor neurone deficits (N=1 1). Thus our data suggest that especially in male patients older than 50 years presenting with painful gait disorder, flaccid paraparesis and genitourinary symptoms but without conclusive diagnostic findings related to the cauda equine or peripheral nerves a congestive myelopathy of the lower spinal cord must be taken into consideration.

2
SURGERY FOR SUSPECTED NEUROGENIC THORACIC OUTLET SYNDROME: A FOLLOW-UP STUDY. Z Matkovic, P Morris, M Donaghy, *Oxford, UK.*

The diagnosis and treatment of thoracic outlet syndrome is controversial. We evaluated 40 patients, 3 months to 20 years (median, 2 years) after surgery for suspected neurogenic thoracic outlet syndrome, in particular to discover if the outcome differed significantly between those with and those without radiographic cervical ribs. Cervical ribs were removed in 23 patients. In the 17 without a cervical rib decompression was by resection of the first thoracic rib in nine and by other operations in 8. Following surgery patients reported improved pain (33/36), sensory disturbance (30/35), hand muscle strength (14/27) and hand function (23/34). The muscle wasting in 17 patients did not alter appreciably. Surgical complications, recorded in 10 patients, were transient and did not result in permanent symptomatic sequelae. Neurological symptoms continued to progress in 3 patients in whom other diagnoses eventually emerged. We conclude that surgical decompression for suspected neurogenic thoracic outlet syndrome gives rise to a similar outcome in patients both with and without a cervical rib. It relieves pain and sensory disturbance in 90% but is less effective for muscle weakness (50%). As established motor abnormalities respond poorly to thoracic outlet syndrome surgery, surgical treatment needs to be considered prior to the development of irreversible denervation.

3
LORENZO'S OIL IN X-LINKED ADRENOLEUKODYSTROPHY (ALD). W Köhler, *Berlin, Germany*

The biochemical defect in ALD is characterized by the incapacity to degrade very long chain fatty acids (VLCFA) from exogen and endogen origin. Glycerol trioleate (GTO) and Glycerol trierucate (GTE) in a 4:1 mixture (Lorenzo's Oil) is recently used to lower VLCFA levels in peripheral blood of ALD patients. Results of several open clinical studies in children and adults indicate that Lorenzo's Oil therapy alone cannot prevent the clinical progression in patients with cerebral involvement dispite VLCFA blood levels are normalized. However the data leave open the possibility that the dietary therapy may slow the rate of progression or even prevent the onset of neurological symptoms. Our own experience in 21 adult ALD patients under treatment with Lorenzo's Oil over 4 years indicate that the therapy may also prevent patients with spinal cord involvement only (Adrenomyeloneuropathy and symptomatic heterozygotes) from further deterioration of neurological disability. Currently a cooperative evaluation of dietary study results from multiple European and North American Study Centers is in progress. For the present Lorenzo's Oil therapy is recommended as a basic therapy in all symptomatic and asymptomatic hemizygotes and symptomatic heterozygote ALD patients.

4
WHAT KIND OF BRAINSTEM LESION IS PREDICTABLE BY MEANS OF CLINICAL SIGNS ONLY? A TOPOGRAPHIC STUDY WITH MRI. T Kammer, J Röther, A Schwartz, M Hennerici, *Mannheim, Germany*

To assess the topographic reliability and predictability of brainstem signs, we studied the concordance of clinically determined sites of the lesion with multiplanar MRI.. We transformed the topography of a brainstem lesion in 28 patients into an anatomical grid on the basis of either clinical signs or MRI data Only cases with a single brainstem lesion were included Clinical and neuroradiological investigators were blinded to the corresponding data. In 9/12 cases with a combination of nuclear and supranuclear signs, the site of the lesion could be predicted in a good concordance to the MRI. Especially in the subgroup with features relating to the dorsolateral medulla, the clinically determined site of the lesion was identical to that on MRI in 6/7 cases. A further 5 cases had signs referring to different

tracts and fibers in the brainstem lacking nuclear involvement. A poor concordance was found in 4/5 cases; in only 1/5 case a good concordance to MRI emerged (compared to the first group, $p < 0.05$). In 7 cases with a pure motor hemiparesis and in 4 cases with ataxic hemiparesis, we did not attempt to clinically determine the site of the lesion. On MRI, locations were found at all pontine levels in these two groups. In conclusion the site of a brainstem lesion can be accurately predicted only in cases of nuclear involvement, whereas localising value of involvement of tracts and fibers alone is poor. This is especially true in cases of pure motor hemiparesis and ataxic hemiparesis.

