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Presidential symposium

Management of stroke

1
Stroke prevention: research with changes practice

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To prevent stroke three complementary strategies are necessary: optimal management of vascular risk factors in all types of strokes, antithrombotic agents in ischaemic strokes, and treatment of the cause when possible.

The objective of the talk is not to make a systematic review, but to focus on a few selected strategies that have changed or will change our practice.

Primary prevention trials

- A meta-analysis of 22 studies showed that smoking doubles the risk of ischaemic stroke. Subjects who stop smoking reduce this risk by 50%. Making public places smoke-free would result in huge benefits.
- A systematic review found hormone replacement therapy to be associated with a small increase in stroke risk (RR 1.44; 95% CI 1.10–1.89). The Women's Health Initiative trial suggested that this risk is increased only in women with hormone use of 5 years or more.
- Antiplatelet agents reduce risks stroke (RR 0.78; 95% CI 0.65–0.94) in patients with non-valvular atrial fibrillation, but warfarin (target INR 2.0–3.0) is more effective than aspirin at reducing stroke (RR 0.36; 95% CI 0.26–0.51), especially in patients who have had a previous systemic embolism (including stroke), over 75 years of age, with high blood pressure or poor left ventricular function. Warfarin was also safe and effective in older individuals. The combination of aspirin and clopidogrel is less effective than warfarin.

Secondary prevention trials

- Antiplatelet therapies reduce vascular events, including non-fatal myocardial infarction, nonfatal stroke and vascular death in patients with previous stroke or TIA (RR 0.78; 95% CI 0.76–0.80). Clopidogrel (RR 0.91; 95% CI 0.84–0.97), and the combination of aspirin and extended release dipyridamole (RR 0.82; 95% CI 0.74–0.91), are slightly more effective than aspirin, but there direct comparison did not find any difference between both strategies.
- Carotid surgery reduces the risk of recurrent disabling stroke or death (RR 0.52) in patients with severe (70–99%) ipsilateral internal carotid artery stenosis. Patients with less severe ipsilateral carotid stenosis (50–69%) may also have a small benefit. Surgery is potentially harmful in patients with stenosis of less than 50%. Carotid surgery should be performed within 2 weeks after the last cerebrovascular event. Patients over 75 years of age also benefit from carotid surgery.
- Several trials have compared surgery and stenting in secondary stroke prevention: they revealed a significantly higher risk of any stroke and death within 30 days after stenting (OR 1.41; 95% CI 1.07–1.87), but after the periprocedural period, both procedure are almost equivalent.

Conclusion: many prevention trials have changed our daily practice during the last 20 years, either by introduction of new drugs or techniques, or by a better determination of those who are the more likely to have a beneficial effect. There is however still a gap between what is proven and how patients are treated in practice. The next step is not only to identify new strategies, but also to make research translate really into practice.

2
Expanding the opportunities for the treatment of acute stroke

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Stroke is a massive burden of disease, still with few effect therapies and limited prevention measures. In contrast to increasingly improving and expanding experimental and clinical research efforts during recent decades, the possibility of therapeutic options is disappointing: regulatory approval for the treatment of acute ischemic stroke is limited to intravenous tPA in a short time-window with rapidly decreasing, albeit excellent early prognosis, within 90 min after onset of symptoms and slowly increasing haemorrhagic complications after 3–6 h. Numerous clinical trials attempting to protect brain tissue in the penumbra of the ischemic core failed whatever stages of the cascade of damage they were suspected to influence according to previous results from experimental studies. Obviously, the concept of bench-to-bedside translation (with the exception of revascularisation) challenges our knowledge about the pathophysiology of ischemic brain injury in man.

Research is needed to increase efficacy and applicability of thrombolysis by extending the time-window by using new thrombolytic compounds and application, such as sonothrombolysis, hypothermia, or CBF augmentation. Although well-known, acute stroke does not only cause deleterious neurotoxic effects but also necrosis of the complex cellular system forming the blood–brain barrier (BBB) and the neurovascular unit. A better understanding of the mechanisms of the BBB maintenance is a prerequisite to understand its response to focal cerebral ischemia, the sequence of circulating blood elements leading to inflammation and apoptosis (e.g. activated microglia/microphages and heterogenic leukocytes producing oxygen and nitroxygen radicals). They play a hey role in subsequent post ischemic inflammation supported by endothelial, glial cells and neurons involving a complex cascade of mediators.

Neuroinflammation aggravates BBB breakdown and neuronal damage, but at the same time and through similar mechanisms and sometimes even identical mediators, confers neural protection and stimulates reorganisation (MMPs and TIMPs). Indeed infections are one of the most important complications leading to final stroke outcome and restoration of the individual patient: systemic inflammation and infections modulate the susceptibility and alter the pathobiology of the delayed and late ischemic cascade. Understanding of these mechanisms may lead to new concepts of support for endogenous neuroprotection and preventive measures using promising candidates to down-regulate ischemic damage, increase the ischemic tolerance and stabilise the BBB. Regeneration and repair after stroke needs to be investigated—again research is needed not only with regard to neurogenesis, reorganisation, new vessel formation and repair, but also to design a new model of stroke for experimental studies and a better selection of criteria to identify the appropriate patients for the clinical study, based on the best experimental model.

In this presentation, I will concentrate on some of these complex conditions underlying acute and delayed stroke ischemia, with regard to revascularisation and reperfusion, neuroprotection and stroke pathobiology, inflammation and BBB response to focal ischemia as well as clinical and lab experimental models for a new translational stroke research.

3
Screening and management of unruptured cerebral aneurysms

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Unruptured intracranial aneurysms are present in around 2% of the population. Main risk factors are female sex, a positive family history, polycystic kidney disease, a previous ruptured aneurysm, increasing age, and smoking, hypertension and alcohol abuse. Unruptured aneurysms may rupture in the near or distant future and sometimes these lesions warrant preventive intervention by means of coiling or surgical clipping. However, in many situations uncertainty abounds, and in many other situations intervention will probably do more harm than good. In these situations follow up imaging to detect growth of the aneurysm is often advised, but data on frequency and effectiveness of this strategy are lacking. It is pivotal to carefully balance the risks and benefits of all treatment options and to take time to counsel the 'patient'. Age is the most discriminating factor, because at a young age the benefit of treatment is large, and the risk of treatment relatively small. Factors that determine the risk of rupture include size and site of the aneurysm, and family history. If an incidental aneurysm is detected, it is important to refrain from descriptions as 'a time bomb in your head' before referring the unfortunate patient to a neuro-interventional centre. For many of these patients no intervention is the best option, but having to live with an untreated aneurysm imposes a threat on quality of life.

Careful counselling and weighing the pros and cons is even more important when screening for aneurysms is considered. Screening often have unrealistic risk perceptions, and screening for intracranial aneurysms is associated with considerable psychosocial effects, both positive and negative. Before intracranial vessels are imaged, the risks and benefits of screening should be weighed up. This balance of risks includes the amount of anxiety before screening, the reassurance that can be given with a negative result, and the anxiety that can be caused by finding an aneurysm. Screening should be considered in individuals with two or more affected first-degree relatives, and in patients with autosomal dominant polycystic kidney disease. If a first screen is negative, repeated screening should be discussed. In individuals with only one affected first-degree relative, screening is not very efficient or effective. Although patients with no family history and no polycystic kidney disease who have survived an episode of haemorrhage are at increased risk for a new episode from a new aneurysm or from recurrence of the treated aneurysm, screening for new aneurysms cannot be recommended in general, but can be considered in patients (especially women) with an initial episode at a very young age and with multiple aneurysms at time of the initial haemorrhage.

Genetic determinants are likely to play a role in the development of intracranial aneurysms. The concept is that aneurysms are a complex disease were multiple genes environmental factors play a role. Despite current efforts the progress in identifying genetic determinants for intracranial aneurysms is modest. In future studies we should not only look for genetic determinants of aneurysms, but also for genetic determinants of rupture of aneurysms. This would help in selecting patients for preventive treatment of aneurysms.

4
Cerebral vein thrombosis: from case-series to recommendations

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Dural sinus and cerebral vein thrombosis (CVT) are less common than other stroke types and challenging to diagnose. The lecture will focus on recent advances and uncertain issues in the diagnosis and treatment of CVT and how they are reflected in available guidelines. Clinical presentation of CVT varies in different demographic groups (children, women, elderly). Worldwide, there is a global variation of associated conditions and risk factors, reflecting the variability of their prevalence in different world regions. The current diagnostic standard for CVT consists of MR with T2* sequences and angio-MR. Venous CT angiography has probably the same diagnostic accuracy as veno-MR. New MR modalities will be necessary to increase our diagnostic ability of this condition, given the limitations of the current screening methods (CT, D-dimers, transcranial Doppler). Screening for genetic and acquired prothrombotic condition should be performed in all patients. New prothrombotic mutations and other biomarkers should be identified in patients with CVT of unknown cause and in those where CVT can herald a systemic disease. The prognosis of CVT can now be stratified using the validated CVT risk score. Anticoagulation remains the fundamental therapeutic measure. Antiepileptic drugs are recommended in patients with seizures and in those with supratentorial hemorrhagic lesions. Concerning the need for long-term anticoagulation, a trial is planned to compare short versus long term prescription. The efficacy and safety of aggressive interventions for the treatment of acute CVT (local IV thrombolysis, hemicraniectomy) will also be evaluated in planned trials and registries.

Symposia

Epilepsy: from pathophysiology to new treatments

5
Epilepsy genetics: academic interest — Help or hindrance for treating our patients?

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Over the past few decades, epidemiologic and molecular research has transformed the field of epilepsy genetics. However, it is very unclear whether, despite the increasing academic interest and research focus, the findings have been helpful in treating our patients. Even well characterized disorders such as Dravet syndrome remain a clinical diagnosis as the gene test for the SCNA1 mutation is only positive in 80% of cases. Although there have been many exciting research advances in both the molecular and epidemiologic areas, what we have learned has not appreciably changed what we tell families, and what we tell them remains relatively reassuring.

A number of genes have been identified that cause idiopathic human epilepsies. However, most identified genes have occurred in rare autosomal dominant families. For most of the genetic epilepsies (as distinct from syndromes such as tuberous sclerosis associated with epilepsy), having a genetic test available is unlikely to alter reproductive choices. As of 15 years ago, we would have told our patient that she had an approximately 5% risk of having a child with epilepsy; recent advances in understanding the genetics of the epilepsies have not yet translated to alter what we as clinicians would tell her, or most other families. The newer data remain reassuring; more than 90% of individuals with epilepsy have no affected relatives, and most parents with epilepsy will have no children with epilepsy. In these early days of the genomic era, we have identified a set of relatively rare single-gene disorders that account for a very small proportion of epilepsy in the population. As our techniques improve, we may approach a better understanding of the complex genetic epilepsies, and discover genes that contribute to more common forms of epilepsy. However, even if tests for these genes

become available, they still may not affect reproductive choices, given the benign nature of many common genetic epilepsies.

6
Cell, gene and focal drug treatments: prospects for the future?

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Despite advances in AED development and epilepsy surgery over the last 20 years, many patients continue to have frequent seizures and urgently require novel approaches. Functional manipulations of focal brain areas (e.g. seizure focus, key trigger or propagation pathways) offer the hope of avoiding the often limiting systemic side effects of AEDs, and reduced risks of adverse effects on normal brain function and are being extensively explored in pre-clinical models. Focal drug delivery has proven short-term (hours–weeks) efficacy including in some instances in well characterised epilepsy models refractory to the same drug given systemically, or using agents such as gap junction blockers that would otherwise have unacceptable toxicity. As limited studies have also been reported in patients undergoing epilepsy surgery, and technical advances mean that focal drug delivery over up to years is now feasible, and indeed used in man in other brain disorders, this approach offers real promise of clinical translation, although further experimental work in appropriate models over longer times is required initially. Genetic manipulation of brain cells, either in vitro prior to grafting, or in host brain using viral vectors can also effect long-term beneficial neurochemical changes in focal regions, and experimentally may also have antiepileptogenic effects. Studies in models with established seizures are less numerous, but at least in a post-status epilepticus model have also shown promise, such that the USA FDA are said to be considering a clinical trial using the same paradigm (Adeno-virus vector induced overexpression of neuropeptide Y following status). However given that not all patients develop epilepsy after status, and other concerns about the longterm safety/efficacy of such manipulations, whether this will come to fruition remains to be seen. Finally, grafting of a range of cell types, including neuronal populations that do establish connectivity and might thus contribute to "network repair", and non-neuronal populations engineered effectively as a "reservoir" for e.g. local neurochemical release, have also been extensively studied in a wide range of seizure models. The concept of network repair whilst attractive is probably less realistic, but studies with cells releasing GABA or adenosine do show promise, if methodological issues relating to long term cell survival, particularly in brain regions that are not acutely injured can be overcome.

7
Advances in molecular epilepsy imaging and influence on management

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Molecular imaging with ictal and interictal single-photon emission computed tomography (SPECT) as well as positron emission tomography (PET) rank among the established functional imaging tests for the presurgical evaluation of epileptic onset zone in patients with intractable partial epilepsy. In temporal lobe epilepsy the sensitivity of these methods was shown to be excellent, in particular if a multimodal platform is used, which combines the functional imaging with the additional morphological information of magnetic resonance imaging (MRI), but was lower in extra temporal lobe epilepsy.

Functional imaging with SPECT and PET reflects seizure related changes of cerebral perfusion, glucose-metabolism and neuroreceptor status.

In this review the usefulness of SPECT and PET imaging in clinical routine in epilepsy as well as the role of different neuroreceptor PET-tracer, which were used in epilepsy are discussed.

The use of perfusion SPECT tracer allows the investigation of ictal activations, but the low temporal resolution of ictal perfusion SPECT often results in the detection of both the ictal onset zone as well as the propagation pathways, an area that has not always need to be resected in order to render a patient seizure free.

The additional use of interictal PET with fluorine-18 fluorodeoxyglucose which measures regional cerebral metabolism or interictal perfusion SPECT enhances the diagnostic accuracy of ictal SPECT and has been shown to be important for a more accurate definition of the ictal onset and the irritative zone.

In recent years PET imaging of different cerebral neuroreceptor-systems e.g. GABAA/Benzodiazepine receptors, serotonin receptors (5-HT1A), opioid receptors as well as dopamine receptors was used to investigate the neurochemical basis of epileptogenesis, seizure propagation and termination. With the exception of Benzodiazepine receptor imaging these approaches have no established clinical role. Currently some of these receptorligands e.g. [18F]-MPPF are also used to investigate non-operative therapeutic approaches, e.g. the modulation of P-glycoprotein a known multi-drug-transporter, which was shown to be overexpressed in drug resistant epileptic patients.

The molecular era of muscle disorders

9
Congenital myasthenic syndromes – From molecule to pathophysiology and therapy

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Congenital myasthenic syndromes (CMS) are a genetically and phenotypically heterogeneous group of rare hereditary disorders affecting neuromuscular transmission. The understanding of the molecular basis of the different types of CMSs has evolved rapidly in recent years. After the identification of mutations in the subunits of the nicotinic acetylcholine receptor (AChR), other genes encoding post-, pre- or synaptic proteins were determined as candidate genes for CMS; to date, mutations in ten different genes have been shown to cause CMS. Pathogenic mechanisms leading to an impaired neuromuscular transmission modify AChRs or endplate structure or lead to decreased acetylcholine synthesis and release. However, the genetic background of many CMS forms is still unresolved. A precise molecular classification of CMS type is of paramount importance for the diagnosis, counselling and therapy of a patient, as different drugs may be beneficial or deleterious depending on the molecular background of the particular CMS.

10
Myotonic dystrophies: knowledge of molecular mechanisms may lead to therapy

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The promise of molecular genetics in medicine is that knowledge of disease pathogenesis at a molecular level will lead to rational design of

treatment. Though this concept is somewhat tarnished due to relatively few specific examples of success, the reality is that moving from gene discovery to treatment requires decades of work. Recent years have seen encouraging pre-clinical developments in several hereditary neuromuscular disorders, such as, spinal muscular atrophy. This presentation will focus on evidence that the RNA-dominant disease process in myotonic dystrophy may be unusually responsive to therapeutic intervention. It now appears that some aspects of the disease are reversible. Promising results of testing in preclinical models will be reviewed.

11
Current trials of molecular therapies in human dystrophies

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Muscular dystrophies have long remained elusive to approaches of molecular therapy because it proved difficult to target an organ that presents ~40% of the total body mass and is at the same time extremely diversified in its molecular and functional setup. More recently, different concepts for molecular therapy have used Duchenne muscular dystrophy (DMD) as a model disease. This is the second most common severe monogenic disease after cystic fibrosis in man. DMD is caused by different mutations of the dystrophin gene, a modular gene where the predominant muscle isoform is composed of 79 exons. In frame deletions of this gene lead to the clinically milder phenotype of Becker muscular dystrophy indicating that partial function of the protein can be retained by partly deleted 'quasi-dystrophins' which most commonly result from deletions maintaining the open reading frame. Recent therapeutic approaches to DMD have used this concept by inducing exon skipping in DMD in order to recover a partially functional quasi-dystrophin. This can be achieved by engineering and administering antisense-oligonucleotides such as morpholinos or 2′Primo-methyl-AONs, and these substances are currently in phase II clinical trials for the skipping of exon 51. A similar approach makes use of an optimized U7 snRNP coupled to AON sequences and delivered through viral systems, either directly into the body using AAV as a shuttle, or using lentivirus to transduce adult stem cells with myogenic potential ex vivo. These techniques are currently evaluated at the preclinical level in different animal models. In addition, nonsense mutations in the dystrophin gene have become the target of a new type of 'pharmaco-gene' therapy where read-through of a nonsense mutation is facilitated by a experimental drug, PTC 124, which is currently in a phase IIb trial. These different approaches can of course be transposed to other forms of muscular dystrophy: a cell therapy trial is ongoing for oculo-pharyngeal muscular dystrophy. Exon skipping approaches are tested for dysferlinopathy. And read-through of nonsense mutations might be applied as a mechanism to numerous muscular dystrophies. These different approaches will be discussed also regarding their complementary aspects.

12
The enigma of hereditary inclusion body myopathy (HIBM): one gene is not enough

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HIBM (also termed DMRV) is a recessive neuromuscular disorder that features quadriceps sparing and rimmed vacuolar muscle pathology. The mechanism that protects the quadriceps through the disease course, despite its similar metabolic and genetic features compares with other muscles, is unknown. Also unclear is the connection between the metabolic defect and the specific pathology, resembling autophagy. HIBM is caused by mutations in the gene encoding the enzyme UDP-N-acetylglucosamine 2 epimerase/N-acetylmannosamine kinase (GNE), which catalyses the rate limiting step in sialic acid production. However, the reduction in this bifunctional enzyme activity is in the range of 30–50% only (an asymptomatic carrier state in 'classical' metabolic myopathies) and a presumed resulting hyposialylation of muscle cells is hard to demonstrate. The muscle disease maybe a result of some specific glycoconjugate hyposialylation or could be due to a defect in another (yet unknown) function of GNE. If the first possibility is the basis of the disease process, substrate supplementation therapy designed for this condition maybe possible by using a metabolic intermediate of the pathway (ManNac), however human trials have not started. Other functions of GNE (e.g. its nuclear presence and the association with muscle filaments) need further investigation using animal models. Such models show also diverse patterns: GNE knockout is lethal (there are also no human patients with double nonsense mutations) and a model of the common human homozygous mutation shows early death due to severe kidney disease that is not present at all in the human myopathy. Only a knock in model (that does not mimic well the human genotype) shows myopathic features with wide spread organ hyposialylation. The ongoing research story of HIBM is an example of how finding a primary causative gene defect, even in a well described metabolic pathway, cannot easily explain the myopathic disease processes.

Critical issues on MS diagnosis and treatment

13
The key role of MRI in a very early diagnosis

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Conventional magnetic resonance imaging (MRI) has been widely used for the study of the natural history of multiple sclerosis (MS) and has become an essential tool for the diagnosis of the disease and monitoring of treatment trials. T2-weighted images of the brain show multiple hyperintense lesions of the white matter in about 50–70% of patients at presentation with clinically isolated syndromes (CIS) suggestive of MS. Among CIS patients with similar clinical characteristics, those with MR-visible lesions on the scan obtained at disease onset have a much higher risk of developing further relapses and evolve towards clinically definite (CD) MS than those without MR-visible lesions. The site of T2-visible lesions has also a role in predicting the subsequent disease evolution: the presence of at least two infratentorial lesions is associated with higher disability at long term. Furthermore, it has been shown that the lesion load accumulated in the first 5 years of disease is predictive of the level of disability at 20 years from onset. In patients with CIS, the risk of converting to CDMS increases if the presence of T2 hyperintense lesions is associated with gadolinium-enhancing lesions on T1 images. Due to its extraordinary sensitivity for MS changes, MRI has gained a key role in the diagnostic criteria of the disease, showing its spatial and temporal dissemination, allowing an earlier diagnosis and treatment in patients at presentation with CIS.

The recent application to the study of MS of quantitative MR techniques, such as magnetization transfer (MT) and diffusion-weighted (DW) MRI, has allowed a better definition in vivo of the pathophysiological substrates of the disease and, as a consequence, a stronger correlation between clinical signs and imaging changes. Nevertheless, in

patients presenting with CIS, the usefulness of these techniques in predicting future conversion to CDMS and accumulation of disability is still to be defined. A recent retrospective multicentre study on a large number of CIS patients has confirmed that the risk of developing CDMS is associated to the extent of T2 lesion burden at onset, but not to the extent of brain atrophy and diffuse damage in the normal-appearing white matter (WM) and gray matter (GM) measured by MT MRI. Furthermore, another longitudinal study with DW MRI has shown a relevant accumulation of tissue damage in both WM and GM already in the first three years from onset, but failed to show correlations between this damage and disease clinical activity. Finally, the application of functional MRI has allowed to show that in patients with CIS the extent of cortical reorganization secondary to diffuse tissue damage might be among the factors influencing clinical evolution. Although these non-conventional MR techniques can add important pieces of information in the study of patients with CIS, their application in therapeutic monitoring is still in a preliminary phase.

14
At the border of MS

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New diagnostic criteria for multiple sclerosis (MS) have been recently defined from evidence based criteria including clinical, CSF and MRI parameters. (Mc Donald et al. 2001; Polman et al. 2005). Without any specific biomarker, however, it is stressed that " there must be no better explanation for the clinical and paraclinical abnormalities than MS for a secure diagnosis to be made". Two recent experts contributions try to help neurologists to make a more accurate diagnosis: one is a consensus based approach (Task Force on Differential Diagnosis on MS, Miller et al. 2008), the other is evidence based mainly focused on MRI diagnosis (Charil et al. 2006).

The first task is to identify MS among a larger spectrum of idiopathic inflammatory demyelinating diseases: acute variants of MS like Balo, Schilder and Marburg diseases, acute disseminated encephalomyelitis (ADEM), and neuromyelitis optica (Devic's disease). Acute variants are unclassified until criteria for dissemination in time and space typical of MS have been reached. ADEM and NMO are true differential diagnosis of MS. There are ADEM criteria, clinically and MRI based which allow a better differentiation with acute form of MS, in adults and children, although in some cases, an erroneous ADEM diagnosis is followed by authentic MS relapses. NMO is the first autoimmune demyelinating disease in which an autoantibody targeting a specific autoantigen, aquaporin 4, a member of water channel family, helps to delineate a new spectrum of CNS autoimmune diseases.