5
CLINICAL AND MOLECULAR BIOLOGY STUDIES OF GM2 GANGLIOSIDOSIS PRESENTING AS JUVENILE SPINAL MUSCULAR ATROPHY. P Rondot, R Navon, B Fontaine, N Bathien, Y Wu, N Baumann, *Paris, France & Tel Aviv, Israël.*

The lower motor neuron syndrome can be provoked by various causes. Some observations have reported juvenile spinal muscular atrophy accompanied by Hexosaminidase A (Hex A) deficiency. We report two similar cases occurring in different families. Both observations (H K. and C B.) presented a KugelbergWelander syndrome, H K. without cognitive syndrome and C.B. with psychosis In both cases the EMG showed a recruitment on maximal effort; nerve conduction was normal without conduction block. On muscle biopsy atrophy predominated on type II fibres. Metabolic studies using radioactive GM2 showed the accumulation of this substrate in cultured fibroblasts. In H K., there was a typical Hex A deficiency; in C B., the existence of the B1 variant of GM2 gangliosidosis was established, as the deficiency was only observed with a synthetic sulfated substrate of 4-MGUS H.K compound heterozygote for a typical adult mutation and for another mutation which has been identified. C.B. was compound heterozygotes for a known B1 mutation and for another previously unidentified mutation in the Hex A gene

6
ASSESSMENT OF HYDRODYNAMIC MECHANISMS IN THE PATHOGENESIS OF THE SYRINX CAVITIES: LONGITUDINAL MRI STUDIES AND DYNAMIC MRI. A Pou Serradell, A Capdevila, MJ Guardiola. *Barcelona; Spain.*

We have analysed 45 new cases of syringomyelia in the period 1988-1993. All of them were submitted to at least two MRI studies in order to compare evolution of cavities and/or the result of surgical treatment. All MRI studies were carried out on a conventional standarts, using T1 and T2 weigted images, and now we are attempting to obtain a relatively simple MRI technique to produce successives images (Cine Phase Contrast with variable flow velocities) of the syrinx cavities. This "dynamic MRI" showed, in large cavities, the turbulent movement of the intracavitary CSF and, in those cases with pure sensitive clinical form of syringomyelia, how this intracavitary CSF establishes communication with the spinal perimedular especes through the entrance of posterior roots or the dilated Virchow-Robin espaces. In no case could be demonstrated anatomical continuity between IV th ventricule and the syrinx. In 3 cases coexisted empty sellae. In tumoral syringomyelia (5 cases), after removing the tumor, MRI controls showed complete disappearance of cavities. We concluded that dynamic MRI studies in syringomyelia offers new insights in the comprehension of its pathogenesis: Syrinx formation cannot be adscribed to the gardnerian theory nor to a pressure gradient between the intracranial and intraspinal espaces but to a difficulty of drainage of the liquid by the spinal cord itself.

7
DIAGNOSTIC VALUE OF LABIAL SALIVARY GLAND BIOPSY IN CHRONIC IDIOPATHIC AXONAL POLYNEUROPATHY. GW van Dijk, NC Notermans, AA Kruize, L Kater, JHJ Wokke, *Utrecht, The Netherlands*

In patients with idiopathic neuropathy the diagnosis of Sjögren's syndrome should be considered. As histopathology and immunocytochemistry of sublabial salivary gland (SSG) biopsy is considered the most specific and most sensitive single test in Sjogren's syndrome, we investigated SSG biopsies in 30 patients who were randomly selected from a group of 100 patients with chronic idiopathic axonal polyneuropathy. In addition we investigated tear gland related keratoconjunctivitis sicca and the presence of anti-Ro/SSA and anti-La/SSB auto-antibodies. Mean age was 63 years (range 50-79). Ten patients had a sensorimotor and twenty a sensory polyneuropathy. Results: 1) In three patients SSG biopsy was diagnostic for Sjogren's syndrome. None of these patients had sicca complaints, two had abnormally Schirmer's test, one abnormally lysozyme test and one had anti-Ro/SSA auto-antibodies. ESR was slightly elevated (14, 24 and 27 mm). 2) In 27 patients with SSG biopsy not diagnostic for Sjögren's syndrome (mean ESR 17 mm, range 4-54) two had sicca complaints, nine had abnormal Schirmer's test and one had abnormal lysozyme test. Autoantibodies were not present in these 27 patients. We conclude that in patients with chronic idiopathic axonal polyneuropathy with or without symptoms or signs of keratoconjunctivitis sicca, SSG biopsy should be considered as a contribution to the diagnosis of Sjogren's syndrome.

Oral Session 42 - General Neurology (3)

1
BOTULINUM TOXIN THERAPY FOR UPPER AND LOWER LIMB SPASTICITY. C Bertelt, S Hesse, H Friedrich, K-H Mauritz, *Berlin, Germany.*

Hemiparetic patients are severely disabled by marked upper limb flexor and lower limb extensor spasticity. To reduce muscle tone and to improve function, botulinum toxin (BOTOX) was injected EMG-guided into 5 muscles of the upper (n=9) and 4 muscles of the lower limb (n=8), the maximum dosage was 100 units per muscle. Upper limb flexor spasticity was reduced, self care abilities (washing of hands, dressing upper extremity) were made easier but motor function was unchanged; a minimum total dosage of 300 units was required. Leg spasticity was diminished by an injection of 100 units BOTOX each into the Mm. gastrocnemius. med. et lat, soleus and tibialis posterior. Gait analysis revealed a functional improvement. Ankle range of motion, gait symmetry and stride length increased, double stance duration was reduced, displacement of the center of pressure and mode of initial contact improved. The tone diminishing effect started on the 3rd. day post injection and lasted up to twelve weeks. Patients and physiotherapists confirmed the results and reported a more effective physical therapy.

2
A SIBSHIP WITH ONSET OF PROGRESSIVE DEMENTIA IN MIDLIFE AND LAMELLAR ULTRASTRUCTURAL INCLUSIONS OF MUSCLE AND LYMPHOCYTES LT Giron, IS Watanabe, D Ewing. *Kansas City, Missouri, Greeley, Colorado, USA.*

Three brothers and 2 sisters were definitely and a brother was probably neurologically affected in a sibship in which 8 achieved adulthood and only in those with hereditary spherocytosis. Since the parents lived to old age with preserved intellect, autosomal recessive transmission of the neurologic syndrome is suspected. In the sibship, normal intellect into midlife was followed by focal higher cortical dysfunction, dementia, dystonia, myoclonus, abnormal gait, dysarthria and dysphagia. Convulsive seizures, visual abnormalities and facial dyskinesias were absent. In 1 affected member, lysosomal enzyme assays were negative and urinary dolichols were non specifically elevated. In 3 autopsies, light microscopic findings of the brain have been non specific with 1 possible exception which revealed sparse, notably non agyrophilic, atypical senile plaques. However, in muscle, lamellar lysosomal inclusions were present to a marked degree in 1 case and to a lesser extent in another. In this kindred, lysosomal inclusions in lymphocytes were distributed without restriction to either spherocytosis or neurologic disease. Although the clinical features suggest corticobasal degeneration and the inclusions suggest a relation to Kuf's disease, neither diagnosis can be made since conventional neuropathology does not show neuronal achromasia and since the morphology of the ultrastructural inclusions in muscle is not specific.

3
CEREBROSPINAL FLUID PULSATIONS IN IDIOPATHIC HYPERTENSION. M Koepp, T Lempert, B Sander, W Poewe, *Berlin, Germany*

We tried to determine whether cerebrospinal fluid (CSF) pulsations on MR Imaging are a reliable measure of raised intracranial pressure (ICP) in

patients with IH. IH has been shown to result from decreased CSF drainage. The compliance of the CSF space is altered in patients with idiopathic intracranial hypertension (IIH). The spinal subarachnoid space, which can store CSF up to a certain limit. Any additional increase in CSF volume leads to an increase in ICP resulting in reduced elasticity of the brain. We compared MRI-CSF pulsations before and immediately after the first diagnostic lumbar puncture (LP) in 5 patients with IH. MRI-CSF pulsations and ICP measurement were repeated one and four weeks later. Results: MRI-CSF pulsations of all studies lay within normal limits. The amount of pulsations did not correlate with the degree of raised ICP. Three patients with decreased ICP on follow-up, however, showed a relative decrease in CSF pulsations. Conclusions: MRI-CSF pulsations are not sensitive enough to detect an elevated ICP in patients with IH. The relative decrease of CSF pulsations in treated patients with normal ICP might be due to a change in the elastic properties of the brain.