Clinically isolated syndrome (CIS) represents the first presentation of relapsing remitting MS. It usually involves the spinal cord, the optic nerve or the brainstem. As CIS syndromes are more or less typical for MS, evaluation of these patients requires (1) to exclude other alternative diagnosis (2) to confirm the clinical characteristics of MS (Mc Donald criteria) (3) to decide the initiation of an immunomodulatory treatment.

Other diseases are true mimics of MS. As stated by the task Force on Differential Diagnostic evaluation strategies apply to individuals with: (1) clinical and paraclinical features are classic for MS without no features suggesting another disease (2) features compatible with MS but the presence of some red flags suggest a possible alternative diagnosis, the confirmation requiring a period of observations with new diagnostic tests (3) clinical and paraclinical features point to a non-MS diagnosis, suggesting the diagnostic of MS improbable (4) clinical and paraclinical parameters suggesting the coexistence of two diseases, MS and another condition. According to the type of MS, relapsing remitting or primary progressive, the alternative diagnosis to evoke are different. Some important red flags will be presented.

The "radiologic isolated syndrome" corresponds to patients having incidentally identified CNS abnormalities meeting specific criteria (Okuda et al 2008). These imaging characteristics helps to differentiate with vascular white matter diseases, the most frequent cause of asymptomatic WM abnormalities. Some of these patients are true presymptomatic MS.

16
How to predict and monitor individual responses to treatment

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Patients with MS that continue to experience clinical or MRI activity despite treatment with disease modifying drugs (DMD) are considered non-responders, although individually it is difficult to establish whether a given patient presents a good response to treatment and if so to what degree. The terms, breakthrough disease, suboptimal response or treatment failure, have also been used in the literature. From the clinical point of view, different criteria of response to therapy have been established based on presence of relapses or disability increase. Definitions based on disability increase are associated with higher specificities to predict confirmed disability in the long term. However, to optimize MS therapy it is very important to identify early on in the course of treatment, those patients who will be non-responders, therefore it may be necessary to evaluate the contribution of MRIs performed at interferon β therapy onset and during follow up, to the identification of non-responders. In our prospective cohort of patients, the presence of more than two active lesions (new or enlarging T2- plus gadolinium-enhancing brain lesions) in the scan performed at 12 months was the most important MRI measure related with treatment response (odds ratio 8.3; 95% confidence interval 3.1–21.9). Other studies have also found that patients treated with DMD presenting more than 2 new or enlarging T2 lesions after 2 years had significantly more EDSS changing (Rudick et al). Finally we have combined both the clinical and radiological information to investigate the predictive value of these measures. Our data show that those patients who present clinical or MRI activity or disease progression in at least two of the three variables analyzed (relapses, increase of disability or MRI activity) after 12 months of treatment are candidates for treatment change, as they are at high risk to have clinical activity and disease progression in the following years (OR between 5.9 and 13.2). Biological markers such as neutralizing antibodies (Nabs) have also been used to monitor treatment response. Persistent Nabs seem to abrogate the IFN β biological response and although clinical use of Nab results are still being debated, the occurrence of Nabs, especially at high titers, seems to reduce the efficacy of IFN on relapse and MRI lesions. Expression of IFN β induced gene products are also potential biomarkers of treatment efficacy.

Parkinson's disease: advances in diagnosis and treatment

17
Where and when does Parkinson's disease start?

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Evidence is accumulating from clinical, neuroimaging and pathological studies on the occurrence in Parkinson disease (PD) of olfactory dysfunction, dysautonomia, mood and sleep disorders years and perhaps even decades before the classical motor symptoms arise.

These data suggests that, at least in some cases, PD may start in the lower brainstem, olfactory structures or in the peripheral autonomic plexuses reaching only later the substantia nigra. It is unclear when these structures become involved in the neurodegenerative process. Neuropathological and imaging data suggest that the substantia nigra is involved at least 5–7 years before motor symptoms appear. Epidemiological and clinical studies suggest that PD related non motor symptoms may already occur a decade or two before motor symptoms begin. And the neurodegenerative process could start years before these non motor symptoms make their appearance. Knowledge on when and where PD starts can greatly contribute to the search of the cause/s of PD. Should a safe and effective treatment with disease-modifying or neuroprotective potential in PD become available, this information will be of great help in initiating treatment at the earliest stages of disease development.

18
Advances in neuroimaging Parkinson's disease

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The Lewy body pathology of Parkinson's disease (PD) targets the substantia nigra and its dopamine projections to the striatum. Nigral structural changes can be detected as hyperechogenicity with transcranial sonography (TCS). Atypical syndromes can also be discriminated from PD by the presence of lentiform nucleus echoes.

Loss of putamen dopaminergic function correlates with motor disability in PD. However, along with motor disability, PD is associated with impaired cognition and dementia, mood disorders and psychosis, sleep disorders and chronic fatigue, and autonomic dysfunction. These symptoms may appear before the onset of the first motor problems.

PD patients with dementia (PDD) show reduced frontal dopaminergic and generalised cortical cholinergic dysfunction relative to non-demented cases. The pattern of glucose hypometabolism in PDD is similar to that seen in Alzheimer's disease (AD) but these patients do not show a raised amyloid load on 11C-PIB PET. 11C-PK11195 PET is a marker of microglial activation. Non-demented PD cases show extensive cortical inflammation to a level seen in PDD suggesting that microglia could drive development of later dementia.

11C-RT132 is a PET tracer which binds with similar affinity to both dopamine and noradrenaline membrane transporters. PD patients with depression have been reported to have lower 11C-RT132 binding in locus coeruleus and areas of the limbic system than non-depressed PD patients. This finding suggests an important role of dopamine and noradrenaline dysfunction in the pathogenesis of depression in patients with PD.

18F-dopa PET, is an in vivo marker of dopaminergic function in PD. In cases with severe fatigue there is a reduction of insukla dopamine storage compared to cases without this problem. Duration of REM sleep in PD has been shown to correlate with midbrain 18F-dopa uptake.

Finally, 11C-raclopride PET can be used to measure changes in dopamine levels in brain regions. With this approach, rewards can be shown induce frontal dopamine release while craving for levodopa can be related to excessive production of ventral striatal dopamine after levodopa.

19
Anatomical and molecular pathology underlying dementia in Parkinson's disease

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Longitudinal studies of patients presenting with typical levodopa-responsive Parkinson's disease (PD) have identified three main clinicopathological phenotypes which pathologically have (1) a loss of dopaminergic neurons in the substantia nigra, (2) abnormal α-synuclein Lewy body aggregates in brainstem and forebrain regions, and (3) cortical cholinergic deficits. They differ clinically in the timing and severity of their dementia - an early, severe rapidly-progressive, dementia-dominant group or dementia with Lewy bodies (DLB), an older onset (around 70 years of age) group who dement within the first decade of PD (PD with dementia or PDD), and those with an earlier onset who may survive to dement exceeding late (typical PD). Autopsy assessment of longitudinally-followed cases shows these groups differ in the timing, severity and mix of cortical neuropathology. The rapidly progressive DLB patients have substantive α-synuclein Lewy aggregates, cholinergic deficits as well as Aβ deposition in the cortex. This pathological group also have a selective loss of hippocampal neurons projecting to the frontal lobe. They often have sufficient tau deposition to fulfill criteria for Alzheimer's disease. The rapidity of their decline supports a rapid pathological process involving multiple mechanisms. Patients with older-onset PDD have a slower disease course but similar substantive α-synuclein Lewy body infiltration in the cortex at autopsy. Many also have substantive cortical Aβ aggregates, consistent with their older age, and a greater cholinergic deficit compared with DLB, due to their longer disease durations. They do not have hippocampal cell loss. In typical PD the timing of cortical Lewy body infiltration is considerably slower—by 13 years 50% of cases have a limbic distribution of Lewy bodies, and by 18 years all will have at least this pathological phenotype - consistent with their much later onset of dementia. These patients do not have hippocampal cell loss (selective for DLB) or cortical Aβ aggregation (found in DLB and PDD), and the density of cortical α-synuclein Lewy bodies is statistically less than that found in the other two groups. Overall autopsy studies of longitudinally-followed cases show that dementia in PD is a unitary process only in typical earlier-onset PD which show a slow infiltration of cortical α-synuclein that associates with dementia. Dementia in PDD and DLB is influenced by age and by the propensity for the induction of multiple neuropathologies in these cohorts. Further research on the effects of age and the identification of the additional factors contributing to the rapidly progressive form of DLB should be research priorities.

20
Genetics versus environment in the etiology of Parkinson's disease

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The role of genetics versus environment in the etiology of Parkinson's disease (PD) has been a matter of debate for long time. Yet, the current evidence supports the view that the common PD form is determined by a complex interplay of several genetic as well as non-genetic factors.

Strong support for the environmental theories came from the occurrence of post-encephalitic parkinsonism, from some geographical clusters of PD-like neurodegenerative diseases (the "Guam complex" and the "Guadeloupean parkinsonism"), and from animal models of parkinsonism induced by toxins such as MPTP, rotenone and proteasome inhibitors. However, despite the epidemiological association of PD with environmental factors such as the occupational exposure to pesticides, a specific toxin causing the disease has not been identified yet. On the other hand, cigarette smoking emerged consistently in epidemiologic studies as a protective factor for PD. The mechanisms underlying this inverse association remain unknown. Recent epidemiological studies have suggested that high plasma urate, history of gout, and some statins might also represent protective factors for the development of PD, but further studies are needed in order to confirm/substantiate these more recent findings.

In the past few years, family-based linkage and positional cloning approaches led to the identification of several monogenic forms of PD, and yet, other PD-causing genes probably remain to be found. Mutations in the SNCA and LRRK2 gene cause autosomal dominant forms, whereas mutations in the PARK2 (parkin), PARK7 (DJ-1), and PARK6 (PINK1) gene cause autosomal recessive forms of PD (usually with early-onset). Perhaps, the most important genetic discovery is that a single, low-penetrance mutation in the LRRK2 gene (Gly2019Ser) is a very common determinant of both familial and sporadic PD in some large North-African and Middle-Eastern populations, providing the proof-of-principle for the existence of a specific genetic factor in the etiology of the common, typical late-onset form of this disease. Furthermore, two different LRRK2 variants (Gly2385Arg, Arg1628Pro) are risk factors for PD in the Asian population.

Although some of the Mendelian forms of PD are rare, they are facilitating the dissection of molecular pathways leading to death of dopaminergic neurons; these pathways might also be implicated in the pathogenesis of the common forms of PD. The several Mendelian forms are also challenging the concept of PD as one disease, as well as the validity of the current clinico-pathological disease definition. Last, mutations in some of these genes (parkin, LRRK2) are frequent enough to have relevance in clinical practice, especially in some populations.

FREE COMMUNICATIONS

Oral Sessions

Oral session 1

Multiple Sclerosis: clinical aspects

O21

Majority of patients with relapsing multiple sclerosis receiving oral fingolimod (FTY720, a sphingosine-1-phosphate receptor modulator) remain free from any inflammatory activity: results of a 4-yr, phase II extension

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Objective: In the 6 M (month) Phase II study in patients ($n = 281$) with relapsing MS, oral fingolimod (1.25 and 5 mg) reduced Gd+ lesions by up to 80% and the annualized relapse rate (ARR) by >50% versus placebo. We report the number of patients free of any new inflammatory activity (defined as percentage of patients with no new T2 and no Gd+ T1 lesions) at M48.

Methods: Placebo-treated patients entering the extension were re-randomized to 1.25 or 5 mg while the fingolimod groups continued. From M15-24 on, all patients received open-label fingolimod 1.25 mg. Gd+T1 and new T2-hyperintense MRI lesions, relapses, Expanded disability status score (EDSS), and adverse events (AEs) were recorded at pre-defined time points. 48 M analyses used descriptive statistics.

Results: At M48, 155 patients were still participating in the extension study and the number (mean/median) of Gd+ T1 lesions (0.1/0.0) and new T2 lesions (0.5/0.0) were low. At M6, the percentage of patients free from new T2 and GD+ T1 lesions compared to M5, for the placebo and continuous fingolimod 1.25 and 5 mg groups, were 47.5, 77, and 80.7%, respectively. At M48, the percentage of patients free of new inflammatory activity since M36, for the placebo/fingolimod 1.25 mg and continuous fingolimod 1.25 and 5/1.25 mg groups, were 88.2, 78.8, and 80, respectively. At M48, patients continuously treated with fingolimod (1.25 or 5/1.25 mg) had a low ARR (0.18 or 0.20), respectively, and 63–70% of these patients remain relapse free; 51% of patients who switched to fingolimod from placebo at M7 were relapse-free. In all groups, most patients (65–75%), were free from 6 M confirmed disability progression. Nasopharyngitis, headache, influenza, fatigue, and back pain were the most frequently reported AEs (>15% patients).

Conclusion: After 4 years, the majority of patients using oral fingolimod remained free from any MRI inflammatory activity, relapses and disability progression. The safety experience with one year longer exposure was similar to that previously reported

Study supported by Novartis Pharma AG, Switzerland.

O22

Clinical efficacy of cladribine tablet therapy in patients with relapsing-remitting multiple sclerosis (RRMS): results from the CLARITY study, a 96-week, phase III, double-blind, placebo-controlled trial

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Objectives: Cladribine tablets are in development for the treatment of multiple sclerosis. Cladribine is a pro-drug, and activation in specific cell types provides targeted and sustained immunomodulation, permitting the investigation of an oral short-course annual treatment. Here we assess the clinical efficacy of cladribine tablets versus placebo in patients with RRMS.

Methods: In the CLARITY (CLAdRIbine tablets Treating multiple sclerosis orallY) study, patients with RRMS (McDonald criteria; expanded disability status scale [EDSS] score 0–5.5) were randomised 1:1:1 to receive placebo or a cumulative dose of 5.25 or 3.5 mg/kg cladribine tablets. Four (5.25 mg/kg arm) or two (3.5 mg/kg arm) courses of 0.875 mg/kg were administered over 4–5 days in weeks 1, 5, 9 and 13; or weeks 1 and 5, respectively. Two further short courses were administered in weeks 48 and 52, to both active arms. The primary efficacy endpoint was qualifying relapse rate over 96 weeks, analyzed using a Poisson regression model.

Results: 1,326 patients were randomised to 5.25 or 3.5 mg/kg cladribine tablets or placebo (ITT population; $n = 456$, 433 and 437, respectively). Groups were comparable for baseline characteristics, including age, gender and relapse rate in the 48 weeks prior to treatment. Cladribine treatment resulted in significant reductions in the annualised rate of qualifying relapses to Week 96 (0.15 and 0.14 vs. 0.33 in the 5.25 and 3.5 mg/kg groups vs. placebo; relative reduction 55 and 58%, respectively, both $p < 0.001$). In addition, significantly more patients were relapse-free at Week 96 in the 5.25 and 3.5 mg/kg groups versus placebo (79 and 80 vs. 61%), with a relative risk to relapse of 0.54 and 0.52, respectively (both $p < 0.001$). The risk of 3-month sustained disability progression was also significantly reduced, with a hazard ratio for relative reduction versus placebo of 0.69 (95% CI: 0.49, 0.96; $p = 0.026$) for cladribine 5.25 mg/kg and 0.67 (95% CI: 0.48, 0.93; $p = 0.018$) for cladribine 3.5 mg/kg. This was accompanied by significant improvements in MRI outcomes and good safety and tolerability, as reported elsewhere.

Conclusions: Treatment with cladribine tablets in the CLARITY study resulted in a significant reduction in relapse rates and prolonged time to sustained disability progression relative to placebo. When taken

alongside the MRI and safety data, the results provide clear evidence supporting the use of cladribine tablets in the treatment of RRMS.

Study supported by Merck Serono S.A., Geneva, Switzerland, an affiliate of Merck KGaA, Darmstadt, Germany.

O23

Long-term study of high-risk patients after a clinically isolated syndrome: 10-year follow-up from CHAMPIONS

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Objectives: CHAMPIONS was an open-label study enrolling 203 patients from 32 of 50 phase 3 CHAMPS sites and followed all patients until 5 years after CHAMPS randomization. The rate of development of clinically definite multiple sclerosis (CDMS) over 5 years in CHAMPIONS was reduced in the group receiving immediate initiation of treatment (IT group) in the CHAMPS trial with IFN β-1a 30 mcg once weekly, compared with delayed initiation of treatment (DT; CHAMPS placebo group) a median of 2.5 years after onset of a clinically isolated syndrome (CIS) (unadjusted hazard ratio 0.65, 95% CI: 0.43–0.97, $p = 0.03$). By 5 years, 43% of patients developed CDMS, 13% reached an expanded disability status scale (EDSS) score of 3.0 or higher, and 2% developed progressive disease. The objectives of this extension were to determine predictors of disease activity and progression and whether immediate initiation of IM IFN β-1a 30 mcg once weekly after a CIS affects long-term outcomes in a population of patients at high risk for developing CDMS.

Methods: Following completion of CHAMPIONS, interested patients were enrolled in an extension study in which they were followed annually for 5 years, until their 10-year (post-CHAMPS enrollment) evaluation. Ten-year outcomes included the development of CDMS, relapses, MRI disease activity, and disease course classification, as well as scores on the EDSS, multiple sclerosis functional composite, 36-item short form health survey questionnaire, and multiple sclerosis quality of life inventory.

Results: Eighty-five percent (155/183) of patients from 24 participating sites enrolled in the 10-year extension ($n = 81$, IT group; $n = 74$, DT group). Study database lock occurred in January 2009, and analyses are ongoing. Preliminary results indicate that 21% of patients developed an EDSS score of 3.0 or higher and 10% of patients developed progressive disease by last study visit.

Conclusion: This is the longest follow-up of well-characterized CIS patients initiating disease-modifying therapy shortly after the development of CIS. Results from this study will help clarify the long-term impact of early disease-modifying therapy and may identify early risk factors responsible for long-term disease activity and progression.

Study supported by Biogen Idec, Inc.

O24

Pneumonia is a predictor of mortality in patients with multiple sclerosis

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Objective: Multiple sclerosis is a chronic disabling neurological illness. Pneumonia has been proven to have a significant association in patients with multiple sclerosis compared with the background population. This study investigated if pneumonia is a predictor of in multiple sclerosis.

Methods: During 2000–2007, 1,152 patients with multiple sclerosis were admitted to a large general hospital in Birmingham. Multiple sclerosis cases and co-morbidities were traced using the ICD-10 criteria. Predictors of in-hospital mortality were determined using the Cox regression model.

Results: Of the 1,152 patients with multiple sclerosis, 98 patients died during the time period. The predictors of mortality in multiple sclerosis were shown to be age ($p < 0.001$), pneumonia ($p < 0.001$). The relative risk of mortality in patients with pneumonia and multiple sclerosis was 6.28 (95% CI; 3.38–11.6).

Conclusion: Pneumonia has been found to be the only predictor of mortality in multiple sclerosis. This is a new finding, with research so far identifying a link between a pneumonia causing a relapse in patients with multiple sclerosis but not as a predictor of in-hospital mortality. Therefore, clinical practice should focus on prevention, anticipation and low thresholds for treatment of pneumonia amongst patients with multiple sclerosis.

O25

Lack of association between APOE-E4 and cognitive impairment in relapsing-remitting multiple sclerosis

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Objective: To assess the association between APOE-E4 and cognitive impairment (CI) in relapsing-remitting multiple sclerosis (RRMS).

Background: Recent data suggest that APOE-E4 allele may be associated with cognitive impairment (CI) in MS, particularly on tasks of verbal memory and in younger individuals. However, due to previous conflicting evidence, this finding must be interpreted with caution and remains to be confirmed.

Methods: In 85 RRMS cases (58 females, mean age 43 ± 8.4, mean disease duration 15.8 ± 9.6, mean EDSS 1.7 ± 1.0) APOE genotype was assessed. In the whole sample cognitive functioning was evaluated through the Rao's brief repeatable battery (BRB). Performance on each test was assessed by applying the normative values for the Italian population. Depression and fatigue were also evaluated. In a subgroup of 50 patients, a brain MR study was performed with measurement of T2 lesion volumes (T2LV), neocortical volume (NCV) and normalized brain volume (NBV). Relationship between APOE genotype, CI and MR variables was assessed through univariate and multivariate logistic regression models.

Results: CI, most commonly involving complex attention and verbal memory tasks, was found in 28 cases (33%). We identified a total of 19 E4 carriers (22.4%), who did not differ from non-carriers for clinical and demographic characteristics. The presence of E4 genotype was associated neither with CI ($p = 0.28$) nor with impairment on each neuropsychological test ($p > 0.32$; corrected for age, gender, disease duration, EDSS, depression and fatigue). APOE genotype and CI were not related also in the subgroup of younger patients (age < 45 years; $p > 0.9$). Moreover, CI was related to higher T2LV ($p = 0.008$) and lower NCV ($p = 0.006$), whereas APOE-E4 was not associated with any MR variables ($p > 0.3$).

Conclusions: In our sample, CI was associated with higher subcortical damage and cortical atrophy but not with APOE-E4 genotype. The role of APOE-E4 as a possible biomarker in MS still remains questionable.

O26

To differentiate the indication to treat the clinically isolated syndrome on the bases of different clinical onsets. The subgroup analyses from a Cochrane meta-analysis

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Objective: To indicate different levels of evidence for the efficacy of early treatment of clinically isolated syndrome (CIS) for different types of presentation.

Methods: We performed subgroup analyses(per protocol; sensitivity analyses)on the bases of different presentations(optic neuritis, brainstem/cerebellar, spinal cord)of the already published (CHAMPS STUDY GR 2001, Beck 2002) papers referring to CHAMPS trial. We further obtain row data from the pharmaceutical companies producing different types of IFN. Outcomes: the number of patients converting to clinically isolated syndrome (CDMS)stratified for different types of presentation.

Results: Analyses performed on Beck's study: in patients whose onset was optic neuritis: no statistically significant difference in treated group compared to placebo group in all the analyses but the "best case scenario"(OR 0.46, 95% CI 0.24 to 0.91, $p = 0.03$; RD -14%, 95%CI -26 to -2%, $p = 0.02$);in patients whose onset was brainstem/cerebellar: the risk of conversion in IFN-treated compared to that in placebo-treated patients was not statistically significant in all the analyses; in patients whose onset was spinal syndromes both in "per protocol" (OR 0.27, 95% CI 0.08–0.92, $p = 0.04$; RD -19% 95% CI -35 to -2%, $p = 0.02$) as well as in "best case scenario" analysis (OR 0.27, 95% CI 0.08–0.92, $p = 0.04$; RD -19% 95% CI -35 to -2%, $p = 0.02$) the difference between the risk of conversion in IFN- compared to that in placebo-treated patients was statistically significant.

Conclusions: This preliminary subgroup analysis shows a slightly increased efficacy of IFN treatment to prevent conversion to CDMS for optic neuritis and spinal cord presentations. We will merge this data with those obtained from pharmaceutical companies in order to obtain a more clear indication to treat on the bases of type of presentation.

Oral session 2

Peripheral neuropathy

O27

The role of ephaptic responses in the prognosis of Guillain–Barré syndrome

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Objectives: Some patients with Guillain–Barre syndrome (GBS) show late reflex responses to motor nerve stimulation, also known as 'ephaptic responses', which point out to the possibility of segmental demyelination at various levels along the nerve. We considered that the underlying pathophysiological mechanism may be different in these cases than in others with no ephaptic responses. Therefore, we aimed at examining if there were differences in the course of the disease, including motor sequellae, in patients with GBS with and without ephaptic responses.

Methods: We carried out a retrospective review of clinical reports and neurophysiological studies in the last 21 patients with GBS evaluated in our institution. We defined ephaptic responses as low amplitude potentials that appeared repeatedly with the same form at a fixed latency, incompatible with F waves. They were considered as abundant, fewer or absent from the exams carried out in leg nerves within the first 18 days after onset of symptoms. The severity of clinical condition was evaluated according to whether the patient had a stage in ICU and the patient's functional motor balance at discharge

Results: Nine patients were considered to have abundant or fewer ephaptic responses. These patients did not show significant differences in age or sex with respect to the 12 patients with no ephaptic responses. Immunoglobulins were used in 77.8% of patients with ephaptic responses and in 100% of patients without ephaptic responses. None of the patients with ephaptic responses was sent to the ICU due to respiratory failure while 33.3% of those without ephaptic responses required mechanical ventilation. Autonomy with performing daily living motor actions at discharge was found in 55.6% of patients with ephaptic responses and in only 33.3% of those without ephaptic responses.

Conclusion: The presence of ephaptic response in the neurophysiological evaluation of patients with GBS may indicate relatively better prognosis than its absence. It is possible that the observation of ephaptic responses marks the spreading of oedema along the nerve path, which would consequently diminish focal pressure at a radicular level and reduce proximal axonal damage.

O28

Outcome measures in Charcot-Marie-Tooth disease type 1A: data from the trial with ascorbic acid (CMT-TRIAAL and CMT-TRAUK)

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Objective: To report data of different outcome measures in the patients recruited in the ascorbic acid trials. CMT-TRIAAL and CMT-TRAUK are parallel, phase III randomized, double blind, placebo-controlled studies with ascorbic acid (1,500 mg/day) or placebo in adults with Charcot-Marie-Tooth disease type 1A (CMT1A). Methods. All the 271 recruited patients (60% females; mean age 42 years, SD 13, range 18–70) have been evaluated at basal assessment. The CMT neuropathy score (CMTNS) is the primary outcome measure and is a specific composite scale taking into account sensory and motor symptoms and signs and electrophysiology (score ranges from 0, normal, to 36, worst score). Other outcome measures were: distal maximum voluntary isometric contraction (MVIC); manual strength assessment (MRC scale); 10-m timed walking (T10 MW); 9-hole-peg test (9HPT); overall neuropathy limitations scale (ONLS); pain and fatigue visual analogue scales (VAS); health-related quality of life (SF-36); electrophysiology.

Results: Mean CMTNS at baseline was 14 (SD 4.8), corresponding to a mild disease severity (CMTNS < 11) in 26%, moderate in 65% and severe in 9% of patients. Age was correlated with disease severity as expressed by CMTNS (p 0.001). Females had higher CMTNS values (mean 14.6, SD 5.0 vs. 13.2, SD 4.2; p 0.02), suggestive of more severe disease, but were older than males (mean 44.5, SD 1.0 vs 39.6, SD 1.2; p 0.002), and multivariate regression analyses confirmed the effect of age (p 0.001) but not of sex on disease severity. ONLS, T10 MW, 9HPT, MVIC, MRC values, SF36 scores worsened with increasing age decades. VAS scores showed that pain 3.68 (SD 3.02) and fatigue 4.87 (SD 2.81) are major complaints in CMT1A. CMTNS values were divided in tertiles (1–12; 13–16; >16) and correlation with other outcome

measures explored: impairment and disability as assessed by MVIC, T10 MW, 9HPT, ONLS and VAS showed good correlation with CMTNS tertiles; patients with higher CMTNS values had worse Quality of Life. Impairment of foot dorsiflexion assessed with a hand-held myometer and a foot stabilising device showed very good correlation with most outcome measures. Conclusion: This is the largest series of CMT1A patients studied thus far, and assessed using several outcome measures. Impairment, disability and QoL worsen with increasing age and the CMTNS is a good measure of disease severity.

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O29

Vocal cord and diaphragmatic paresis in GDAP1-associated neuropathy

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Cranial nerve involvement due to Charcot-Marie-Tooth disease (CMT) is rare, though there are a number of CMT syndromes in which vocal cord paralysis is a characteristic feature. CMT disease with mutations in the ganglioside-induced differentiation-associated protein 1 gene (GDAP1) has been reported to be associated with vocal cord and diaphragmatic palsy. In order to asses the contribution of the GDAP1 mutations on these complications we evaluated vocal cord and respiratory function in nine patients from eight unrelated families with CMT showing different GDAP1 gene mutations. Hoarseness of the voice and the inability to speak loudly had been suffered by eight patients and one of them complained of respiratory insufficiency symptoms as well. All patients were investigated by means of peripheral and phrenic nerve conduction studies, flexible laryngoscope, pulmonary function studies and polysomnography. Nerve conduction velocities and pathological studies were compatible with axonal CMT (CMT2). Flexible laryngoscopy showed left vocal cord palsy in four cases, bilateral cord palsies in four cases, and was normal in one case. The eight patients with vocal cord palsies were wheelchair-bound dependent and all of them presented restrictive respiratory dysfunction and neurophysiological findings of phrenic nerve dysfunction. The only patient with normal vocal cord and normal pulmonary function had a less severe clinical course.

CMT patients with GDAP1 mutations develop severe disability due to weakness of the limb muscles, but the disease can also affect frequently laryngeal and respiratory muscles. The early and predominantly involvement of left vocal cord can be the result of a length-depending pattern nerve degeneration, provided that left recurrent laryngeal nerve runs a longer course. Respiratory function should be thoroughly investigated in these patients because life expectancy can be compromised due to respiratory failure

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O30

Treatment of experimental autoimmune neuritis with clodronate (Bonefos^{TM})

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Objectives: Experimental autoimmune neuritis (EAN) serves as an animal model for human Gullain–Barre syndrome (GBS), an autoimmune disease causing demyelination and inflammation of peripheral nerves. Macrophages, which play a major role in this autoimmune inflammatory process, can be selectively targeted by high doses of bisphophonates. The aim of the present study was to examine the effect of the bisphosphonate, clodronate, on the severity of the EAN induced in rats.

Methods: EAN was induced in female adult rats by immunization with bovine peripheral myelin. A number of treatment protocols with clodronate were used based on the common dosage regimen of 20 mg/kg in humans starting with the appearance of clinical signs on day 10 post immunization. Regimens included 20 mg/kg given every second day or every day and 40 mg/kg every second day. Control animals were treated with saline. The clinical parameters measured included: a clinical score, a motor performance test performed on a Rotarod, and body weight. The expression of the matrix metaloproteases (MMP9 and MMP2) in the sciatic nerves were measured as markers of inflammatory macrophages.

Results: Treatment with clodronate significantly reduced the disease severity (a 75% decrease in severity, $p < 0.01$ by ANOVA) as measured by the clinical score, compared to controls only in rats treated with the higher doses of clodronate 20 mg/kg daily and 40 mg/kg every 2 days. Performance on the Rotarod test and body weight confirmed the clinical score findings. MMP2 expression levels were significantly lower in the sciatic nerves of high dose clodronate treated rats.

Conclusions: The present findings support the efficiency of clodronate in inflammatory diseases of the peripheral nervous system. The mechanism of action includes inhibition of inflammatory macrophages. The results suggests the use of bisphosphonates be considered in humans with GBS.

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O31

Clinical features of peripheral neuropathy in primary Sjögren's syndrome: a study of 25 cases

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Introduction: Primary Sjögren's syndrome (PSS) is a chronic inflammatory autoimmune disease that mainly affects exocrine glands (salivary and lacrimal) leading to sicca syndrome. The clinical diagnosis of PSS requires a high index of suspicion especially when the first clinical manifestation of the disease is neurologic, since peripheral neuropathy may precede the sicca syndrome in many patients.

Objective: To study the clinical features of peripheral neuropathy in PSS

Patients and methods: Twenty five consecutive patients with peripheral neuropathy associated with PSS were retrospectively studied. All patients fulfilled the American-European Classification Criteria for Sjögren Syndrome revised in 2002. Patients were divided in group A (sicca syndrome preceded neurologic involvement) and group B (peripheral neuropathy preceded sicca syndrome).

Results: All 25 patients were female with ages between 34 and 82 years (mean age of 52.48 $\pm$ 16.16 years). The mean disease duration interval ranged from 3 to 180 months (mean 52.80 $\pm$ 45.59 months). Eighteen patients (72%) were located at group A and the mean interval between sicca syndrome and peripheral neuropathy was 14.1 $\pm$ 15.0 months. Seven patients (28%) were located at group B and the mean interval between peripheral neuropathy and sicca syndrome was 23.36 $\pm$ 28.20 months. Twenty patients (80%) presented with small fiber polyneuropathy (SFP), three patients (12%) with polyganglioneuropathy (PGNP) and the last two patients (8%) with sensory-motor

polyneuropathy (SMP). Antibodies to Ro/SSA and neuropathic pain (not simultaneously) were detected in 100% of patients with SMP and with PGNP and in 90% of patients with SFP. Sensory nerve conduction was abnormal in 50% of patients with SFP. We didn't find any case of plexopathy. Sural nerve biopsy was performed in 23 patients and showed microvasculitis in 100% of patients with SMP, in 77.78% of patients with SFP and in 0% of cases of PGNP ($p = 0.020$).

Conclusion: Peripheral neuropathy may precede sicca syndrome and be the first manifestation of PSS. The recognition of PSS in patients with peripheral neuropathy is important mainly in those with involvement of small fibers. Some patients present with an unfavourable clinical course and immunosuppressive therapy can be beneficial. A screening for primary Sjögren's syndrome must be made systematically in patients that develop peripheral neuropathy with the objective of early diagnosis and treatment.

O32

Association of integrin β-3 polymorphism at residue 33 with development of chronic oxaliplatin-induced peripheral nerve damage

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Background and purpose: Peripheral neuropathy (PN) is widely recognised among the major non-haematological dose-limiting toxicities of oxaliplatin (OXL). The integrin β-3 (ITGB3) polymorphism at residue 33 (L33P) has been previously associated with altered adhesion ability and ERK2 activation. Thus it may affect neuronal survival. The current study sought to assess the significance of the ITGB3 polymorphism at residue 33 in the development of chronic OXLIPN.

Methods: Thirty four patients, 22 males and 12 females, with advanced colorectal cancer (CRC) were genotyped. Genotyping was performed using allele specific primers and sybr green in real time polymerase chain reactions. All patients had received adjuvant oxaliplatin-based chemotherapy consisting of the formal FOLFOX-4 or XELOX regimen. The severity of the OXLIPN was defined by means of total neuropathy scores (TNS), corresponding to the WHO grading scales 1–3 for chemotherapy-induced PN. Following the discontinuation of treatment, 20/34 patients (58.8%) developed OXLIPN. Among patients developing OXLIPN, 13 were males and 7 females with mean age 65.6 ± 9 years. According to the TNS, mild, grade I neurotoxicity was revealed in 6 (30%) patients and moderate grade II neurotoxicity in 14 (70%) patients.

Results: Patients with normal peripheral nerve function ($n = 14$) were 14.3% homozygous for C, 28.6% heterozygous and 57.1% homozygous for T. The corresponding percentages for patients who developed OXLIPN did not differ significantly and were 5, 25 and 70%, respectively. Half of patients (50%) with mild OXLIPN (grade I) were heterozygotes (16.7% CC and 33.3% TT). The majority of patients with moderate OXLIPN (grade II) were homozygous for TT (85.7%) with the remaining 14.3% being CT. The TT genotype was associated with increased severity of OXLIPN compared to the genotypes containing the C allele ($p = 0.046$).

Conclusion: The ITGB3 polymorphism at residue 33 seems to be unrelated to the development of OXLIPN but appears to be related to the severity of OXLIPN. Further study on this issue with significant clinical application is warranted.

Oral session 3

Neuro-ophthalmology

O33

Structural brain changes following peripheral audio-vestibular deafferentation may indicate multisensory compensation

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Vestibular deafferentation is known to elicit functional brain plasticity which may be related to vestibular compensation. However, little is known about structural (morphological) changes in the human brain which might contribute to central vestibular compensation and account for the great variability of clinical recovery following peripheral vestibular lesions. We compared regional gray matter changes in patients (mean age: 56.6 ± 8.9 years) after surgical removal of a unilateral acoustic neuroma with age-matched control subjects (mean age: 56.0 ± 9.1 years). We hypothesized morphometric changes in the vestibular and auditory cortices which may be related to functional disability scores.

Patients were examined with a battery of neuro-otological tests and clinical scores to assess vestibular and auditory disability. Using voxel-based morphometry (VBM, SPM2) categorical comparison between patients and controls within defined regions of interest according to the a priori hypothesis revealed gray matter volume (GMV) increase bilaterally in primary somatosensory cortices and motion sensitive areas in the medial temporal gyrus (MT). Simple regression analysis revealed the GMV increase (1) in the contralesional superior temporal gyrus/posterior insula to be correlated with decreasing clinically assessed vestibular deficits; (2) in the contralesional inferior parietal lobe with decreasing functional impairment of daily living activities; and (3) in the contralesional auditory cortex (Heschl gyrus) with decreasing hearing impairment.

In conclusion, these data suggest structural cortical plasticity in multisensory vestibular and auditory cortex areas of patients following unilateral irreversible vestibular deafferentation which is related to functional vestibular and auditory function. More specifically, increase of GMV was related to better vestibular and auditory function suggesting that structural alterations are related to central mechanisms of compensation.

O34

Sequential micro-PET based brain imaging in the unilateral labyrithectomy rat model: insights to compensatory brain plasticity

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Objectives: Characterization of dynamic brain activation patterns in vestibular damage and compensation.

Methods: Left-sided unilateral labyrinthectomy (UL) was performed by drilling into the vestibule and removing its contents through aspiration in 3-month old Sprague–Dawley rats ($n = 6$). As a

control group animals were given a surgical sham treatment identical to the UL procedure, but without damage to the inner ear ($n = 6$). Sequential [18F]-Fluoro-deoxyglucose micro-PET imaging was done in all animals on day 1 before and days 1, 2, 5 and 12 after UL or sham surgery. At same time points vestibular deficits were scored for the three components nystagmus, head roll tilt and postural asymmetry. Individual brain images were normalized to a rat brain template and mean brain activation maps calculated by group analysis.

Results: Dynamic changes of the regional cerebral metabolic rate for glucose (rCMRglc) could be shown in the UL but not in the sham group, which could be categorized into four stages: (1) Stage of vestibular imbalance: At day 1 after UL a significant asymmetry of rCMRglc appears showing reduced glucose consumption in the ipsilateral vestibular nucleus, contralateral tegmental mesencephalic nuclei (interstitial nucleus of Cajal, parabrachial nucleus, raphe nucleus), the contralateral posterolateral thalamus and temporoparietal cortex and increased glucose consumption in the ipsilateral posterolateral thalamus. (2) Stage of early vestibular compensation: At day 2 after UL rCMRglc equalizes in the vestibular nuclei and the mesencephalic nuclei at a level below baseline parallel with concomitant gradual normalization of behavioural signs of vestibular imbalance. (3) Stage of vestibular hypercompensation: At day 5 after UL the contralateral vestibular nucleus, ipsilateral tegmental mesencephalic nuclei and posterolateral thalamus show significant increase in rCMRglc. (4) Stage of late vestibular compensation: At day 12 after UL rCMRglc of the vestibular nuclei, the tegmental mesencephalic nuclei, the posterolateral thalamus and the cortex was symmetric and back to baseline.

Conclusions: In the present study, highly dynamic changes of brain activation are shown in the time course after unilateral vestibular damage reflecting compensatory mechanisms. Four stages can be differentiated based on rCMRglc patterns. The presented model provides a useful tool for imaging brain stem activity patterns during vestibular compensation.

O35

Imaging human supraspinal locomotor centres across the age spectrum

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Objectives: Characterization of supraspinal locomotor regions in a group of normal persons of different ages during imagined locomotion.

Methods: 60 normal subjects (age: 24–78 years) were trained for the conditions lying, standing, walking and running in order to imagine these conditions on command in 20-s sequences with eyes closed while lying supine in a MRI scanner (3T, GE). For functional imaging a T2 -weighted gradient echo multislice sequence (EPI, TR 4500 ms, TE 60 ms, voxel size $3.75 \times 3.75 \times 3.75$ mm^3, matrix 64×64) was used to acquire 34 slices covering the whole brain and the cerebellum. Each condition was tested 14 times per subject. Data processing was done using statistical parametric mapping software (SPM5). SPMs were computed for the comparisons standing versus lying, walking versus lying, running versus lying. Both BOLD (blood oxygen level dependent) signal increases and decreases were calculated and considered significant for $p < 0.05$, corrected for multiple comparisons using the FDR method.

Results: During locomotion the most prominent infratentorial activations were found in the vermal and paravermal cerebellum, with extension via the superior cerebellar peduncle bilaterally in the pontomesencephal brainstem tegmentum (involving the cuneiform and pedunculopontine nuclei). Furthermore BOLD signal increase was shown in the parahippocampal gyri and visual cortical areas, both of which are important for visually guided navigation, and in the prefrontal region. Significant deactivations were found in the posterior insulae and the supramarginal gyri, which are related to vestibular function (parieto-insular vestibular cortex), and in the anterior cingulate. The basic patterns of activation and deactivation in the locomotion network were found irrespective of age.

Conclusions: The most important locomotor centers are the mesencephalic, the subthalamic, and the cerebellar locomotor region. Prefrontal cortex activity influences the brainstem regions via the basal ganglia. Locomotor signals are transmitted from the midbrain to the spinal cord via the ponto-medullary reticular formation and integrate multisensory input at different levels. The basic locomotion network is conserved up to advanced age.

O36

A longitudinal evaluation of the disease mechanisms of non-arteritic anterior ischaemic optic neuropathy using functional magnetic resonance imaging

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Background: Non-arteritic anterior ischaemic optic neuropathy (NA-AION) results in infarction of the optic nerve head and is the most common cause of acute optic neuropathy in the middle-aged and elderly population. Some authors claim that significant visual recovery is rare, but other studies have shown that about 30% of patients achieve visual acuity improvement of several lines at 24-months follow-up. Neuroplasticity has hitherto not been studied in NA-AION.

Objectives: We aimed to investigate the longitudinal relationship between recovery after NA-AION and task-related brain activation during monocular visual stimulation as measured using functional MRI (fMRI).

Methods: fMRI was used to study the brain activation pattern induced by a monocular visual stimulation in nine patients who had ischemic optic neuropathy at 1–6 months. Four of these patients were also assessed in the first 2 weeks from the onset. Visual acuity was recorded as the 4 m logMAR and the visual field was measured using the Humphrey visual field mean deviation (HMD). Functional images were analyzed using statistical parametric mapping (SPM5).

Results: For the affected eye, it was found no activation in primary visual areas (V1), early after symptom onset, in four out of nine patients. In two subjects, V1 activation correlated with better visual acuity over time. For the fellow eye, V1 activation increased in four out of nine patients over time. In three subjects V1 activation correlated with better visual acuity over time.

Conclusions: There is individual variation in fMRI activation following NA-AION. In some patients there are significant associations between fMRI response and visual function.

O37

Ocular maximal saccade velocity is reduced even in presymptomatic stages resulting from polyQ toxicity in SCA2

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Objective: (1) We sought if Maximal Saccade Velocity is affected at earliest stages even before ataxia debut in SCA2 carriers. (2) To trace the progression of SCA2 neurodegeneration using the endophenotype in 110 patients from an SCA2 founder population, 70 non-symptomatic first-degree relatives and 107 controls. (3) To identify association between endophenotype and disease duration, polyglutamine expansion size, age at onset, ataxia score, age and sex.

Methods: Eighty two SCA2 patients, 53 asymptomatic carriers and 82 healthy controls were studied by an electronystagmographical technique to evaluate the saccade velocity, latency and deviation. For a longitudinal study, 50 SCA2 patients and controls were studied three times each two years.

Results: Significant reduction of MSV in SCA2 was found for visually guided saccades of 10o, 20o, 30o, 60o amplitude, and even at earliest disease stages there was little overlap with normal values. Multivariate analysis with stepwise regression found 60o MSV to be influenced strongly by the expansion size, and still significantly by disease duration.

Conclusion: This defect has been attributed to neuronal degeneration in the brainstem centers. Secondly, there are deficits in the higher-level control of these premotor centers, as in evident from increased latencies and difficulty in initiating appropriate saccades. The data suggest that saccade velocity is a sensitive objective SCA2 endophenotype, useful to search polyglutamine modifier genes similarly to the subjective age of onset. On the other hand, it has been claimed that saccadic eye movements dysfunction occur at a preclinical stage and could serve as an early marker of future SCA2 among the offspring of SCA2 patients.

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Oral session 4

Parkinson's disease

O38

Iowa Gambling Task in young patients with Parkinson's disease without the history of pathological gambling

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Objectives: There is increasing knowledge about higher incidence of some types of compulsive behaviour in patients with Parkinson's disease (PD) in contrast to other population. These impulse control disorders (such as pathological gambling, hypersexuality, compulsive shopping, compulsive eating, punding, compulsive overusing of dopaminergic drugs) can lead to monetary loses or worsened social handicap of patients. The risk factors of the pathological gambling are: dopaminergic agonist in medication, young onset PD, personal or family history of alcohol abuse, tendency to novelty-seeking and tendency to impulsive behaviour generally. The aim of our study was to detect a tendency to impulse behaviour in patients with PD registered in our Movement Disorders Centre. With regards to the risk factors we had chosen a group of patients with onset of PD in young age till 45 years.

Methods: We have examined 20 patients with PD (onset of PD up to 45 years) and 20 age-matched control subjects. We used computer version of Iowa Gambling Task (IGT), which is used for studying limbic functions and for detection of impaired decision making. All the subjects made a set of questionnaires viewed to pathological gambling (South Oaks Gambling Screen, modified Minnesota Impulse Disorders Inventory).

Results: Patients with PD gained significantly lower IGT-score (difference between a number of advantageous and disadvantageous choices) during the performance of IGT when compared with control group (mean −10.9 in patients versus 8.7 in control subjects). None of the subjects were considered to be a gambler according to South Oaks Gambling Screen nor modified Minnesota Impulse Disorders Inventory.

Conclusions: Our results show the tendency to impulsive decision in young patients with PD without the history of pathological gambling. It is necessary to consider pathological gambling in young PD patients with regards to their treatment and possible clinical and sociological outcomes.

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O39

Sleepwalking in patients with Parkinson's disease

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Introduction: Sleepwalking (SW) corresponds to a complex sleep-associated behavior, which includes locomotion, mental confusion, and amnesia. SW is present in about 10% of children and 2–4% of adults, but only 0.6% of adults report SW "de novo". In a series of 165 consecutive patients with Parkinson's disease (PD) we found SW "de novo" in 6 (3.6%). The aim of the present study was to assess the frequency and the characteristics of SW in patients with PD.

Methods: A questionnaire including items on sleep quality, sleep disorders, in particular SW and REM sleep behavior disorder (RBD), PD characteristics and severity, was sent to the members of the national PD patients organization in Switzerland.