4
MOTOR LESION OF THE FIFTH CERVICAL ROOT DUE TO ANTEFLEXION. TRAUMA OF THE CERVICAL VERTEBRAL COLUMN AFTER MOTOCROSS RACING ACCIDENT. U Kauerz, HM Mehdorn, J Hezel, W Eickhoff, *Kiel, Hamburg, Germany*

The European champion of motocross racing, a 17 year old young patient came to the neurosurgical dept. of Kiel university. Due to an accident during a training race he was injured. He suffered from an anteflexion trauma of the cervical vertebral column with extreme stretching of the fifth cervical root. Soon after the trauma he notices a paresis of the left deltoid muscle but no pain, non sensory deficit. Neurological examination disclosed a severe paresis of the deltoid muscle and a light paresis of the biceps muscle. No differences of reflexes could be seen. Retroflexion and turning left of the head led to discrete pain near the middle paravertebral region of the cervical vertebral column. Radiologic examination revealed a stepwise discontinuity between the fourth and fifth cervical segment. MRT investigation showed an edema in the periphery of the fifth cervical root. obviously, due to the maximum anteflexion a subluxation of the fourth and fifth vertebral segment had led to an overstretching mechanism of the cervical root.- Nerve conduction time of the nervus axillaris showed normal values- even when compared with the right (healthy) side. only the F-wave latency was markedly increased as a hint for the lesion of the motor part of the fifth cervical root. Electromyography showed spontaneous activity in the deltoid muscle 6 days after the trauma.- The therapeutical intervention was planned with physiotherapy and corticosteroids. Due to the lack of pain- the patient was not compliant: three weeks after the trauma he was back to training. His father took a video: the functional deficit and the compensatory false posture of the shoulder during motocross race could be exactly observed.- Electrophysiological controls, clinical examination and MRT course is presented over the follow-up of one year.

5
CORRELATION OF CLINICAL MANIFESTATIONS AND MRI FINDINGS IN WILSON'S DISEASE. J U Gajda, A Czlonkowska, T Kryst; *Warsaw, Poland.*

Wilson's disease is an autosomal recessive disorder of copper transport resulting in accumulation in liver and brain tissue. Ninety-one patients with biochemically proven Wilson's disease underwent magnetic resonance imaging of the brain. We studied correlations between MRI findings and clinical manifestations of the disease. Fourteen patients had normal scan, 17 had multiple lesions of the white matter, 43 had diffuse brain atrophy, 21 had cerebellar atrophy, 26 had hydrocephalus, 54 basal ganglia lesions, 5 lesions of the caudate nuclei, 29 brain stem lesions and 26 deep cerebellar lesions. Nine newly diagnosed patients underwent follow-up MRI examination after one year of treatment. We found out that the lesions in the basal ganglia, thalamus, cerebellum and brain-stem had become smaller and less intensive. At the end of the study clinical and MRI data were statistically analysed and correlated. A marked correlation was see between dystonia and putaminal lesions.

6
INTEREST OF "HELICAL". ANGIOSCAN IN THE STUDY OF THE CAROTID WALLS. S Timsit, D Gardeur, F Koskas, E Kieffer, G Rancurel, *Paris, France*

"Helical" angioscan (HAS) is a technique which allows to study neck vessels structure with axial slice and 3D reconstruction after intravenous contrast injection. Eighty four patients were submitted to HAS, 100 carotid or vertebral arteries. All had an ischemic stroke, a CT Scan, doppler-echo of the neck vessel and a cerebral angiogram. Among those, different aspects were found: For internal carotid atherosclerotic lesion(n=89): mediacalcose, wall thickening, presence of mural hypodensity which could be due to either intra-plaque hemorrhage or thrombus at the lumen, and sometimes ulceration. For carotid and vertebral dissections (n=ll) the typical image on an axial slice was a target aspect, and a string sign on 3D reconstruction. In both lesional types, HAS allowed us to quantify the degree of the stenosis, but also revealed(n=2) a carotid pseudo-occlusion. HAS can give accurate is a technique which can analyse precisely the pathological arterial wall and may be its own embolic potential. Further study will concentrate on radio-pathological correlations from surgical specimens.