Results: 420 questionnaires were received. Three patients had to be excluded for diagnoses other than idiopathic PD. 36/417 patients (9%) reported adult SW, of them 22 (5% of the population studied) had SW "de novo". Patients with SW had significantly longer disease duration ($p = 0.035$), they reported more often hallucinations ($p = 0.004$) and nightmares ($p = 0.003$), their dream content was more variable ($p = 0.046$) and they had higher scores, suggestive for RBD in a validated questionnaire ($p = 0.001$). Patients with SW also had a trend for a higher Epworth sleepiness scale score ($p = 0.055$).

Conclusion: Our results suggest that SW in PD patients is more common then in the general populations. SW appears to be a late manifestation of PD. Most patients with SW also had questionnaire scores suggestive for RBD. The simultaneous occurrence of SW and RBD suggests a complex disturbance of arousal, locomotion and muscle tone during REM and NREM sleep in PD.

O40

Improvements in nocturnal symptoms and sleep with ropinirole prolonged-release in patients with sleep impairment in advanced Parkinson's disease not optimally controlled with L-dopa

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Objective: Examine the effect of ropinirole prolonged release on nocturnal symptoms in patients with advanced Parkinson's disease (PD) not optimally controlled with L-dopa.

Methods: A Phase III, double-blind, parallel-group, 24-week study compared the safety and efficacy of adjunctive ropinirole prolonged release with placebo (EASE-PD Adjunct; 101468/169). Patients were randomized to once-daily ropinirole prolonged release (2–24 mg/day) or placebo. Nocturnal symptoms were assessed by mean change from baseline in Parkinson's disease sleep scale (PDSS) total score (range: 0–150; ≤ 100 = sleep dysfunction). Post-hoc analysis of grouped items on the PDSS for nocturnal restlessness (items 4&5), nocturnal motor symptoms (NMS: items 10–13), daytime sleepiness (items 14 and 15), dopaminergic symptoms (DopaS: items 1, 3–5, 8, 10–13) and global quality of nocturnal sleep (GQNS: items 1, 3 and 14) was carried out. The magnitude of change in grouped PDSS score depended on the number of items included (e.g. NMS = 3 items, possible range = 0–30; DopaS = 9 items, possible range 0–90).

Results: Of patients receiving ropinirole prolonged release, 94/200 (47%) had a baseline PDSS total score ≤ 100, versus 90/190 (47%) receiving placebo. For patients with PDSS total score ≤ 100 at baseline, mean (SD) change from baseline in PDSS total score was greater for ropinirole prolonged release than placebo at Week 12, Week 24 observed case (OC) and Week 24 last observation carried forward (LOCF) (10.3[24.44], $p = 0.0001$ vs. baseline; vs. 2.5[20.96], $p = 0.2762$ vs. baseline). Patients with PDSS total score >100 at baseline, demonstrated no clinically relevant change from baseline to Week 12 or 24 OC/LOCF in either treatment group. In patients with baseline PDSS scores ≤ 100 receiving ropinirole prolonged release, improvements were seen in PDSS grouped scores at Weeks 12, 24 OC and 24 LOCF for all item groups. Differences vs placebo at Week 24 (LOCF) were most pronounced for NMS (4.1[9.22] vs. 0.3[9.08]), DopaS (7.5[16.26] vs. 2.3[14.98]) and GQNS (2.1[7.41] vs. 0.2[6.76]). Changes in grouped items in patients receiving ropinirole prolonged release with a PDSS score >100 at baseline were minimal.

Conclusion: In patients with PD exhibiting sleep dysfunction at baseline, ropinirole prolonged release improves nocturnal symptoms compared to placebo as measured by PDSS total score. Particular improvements were seen in the PDSS items related to dopaminergic and nocturnal motor symptoms, and in global sleep quality.

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O41

Rotigotine transdermal system for perioperative administration in Parkinson's disease

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Background: Despite increased medical need due to frequent surgical procedures in Parkinson's disease (PD) patients, perioperative management has remained unchanged for decades. Therapeutic strategies are sparse, invasive, complicated, partly ineffective and expensive: levodopa either via nasogastral tube or intraduodenally, amantadine intravenously and continuous subcutaneous administration of apomorphine. In most cases oral therapy is even discontinued. A retrospective analysis of two large multicenter trials of rotigotine, a non-ergot D3/D2/D1 dopamine receptor agonist, suggested that transdermally applied rotigotine might provide a novel perioperative treatment option for PD patients (Korczyn et al. 2007).

Objective: To investigate the feasibility of an administration of transdermally administered rotigotine in PD patients throughout the perioperative period.

Methods: Prospective multicenter open-label pilot trial in PD patients undergoing a surgical procedure with the need for general anaesthesia. PD patients were substituted with transdermal rotigotine following usual oral anti-parkinsonian medication. Administration of rotigotine started in the evening of the preoperative day and continued until the intake of the usual medication was possible again.

Results: 14 PD patients (7/7, mean age 69 years, HY I-IV) were enrolled in the study. Feasibility of the perioperative administration of rotigotine was assessed using questionnaires and rated positive in all dimensions by the anaesthesiologist, the neurologist and the patient, respectively. Tolerability was generally well. Throughout the entire study, 5 Serious Adverse Events with the outcome of full recovery were recorded. Plasma levels of rotigotine were within the expected range.

Conclusion: PD patients suffer from a variety of problems during the perioperative phase probably in part as a result of discontinuation of the oral dopaminergic therapy (Mueller et al, 2008). Currently available data indicate that the transdermal application of rotigotine is a feasible measure to treat PD patients throughout the perioperative period.

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O42

Long-term clinical and cognitive follow up in patients with advanced Parkinson's disease treated with subcutaneous apomorphine infusion or deep brain stimulation

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Objective: To compare clinical and neuropsychological long term outcomes (5 years) following subcutaneous apomorphine infusion (APO) and chronic deep brain stimulation of the subthalamic nucleus (STN-DBS) in advanced PD patients.

Methods: Patients with advanced PD and medically untreatable fluctuations were offered either APO (12 patients) or STN-DBS (12 patients). All patients were yearly evaluated by means of UPDRS and neuropsychologically evaluated at baseline, at 1 year and at last

follow up visit with MMSE, HAMD-17 and Neuro-Psychiatric Inventory (NPI). Subjects with STN-DBS were also tested with Paired Word Learning test, Raven's Coloured Progressive Matrices, phonemic and category fluency (CF) tests; patients with APO performed the California Verbal Learning test and Corsi test.

Results: One patient only was receiving APO at 5 years, with benefit. Two subjects discontinued APO after 4 years: one switched to duodenal infusion of levodopa and one to STN-DBS due to subcutaneous nodules and severe dyskinesias, respectively. In the first 4 years, three subjects discontinued APO because of untreatable dyskinesias (one with additional "offs" episodes) and one because of subcutaneous nodules and panniculitis; three patients died because of unrelated pathologies; two patients were lost at follow up. The overall adverse event rate responsible for APO discontinuation was 0.28 event/year (excluding death).
All STN-DBS patients were actively stimulated at 5-year follow up. One patient had leads infection that was treated successfully (0.01 event/year of stimulation per electrode).
In both cohorts, clinical improvement at 1 year was maintained in all successive yearly examinations. Starting at first year, all patients experienced a significant reduction of daily "off" time. In addition, subjects with STN-DBS showed a significant reduction in total levodopa daily intake and dyskinesias duration and severity. NPI and CF significantly worsened in four subjects with STN-DBS (0.11 event/year stimulation). No worsening at any NPS tests was found in the APO group.

Conclusions: Both APO and STN-DBS resulted in significant clinical improvement. STN-DBS allowed greater reduction in levodopa daily doses and provided more benefit on dyskinesias, but four subjects experienced apathy, anxiety, and depression after stimulation. A higher incidence of adverse events and dropouts were observed in the APO cohort with only one subjects able to continue APO infusion over 5 years.

O43
Impact of multitrajectoral stimulation and microelectrode mapping for intraoperative target validation in surgery for thalamic deep brain

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Objectives: Thalamic high-frequency stimulation is an established therapy for severe tremors. Because the best anatomical target for deep brain stimulation (DBS) in tremors is still not clearly identified and the target region is difficult to visualize, it is essential to verify clinical benefit and adverse event threshold by intraoperative electrophysiological techniques. Here, we analyze why and how often multitrajectoral mapping leads to deviation from the originally planned trajectory.

Methods: We retrospectively analyzed data of 85 electrode implantations into the ventrolateral thalamus in patients with severe tremor (electrode implantations in essential tremor, $n = 44$, multiple sclerosis tremor, $n = 35$ and other tremors, $n = 11$). In all procedures, we performed multitrajectoral microelectrode mapping with up to five parallel microelectrodes ("Bens-Gun"). The target was calculated by AC-PC based atlas coordinates and individual MRI with the central trajectory of the Ben-Gun array aiming at this target. Microelectrode recording and macrostimulation were used to refine the final electrode position based on the presence or absence of typical thalamic neuronal discharges and the clinical responses to high frequency stimulation.

Results: The permanent electrode was implanted in the central trajectory in 42.4%, in the medial in 41.2%, in the posterior in 9.4%, in the anterior in 4.7% and in the lateral trajectory in 2.4% of the hemispheres. Reasons for choosing other trajectories than the central one were adverse effects and less efficacy in tremor reduction in 22 %, the induction of adverse effects only in 51% and less efficacy in tremor reduction only in 24% of implanted hemispheres. In only one case the decision was based on more typical microelectrode recordings. The clinical outcome did not differ significantly between the groups implanted in the predetermined anatomical target (central trajectory) and surrounding trajectories.

Conclusion: The implantation of the permanent electrode in others than the anatomically predefined trajectory in 57.6% emphasizes the relevance of additional intraoperative neurophysiological mapping for defining the clinically optimal site for long-term tremor reduction and a high threshold for stimulation induced adverse events. Whereas microelectrode recordings contribute little, macrostimulation for efficacy and adverse events is crucial.

Oral session 5

Motor neuron disease

O44
Diffusion tensor MRI tractography study of the brain white-matter pathways in amyotrophic lateral sclerosis

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Objective: Amyotrophic lateral sclerosis (ALS) is the most common adult-onset motor neuron disease. The diagnosis of ALS is based on clinical criteria and no diagnostic biomarkers are available. Objective biomarkers are warranted to monitor disease progression, and the effects of potentially disease-modifying treatments. Aim of this study was to explore the ability of diffusion tensor (DT) MRI tractography to assess the structural damage to the corticospinal tracts (CST) as well as to the major cerebral white matter (WM) pathways in ALS patients with mild disability.

Methods: Brain conventional and DT MRI were obtained from 25 patients (14 men and 11 women, mean age = 54.1 years, mean disease duration = 39 months) with ALS and mild disability, defined as a score equal to or greater than 20 at the ALS Functional Rating Scale. Six patients had a bulbar-onset and 19 patients had a limb-onset disease. None of the patients had clinical evidence of frontotemporal dementia. Eighteen sex- and age-matched healthy subjects (11 men and 7 women, mean age = 52.2 years) were also studied. DT MRI tractography was used to investigate the CST, corpus callosum, cingulum, fornix, uncinate fasciculus, inferior fronto-occipital fasciculus, and inferior longitudinal fasciculus. From each tract, axial and radial diffusivity, mean diffusivity (MD), and fractional anisotropy (FA) were obtained.

Results: Compared with controls, ALS patients showed significantly decreased average FA and significantly increased radial diffusivity and MD in the CST, bilaterally (p values ranged from 0.002 to 0.02). No DT MRI changes were found in the other WM tracts.

Conclusions: ALS patients with mild disability and no cognitive impairment have a selective damage to the CST.

O45

Motor axon excitability changes in ALS and Wallerian degeneration

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The mechanisms involved in selective motor neuron degeneration in amyotrophic lateral sclerosis (ALS) remain unknown. By means of "threshold tracking" excitability of motor axons was found to be abnormal in some ALS patients. The reported abnormalities were heterogeneous possibly depending on disease stage. In the clinical setting it is not possible to distinguish whether abnormalities in axonal excitability reflect a specific pathogenic mechanism of ALS or the process of axonal degeneration itself.

Transgenic mouse models with mutations in the gene encoding Cu/Zn superoxide dismutase (SOD1) gene develop late onset progressive death of motor neurons reminiscent of ALS. The G127X-C57Bl mouse line 716 transgenically overexpresses 19 copies of a human mutant SOD1 gene (G127insTGGG) which leads to the synthesis of a C-terminally truncated unstable mutant protein lacking SOD activity that is rapidly degraded. The G127X SOD1 mutant protein is most abundant in the ventral horns, however, it does not enter the axonal transport system possibly due to its instability.

We compared the excitability of tibial nerve motor axons in G127X homozygote (G127X) mice and wild-type C57Bl mice prior to and during Wallerian degeneration following sciatic nerve crush.

Serial electrophysiological observations were carried out under anesthesia. Tibial nerve was stimulated at ankle and plantar responses were tracked using the clinically available multiple excitability protocol.

The mean survival for the G127X mice was 30 weeks. The disease course in the G127X mice was only 1 week after the first symptoms. In presymptomatic G127X mice (n=6), excitability was undistinguishable from wild-type controls. In terminally ill G127X mice ($n = 3$) the excitability measures appeared slightly abnormal: increased threshold deviations during threshold electrotonus, enhanced superexcitability during the recovery cycle, increased rheobase and chronaxie. These excitability deviations were similar to those observed in wild-type axons, just prior to conduction failure, at 14 hours following axotomy ($n = 15$).

Our preliminary data suggest that the excitability changes of peripheral motor axons in symptomatic G127X SOD1 mutant mice are secondary to the process of axonal degeneration. Thus, at least in some ALS variants, the excitability abnormalities do not reflect the disease-specific axonal involvement.

O46

The epidemiology of MND in the Netherlands, 2006–2008

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Objectives: Determining the epidemiology and spatial distribution of motor neurone disease (MND) in the Netherlands

Methods: In a nationwide population based study, we have collected data from patients diagnosed with amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS) or progressive spinal muscular atrophy (PSMA) according to the El Escorial criteria. Cases were ascertained from five sources. These include: (1) the Dutch ALS center, (2) neurologists, (3) consultants in rehabilitation medicine, (4) the Dutch Neuromuscular Patient Association and (5) patients were able to register at a website.

Incidence was measured from 1 January 2006 to 30 June 2008. Prevalence was measured at 31 December in 2006 and 2007. A capture-recapture analysis was performed to correct incidence rates for the estimated number of missing patients. Spatial distribution of all incident patients was tested for clustering.

Results: According to the preliminary results, the crude incidence of MND in the Netherlands was 1.82 and 1.66 per 100,000 person-years in respectively 2006 and 2007. The crude prevalence at 31 December was 4.43 and 4.70 per 100,000 persons for respectively 2006 and 2007. The peak incidence for both male and female was between 60 and 75 years. The male:female incidence ratio was 1.31:1.

Capture-recapture analysis shows a total coverage of 90.7% for all sources combined. This results in an estimated incidence of 2.0 per 100,000 person-years in 2006.

Analyzing the 2006 incident cases we found two significant clusters in the Netherlands, one with a relative risk of 3.1 (radius 14 kilometers, p value 0.015) and one with a relative risk of 1.8 (radius 27 kilometers, p value 0.034).

At the 19th meeting of the European Neurological Society the epidemiologic results and the results of the capture-recapture and cluster analyses for the whole study period will be presented.

Conclusion: We report the epidemiology of MND in the largest study group described until now. The incidence and prevalence is comparable to other population based studies in western countries. Two significant clusters were detected which need further investigation and may provide clues to the etiology of MND.

O47

Prognostic markers in amyotrophic lateral sclerosis: proteome analysis of cerebrospinal fluid

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Objectives: We aimed to identify biomarkers of disease-progression in amyotrophic lateral sclerosis (ALS). ALS is the most common form of motor neuron disease. Though in most patients the disease takes a fatal course within about 2 years, the progression of disease can be much slower in some patients. Cerebrospinal fluid (CSF) is a promising source for biomarkers of disease progression in ALS since the CSF compartment is in close anatomical contact with the brain interstitial fluid, where biochemical changes related to the disease are reflected.

Methods: We used the two-dimensional difference in gel electrophoresis (2-D-DIGE) to compare CSF samples from patients with ALS that showed a rapid progression of disease over follow-up of 2 years in a prospective study (ALS-rp, $n = 9$) with ALS that showed a slow progression over follow-up (ALS-sl, $n = 9$). Protein spots that showed a significant difference between the groups over three independent 2-D-DIGE gels were selected for further analysis by MALDI-TOF mass spectrometry. For validation western blot analysis was performed.

Results: Analysis of only those spots with a significant difference over all three gels between ALS-rp and ALS-sl revealed 11 spots, corresponding to 6 different proteins and their isoforms, which were all upregulated in ALS-rp as compared to ALS-sl (heat shock protein1, α-1 antitrypsin,, α-2-HS-glycoprotein precursor, transferrin, transthyretin, nebulin-related anchoring protein).

Conclusions: A-2-HS-glycoprotein and nebulin have not been implemented in ALS pathology so far. In contrast, several other proteins (transferrin, transthyretin) seem to be unspecifically affected in different neurological diseases and may therefore be of limited

value as disease-related biochemical markers in ALS. Though the pathophysiological role of the above mentioned proteins still remains to be further elucidated, our findings may have a relevant impact on the identification of biomarkers of disease progression in ALS.

O48

Treatment with a soluble activin receptor type llB attenuates loss of lean tissue and grip strength in SODG93A mice

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Objective: Amyotrophic lateral sclerosis (ALS) is a motor neuron disease which results in the loss of neurons responsible for coordinating voluntary muscle control. Muscles become progressively weaker and atrophy as motor neurons are lost. SODG93A mice express the mutant human Cu/Zn superoxide dismutase gene and display progressive muscle weakness, muscle atrophy and paralysis, similar to ALS patients. Activin receptor type llB (ActRIIB) mediates the effects of TGF β family members that negatively regulate muscle mass. We have previously shown that ActRIIB inhibition by administration of a soluble ActRIIB receptor comprised of a form of the ActRIIB extracellular region fused to an IgG Fc domain (RAP-031) results in dramatically increased muscle mass and muscle strength. This study evaluates the potential beneficial effects of ActRIIB inhibition on muscle mass and strength in late-stage SODG93A mice.

Methods: 93-day old SODG93A mice were divided into male and female groups and received either vehicle or RAP-031 weekly for 4 weeks. Forelimb grip strength and body composition were measured at baseline and study end.

Results: At study completion, RAP-031 treated groups had significantly higher body weights compared to their respective vehicle control groups. Body composition measurements demonstrated that the body weight differences between RAP-031 and control cohorts was attributable to differences in lean mass. Over the course of the study, the male vehicle group lost lean tissue mass (−5.9%) whereas the male RAP-031 group gained lean tissue mass (+9.2%). While the female vehicle mice did not lose significant lean mass (−0.75%), the female RAP-031 group gained lean tissue mass (+11%). To determine if the increased lean tissue mass provided functional benefit to SODG93A mice, we assessed forelimb grip strength. Between baseline and study end, the male vehicle control group lost significantly more grip strength (−34.9%) compared to the male RAP-031 treated group (−12.9%). The female vehicle control group also lost significantly more grip strength (−30.8%) compared to the female RAP-031 treated group (−9.4%).

Conclusions: These data demonstrate that RAP-031 increases body weight, lean tissue mass, and improves grip strength in late-stage SODG93A mice and could therefore provide clinical benefit to ALS patients.

This work was fully supported by Acceleron Pharma.

O49

Neural stem cells derived from genetically engineered, lineage-selectable ES cells improves the phenotype of a mouse model of spinal muscular atrophy

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Currently, spinal muscular atrophy (SMA), a motor neuron disease and one of the most common genetic causes of infant mortality, has no cure. Stem cell transplantation is a potential yet undeveloped therapeutic strategy for SMA. We recently reported that primary neural stem cell (NSC) transplantation can ameliorate the disease phenotype in a mouse model of SMA.

Here, we investigate the therapeutic potential of NSCs derived from a genetically engineered murine embryonic stem cells (ES) lineage (sox2-ßgeo/oct4-tk ES cells, OSG cells). By treating the doubly targeted ESCs with both gancyclovir and G418, undifferentiated ESCs could be selected against (increasing their safety) and neuroepithelial cells could be selected for, to promote neuronal differentiation. We differentiate OSG cells into NSCs cells that are positive for neural stem marker with a two fold higher efficiency than wild-type ES cells. Indeed OSG-NSCs can be differentiated by exposure to a growth factors cocktail (priming) followed by Retinoic-acid and Sonic-Hedgehog into motorneurons that can generate neuromuscular junctions in myotubes co-culture.

Then, we transplanted the OSG-NSCs, after priming, intratechally in SMA mice. Intrathecally grafted NSCs migrated into the SMA parenchyma and generated a small proportion of motor neurons. Treated SMA mice had improved neuromuscular function, increased life span (21 vs. 13 days, $p < 0.00001$) and ameliorated motor unit pathology. Any side effect such as teratoma formation was observed. To define the molecular mechanisms through which OSG-NSCs may ameliorate the SMA phenotype, we analyzed by ELISA the levels of neurotrophins demonstrating that these cells secreted significant amounts of GDNF, BDNF and VEGF.

OSG-NSC transplantation improves the SMA disease phenotype, suggesting that genetic modification may also be useful for producing human stem cells for cell mediated therapy.

Oral session 6

Clinical neurophysiology 1

O50

Periodic epileptiform discharges: prognostic implications

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Introduction: Periodic lateralized epileptiform discharges (PLEDs) are an abnormal finding on electroencephalograms (EEGs) of uncertain significance. While many studies have indicated that PLEDs are associated with a poor prognosis, little attention has focused on determining the factors that are involved in the clinical outcome. Objective: We retrospectively analyzed the outcome of patients diagnosed with PLEDs over a 7 year period.

Methods: We abstracted and tabulated clinical parameters from the time of EEG recording, imaging findings, EEG measurements, and subsequent clinical outcome from the medical records. We used descriptive, inferential and logistic regression analysis to determine the factors associated with clinical outcome in patients diagnosed with PLEDs.

Results: Of the 162 patients diagnosed with PLEDs, we obtained complete clinical, neuroimaging, neurophysiologic and long-term outcome data in 118 patients. In the subgroup of patients with PLEDs, absence of seizures at onset (OR 0.21/point (CIs: 0.04–0.97)) and an acute etiology for the PLEDs (OR 0.14/ point (CIs: 0.03–0.72)) were associated with death. A non-neoplastic cause for the PLEDs was associated with independence functionality (OR: 0.45/point (CIs: 0.3–0.67)).

Conclusion: In patients with PLEDs, absence of seizures at the time of detection and presumed acute etiology are associated with death whereas a non-neoplastic etiology was associated with a good clinical outcome.

O51

Low resolution electromagnetic tomography (e/sLORETA) study in patients with migraine

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Objective: On the basis of differences in clinical features and therapeutic response, it has been suggested that migraine with aura and without aura might be consequence a different underlying mechanisms. The aim of the present study was to search for differences in EEG background activity between patients with migraine and controls, and between migraine with and without aura using e/sLORETA (exact/standard Low Resolution Tomography).

Method: Eighteen patients with migraine (with no MRI lesions) were studied. Ten patients had aura (age 38.6 ± 8.6; 9 F), 8 no aura (age 38.6 ± 14; 6 F). Five minutes of resting 29-channels EEG, with closed eyes were recorded in the attack-free period. Data underwent e/sLORETA analysis and compared with those from a migraine-free control group with similar gender and age distribution (10 subjects) for the following frequency bands: Delta (1–3 Hz), Theta (4–7 Hz), A (8–12 Hz), B1 (13–18 Hz), B2 (19–21 Hz) and B 3 (22–30 Hz).

Results: Compared with controls, patients with migraine without aura showed increased current source density in frontal and limbic regions (bilaterally) for Delta and Theta. Patients with aura showed increased current source density in temporal and limbic regions for B1 (bilaterally) and B 2 (Right hemisphere) bands. Comparison between the two migraine subgroups showed increased activity in the right Anterior Cingulate cortex in patients without aura.

Conclusions: These preliminary findings suggest possible different mechanisms underlying migraine with and without aura. A key role of the ACC dysfunctions in patients without aura and of the limbic and temporal regions in those with aura might be hypothesized.

O52

Reduced short latency afferent inhibition in severe brain injury patients with impaired consciousness

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Objectives: Peripheral nerve inputs may have an inhibitory effect on motor cortex at short intervals (short latency afferent inhibition, SAI), thought to reflect cholinergic cortical modulation. SAI can be tested by coupling electrical stimulation of the peripheral nerve with transcranial magnetic stimulation (TMS) of the motor cortex. In our study, we evaluated SAI in patients with impaired consciousness due to severe brain injury.

Methods: Seven patients (7 male, mean 45 years, range 23–76) and nine healthy subjects (mean 32 years, range 23–59) were recruited. Patients had chronic brain injury (mean interval after injury 6 months, range 1–12) of traumatic ($n = 5$) and non-traumatic ($n = 2$) aetiology and met the criteria defining vegetative ($n = 2$) or minimally consciousness state ($n = 5$). SAI of the motor cortex was studied using a paired-pulse stimulation technique: conditioning electrical stimuli were applied to the median nerve at the wrist; test TMS stimuli were applied to the motor cortex. Interstimulus intervals (ISI) were determined relative to the latency of the N20 component of the somatosensory evoked potentials. We investigated ISIs minus 2 ms and plus 14 ms of the obtained N20 component latency (in steps of 2 ms). The amplitude of the conditioned motor evoked potentials (MEP) was expressed as the percentage of the amplitude of the unconditioned MEP.

Results: In one vegetative patient neither sensory nor MEPs could be elicited. In healthy subjects the most prominent SAI was observed at the ISI of N20 plus 2 ms ($p = 0.0015$, paired t test). In patients no inhibition was observed at this ISI compared with controls (mean 120 ± 19 vs. 55 ± 26% of the test size; $p = 0.029$, unpaired t test). Patients also tended to have a high resting motor threshold and less pronounced inhibition at other ISIs, but these differences were not significant.

Conclusion: The assessment of motor cortical excitability in vegetative and minimally conscious patients may offer a better understanding of their underlying disordered cortical excitability. Our preliminary findings suggest that SAI of the motor cortex, a putative marker of cholinergic cortical activity, is significantly reduced in patients suffering from chronic disorders of consciousness.

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O53

Dominance effect on the degree of overlap of hand muscle cortical representations in right and left handers: a TMS study

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Objectives: To investigate the effect of hemispheric dominance on the degree of overlap of cortical representation of three upper limb muscles in right and left handers.

Methods: Motor cortical mapping using focal TMS, with simultaneous recording of three upper limb muscles (abductor pollicis brevis–APB; abductor digiti minimi–ADM; extensor carpi radialis–ECR) was performed in 15 right-handed volunteers (RH) (8 males, age 26.43 ± 3.6 years) and 7 left-handed volunteers (LH) (4 males, age 26.14 ± 3.18 years). The number of responsive sites were determined for each muscle and the degree of overlap was expressed as the ratio between the global area covered by the three maps and the mean of their sum in both groups. Upper limb dexterity was measured using Nine Hole Peg Test (NHPT).

Results: The dominant hemisphere had a higher representation compared to the non-dominant concerning map area both in RH ($p = 0.007$; Paired t test) and LH ($p = 0.04$; paired t test) even if the inter-hemispheric difference was smaller in LH compared with RH ($p = 0.005$; ANOVA). When map representations of the three muscles were superimposed, a significantly larger degree of overlap (1.18 ± 0.15 vs. 1.30 ± 0.18) was present for the dominant side compared to the non dominant one in RH ($p = 0.03$; Paired t test) but not in LH. At NHPT, the dominant hand performed significantly better than the non-dominant one in RH ($p = 0.002$; paired t test) but not in LH. In RH, but not in LH, the degree of overlap of the non dominant hemisphere was correlated to NHPT performance ($r = 0.6$, $p = 0.03$; Pearson correlation).

Conclusions: Our finding of higher motor cortical representation in the dominant compared with the non-dominant hemisphere in both groups, consistent with previous neuroimaging and TMS mapping studies, may be determined by plastic changes related to a preferred use of the dominant hand, or may develop early during ontogenesis. The lack, in LH, of significant asymmetries both in cortical hand representation and in the degree of overlap, to be confirmed by larger studies, is consistent with previous neuroimaging and neurophysiological evidence, and may be explained by a less strict hand preference in everyday activities. The higher degree of overlap in the dominant hemisphere in RH could be related to a more frequent simultaneous use of the three muscles in skilled hand movements.

O54

Simple, choice and go/nogo reaction time tasks: a feasibility study of simultaneous event-related potentials and functional magnetic resonance imaging

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Objectives: EEG monitoring during functional magnetic resonance imaging (fMRI) experiments is increasingly applied for studying physiological and pathological brain function. However, the large EEG artefacts induced by the magnetic fields sometimes preclude simultaneous EEG and fMRI recordings, restricting study design. Here, we demonstrate the feasibility of recording event-related potentials (ERPs) during fMRI using three different types of visual Reaction Time tasks and involving a small number of trials for each stimulus in a single recording session.

Methods: Nine healthy subjects performed the three different tasks using two types of visual stimuli. Subjects were instructed to press: (a) always the same response key upon appearance of both types of stimuli in the simple reaction time task (SRT); (b) always either the right or left button keys according to stimulus type in the Choice Reaction Time task (CRT); (c) the response key only upon appearance of a "Go" stimulus and withhold response upon appearance of "NoGo" stimulus in the Go/NoGo task. These different conditions, in which a same stimulus served as many response targets as response inhibition, allowed us to separate inhibition-related process from mere response-related effects. EEG data were recorded using a 32-channel system, during simultaneous echo planar gradient-echo acquisition carried out on a 1.5 Tesla scanner. Different number of processing techniques for the cancellation of fMRI environment disturbances were performed.

Results: After averaging, P1, N1, P2, N2 and P3 components were clearly identified associated to visual information processing during the different tasks. In line with previous studies, there was an enhanced N2 amplitude between Go and NoGo conditions. Significantly enhanced amplitude for NoGo–N2 component compared with SRT and CRT tasks, as well as for NoGo-P3a with respect to SRT, were also detected, which could be consistently linked to response inhibition in comparison to a simple response.

Conclusions: ERP signatures of response- and inhibition-processing could be identified, confirming previous research based on recordings outside the scanner. Our study demonstrates that ERP effects are preserved in simultaneous recording with fMRI. The simultaneous EEG/fMRI recordings approach using different cognitive tasks will significantly enhance our ability to investigate important aspects of brain function, and will reduce the time needed for evaluation in healthy subjects as well as in neurological patients.

O55

Asymmetry of interhemispheric interactions in drug-naïve asymmetric PD: a study on ipsilateral silent period to TMS

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Objectives: The aim of our study was to evaluate interhemispheric inhibition and motor overflow in patients with early and asymmetrical Parkinson disease (PD) using transcranial magnetic stimulation (TMS) and to compare the results with controls.

Methods: In a group of eight right-handed drug-naïve PD patients (5F; age mean: 66,5; UPDRS III score: 22.57 in OFF; 13,7 in ON) we evaluated the suppression of ongoing maximal voluntary EMG activity in abductor pollicis brevis (APB) induced by focal transcranial magnetic stimulation (TMS) on the ipsilateral hand motor cortex (iSP) at 90% of stimulator output. All patients had asymmetric involvement (5 worse on left side) according to symptoms and UPDRS motor scores in OFF. Each subject was studied within the same experimental session during two conditions: prior to administration of any antiparkinsonian drug (OFF) and during acute levodopa challenge (ON) with a dose of 3 mg/Kg. Motor threshold and iSP amount (% of baseline EMG) were compared with a group of 8 right-handed controls (4 F; age mean: 63.25).

Results: Motor threshold did not significantly differ between the two groups, nor between the two hemispheres in any group and between OFF and ON conditions in PD. In controls, no significant iSP differences were found between dominant and non-dominant hemispheres. While no significant differences were found between the less affected side of PD patients and normal controls, both ON and OFF drug, the most affected hand revealed a statistically significant ($p < 0.05$; T test) increase of iSP amount both OFF and ON, with no significant drug-induced changes. Moreover, in the PD group, iSP over the more affected hand was significantly greater compared with the less affected ($p < 0.05$, T test), both in ON and OFF.

Conclusions: our results revealed a different ability in interhemispheric inhibition in early, drug naïve PD patients, being the more affected hemisphere more inhibited by the contralateral, less affected hemisphere. Single, acute levodopa challenge does not seem to normalize this finding, possibly because long-term changes are required to influence non-dopaminergic circuitries responsible for iSP. Follow-up studies are needed in order to investigate long-term dopaminergic effects on ipsilateral silent period

Oral session 7

Epilepsy

O56

Oganic mental disorders (other than memory disorders, depression and psychosis) after temporal lobe epilepsy surgery

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Objectives: To review the occurrence and type of organic mental disorders (OMDs) after temporal lobe epilepsy surgery (TLES) in the literature, and to outline the structure of a pilot questionnaire for use in the evaluation of these disorders in future prospective longitudinal controlled studies.

Methods: The information for this study was extracted from a database search of the literature of the last 40 years and from a scrutiny of the reference lists of all the relevant papers. Follow-up descriptive, retrospective or prospective studies as well as case reports of adults, male or female, who underwent any resective temporal lobe procedures, with or without pre-surgical OMDs were included. No sample size restriction was applied but studies in French and English only were considered. The three main instruments used in psychiatry for the classification of OMDs (DSM-IV, ICD-10, and the Lindqvist-Malmgern scheme) and the traits identified by Bear and Fedio in patients with temporal lobe epilepsy were used to define these organic disorders.
A total of 28 studies and two conference proceedings relevant to this study were obtained.
[N. B. Depression, anxiety, psychosis and memory disturbances after TLES have been well documented and are therefore excluded from this study.]

Results: The reported cases from the literature review can be divided into eight main categories: astheno-emotional and emotional motivational blunting disorder, interictal dysphoric disorder, mood disorders, obsessive-compulsive disorders, personality disorders, behavioural disorders, sexual disturbances, suicide and suicide attempts.
A pilot questionnaire is proposed to identify the above mentioned categories in patients before and after TLES. It is intended to be administered by a psychiatrist in a face to face semi-structured interview of the patient. Each disorder will be scored separately before and after surgery. The results will then be compared within the same patient pre- and postoperatively, and in a non-operated control group based on serial prospective scores. The use of validated existing scales is referred to where necessary.

Conclusion: OMDs are rarely assessed in the course of TLES and there is a surprising dearth of cases documented in the literature, in spite of their frequent occurrence and potential importance. For the first time, eight main categories of OMDs following TLES were outlined and a pilot questionnaire to be used in the diagnosis of these disorders designed.

O57

The role of nicotinic acetylcholine receptors in nocturnal frontal lobe epilepsy: a clinical and genetic study of 22 affected families

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Objectives: Specific mutations in genes coding for the $\alpha 4$, $\beta 2$ and $\alpha 2$ subunits of the neuronal nicotinic acetylcholine receptor (nAChRs) were associated with autosomic dominant frontal lobe epilepsy (ADNFLE), a rare non lesional epileptic disorder.
The purpose of our study was to identify new families suffering from ADNFLE and, within those families, to assess range and incidence of mutations in neuronal subunits of the nAChR, which bear significant homology.

Methods: Probands from 22 unrelated families who had been referred to epileptology department of the Pitié-Salpêtrière Hospital for paroxysmal nocturnal events with familial recurrence underwent precise clinical phenotyping and complementary examination (electroencephalogram and 1,5T magnetic resonance imaging of the brain). Adopting a candidate gene approach, all probands were screened for mutations in genes coding for the 9 neuronal subunits of nAChR by direct sequencing of the genes coding sequence. New variants were tested in available family members.

Results: Eighteen out of 22 index cases had non lesional nocturnal frontal lobe epilepsy, 8 of them reported positive personal or family history for slow wave sleep arousal parasomnias (SWSAP) consistent with previous findings.
A new missens mutation, Leu290Val in the $\alpha 4$ subunit, was identified in one family. Affected kindred featured ADNFLE, and in some cases, SWSAP and mental retardation.
Further, two potential mutations, Leu17Phe in $\beta 2$ and Thr158Ala in $\alpha 2$ were found. Several new variants were present only in epileptic index cases but not in relatives with SWSAP indicating a possible digenic inheritance.

Conclusion: Mutations of nAChR subunits account only for a minority of ADNFLE. Nevertheless, some cases might be explained by a more complex inheritance. The frequent association of SWSAP with ADNFLE might point towards a possible common genetic background or shared pathological mechanisms.

O58

Thalamic hyperperfusion during nocturnal hypermotor seizures

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Introduction: Previous studies using ictal single photon emission computed tomography (iSPECT) during nocturnal frontal seizures have demonstrated increased perfusion of the anterior cingulum.
We report thalamic hyperperfusion as an iSPECT finding in two patients with nocturnal hypermotor seizures.

Methods: Two patients with nocturnal frontal lobe epilepsy (NFLE) since childhood underwent presurgical evaluation for surgical treatment of frequent pharmacoresistant sleep bound seizures. Technecium-99 m was injected intravenously during a typical major seizure arising from slow wave sleep (SWS), and a brain scan was performed the next morning. Ictal images were compared to an interictal SPECT obtained after tracer injection during the same sleep stage on a subsequent night.

Results: Patient 1: Seizures in this 36-year old started with a feeling of chest tightness and palpitations, and progressed to dystonic posturing of the head and limbs, with hypermotor activity including pedaling. Consciousness was preserved. The tracer was injected 12 s after onset of a typical seizure which lasted 82 s in total. iSPECT showed increased striatal and thalamic perfusion bilaterally, and hypoperfusion in the left frontal area. The latter corresponded to the seizure onset zone determined previously by intracranial EEG recordings. Patient 2: Seizure in this 24-year old woman were characterized by prominent oral automatisms with tongue protrusion and dystonic posturing of the arms with superimposed stereotypic movements. The patient had no recollection of the seizures. The tracer was injected 4 s after onset of a typical seizure lasting 50 s in total. iSPECT documented increased thalamic perfusion bilaterally.

Conclusion: Our results suggest a major activation of the thalamus during sleep bound hypermotor seizures. They also show that nocturnal frontal seizures can be associated with local hypoperfusion of the epileptic focus, in contrast to the ictal hyperperfusion that is generally reported.

O59

Mesial temporal lobe epilepsy in chorea-acanthocytosis

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Objectives: Although at least 40% of patients with Chorea-acanthocytosis (ChAc), a hereditary movement disorder caused by mutations in the VPS13A gene, have epileptic seizures there is very limited information about the exact type and physiopathology of the associated epileptic syndrome.

Methods: Case histories and findings of serial MR-imaging of three ChAc-patients with primary epilepsy. Review of the literature.

Results: Three male patients, of whom two were siblings, gradually developed mesial temporal lobe epilepsy at the ages of 14, 23, and 30 years, respectively. There were no movement- or psychiatric abnormalities at that time. The diagnosis ChAc was made by Chorein Western-blots after time intervals of two months, four and nine years, respectively. For the first time in this context, serial MRI-data demonstrate the gradual development of hippocampal sclerosis (HS).

Conclusions: Our findings support the notion that ChAc must be added to the spectrum of familial temporal lobe epilepsies (FTLE). The demonstration of a pathological process in associated anatomical structures strongly argues for an autochthon physiopathology and against a classification as pseudotemporal seizures. The molecular pathogenesis of an affection of the medial temporal lobe(s) in ChAc needs further clarification.

O60

Electrographic seizures and their clinical correlation in a neurological intensive care unit

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Objectives: In order to assess the need of continuous EEG monitoring in a Neurological Intensive Care Unit (NICU), we investigated in a population of critical neurological patients the frequency and characteristics of epileptic or paroxysmal electrographic activity present in standard EEG studies and its association to clinical manifestations.

Methods: We reviewed all EEGs performed in 229 patients during their recovery in a NICU over a 2 years period and investigated epileptic activity recorded, particularly the presence of electrographic seizures. We subsequently searched in medical and nursing records to determine if patients with a positive EEG had presented or not identifiable seizure manifestations in any moment of their hospitalization in the NICU or in the immediate days before. Finally, we investigated the frequency of seizure manifestations detected simultaneously during single EEG ictal recordings.

Results: Out of 229 patients, 100 patients (43,67%) presented EEGs with paroxysmal activity. From these patients, 42 (42% in the subgroup, 18,34% of the total) showed at least one EEG with a well defined electrographic seizure or a highly suggestive continuous paroxysmal activity. In 32 of these cases (76,19%) clinical seizures were documented during recovery, in 7 cases (16.66%) there was no evidence of clinical seizures and in the 3 remaining cases not reliable information could be found. The NICU team was able to report a focal seizure onset in 59.4% of cases with evident clinical manifestations. These signs were limited to the face in 15.6%. Finally, just in 12 (28.57%) of these 42 patients, seizures could be simultaneously detected while recording the EEG. The remnant 58 cases showed just interictal paroxysmal activity in their performed EEG.

Conclusions: Patients admitted in NICU may frequently present electrographic seizures without clinical correlation. Since seizures may present in the same patient alternatively with or without clinical detectable manifestations and in some cases, clinical correlation is completely absent, the "gold standard" would be that of continuous EEG monitoring, at least in selected cases. Just in this way we will be able to adequately asses the frequency of non convulsive seizures and non convulsive status epilepticus and early influence patient's clinical course in a population of critical neurological patients.

O61

A case of Brugada syndrome and epilepsy: a ion-channels unifying disease?

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Objectives: To report a case of a first generalized convulsive seizure in a patient with previous diagnosis of West Syndrome in childhood and evidence of abnormal ECG findings typical of Brugada syndrome.

Methods: Observational case report.

Results: A 23-year-old man presented with a convulsive seizure at our Emergency Department. His past medical history revealed infantile spasms, associated with EEG hypsarrhythmia and arrest of psychomotor development suggestive of West Syndrome, successfully responsive to ACTH. He had a family history of sudden death. On admission EEG showed continuous fronto-temporal spike and wave activity with a left prevalence. A brain MRI was normal except for a small T2 hyperintensity over the left parietal cortex without enhancement. A screening ECG showed ST-segment elevation in V1-V2 leads with a type 2 Brugada pattern that together with a family history of sudden death and a past undefined episode of loss of consciousness, was suggestive of Brugada Syndrome. The diagnosis was confirmed by the ECG pattern (type 1 "coved" Brugada) induced by a provocative pharmacological test with intravenous application of class Ic sodium canal blocker (flecainide 2 mg/Kg). Three days later a monocameral cardioverter defibrillation was implanted. Further genetic characterization is going on.

Conclusions: Brugada Syndrome is an autosomal dominant condition associated with sudden cardiac arrest in the setting of a structurally normal heart due to a voltage-dependent cardiac sodium channel mutation (most affecting the alfa subunit of SCN5A gene). In West syndrome a neuron hyperexcitability is induced by the mutation of a gene encoding the alfa subunit of voltage-gated sodium channel (especially SCN1A) - near the carboxy terminus-which is particularly important for fast inactivation of the channel. Our patient presented with two different clinical patterns (epilepsy and Brugada) of a possible similar underlying pathogenesis (sodium channel dysfunction). We argue that a sodium channel mutation harbours biophysical defects associated with a pleiotropic clinical manifestations on the basis of its tissue expression. Another possibility is that the mutation affects an overlapping subunit of the two channels. Our case underlines the importance of further genetic studies to reveal the relationship of these two syndromes in order to better understand their pathogenesis.

Oral session 8

Mechanisms in cerebrovascular disorders

O62

Kinetics of vasogenic oedema formation in the first three hours of ischaemic stroke

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Background: Brain edema formation is a serious complication of ischemic stroke and can lead to mechanical compression of adjacent brain structures, cerebral herniation and death. The space-occupying effect of edema furthermore impairs regional cerebral blood flow, which would be of particularly importance in the penumbra-phase of stroke.

The present work evaluates the natural course of edema formation in the hyperacute phase of focal cerebral ischemia.

Methods: Using the macrosphere embolisation technique, middle cerebral artery occlusion (MCAO) or a sham procedure was performed in rats within the MRI-scanner (in-bore occlusion). Pre- and postischemic images thus could be compared on a pixel-by-pixel base. T2-relaxation time (T2-RT), a marker for brain water content, was measured in regions of interest. Evans blue extravasation was assessed in additional animals 20 and 155 min after MCAO.

Results: A significant increase in T2-RT was detectable as early as 20–45 min after MCAO ($p < 0.05$). At this early time-point the midline-shift (MLS) amounted to 0.214 ± 0.092 cm in the MCAO- and to 0.061 ± 0.063 cm in the sham-group ($p < 0.01$). T2-RT and MLS increased linearly thereafter. Evans blue extravasation was visible in all animals indicating in increased permeability of the blood brain barrier (BBB) at 20 and 155 min.

Conclusions: Vasogenic brain edema occurs much earlier than expected following permanent MCAO and results in MLS and mechanical compression of adjacent brain structures. Since compression effects can impair regional cerebral blood flow, early edema formation might contribute significantly to infarct formation and thus represents a rewarding target for neuroprotection.

O63

The detrimental effect of T-cells in experimental stroke does not require antigen recognition and does not involve thrombus formation

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Objectives: Ischemic stroke induces local and systemic inflammatory reactions. T cells critically contribute to brain ischemia/reperfusion (I/R) injury, but the underlying molecular mechanisms are unknown. In the present study we used transgenic mice with clonal T cell receptors (TCR) and mutations in co-stimulatory molecules to define the minimal immunological requirements for T cell mediated ischemic brain damage.

Methods: Focal cerebral ischemia was induced in recombination activating gene 1 deficient (RAG1−/−) mice devoid of T and B cells, TCR transgenic mice bearing one single CD8+ (2C/RAG1, OTI/RAG1 mice) or CD4+ (OTII/RAG1, 2D2/RAG1 mice) TCR, and mice lacking essential accessory molecules of TCR stimulation (PD1−/−, B7H.1−/− mice) by transient middle cerebral artery occlusion (tMCAO). Infarct volumes and neurological deficits were assessed at day 1.