Additional abstracts for POSTER SESSION 1

127
ANTIBODIES AGAINST DEFINED OLIGOSACCHARIDE IN SPINAL CORD FLUID. Mitermayer Galvao dos Reis, E Secor, A Andrade Filho, M Cardoso Silva, SR Silveira Santos, G Vasilaski, EA dos Reis, P Velupillai, DA Harn. *Salvador, Bahia, Brazil.*

Antibodies against carbohydrates may play a major role in the pathology of various infectious diseases. We analysed the presence of antibodies against SEA, KLH and defined oligosaccharides in the CSF of 22 patients with neurological disorders. CSF of patients with *S. mansoni* or HTLV-1 infection having an associated neurologic disorder reacted with SEA and KLH; SEA & KLH share some prospective carbohydrate epitopes. Previously, Harn reported that the anti-SEA monoclonal antibody (E5) reacts with the fucosylated sugar, lacto-N-fucopentaose (LNFP-III).Therefore, it was our interest to test CSF for antibodies against defined oligosaccharides Interestingly, CSF from these patients reacted with the different fucosylated oligosaccharides: LNFP-III, Lewis-y and Lacto-N-difucohexaose. The samples did not show any reactivity towards a non-fucosylated homologue of LNFP-III, lacto-N-neotetraose or the carrier molecule, human serum albumin. Spinal fluid from a normal subject did not react with any of these antigens or sugars. Samples with antibody reactivity against SEA, KLH and sugars also had elevated levels of IL-10. These findings suggest that the presence of antibodies against carbohydrates in the CSF might correlate with the neurologic disorders.

128
LEVAMISOL, A NEW TREATMENT FOR CEREBRAL INFARCTION. J Garcia Tigera, R Martinez Dreke; *Havana, Cuba*

A double blind controlled study was carried out in 49 patients during the acute phase of the cerebral infarction. Twenty four patients took Levamisol (150mg.per day) and twenty five took aspirin (500mg.per day) for 11 days. After this both group continued with a uniform treatment of Dipiridamole and Aspirin at the usual doses. 29 patients were men (59.1%), 28 were women (48.9%) and 38 patients were white (77,5%). Most patients were in the 7th and 8th decade of life and the carotid territory was the most affected vascular territory with 45 patients (91.8%). The clinical efficiency of the drug was evaluated according to Matthew's Scale. Some degree of motor impairment remained in 60% of the patients treated with Aspirin, compared to 54.1% in the levamisol group. Language disturbances were also slightly more frequent and severe in the Aspirin group (40%) than in the Levamisol group (33.3%), but these differences were not statistically significant. Both medications proved to have a similar therapeutic efficiency.

129
TREATMENT OF VASCULAR DEMENTIA WITH NICERGOLINE. J Garcia Tigera; R Piedra Crespo. *Havana, Cuba.*

The therapeutic efficiency of Nicergoline in 20 patients with slight or moderate vascular dementia was studied. Nicergoline was administered orally at a dose of 90 mg per day during 3 months.The Geriatric Appreciation Scale from Sandoz Clinic (GASC) and the Scale for Neuropsychologic Evaluation of Organic Impairment from Juvert Guart and Navarra (SNEOI) to measure the efficiency of the drug were employed. With both scales a noticeable improvement was detected with respect to absolute values, as well as percentage of impairment in some of the mental functions studied. For both scales the total magnitude of improvement was 70%. Quantitative EEG results were compatible with the clinical findings and were characterized by a decrease of the slow activities and an increase of the fast. In the cerebral blood flow studies an improvement of the hypoperfusion in the temporal, parietal and frontal zones was observed in that order. No adverse reactions were registered with the drug.

130
ISCHEMIC STROKE AS AN EARLY MANIFESTATION OF PRIMARY THROMBOCYTHEMIA. A Arboix, C Besses, P Acin, J Massons, L Florensa, M oliveres, J Sans-Sabrafen, *Barcelona, Spain*

Six cases of ischemic stroke (IS) as an early manifestation of primary thrombocythemia (PT) have been analysed. From the Stroke registry of the Alianza-Central of Barcelona (Spain), which consisted of 1-099 consecutive patients with first ever stroke (908 WITH IS: 82%) 14 patients presented IS attributed to hematologic disorders (1,5%). Is due to PT was the most frequent haematological disease (6/14: 42.8%). The mean age was 62.5 (range 32-79) years old. Four patients were male. The IS subtypes were: transient ischemic attack (n=1), lacunar infarcts (n=2) and hemispheric large infarcts (n=3). Platelet counts ranged from 414 to 760× 10^9/1. All patients were in accordance with the diagnostic criteria of the polycythemia vera study group. Spontaneous megakaryocytic and/or erythroid colony formation from peripheral blood were seen in all six patients. The latency period between the IS an the PT'S diagnosis was 4.5 (range 1-12) months. The results indicate that 1) PT was in our registry, the most frequent hematologic disorder responsible from IS; 2) IS can be the first manifestation of PT even with platelet counts below 800×10^9/1 and 3) spontaneous megakaryocytic and/or erythroid colony formation study are useful in the diagnosis of PT in patients with stroke and thrombocytosis.