Results: RAG1−/− mice developed significantly smaller brain infarctions (18.6 ± 12.5 mm^3 versus 67.9 ± 16.7 mm^3; $p < 0.01$) and less neurological deficits ($p < 0.01$) compared to wild-type controls. In contrast to RAG1−/− mice, TCR transgenic mice or mice lacking co-stimulatory TCR signals were fully susceptible to tMCAO ($p > 0.05$). Platelet adhesion and thrombus formation after FeCl3-induced vessel injury was not impaired in RAG1−/− mice.

Conclusions: Our data confirm that T cells critically contribute to focal cerebral ischemia, but their detrimental effect does neither depend on antigen recognition nor TCR co-stimulation. Since T cells are also dispensable for thrombus formation, other mechanisms such as T cell mediated activation of the cerebral endothelium must be functional in stroke.

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O64

Study of cerebral microcirculation at rest and during vasomotor reactivity by innovative near-infrared spectroscopy

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Background: By near infrared light near–infrared-spectroscopy (NIRS) measures oxygenated (HbO2) and deoxygenated (Hbr) haemoglobin concentration and the relative Cerebral Tissue Oxygen Saturation (StcO2) of the brain that reflects cerebral function and metabolism. Infrared light can penetrate the skull of adult human, enabling investigation of cerebral microcirculation until to 3 cm of depth. Recently some authors have documented by NIRS the presence of Arterial Pulse Wave in the Cerebral Microcirculation (APWCM) caused by the heartbeat pressure pulse and correlated to the changes of cerebral blood flow (CBF) in piglets during vasomotor reactivity (VMR) test.

Objective: To study cerebral microcirculation in healthy human at rest and during VMR test by NIRS evaluating a possible correlation between the amplitude of APWCM and the mean blood flow velocity (MBFV) by Transcranial Doppler (TCD).

Material and methods: We studied 15 healthy human volunteers, 10 F and 5 M, aged 21–48 years, by TCD and NIRS (CW mode, portable, 760 and 850 nm as source, 4 cm source-detector separation, high signal/noise; by real time acquisition it's possible to detect APWCM and SctO2 of frontal, parietal, temporal and occipital lobe.

Results: At rest we found mean value StcO2 = 74% + 5,3 SD and the amplitude of APWCM = 0.48 U-NIRS + 0.05 SD in frontal, parietal, temporal and occipital lobe of the brain and the MBFV = 65 cm/s ± 5 SD in bilateral middle cerebral artery (MCA). During VMR test we found a significant correlation between the amplitude of APWCM measured on frontal lobe (C4) and MBFV in the MCA of the same side by TDC (apnea max: r 0.84 $p < 0.001$; hyperventilation for 180 s: r 0.91 $p<0.001$) and the relative changes of CBF measured by TDC from moment that recent studies report no significant variation of MCA diameter during test.

Conclusions and future work: Preliminary results suggest that innovative NIRS device can provide important information at rest and during vasomotor reactivity about cerebral microcirculation in adult human brain. Combinations of StcO2 and APWCM parameters can be use to derive other physiologically clinally interesting parameters such as the tissue metabolic rate of oxygen consumption.

O65

Exacerbation of stroke symptoms by infection and metabolic perturbations – A diffusion-weighted MRI study

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Objective/Background: Acute ischemia secondary to a thromboembolic event is the most common cause of stroke in adults. It is important to distinguish new ischemia from exacerbation of prior ischemic deficits. Conventional teaching has emphasized that acute exacerbations of prior neurological deficits may happen in conjunction with acute microbial infection or metabolic derangement. However, there is no study that has actually demonstrated this fact. To date, Diffusion-weighted Magnetic Resonance Imaging (DW-MRI) remains the most sensitive and specific marker for new ischemia.

Design/Methods: Case series.

Results: Our initial analysis included patients with history of previous strokes, who presented with acute-onset of worsening of their prior neurological deficits ($n = 33$), DW-MRI was performed on 27 patients. DW-MRI analysis in most instances ($n = 15$) did not reveal any new strokes. In these patients, infection or metabolic abnormality was concurrently noted.

Conclusions/Relevance: It is commonly believed that systemic infections exacerbate "old" stroke symptoms. Our study bolsters such an idea with evidence from DW-MRI. A history of past strokes and a concurrent infection most likely identifies a state were old symptoms are exacerbated by infection rather than a new stroke event. A larger study of this kind may yield predictive features that would help an emergency room physician or stroke neurologist distinguish new ischemia from simple worsening where emergent DWI is not available and prompt appropriate treatment.

O66

Endothelial dysfunction in CADASIL patients is worsened by the risk factor profile

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Objectives: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), caused by mutations in the 33-exon NOTCH3 gene, is characterized by recurrent strokes, severe motor disability with pseudobulbar palsy, and subcortical dementia. Endothelial alterations are observed in brain arterioles and patients show endothelial dysfunction (ED) by lengthened and delayed response to reactive hyperemia. ED, a marker and prognostic predictor in cardiovascular (CV) diseases, is associated with defective endothelial production of nitric oxide (NO) through the tetrahydrobiopterin (BH4)-dependent enzyme NO synthase. Exogenous BH4 administration improves ED in experimental and human studies. We designed a randomized, double-blind placebo-controlled, parallel-group study to determine whether chronic BH4 administration to CADASIL patients improves endothelial function, as assessed by the flow-mediated dilation (FMD) technique, ultimately reducing the occurrence of new strokes and slowing disease progression. We report here baseline FMD data of 47 patients enrolled until 2008.

Methods: Sixty consenting patients (30-60 years) with molecularly-confirmed CADASIL were randomized to receive BH4 or matching placebo for 24 months. Baseline and end-of-study tests include neurological evaluation, disability scales, brain MR imaging, plasma thiol determination, and FMD. FMD is assessed by non invasive pletismographic assessment of pulse arterial volume at the fingertips, before and after reactive hyperemia induced by occlusion of the brachial artery at the non dominant forearm level (EndoPAT Itamar Israel).

Results: Among the first 47 enrolled patients (27 M and 20 F) 11 had a history of stroke and 8 of TIA. Median age was 46 [39–52] years, Barthel index was 100 in 86%, modified Rankin scale was 0 in 74%, 1 in 21% and $\geq$2 in 5%. Median PAT score was 1.88 (1.57–2.48), 32% below the reference method cut-off value. We are currently collecting PAT data in an age- and RF-matched control population. Among CADASIL patients, despite similar age and gender distribution, PAT score was significantly lower ($p = 0.03$) in subjects with $\geq$1 RF [$n = 19$, 1.68 (1.44–1.92)] than in those with no RF [$n = 28$, 2.01 (1.77–2.60)].

Conclusion: Our findings underscore the importance of specific treatments aimed at correcting CV risk profile in CADASIL patients to improve ED.

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O67

Magnesium therapy in subarachnoid haemorrhage: a systematic review

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Objectives: Secondary ischaemia occurs in up to one third of patients with an aneurysmal subarachnoid haemorrhage (SAH) and is an important cause of death and dependency. Magnesium acts as a non-competitive antagonist of voltage dependent calcium channels, as a NMDA-receptor antagonist and has neuroprotective and vasodilatory properties. Magnesium has been shown to reduce cerebral vasospasm and infarct volume after experimental SAH. Recently, clinical trials have been performed with magnesium in patients with subarachnoid haemorrhage. The objective of this systematic review was to assess whether magnesium decreases the occurrence of secondary ischaemia and poor outcome after aneurysmal subarachnoid haemorrhage.

Methods: We sought to identify all unconfounded randomised controlled trials with magnesium in patients with aneurysmal SAH. Trials were identified in the Stroke Group Trials Register of the Cochrane Library, PUBMED and MEDLINE. Outcome measures were poor outcome (death or dependency), death, secondary ischaemia (both clinical and infarction on CT scan) and rebleeding. An estimate of the treatment effect across trials was calculated with the Mantel–Haenszel method according to the intention-to-treat principle.

Results: Four trials totalling 437 patients were included in the review. There were no losses to follow-up. All studies randomised patients for magnesium sulphate or placebo in addition to nimodipine. The overall relative risk (RR) for poor outcome was 0.74 (95% CI 0.57–0.96), for death 0.92 (95% CI 0.62–1.37), for clinical signs of secondary ischaemia 0.67 (95% CI 0.47–0.96), for infarction on CT scan 0.83 (95% CI 0.53–1.29) and for rebleeding 1.10 (95% CI 0.57–2.14).

Conclusion: Magnesium is a promising agent to prevent the occurrence of secondary ischaemia and to improve outcome in patients with SAH. Because most studies did not have poor outcome as primary outcome measure, and because of the relatively small number of patients, magnesium cannot be routinely administered in SAH patients yet. Currently 2 large phase III trials are being

conducted that will hopefully provide definite evidence whether magnesium treatment is beneficial in SAH patients.

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Oral session 9

Muscle disorders

O68

Management of myasthenic crisis: a retrospective review of 51 patients

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Objectives: Myasthenic crisis (MC) is a medical emergency requiring ICU management. The prevalence of MC is relatively high and up to 20% of myasthenic patients can experience MC episode, most often within the first 3 years from the disease onset. This study investigated clinical outcome and hospital mortality in MC patients treated with different therapeutic options.

Methods: We retrospectively analyzed all patients with MC treated at our Department from 1989 to 2008. There were 59 MC episodes in 51 myasthenic patients (16 men, 6 patients had >1 MC). In 88% of cases the first MC episode occurred within 3 years from disease onset, and 26 patients underwent thymectomy in the past. We determined the cause of MC in 36 cases: infection ($n = 22$), high-dose corticosteroids ($n = 6$), corticosteroids titering ($n = 3$), aspiration ($n = 2$), and pregnancy ($n = 3$). In 23 cases the MC was attributed to the deterioration of myasthenic symptoms.

Results: 81% of cases ($n = 48$) were extubated after a mean 10-day period (range 5–20 days). Tracheostomy was performed in 8 patients within mean period of 26 days (range: 21–29) due the necessity of prolonged artificial ventilation. There were 9 deaths including 5 patients with tracheostomy: 6 due to pulmonary complications, one due to complications of tracheostomy, one due to myocardial infarction, and one was caused by mediastinal empyema after thymectomy. The patients were treated with plasmapheresis ($n = 25$), intravenous immunoglobulin ($n = 17$), and high-dose corticosteroids i.v. ($n = 19$). Oral corticosteroids were used either from the beginning of treatment or as a continuation of i.v. treatment ($n = 40$). In 2 cases all three therapeutic methods were used, starting with plasmapheresis.

Conclusions: Despite NICU management including artificial ventilation and intensive immunotherapy the risk of early mortality in MC remains high (15%). The need for tracheostomy, complications of mechanical ventilation and age > 60 years were predictors of worse outcome.

O69

Long-term management of treatment-resistant MuSK-positive Myasthenia gravis with IgG immunoadsorption and cyclophosphamide

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MuSK-associated myasthenia gravis (MG) is characterized by severe involvement of oculobulbar muscles with relative sparing of the limbs, and frequent relapses with respiratory insufficiency. The response to immunosuppression is often inadequate. Interestingly, even though the efficacy of standard pharmacological treatments can be limited, plasmapheresis (PE) is rapidly and dramatically effective in improving bulbar dysfunction, at least for a short period of time. Therefore, MuSK-associated MG can be a therapeutic challenge in treatment-resistant patients needing frequent PE or intravenous immunoglobulins to avoid severe relapses. Long-term IgG immunoadsorption with protein A (IA) removes circulating IgG selectively from plasma without affecting other plasma components, overcoming the drawbacks of frequent large volume plasmaexchanges. To our knowledge no reports on long-term management of treatment-resistant MuSK-associated MG with IA is available in the literature. We treated three MuSK-positive patients refractory to common immunosuppressive therapies with repeated IA. Patient were submitted to a first course of 3 every other day sessions followed by maintenance treatment of one session every 4 to weeks. We evaluated clinical efficacy as well as IgG and MuSK-antibodies removal from patients' plasma; modifications of circulating cytokines (IFN-γ, TGF-β, IL-4, IL-6, IL-7, IL-10, IL-12, IL-17, IL-18) is under way. Cyclophosphamide was used in place of other immunosuppressive drugs when the ongoing treatment was considered not effective, but started after improvement related to IA was definitely recorded. All patients improved dramatically by long-term IA; the Myasthenia Gravis Foundation of America (MGFA) Postintervention Status at the end of the follow-up period was improved in one patient and pharmacologic remission in the remaining two. The time course of clinical improvement was strictly related in time with IA. 33% reduction of prednisone was recorded in one patient, while it was completely stopped in another one. The efficiency, clinical efficacy and tolerability of IA make this technique suitable for long-term management of treatment resistant patients with MuSK-associated MG; since the disease shows a worse outcome compared with MG associated with anti-acetylcholine receptor antibodies, we suggest the early application and investigation of IA to severe patients to improve their clinical course and reduce side effects from long-term steroids.

O70

Clinical evaluation of muscular dystrophies: new tools from BioEngineering

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Introduction: Muscular dystrophies (MD) are associated with loss of muscle function over time. Symptoms of respiratory insufficiency can be subtle and the routinely applied methods are not always capable to unravel early alterations.

We analysed the respiratory function (through spirometry) and the breathing pattern (through Optoelectronic Plethysmography, OEP) of a large cohort of patients affected by muscular dystrophies.

Materials and methods: 62 adult patients with MD (27 Limb-Girdle Muscular Dystrophy,LGMD, age 35.2 + 14.7 years (y); 14 Becker Muscular Dystrophy, BMD, 35.8 + 12.1 years; 21 Facio-scapulo-humeral dystrophy, FSHD, 40.5 + 18.3 years) and 20 healthy age and sex matched volunteers (Control Group, CG, age 32 + 9.2 years) were recruited.

OEP is a technique that starting from 3D coordinates of 52 reflective markers positioned on trunk from clavicles to pubis and acquired by an optoelectronic system allows to calculate ventilatory parameters, chest wall (CW) and its thoraco-abdominal compartments volume variations during breathing.

Three minutes of quiet and spontaneous breathing (QB) in the supine position and two slowed vital capacity (SVC) were performed.

Results and discussion: Spirometry data showed a mild restrictive respiratory pattern (normal FEV1/FVC but decreased VC, FVC and TLC and increased RV) in all the three pathologic groups. During QB no significant differences were found in ventilatory and CW compartments parameters between pathological groups and CG. In SVC trial, dystrophic subjects presented ventilatory parameters and breathing pattern that markedly differentiated from those calculated for healthy subjects. The most evident difference with CG was obtained for VC values (LGMD: 3.5 ± 1.3 L, BMD :4.2 ± 0.9 L, FSHD: 3.5 ± 1.1 L, CG: 4.9 ± 0.8 L), particularly evident for non ambulant patients, suggesting expiratory muscles weakness. The pattern of CW compartments of FSHD patients strikingly deviated from normality especially during the inspiration phase, where the diaphragm and the muscles of abdomen were recruited more than CG and the other pathologic groups, probably due to weakness of upper trunk muscles.
Based on OEP data, it was possible not only to evidence and quantify differences in ventilatory parameters between MD groups and healthy subjects, but also to identify a breathing pattern specific for different dystrophies and then to unravel early signs of respiratory deficiency.

O71

Myotonia permanens with neonatal onset associated with a p.Gly1306Glu mutation in the SCN4A gene

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Objectives: Myotonia permanens has been associated with a p.Gly1306Glu mutation in the SCN4A gene in a few patients and a recent novel p.Asn1297Lys of the voltage-gated sodium channel gene has been associated with a severe neonatal non-dystrophic myotonia associated with involvement of respiratory muscles, psychomotor delay, and fatal outcome in one other patient. We describe the clinical features, laboratory findings and treatment strategies in one patient with severe neonatal, painful and cold-sensitive myotonia, associated with involvement of oro-pharyngeal and respiratory muscles together with transitory episodes of flaccid paralysis.

Methods: Muscle strength assessment, EMG studies, muscle biopsy, genetic testing as well as blood tests, respiratory function tests, chest X-rays and ECG were performed.

Results: Severe and diffuse myotonia as well as muscle hypertrophy were present at birth. Involvement of respiratory muscles led to episodes of apnoea and involvement of oro-pharyngeal muscles was associated with swallowing difficulties and vomiting. EMG studies showed diffuse myotonic discharges. Mexiletine 40 mg, tid was started at 4 months of age with improvement. Dosage was increased to 100 mg tid at 3 years of age as myotonia persisted and had become increasingly painful. Contractures and skeletal deformities in the hands, neck and elbows developed. At age 17 mexiletine treatment was further increased to 400 mg tid with regular ECG monitoring. Myotonia improved until age 18 when episodes of transitory flaccid paresis became apparent. EMG studies confirmed diffuse myotonic discharges. Chest X-rays were normal. Molecular analysis ruled out Schwartz-Jampell syndrome and common mutations in the chloride channel gene and revealed a c.3917G>A mutation on exon 22 of the SCN4A gene consistent with the p.Gly1306Glu mutation associated with myotonia permanens. Acetazolamide 125 mg tid was introduced with improvement.

Conclusions: The cold-sensitive episodes of stiffness and diffuse myotonic discharges associated with transitory weakness suggested a muscle channelopathy. The neonatal onset and severity of myotonia associated with involvement of respiratory and oro-pharyngeal muscles resulting from a mutation in the SCN4A gene expands the phenotypic spectrum of sodium channelopathies and emphasizes the potential benefit of combined treatment options.

O72

Muscle gene expression profile in adult-onset patients with Pompe disease

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Objectives: The main purpose of this study was to investigate muscle gene expression in patients with late-onset Pompe disease with different morphological features.

Background: Pompe disease or glycogenosis type II (GSD II) is an autosomal recessive disorder due to deficiency of the lysosomal enzyme, α-glucosidase (GAA). The adult form is clinically heterogeneous, and may present as a slowly progressive limb-girdle syndrome with or without respiratory distress. Asymptomatic subjects can be incidentally diagnosed because of elevated creatine kinase levels. GSD II muscle biopsies showed great morphological variability ranging from a vacuolar myopathy with high glycogen content to minimal unspecific changes. So far more than 200 mutations in GAA gene have been reported but there are no clear phenotype-genotype correlations. It is conceivable that other conditions such as non-genetic factors and/or modifying genes may determine GSD II clinical pattern.

Methods: Muscle specimens from 10 GSD II patients and from 5 normal controls were studied. We divided muscle samples in two groups according to pathological features: one group (G1) characterized by a vacuolar myopathy with increased glycogen content and a second group (G2) with minimal or absent changes and no glycogen storage. Microarray experiments were performed using amplified RNA isolated from muscle specimens hybridized in a GeneChip microarrays panel of the whole human Genome containing approximately 44,000 genes.

Results: Gene expression analysis revealed an upregulation of transcripts for calcium binding proteins and myosin light-chain kinase in G1. Ion channels family was downregulated in G1, whereas voltage-gated cation channels such as potassium channel were upregulated in G2. Folding, sorting and degradation protein family genes, such as ubiquitin and proteasomes, were overexpressed in G1. Several genes, involved in the autophagic pathway, resulted also overexpressed (ATG8, LC3, FOXO3 etc.).

Conclusions: Our data support the hypothesis that additional genetic factors strictly linked to autophagy and protein catabolism pathways could play a role in the pathogenesis of GSD II.

O73

The mitochondrial disulfide relay system protein GFER is mutated in autosomal recessive myopathy with congenital cataract and COX deficiency

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A disulfide relay system (DRS) has recently been identified in the yeast IMS that consists of two essential components: the sulfhydryl

oxidase Erv1 and the redox-regulated import receptor Mia40. The DRS drives the import of these cysteine-rich proteins into the mitochondrial intermembrane space (IMS) by an oxidative folding mechanism. Erv1p is reoxidized within this system, transferring its electrons onto molecular oxygen via interaction with cytochrome c and Cytochrome c Oxidase, thereby linking the DRS to respiratory chain activity.

The role of the human homologue of Erv1, named GFER, in DRS has been poorly explored. Through a family-based approach we discovered that mutation in the GFER encoding gene causes an infantile progressive mitochondrial myopathy.

The consequence of the mutation at the patient's muscle and fibroblast levels are: (1) a reduction of mitochondrial Complex IV activity, which is restored by overexpressing the wild-type protein; (2) an impaired import of human cysteine-rich proteins, known to be imported through the DRS only in yeast, into mitochondria; (3) an abnormal mitochondrial ultrastructural morphology, with enlargement of the IMS space; (4) defective mtDNA maintenance, with accelerated time-dependent accumulation of multiple mtDNA deletions. Moreover, the Saccharomyces cerevisiae erv1R182H mutant strain reproduced the Complex IV activity defect and showed genetic instability of mtDNA and mitochondrial morphological defects.

These findings shed light on novel mechanisms of mitochondrial biogenesis and mtDNA maintenance, establish for the first time the role of ERV1 homologue in the human DRS, and promote the understanding of pathogenesis of a novel form of mitochondrial-related disease.

O74

Clinical, morphological and molecular analyses of patients with progressive external ophthalmoplegia and mitochondrial DNA mutations

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Progressive external ophthalmoplegia (PEO) may occur due to primary mitocondrial DNA (mtDNA) mutations, presenting as sporadic cases or with a maternal pattern of inheritance, or may be associated with multiple mtDNA deletions, showing a mendellian inheritance.

Objectives: Report clinical, histoenzimological and molecular findings in patients with PEO (6 multiple mtDNA deletions-group I; 17 primary mtDNA mutations-group II) and compare clinical findings between the groups.

Patients and methods: Clinical, histoenzymological and molecular findings in 23 patients with PEO (6 multiple mtDNA deletions-group I; 17 primary mtDNA mutations-group II). Results: Mean age at onset was 42.2 years (group I) and 13.4 years (group II). Five patients (group I) showed mendellian inheritance (AD-1 patient; AR-4 patients). 17 patients (group II) were sporadic cases. Most frequent clinical signs were muscle weakness, heart conduction disturbances and dysphagia. Comparison between groups showed more diffuse muscle weakness and more severe heart conduction disturbances in group II. In this group, mialgia and lower vital pulmonary capacity were frequent findings rarely referred in scientific literature. Post exercise serum lactate levels were elevated (4 patients-group I; 9 patients-group II). Electroneuromyography showed myopathic changes (1 patient-group I; 6 patients-group II); axonal neuropathy (1 patient in each group). All patients showed ragged-red fibers (RRF) in muscle, most of which were COX-negative. Some RRF with preserved COX activity were found in 1 patient of each group, and were associated with a higher proportion of RRF. Molecular analysis showed multiple mtDNA deletions (6 patients-group I), A3243G point mutation (2 patients-group II) and single deletions (15 patients-group II).

Conclusion: Although PEO with multiple mtDNA deletions or primary mtDNA mutations are clinically similar, some clinical findings were different between the groups. Defining the clinical boundaries of such disease may help to direct clinical investigation and genetic counseling.

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Oral session 10

Movement disorders and neuro-imaging

O75

MRI measurements of brainstem structures in patients with Richardson's syndrome, progressive supranuclear palsy-parkinsonism, and Parkinson's disease

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Objective: MRI measurements of brainstem structures distinguish patients with typical progressive supranuclear palsy (PSP) (PSP-Richardson's syndrome [PSP-RS]) from those with Parkinson disease (PD). PSP patients, however, can present with an atypical asymmetrical extrapyramidal syndrome and a positive response to levodopa (PSP-parkinsonism [PSP-P]). In PSP-P, an early diagnosis may be even more challenging. We investigated whether brainstem MRI measurements can differentiate patients with PSP-P from those with PD.

Methods: 20 PSP (10 PSP-RS, 10 PSP-P), 25 PD, and 24 matched healthy controls were studied. PSP were categorized as PSP-RS or PSP-P on the basis of published clinical criteria. Midbrain (M) and pons (P) areas, as well as the superior (SCP) and the middle cerebellar peduncle (MCP) widths were measured on 3D-T1 weighted images. The P area-M area ratio (P/M), the MCP width-SCP width ratio (MCP/SCP), and the MR parkinsonism index ([P/M]*[MCP/SCP]) were calculated.

Results: PSP-RS showed significantly decreased M area vs. both controls and PD ($p < 0.001$), as well as decreased SCP and MCP widths vs. PSP-P, PD, and controls (p from <0.001 to 0.05). PSP-P had a significantly decreased M area vs. controls ($p = 0.005$), while no difference was found between PSP-P and PD. P/M was significantly higher in PSP-RS and PSP-P vs. controls ($p < 0.001$) and PD ($p < 0.001$ and $p = 0.01$). PSP-RS also had a significantly higher P/M versus PSP-P ($p = 0.006$). MCP/SCP was significantly higher in PSP-RS vs. PD ($p = 0.02$). MR parkinsonism index was significantly higher in PSP-RS and PSP-P vs. controls ($p < 0.001$ and $p = 0.02$) and PD ($p < 0.001$ and $p = 0.01$). PSP-RS also had a significantly higher MR parkinsonism index versus PSP-P ($p = 0.01$). When the MR parkinsonism index was used for differentiating PSP-RS from controls and PD patients, no patient with PSP-RS received a misdiagnosis (sensitivity 100%, specificity 92%). The MR parkinsonism index distinguished PSP-P patients from controls with a sensitivity of 70% and a specificty of 80%, while an overlap of individual values among groups was found between PSP-P and PD patients.

Conclusions: Atrophy of the midbrain is a common MR feature across PSP syndromes, while SCP atrophy seems to be specific for PSP-RS. The MR parkinsonism index can contribute distinguishing PSP-RS patients from those with PD on an individual basis, while it fails to aid in the differentiation of PSP-P patients from patients with PD.

O76

Clinical and [123I] FP-CIT SPET imaging follow-up in patients with drug-induced parkinsonism

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Objective: Drug-induced parkinsonism (DIP) may develop in individuals treated with dopamine receptor blocking agents(DRBAs). DIP is clinically not easily distinguishable from Parkinson's disease because similar clinical signs may occur in both diseases. Recently we assessed [123I]FP-CIT SPET in 32 consecutive patients treated with DRBAs who had developed DIP (Tinazzi et al. Mov Disord 2008). We observed normal putamen [123I]FP-CIT SPET binding in 18 patients (Group I) and reduced in the remaining 14 (Group II).

In the present study we reassessed clinical features and DAT binding in 19 of the original 32 patients (10 of Group I and 9 of Group II) after a 19- to 39-month follow-up period and tested the effects of chronic levodopa treatment in both cohorts of patients.

Methods: A total of 19 out of 32 patients (10 out of 18 patients of Group I and 9 out of 14 patients of Group II) underwent to a clinical (UPDRS III) and SPECT-DaT Scan re-assessment.

Results: In Group I, [123I]FP-CIT SPET was still normal in all patients at follow-up; DAT binding and UPDRS motor score values did not differ from baseline.

In Group II, [123I]FP-CIT SPET was still abnormal at follow-up. Putamen DAT binding was significantly reduced and UPDRS III score higher compared to baseline.

Levodopa treatment improved motor symptoms in 3 out of 10 patients of Group I and in 8 out of 9 patients of Group II. No adverse psychiatric effects were observed in any of the patients.

Conclusion: The present study shows that DAT binding imaging may help to identify subjects with DIP secondary to a loss of dopamine nerve terminals in the context of a progressive degenerative parkinsonism. Patients with DIP may benefit from levodopa therapy, particularly when dopamine nerve terminal defects are present and this should be considered in the therapeutic management of these patients.

O77

Sensory-temporal discrimination and mental rotation of corporal objects in patients with early-onset parkinsonism, positive or negative for mutations in the Parkin gene, compared to healthy controls

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Objective: To test whether sensory temporal discrimination and mental rotation can reveal differences between patients with early-onset parkinsonism, positive or negative for mutations in the Parkin gene compared to healthy controls. Abnormalities in temporal discrimination and mental rotation have been described in various studies in primary dystonia and Parkinson's disease supporting the hypothesis of impaired sensory processing and sensorimotor integration in those disorders. So far these methods have not been applied to patients with early-onset parkinsonism and mutations in the Parkin gene.

Methods: 6 Parkin positive and 6 Parkin negative patients with early-onset parkinsonism, and 6 age matched controls were asked to discriminate whether pairs of unimodal (visual, tactile) and cross-modal (visuo-tactile) stimuli were simultaneous or sequential (temporal discrimination threshold, TDT) and which stimulus preceded the other (temporal order judgement, TOJ). In the mental rotation task subjects had to judge the laterality of hands, feet, and whether a black patch in a face covered the left or the right eye. Reaction times and accuracy were measured.

Results: Patients with mutations in the Parkin gene showed significantly higher thresholds for cross-modal TDT and TOJ, whereas Parkin negative patients were only impaired in cross-modal TOJ. Accuracy in mentally rotating feet was significantly lower in Parkin positive patients than in controls, whereas reaction times revealed no differences between the groups.

Conclusion: Since temporal discrimination of cross-modal stimuli in contrast to unimodal stimulation requires the integrity of multisensory integration in addition to temporal processing our results rather point to a dysfunction of the former than to defective timing per se. Parkin positive patients were less accurate in rotation of feet task and this and interestingly there is a higher frequency of foot dystonia in these patients. However, we did not find significant differences between patients with and without mutations in the Parkin gene, thus rather pointing to a more general deficit of sensory processing and sensorimotor integration in Parkinson's disease than to an association between the deficits and specific genes or pathological processes.

O78

The pattern of brain atrophy distinguishes progressive supranuclear palsy-parkinsonism from Richardson's syndrome

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Objective: Progressive supranuclear palsy (PSP) has been recently classified into two major clinical entities. Compared to the most common form (i.e., the classic Richardson's syndrome [PSP-RS]), the PSP-parkinsonism (PSP-P) is associated with less severe tau pathology burden, decreased PSP genetic risk, and a more favorable disease course. In this study, we investigated in vivo the regional pattern of grey (GM) and white matter (WM) atrophy in patients clinically categorized as PSP-RS and PSP-P, to determine (a) regions of common brain atrophy across PSP syndromes relative to controls, and (b) regions of atrophy specific to each clinical syndrome compared to the other.

Methods: Twenty PSP patients were diagnosed based on clinical criteria, and charts were reviewed to classify patients as PSP-RS or PSP-P. Using the Statistical Paramentric Mapping (SPM5) and the recent Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) method, voxel-based morphometry (VBM) was used to assess GM and WM atrophy in PSP patients compared to 24 age- and sex-matched healthy controls.

Results: Both PSP-RS and PSP-P comprised 10 patients each. Compared with controls, regions of GM loss across PSP syndromes were located in the brainstem, in the cerebellum, in the caudate nucleus, in the hippocampus and in the frontotemporal cortex, bilaterally. Regions of common WM atrophy were found in the midbrain, in the left superior cerebellar peduncle, in the bilateral

internal capsule, and in the left premotor and bilateral prefrontal regions. When compared to PSP-P, patients with PSP-RS showed additional regions of GM atrophy in the midbrain, in the left cerebellum, and in the bilateral dentate nucleus. PSP-RS was also associated with most significant WM atrophy in the midbrain, and in the bilateral internal capsule and frontal lobe. Compared to PSP-RS, PSP-P patients showed most significant GM atrophy in the frontal cortex, while no additional regions of WM atrophy were found.

Conclusions: The general pattern of brain atrophy associated with PSP appears remarkably consistent despite the broad spectrum of clinical features recorded in life. However, in addition to the largely overlapping atrophy patterns, anatomical differences are associated with distinct PSP clinical syndromes and may account for the early clinical differences between PSP-RS and PSP-P.

O79

Brain activation patterns during real locomotion in progressive supranuclear palsy

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Objectives: Characterization of pathological changes in the supraspinal network of locomotion in patients with progressive supranuclear palsy (PSP) during real locomotion.

Methods: 12 PSP patients and 16 age- and sex-matched healthy controls were included in the study. As a locomotion paradigm persons had to walk with a medium velocity in a basement floor providing uniform visual environment for 10 minutes. Then [18F]-Fluoro-deoxyglucose ([18F]-FDG, max. 200 MBq) was injected intravenously while the subject continued walking for further 10 min. Imaging started 30 min after tracer injection. In all participants a second [18F]-FDG scan was done under resting conditions (in lying position with eyes open). For analysis the [18F]-FDG-PET images were normalized to individual T-1 weighted high-resolution MRIs to account for atrophy effects. Imaging data at locomotion and rest were compared separately for both groups by a paired t test ($p < 0.005$, uncorrected values). Mean images of the locomotion and rest condition were statistically compared between the PSP and control group using an unpaired t-test ($p < 0.005$, uncorrected values).

Results: At locomotion relative to rest, PSP patients and controls similarly showed strong increase in glucose uptake in the vermal cerebellum, the parahippocampal and the precentral gyrus while walking. However when comparing the PSP patients and controls during locomotion a significantly higher glucose uptake was found bilaterally in the postcentral gyrus, the primary visual cortex (V1) and motion-sensitive visual area V5 and the superior temporal and inferior parietal gyri (parieto-insular vestibular cortex). Relative reduced glucose uptake in PSP patients during locomotion was seen in the anterior cingulate gyrus and the pontomesencephalic tegmentum (involving the peduncopontine nuclei). Same deactivations were present, when comparing the resting condition in PSP patients versus controls.

Conclusions: In the present study it could be shown, that PSP patients use significantly more multisensory information (visual, vestibular, perceptual) during locomotion as compared to normal persons, thereby trying to counterbalance postural instability. Dysfunction of balance and gait in PSP patients may result from disruption of supraspinal neuronal locomotion circuits at the mesencephalic level by degenerative changes of locomotor centers (e.g. pedunclo-pontine nucleus) or connections (e.g. vermal-midbrain projections).

O80

Diffusion tensor-based tractography and voxel-based morphometry in progressive supranuclear palsy

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Objective: Progressive supranuclear palsy (PSP) is a neurodegenerative disorder within the category of tauopathies. PSP is associated with midbrain and superior cerebellar peduncle (SCP) atrophy. Frontal grey matter (GM) and white matter (WM) involvement has also been described. The aim of this study was to explore the ability of diffusion tensor (DT) MRI tractography to assess the structural damage to the major cerebral and cerebellar WM pathways in PSP. We combined DT MRI findings with GM and WM volumetry data, obtained by voxel-based morphometry (VBM).

Methods: Brain conventional and DT MRI were obtained from five PSP patients (mean age: 73 years, women: 4; mean disease duration: 4.6 years; mean unified Parkinson disease rating scale III [UPDRS III]: 39.6) and 18 healthy controls (mean age: 69, women: 10). Mean diffusivity (MD), fractional anisotropy (FA), as well as parallel and radial diffusivities were measured in the normal-appearing WM of superior (SCP) and middle (MCP) cerebellar peduncles, corpus callosum, cingulum, superior longitudinal fasciculus (SLF), uncinate fasciculus, inferior longitudinal (ILF), and inferior fronto-occipital (IFO) fasciculi, using an atlas-based automated technique. Using the Statistical Parametric Mapping (SPM5), VBM was used to assess GM and WM atrophy in the same patients.

Results: Compared with controls, PSP patients had significantly higher MD, parallel diffusivity and radial diffusivity and lower FA in the SCP (p from 0.004 to 0.001). PSP patients also had higher radial diffusivity ($p = 0.04$) and lower FA ($p = 0.03$) in the CST, and higher parallel diffusivity ($p = 0.02$) and lower FA ($p = 0.03$) in the cingulum. No change was found in the MCP, corpus callosum, SLF, uncinate fasciculus, ILF and IFO. VBM results showed that patients with PSP had GM loss in the bilateral caudate nuclei, anterior cingulum, dorsolateral frontal cortex, and insula ($p < 0.001$, uncorrected). They also demonstrated a significant cluster of WM atrophy in the midbrain ($p < 0.05$, corrected for multiple comparisons).

Conclusions: This is a pilot, multiparametric MRI study which shows that modern MR techniques are able to detect in vivo the cerebral and cerebellar structural changes known to be associated with PSP.

Oral session 11

Neurorehabilitation

O81

Subcategorising the minimally conscious state based on cerebral metabolism PET studies

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Objectives: Patients in a minimally conscious state (MCS) show restricted signs of awareness but are unable to communicate consistently and reliably [1]. We here tested the hypothesis that this

heterogeneous clinical entity can be subcategorized in low-MCS (i.e., patients showing movements to command) and high-MCS (i.e., patients only showing non-reflex behavior such as visual fixation or pursuit or localization of noxious stimuli), each characterized by its own specific residual cerebral brain function.

Methods: Using FDG-PET, we assessed regional cerebral glucose metabolism (rCMRGlu) in 16 low-MCS (10 men; mean age 46 [SD 19] years; 5 traumatic) and 21 high- MCS (16 men; mean age 39 [SD 15] years; 11 traumatic). Data were preprocessed and analyzed by means of statistical parametric mapping (SPM5). Results were thresholded for significance at $p<0.05$ corrected for multiple comparisons.

Results: Compared to low-MCS, high-MCS patients showed higher rCMRGlu in Broca's and Wernicke's regions (areas 44 & 45, peak voxel *x y z* stereotaxic coordinates −42 12 4 mm; *T* value = 2.50). Other identified areas were premotor,, postcentral and precentral cortices (areas 6, 3 and 4; coordinates −8 −6 66 mm; $T = 3.62$).

Conclusion: The difference in brain metabolism between high- and low-MCS was not identified in widespread frontoparietal "consciousness areas" but in language, sensorimotor and premotor areas. These findings suggest that the main difference between these two subcategories of MCS, clinically separated by the presence of command-following, is their ability to express consciousness (verbally or non-verbally) rather than their level of consciousness per se.

Reference:

1. Giacino et al (2002) The minimally conscious state: definition and diagnostic criteria. Neurology

O82

Attitudes towards disorders of consciousness: do Europeans disentangle vegetative from minimally conscious state?

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Objectives: The vegetative state (VS) is characterized by wakefulness without awareness. In chronic VS (i.e. >1 year), medical guidelines consider treatment withdrawal (artificial nutrition and hydration; ANH) ethically justifiable. The minimally conscious state (MCS) characterizes patients with more than reflex behavior (i.e., inconsistent but clearly discernible evidence of consciousness, lack of interactive communication or functional object use). At present, there are no generally accepted standards of care for MCS patients. We here surveyed the attitudes of European doctors, paramedical professionals and non-medical professionals on end-of life decisions in these challenging patients.

Methods: A questionnaire on end-of-life issues was presented to attendees of meetings on coma and disorders of consciousness. Data were obtained from 1,739 respondents (mean age 40 ± 14 years, range 16–83; 51% women; 48% Belgian and 52% other EU citizens).

Results: 65% of all respondents considered it acceptable to stop ANH in patients in chronic VS (2% non-respondents). A significant disagreement with ANH withdrawal was expressed by religious respondents (vs. non-religious; $B = -0.454$, $p < 0.0001$) and by women (vs. men; $B = -0.364$, $p = 0.003$). There was no effect of professional background on this statement($\times 2(2,1) = 0.998$, $p = 0.607$). The vast majority (81%) of all respondents would not like to be kept alive if they themselves were in permanent VS (1% non-responders). The majority (78%) also considered that being in a permanent VS is worse than death for the patient's family (51% considered it worse than death for the patients themselves).

Twenty-nine percent of responders considered it acceptable to stop ANH in patients in chronic MCS (1% non-respondents). Religious respondents disagreed significantly more with this statement as compared to non-religious respondents ($B = -0.634$, $p < 0.000$). 67% would not like to be kept alive if they themselves were in chronic MCS (1% non-respondents). 44% considered that being in a MCS is worse than VS for the patient's family (52% considered it worse than VS for the patientS themselves).

Conclusion: The sampled European respondents report different end-of-life attitudes towards VS and MCS patients. These findings raise important ethical issues concerning our care for patients with chronic disorders of consciousness. In light of the high rates of diagnostic error in these patients, the necessity for adapted standards of care for MCS as compared to VS is warranted.

O83

Inpatient and outpatient rehabilitation in subjects with multiple sclerosis. A prospective and 6 months follow-up study

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In this study we evaluated differences in clinical and functional outcome of inpatient and outpatient rehabilitation in two different cohorts of patients with Multiple Sclerosis (MS) to detect how this treatment could impact in these outcomes after a 3 months follow-up evaluation.

We selected a group of 21 consecutive patients with both relapsing-remitting (RRMS) and secondary-progressive (SPMS) course of disease in two different region of Italy. All patients should have had worsening of their neurological condition of at least 1.0 point at Expanded Disability Status Scale (EDSS) in the last 12 months without superimposed relapses in the previous 3 months. Moreover they should be able to walk and with EDSS score between 3.5 and 6.5. A total of 9 subjects (3 RRMS, 9 SPMS) underwent to inpatient intensive rehabilitation programme in a Neurorehabilitation Dept. in Northern Italy and 12 patients (6 RRMS, 6 SPMS) followed the same programme in a outpatient clinic in Southern Italy. As outcome measure we evaluated EDSS, Barthel Index (BI), time to walk 15 feet (t15F) and 9-Hole-Peg-Test (9HPT). Both groups are similar in basal data such as age, sex, duration of disease, EDSS, BI, 9HPT; we evaluate outcome at the end of rehabilitation programme and after 3 months of follow up in which outpatient group continued its rehabilitative programme.

We found that inpatient and outpatient rehabilitation gave a significant improvement in EDSS score ($p < 0.0001$), 9HPT (right hand $p < 0.02$, left hand $p < 0.0001$), BI ($p < 0.02$) while seems to be no effective in t15F ($p = 0.09$). If we compare inpatient versus outpatient outcome, we found that first group have more significative improvement in EDSS, 9HPT and BI respect of outpatient group at the end of the intensive rehabilitation programme. This clinical benefit decrease progressively in the inpatient group in the first 3 months of follow-up. These results were confirmed at the end of the study, after 6 months.

Intensive rehabilitation seems to give a stronger beneficial effect in term of impairment and disability than the outpatient treatment; nevertheless the follow-up analysis showed that this gain is lost into few months in absence of an outpatient rehabilitative program.

O84

Post-stroke cognitive assessment and rehabilitation: a new ecological virtual reality task

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Objectives: We developed a virtual reality (VR) task for the cognitive assessment and treatment of people with focal brain lesions due to stroke. A cognitive procedure, conceived as a hierarchical serie of tasks, starting from a single-task condition and ending with successive multiple tasks, has been implemented in a virtual supermarket.
The pilot study performed was aimed at investigating the feasibility of a virtual shopping task in stroke patients and in a normative sample of healthy subjects.
Data analysis have been conducted in order to compare the two groups performances, and to identify correlations between traditional neuropsychological testing and VR test.

Methods: Twenty-one healthy subjects, aged from 50 to 72, and 10 patients aged from 50 to 86, referring to our Institute Stroke Unit, were enrolled.
We customized a virtual supermarket, developed via the NeuroVR software (http://www.neurovr.org) and displayed on a desktop monitor. With the aid of a joystick, participants were instructed to navigate around 96 aisles and to collect products. Audio announcements were used to introduce additional tasks.
The cognitive procedure was composed of two main rules that subjects had to satisfy: a primary rule (to purchase a list of four supermarket products in a pre-set order) and a secondary one (to temporarily modify the primary rule, following an audio instruction). There was an increasing difficulty in secondary rule, in relation to order and number of items to be collected. Subjects were stopped if they made more than three errors in a trial.
Patients also underwent an exhaustive traditional neuropsychological assessment.

Results: Execution times (ET), errors (E) and complexity level (CL) were collected for each trial.
Mann–Whitney *U* test showed the presence of a clear difference between patients and healthy subjects in the complexity level reached; moreover, there was a trend, even if not significant, for what trial 13 (which is the task highest difficulty level) (E) is concerned.
A correlation between trial 13 and TOL, Trial Making Test and Short Story Recall scores was also found.

Conclusions: This pilot study shows that our VR task partially highlights stroke patient difficulties, also correlating with traditional neuropsychological tests, in particular executive and frontal measures. The task developed seems to ecologically reflect complex real life situations. Further studies will investigate the feasibility of such procedure for cognitive rehabilitation purposes

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O85

Action observation and imagery conducted with stroke patients stimulate both hemispheres: the affected and non-affected

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Objectives: The application of the mirror neuron system (MNS) has extended into the field of stroke rehabilitation through mirror- or video-therapy. Current literature has demonstrated that action observation exclusively or predominantly stimulates the non-affected hemisphere [1, 2]. The aim of this study was to use the fMRI (functional magnetic imaging) to investigate whether the affected and non-affected hemispheres are stimulated to the same extent during action observation and imagery conducted in stroke patients.

Methods: fMRI in block design applying action observation or action imagery with open eyes. Stimuli consisted of object-related, simple hand actions. Eight right hemispheric and eight left hemispheric stroke patients with incomplete hand pareses participated in the study.

Results: Action observation as well as simultaneous action observation and imagery induced activation in a well known network of occipital, superior and inferior parietal and dorsolateral and ventrolateral premotor cortical areas. Cortical activation encompassed a symmetrical bilateral pattern: the affected hemispheres were stimulated to the same degree as the non-affected hemisphere.

Conclusion: This study confirms that action observation has facilitatory effects in the affected and non-affected hemispheres, respectively. Data support applicability of video-therapy in stroke patients.

1. Kimberley TJ et al (2006) Neurorehabilitation and Neural Repair 20:268–277
2. Stinear CM et al (2007) Clin Neurophysiol 118:1794–1801

Oral session 12

Clinical neurophysiology 2

O86

Autonomic innervation feature in multiple system atrophy and pure autonomic failure

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Objectives: Progressive autonomic failure (Pure Autonomic Failure or PAF) and multiple system atrophy with autonomic failure (MSA) are characterized by chronic autonomic failure. The underlying lesion site of dysautonomia is supposed to be different considering pathological data although tests of autonomic function often reported contrasting findings. Recently we reported that skin biopsy associated with microneurography were effective in detecting the underlying sudomotor lesion site in patients with generalized anhidrosis. Here we extended this approach to PAF and MSA in order to define the underlying autonomic dysfunction and to verify a different sympathetic lesion site which may contribute to differentiate these two conditions.

Methods: We have studied six patients with multiple system atrophy (MSA) and seven patients with pure autonomic failure (PAF) according to the consensus statement diagnostic criteria. Tilt-table test disclosed neurogenic orthostatic hypotension in all patients. A skin biopsy was taken to evaluate autonomic skin innervation by immunofluorescence analysis. Microneurography from the peroneal nerve was performed in all patients with the aim to analyse the skin sympathetic nerve activity (SSNA) and the muscle sympathetic nerve activity (MSNA).