131
QUANTITATIVE ASSESSMENT AND EVALUATION IN POLYNEUROPATHY. E M Wicklein, G Pleiffer, K Kunre, *Hamburg, Germany*

We designed a PN-Scaling-system (PN-S-S) consisting of 40 items comprising essential motor functions (pos. and neg) sensory abnormalities as well as functional capabilities of daily life activities, commonly affected in PN. The PN-S-S was applied in 25 patients with clinical and electrophysiological evidence of generalised neuropathy, interrater-reliablity was tested by independent scoring through 3 physicians. Assessment per patient was performed twice in the course at a minimum. Sensitivity of the PN-S-S towards clinical improvement or deterioration was compared to sensitivity of the Rankin-score and the Ambulation index. Results: The PN-S-S is relevant to degree of a present PN and to functional impairment, it is predictive of the course of the disease. Interrater-reliability is sufficient, Sensitivity towards Clin, changes is higher in comparison to Rankin-score and Ambulation index. The PN-S-S is suitable for assessing changes in severity of a PN and for estimating therapeutic impact.

This abstract belongs to Oral session 42 in POSTER SESSION 3

7
INTERNUCLEAR OPHTHALMOPLEGIA AND SKEW TORSION IN LESIONS OF THE MEDIAL LONGITUDINAL FASCICULUS. M Dieterich, Th Brandt, *Munich, Germany*

In 85 patients with acute unilateral ponto-mesencephalic infarctions incidence and coincidence of internuclear ophthalmoplegia (INO), skew deviation, and ocular torsion were studied. The major question was: Can typical patterns be identified which indicate lesions of a particular brainstem level or ocular motor structure? Ischemic lesions were classified according to the level and side of the brainstem by the clinical syndrome and by neuroimaging. Neuro-ophthalmological and orthoptic examinations were performed as well as electronystagmography and measurements of ocular torsion by repeated fundus photographs. Twenty-eight (33%) of the 85 patients presented with skew deviation which was always combined with ocular torsion towards the undermost eye. Eighteen (21%) patients had unilateral INO. In the patients with "skew torsion" 10 of 28 (36%) had additional INO. In caudal pontine lesions skew torsion was inevitably ipsiversive (ipsilateral eye down) without concomitant INO. In ponto-mesencephalic lesions all patients with combined skew torsion and INO exhibited contraversive skew torsion. Projections of well demarcated-infarcted areas (MRI) onto the appropriate sections of a stereotaxic brainstem atlas (Olszewski and Baxter, 1982) revealed the paramedian medial longitudinal fasciculus (MLF) as the most likely structure a lesion of which causes both INO and contraversive skew torsion. The latter indicates that graviceptive pathways which maintain the vestibular tone in the roll plane (skew torsion indicates a tone imbalance by a unilateral lesion) travel along the contralateral MLF to the supranuclear ocular motor centres in the rostral midbrain.

The following abstract belongs to POSTER SESSION 4

35
NEUROLOGICAL COMPLICATIONS OF ORTHOTOPIC LIVER TRANSPLANTATION. M Guarino, A Stracciari, P Pazzaglia, R D'Alessandro, I Santilli, M Donato, F Erminio, R Sterzi, *Bologna, Milano, Italy*

Among the post-operative complications of ortothopic liver transplantation (OLT) neurological symptoms are very common and has been reported in 18-33% of patients. We studied 184 consecutive patients (115 males; age range: 7-60 years) receiving 202 OLT. Neurological complications occurred in 59 cases (30%), mostly within 30 days after surgery. 20 patients had more than one complication. 92.3% had a central nervous system (CNS) involvement and only 15.2% had sign of peripheral nerve lesions. The most frequent CNS complications were: coma and encephalopathy (41 cases; 69.5%) and seizures (15 cases; 25.4%). Less frequent symptoms were: dysarthria (5 cases); hemiplegia (5); cortical blindness (3); visual hallucinations (1); hemianopia (1); spastic tetraparesis (1); convulsive syncope (1). Peripheral syndromes included: polyneuropathy (4); multiple mononeuritis (3); brachial plexopathy (2). The most frequent causes were: metabolic encephalopathy; rejection; ciclosporine A toxicity. They were not seldom associated in the same patient. We conclude that neurologic complications after OLT occur commonly and early and they are frequently multifactorial.