Results: In patients with MSA, immunofluorescence analysis showed a normal amount of both cholinergic and adrenergic sympathetic skin nerve fibers while sympathetic activity was not recorded during microneurography evaluation suggesting a pre-ganglionic sympathetic dysfunction. In patients with PAF sympathetic skin

innervation was poor and deranged at the immunofluorescence analysis and microneurography did not disclose sympathetic activity supporting a post-ganglionic disorders.

Conclusion: Skin biopsy associated with microneurography proved reliable diagnostic tools in detecting the possible site of the autonomic dysfunction in patients with PAF and MSA. This diagnostic approach may be useful in differentiating the two conditions characterized by a different prognosis and disability.

O87

Temperature-induced electrodermal activity in patients with primary palmar hyperhidrosis

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Introduction: Electrical stimuli are commonly used for the analysis of the sudomotor activity of the hands in patients with primary palmar hyperhidrosis (PPH). However, effects of thermoalgesic stimuli have not been yet examined. We recorded the electrodermal activity (EDA) in response to slow and tonic thermal stimuli before and after thoracoscopic sympathectomy (TS).

Methods: We carried out a study in 18 PPH patients and 20 controls. We assessed a visual analogue scale for sweating (s-VAS) and for compensatory sweating (CSS). We also measured the ongoing EDA in the hands and concomitant temperature perception (t-VAS) in response to thermal stimuli given over the forearm. The EDA was analyzed according to different phases of t-VAS: pre-perception, warm, pain and post-perception phases.

Results: In patients with PPH, thresholds for warm sensation were lower, while the EDA was higher in all t-VAS-based phases in comparison with controls. After TS, both variables normalized. A period of absent sudomotor activity right after the pain-sensation phase was present in all controls, but not in PPH patients, even after TS. There was a significant positive correlation between preoperatively EDA and CSS ($r = 0.45$–0.57), but not between preoperative s-VAS and CSS ($p > 0.05$).

Conclusions: Apart from the increased sweating, patients with PPH showed a high sensitivity for warm sensation, that were both normalized after TS. However, signs of increased autonomic reactivity to temperature stimuli were not modified after the procedure. The recording of temperature-induced EDA may help in the understanding of the pathophysiological mechanisms underlying PPH.

O88

Motor cortex excitability abnormalities in patients with peripheral neuropathy before and after fatiguing test

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Objective: Fatigue, the reduced capacity of maintaining a sustained muscle effort, is a frequent complaint in peripheral neuropathies. Aiming to investigate central mechanisms of fatigue, we analysed the curve of motor cortex excitability measured with paired-pulse transcranial magnetic stimulation (TMS), before and after 2 repeated fatiguing exercise.

Methods: We selected two groups of patients with chronic sensory-motor neuropathy, either acquired (12 patients) or hereditary (16), and compared them with 12 healthy controls; all neuropathic patients experienced moderate/severe fatigue. We evaluated motor evoked potentials (MEP) latency, amplitude and motor threshold, as well as the ratio of amplitude between conditioned and unconditioned MEP (MEP/R) at different interstimulus intervals (1, 3, 15 e 20 ms). This MEP/R was considered as a marker of the intracortical inhibition, that is one of the mechanisms which modulate the motor output descending from motor cortex.

Results: The study demonstrated that normal adaptation of motor cortex to sustained effort is mediated by a hyperexcitability, expressed as a progressive reduction of intracortical inhibition after each fatiguing exercise at ISI 1 ms. Patient with hereditary neuropathies displayed similar adaptative patterns through subsequent test of fatigue, with significant increases of motor cortex excitability after effort, which differed from normal curve in that hyperexcitability was quantitatively more evident. Most striking differences were found, however, in the acquired neuropathies group, where an unexpected hyperexcitability of motor cortex was found in basal conditions, before any fatiguing test; adaptation to fatigue was characterised by a paradoxical enhancement of intracortical inhibition.

Conclusion: This study suggests that sustained motor efforts disrupt normal excitatory/inhibitory balance of motor cortex, leading to a hyperexcitability of motor system, which is also observed in hereditary neuropathies, even though at a higher excitability level as compared to controls. Notably, in patients with acquired neuropathies, motor cortex hyperexcitability is found even in basal condition, probably due to the release of an inhibitory peripheral feed-back. The exhaustion of cortical functional reserve in basal conditions could easily explain the failure of mechanisms allowing the motor cortex to compensate fatigue through the increase of motor excitability level seen in normal subjects.

O89

Increased jaw-jerk reflex excitability in early-stage ALS patients

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Objective: The Jaw-Jerk Reflex (JJR) is the trigeminal equivalent of monosynaptic myotatic reflexes in limb muscles. JJR excitability could be a sensitive method to evaluate the influence of supra-segmental structures on brainstem motor circuits. There are no previous studies of JJR in patients with amyotrophic lateral sclerosis (ALS). The aim of the present study was to describe the electrophysiological features of the JJR in patients with early-stage ALS.

Methods: We studied 21 patients with a diagnosis of definitive ALS at the early stages of the disease (<1 year of evolution)and 18 age-matched healthy controls. The JJR reflex was evoked by tapping the subject's chin at rest with a modified neurologist's reflex hammer that also triggered the oscilloscope recordings. The responses were recorded with surface electrodes placed over the masseter muscle. All subjects were stimulated 20 times, at intervals of 30 s. Average onset latency, peak to peak amplitude, as well as the percentage of occurrence of the responses, were measured in all subjects.

Results: ALS patients showed significantly increased JJR amplitudes as compared to controls {647 ± 45 uv. vs. 307 ± 36 uv.), $p < 0.05$}. No significant differences were found between groups for the persistence of JJR responses {ALS: $75.5 \pm 21.3\%$ vs. Controls: $65.5 \pm 34.2\%$) and onset latencies {ALS: 8.48 ± 1.5 ms. vs. Controls: 8.25 ± 1.3 ms}.

Conclusion: These findings demonstrate that patients with early stage ALS have a facilitated JJR. This enhancement could be explained by two reasons: (1) Increased suprasegmental excitatory influences on brainstem motor circuits. (2) Decreased cortico-bulbar inhibitory influences on brainstem motor neurons, as happen with the other myotatic reflexes. The evaluation of JJR could provide evidence of upper motor neuron involvement in ALS patients, independent of cervical spinal cord compression, which could be helpful to support ALS diagnosis.

O90
Gravity perception in cerebellar patients

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Purpose: Patients with midline cerebellar atrophy typically suffer from impaired postural balance. We asked whether this deficit is in part caused by a deficient perception of body position relative to gravity and therefore measured the subjective visual vertical (SVV) in patients with idiopathic late-onset cerebellar ataxia ($n = 11$) and age-matched controls ($n = 8$).

Methods: Using a motorized turntable, subjects were placed in different roll positions [0, 75° right ear down (RED), 75° left ear down (LED)] and aligned a luminous arrow with the perceived earth-vertical.

Results: Both SVV deviations and intra-individual SD of SVV-adjustments in all positions studied were not significantly different between patients and controls. Four patients with long-standing cerebellar ataxia and prominent cerebellar atrophy demonstrated increased SVV deviations from earth-vertical and larger SD in upright position in comparison to the average. Interestingly, three of these patients also exhibited markedly reduced VOR gains.

Conclusion: Our findings suggest that perception of verticality in patients with cerebellar ataxia may only deteriorate in a more advanced stage of the disease, whereas postural imbalance is often an early sign of the disease. To which degree the deterioration of perceived vertical is caused by a collateral vestibular impairment, needs further clarification.

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O91
Brain polarisation: effects of transcranial direct current stimulation on motor-evoked potentials in the mouse brain

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Objectives: Weak direct current stimulation (DCS) of animal brain induces long-lasting alteration of cortical excitability. Aftereffects depend on polarity, duration of stimulation and current density. A non-invasive method to apply this stimulation is transcranial DCS, or tDCS. It has been shown that tDCS is able to increase motor evoked potentials (MEP) amplitude in human brain after anodal (+) and decrease them after cathodal (−) stimulation. Moreover, tDCS has been used in preliminary studies for improving symptoms in neuropathological conditions such as depression, stroke, Alzheimer or epilepsy. So far, there are no studies of tDCS effects on MEPs in animals, such as mouse. Since mice are the most used animal model of diseases, we developed a method for stimulating the mouse brain and recording motor evoked potentials.

Methods: We measured MEP amplitude in adult C57 female mice of 2–3 months of age immediately before (T0) and after (immediately-T1, 5-T2 and 10-T3 minutes) anodal and cathodal tDCS, applying a current intensity of 250 microA for 10 min over the motor area (M1).

Results: Cathodal tDCS significantly decreased MEP amplitude by about 20% at t1 with respect to baseline. An opposite, non significant trend was observed after anodal tDCS, with MEPs increased by about 5%. All the aftereffects tended to return to baseline within the 10 minutes of post-stimulation analyzed.

Conclusions: These preliminary observations suggests that our paradigm of short-duration tDCS stimulation is able to induce rapid changes in corticospinal excitability, as demonstrated by the difference in MEP amplitude before and DCS.

Oral session 13

Multiple sclerosis: pathogenesis

O92
Replication phase of a whole-genome association study in progressive forms of multiple sclerosis

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Objectives: The clinical heterogeneity of multiple sclerosis (MS) can be partly explained by genetic factors. The aim of this study is the genetic characterization of the progressive forms of MS.

Methods: We applied a genome-wide high-density single-nucleotide polymorphism (SNP) genotyping approach (Affymetrix 500 k chip) in 197 patients affected with the less common course of primary progressive (PPMS), progressive-relapsing (PRMS) and single attack progressive (SAP) multiple sclerosis and 234 age- and sex-matched controls. We also tested the association with HLA DRB1*1501 in this group of patients.

Results: The HLA class II region was confirmed to be strongly associated with progressive forms of MS (odds ratio: 2.71, 95% CI 1.36–5.40). Moreover, additional markers in several genes, including DPP6, NRG1, have been found to be associated ($p < 10\text{-}4$) with progressive MS.
We are replicating best hits of this preliminary study on additional independent case-controls samples of progressive MS patients.

Conclusion: The selection of more clinically homogeneous phenotype at the cost of a lower sample size could represent an alternative strategy for the identification of causative genetic variants in MS.

O93

A 50 kb LD block in the CLEC16A gene is highly associated with multiple sclerosis in a German population

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Objectives: Recently, the association of several single nucleotide polymorphisms (SNPs) within the CLEC16A gene (also known as KIAA0350) with multiple sclerosis (MS), type I diabetes and primary adrenal insufficiency was described. We performed Linkage Disequilibrium (LD) mapping of this gene, aiming at narrowing down the associated region.

Methods: 603 German patients (591 with MS according to the McDonald or Poser criteria, 12 patients with clinically isolated syndrome) and 825 controls were enrolled in this study. SNP genotyping was performed on HumanHap300 and HumanCNV370-2 Whole-Genome Genotyping BeadChips (Illumina Inc, San Diego). 31 SNPs mapping to the CLEC16A gene were considered in the analysis.

Two-sided P values were calculated by logistic regression analysis. Correction for multiple comparisons was done by permutation thus implementing a Westfall-Young method controlling the family-wise error rate. Forward stepwise logistical regression was performed in order to evaluate the independence of the association.

Results: We found four significantly associated SNPs, all located in the same intron of CLEC16A. One of these SNPs, rs2041670, showed a stronger association to MS than all SNPs previously reported. We also observed an association with rs2080272. This SNP is in strong LD with rs6498169, which was found to be associated with MS in two studies. We replicated the association of rs725613 with MS, a SNP which is also associated with type I diabetes and describe an association of rs998592 with MS—a SNP in strong LD ($r2 = 1.0$) with rs12917716, which was found to be associated with primary adrenal insufficiency previously.

Conclusion: We replicated the association of CLEC16A with MS and delineated a LD block of approximately 50 kb within this gene, playing a pivotal role in susceptibility to MS and possibly other autoimmune diseases such as type 1 diabetes and primary adrenal insufficiency.

O94

CSF proteome analysis in clinically isolated syndrome: candidate markers for conversion to definite multiple sclerosis

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Objectives: In most patients who later develop multiple sclerosis (MS), the disease initially presents with an acute or subacute episode of neurological symptoms which is known as clinically isolated syndrome (CIS). Given the importance of an early treatment of MS, the clinical challenge in CIS is to predict the risk of future events that would confirm the diagnosis of definite MS. Cerebrospinal fluid (CSF) is a promising source of biomarkers in CIS that could help to identify patients at risk to develop definite MS.

Methods: Using the two-dimensional difference in gel electrophoresis (2-D-DIGE), we compared CSF samples from patients with CIS that remained CIS (CIS-CIS, $n = 8$) over a follow-up time of 2 years and from patients with CIS that developed definite MS of the relapsing-remitting subtype (CIS-RRMS, $n = 8$) over the same period. Protein spots that showed significant differences between patients and controls were selected for further analysis by MALDI-TOF mass spectrometry. For validation of identified spots ELISA experiments were performed.

Results: We identified 1 protein that was upregulated in CIS-RRMS (serin peptidase inhibitor) and 8 proteins (α-1-B-glycoprotein, Fetuin-A, apolipoprotein A4, haptoglobin, human Zinc-α-2-glycoprotein (ZAG), Retinol-binding protein, superoxide dismutase 1, transferrin) that were down-regulated in CIS-RRMS versus CIS-CIS. For Fetuin-A, our findings could be confirmed by ELISA.

Conclusion: Our study provides new CSF candidate markers of disease progression to definite MS in patients with CIS. The validity of the 2D-proteomic results could be confirmed for one of the identified proteins (Fetuin-A) using ELISA analysis. While the pathophysiological role of Fetuin A in CIS and MS is unclear, the observation of low CSF Fetuin-A in CIS-RRMS as compared to CIS-CIS is in line with findings of a previous study that observed Fetuin-A to be lower in CSF of RRMS as compared to normal controls. Consequently, Fetuin-A is a promising candidate marker for conversion of CIS to MS that warrants further evaluation on a larger cohort of patients.

O95

HLA-DRB1 and multiple sclerosis in a spanish population

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Objective: The association of the HLA class II with susceptibility to multiple sclerosis (MS) has been consistently reported although its effect on the clinical phenotype is still controversial. The objective of this study is to investigate the frequencies of the HLA-DRB1 alleles and its influence on the genetic susceptibility to MS in a Spanish population. Moreover, we study the impact of the different alleles on several clinical variables.

Methods: HLA-DRB1 typing was performed by PCR-SSP in 432 patients diagnosed of MS and 1088 unrelated healthy controls. We compared the frequency of each allele in both groups using binary logistic regression method. In addition, we studied the correlation between the more frequent alleles and age at onset, course of the disease, time to reach the progressive phase of the disease and time to extended disability status scale (EDSS) score of 3. The statistical methods used were Kaplan Meier survival analysis, chi-square, *T* test and Cox Regression as appropriate.

Results: The HLA-DRB1-15 in MS patients was the allele more frequently found and it had a statistically significant higher frequency when compared with controls (19.1% in MS patients vs. 10.1% in controls, 95%CI = 1.66–2.64, $p < 0.001$). The HLA-DRB1-03 had also a higher frequency in patients versus controls (16.2 vs. 12.5%, 95%CI = 1.07–1.70, $p = 0.012$). The frequency of HLA-DRB1-11 was lower in patients when compared with controls (8.4 vs. 12.4%, $p = 0.004$) as well as HLA-DRB1-16 (1.2 vs. 2.8%, $p = 0.022$). When analyzing the relation of the different alleles and the clinical variables we found the HLA-DRB1-13 allele

overrepresented in the primary progressive patients when comparing with the other patients (58.3 vs. 20.5%, $p = 0.005$). No other correlation was found between the alleles and age at onset or time to reach disability.

Conclusions: We found a higher incidence of HLA-DRB1-15 and DRB1-03 MS patients when comparing with unrelated healthy controls in a Spanish population. A lower frequency of HLA-DRB1-11 and DRB1-16 was identified in patients compared with controls. The HLA-DRB1-13 is overrepresented in primary progressive MS patients.

O96

Wallerian degeneration contributes to axonal damage in plaques and periplaque white matter in patients with multiple sclerosis

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Objectives: Axonal damage is a morphological substrate of permanent clinical disability in patients with multiple sclerosis. Axonal injury takes place in plaques, but it could also affect white matter. Axonal transaction within the plaques could result in Wallerian degeneration in periplaque white matter (PPWM). The aim of our study was to assess the extent of axonal damage and contribution of Wallerian degeneration to injury of PPMW in patients with multiple sclerosis.

Methods: Axonal density was quantified in 44 plaques and 40 areas of PPWM obtained during biopsy from patients with early stage of multiple sclerosis and compared to 4 patients with epilepsy. To assess axonal injury we used the antibodies against phosphorylated neurofilaments (anti-SMI-31), unphosphorylated neurofilaments (anti-SMI-32), and amyloid precursor protein (anti-APP). Wallerian degeneration was visualised using the antibody against neuropeptydy-Y1 receptor (NPY-R).

Results: The number of SMI-32-positive axons was significantly higher in both PPWM and plaques compared to control white matter. The total number of axons (Bielschowsky staining) as well as SMI-31-positive and APP-positive axons did not differ significantly between PPWM and control white matter. The number of NPY-R-positive axons was significantly higher in PPWM (median: 335/mm^2) and plaques (median: 200/mm^2) than in control white matter (median: 7/mm^2).

Conclusions: The results of our study suggest that axonal injury defined as dephoshorylation of neurofilaments has place in PPWM in early phase of multiple sclerosis and that Wallerian degeneration contributes to axonal damage in plaques and PPWM.

O97

Repetitive pertussis toxin prevents CNS autoimmune disease: expansion of regulatory T-cells

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Objective: Pertussis toxin (PTx), the major virulence factor of Bordetella pertussis, is widely used to enhance incidence and severity of experimental autoimmune encephalomyelitis (EAE), the animal model of multiple sclerosis (MS). Its adjuvant effect is mainly attributed to a facilitated migration of activated immune cells across the blood brain barrier into the central nervous system (CNS). While data indicate that certain bacterial agents may also have protective properties suppressing CNS autoimmune disease, the underlying mechanism remains elusive. In this study, we investigated the immunological effects of repetitive PTx administration in EAE-susceptible mice.

Methods: Age-matched female C57BL/6 mice were injected weekly with 300 ng PTx or control antigen intravenously for up to 6 months prior to EAE induction with MOG p35-55. T cell proliferation and differentiation in response to PTx, PHA, aCD3/aCD28 and MOG p35-55 was evaluated by H3thymidin-incorporation and ELISA, respectively. Development of CD4+CD25+ FoxP3+ regulatory T cells was evaluated by FACS.

Results: Mice exposed repetitively to PTx were largely protected from subsequent EAE induction (mean clinical score $\pm$ SEM, 1.1 ± 0.48 vs. 4.3 ± 0.44; $p = 0.0001$), despite the fact that T cell responses to non-specific stimuli had remained unchanged. EAE resistance was reflected by decreased proliferation and pro-inflammatory differentiation of myelin-specific T cells. Splenocytes isolated from these mice produced large amounts of IL-10 upon re-stimulation with PTx, but not in response to PHA, aCD3/aCD28 or MOG p35-55. Longitudinal analyses revealed that pre-exposure of mice to PTx elevated serum levels for TGF-b and IL-10 prior to disease induction. Most strikingly, repetitive PTx treatment had promoted a significant incrase in the frequency of CD4+CD25+FoxP3+ regulatory T cells.

Conclusion: Our findings indicate that repetitive PTx treatment protects mice from CNS autoimmune disease through IL-10 and TGF-b meduated expansion of CD4+CD25+FoxP3+ regulatory T cells. Ongoing studies aim to clarify the molecular mechanism by which this effect is achieved. Besides its therapeutical implication, these data suggest that encounter of the immune system with microbial agents may not only be part of the pathogenesis of CNS autoimmune disease but also of its regulation.

Oral session 14

Diagnosis and workup in cerebrovascular disorders

O98

Grading carotid artery stenosis with non-invasive imaging modalities: comparison of NASCET and ECST ratio with absolute methods of measurement

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Background: NASCET and ECST ratios are validated methods for grading carotid artery stenosis. Designed for intra-arterial angiography, they are routinely used with colour-coded duplex ultrasound (CDUS) and CT-angiography (CTA). However, they are time-consuming and not always easy to perform.
We investigate the potential interest of the absolute minimal residual lumen diameter (MRLD) and PSV (pick systolic velocity) as compared to NASCET or ECST degree of stenosis determined on CDUS and CTA.

Methods: 95 atheromatous cervical carotid stenosis (CCS) was examined in a series of 52 consecutive patients. The MRLD and the bulb and distal internal carotid artery diameters were determined on

axial plan on CDUS and CTA and NASCET and ECST ratio were calculated. We also recorded the PSV by CDUS. Pearson correlation coefficients were calculated between the absolute methods of measuring (MRLD, PSV) and NASCET, ECST ratios. Receiver operating curves (ROC) were used to determine the optimum threshold of MRLD and PSV for predicting 50% NASCET or equivalent 70% ECST stenosis.

Results: With CDUS, MRLD correlated better with ECST ($r^2 = 0.829$) than with NASCET ($r^2 = 0.792$), and PSV correlated better with ECST ($r^2 = 0.774$) than with NASCET ($r^2 = 0.617$). Conversely, with CTA, MRLD correlated better with NASCET ($r^2 = 0.888$) than with ECST ($r^2 = 0.735$). The correlations with PSV were less strong (PSV-ECST $r^2 = 0.369$; PSV-NASCET $r^2 = 0.350$). The ROC curves show that a CDUS MRLD $\leq$2.2 mm had a sensitivity of 100% and a specificity of 96% to detect a >70% ECST stenosis slightly better in this series than the PSV hemodynamic criterion (sensitivity of 91% and a specificity of 82% for PSV $\geq$110 cm/s). The CTA MRLD $\leq$2.4 mm had a sensitivity of 92% and a specificity of 99% to detect a >50% NASCET stenosis.

Conclusions: These data suggests that MRLD may be an interesting parameter to standardize grading of carotid stenosis across different non-invasive imaging techniques, and a 2.2–2.4 mm MRLD appears to be a consistent threshold to detect a potentially surgical carotid stenosis (i.e >50% NASCET and/or 70% ECST) with CDUS or CTA.

O99

Knowledge of stroke risk factors and warning signs in the older general population in north-eastern Nigeria

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Reduction in the risk of stroke and increase in the speed of hospital presentation after stroke depends on the level of knowledge of stroke in the general population. Knowledge among older people, who are most vulnerable to stroke, is particularly important.

Objective: The aim of this study was to assess baseline knowledge regarding stroke risk factors and warning signs in older urban community dwelling Nigerian adults.

Methods: A cross sectional study was carried out on a randomly selected community based older people aged 65 and above in their homes. Three hundred and thirty-eight participants responded to questions relating to their knowledge of stroke risk factors and warning, and personal risk factors for stroke.

Results: Of the overall sample, 15.3% had previously experienced a stroke or transient ischaemic neurological deficit (RIND). Eighty-nine (26.3%) correctly identified the brain as the affected organ in stroke. When asked to identify stroke risk factors from a provided list, less than a tenth identified established risk factors (e.g., smoking, hyperlipidaemia, diabetes mellitus), hypertension being the only exception (identified by 30%). Similarly, with the warning signs, less than a quarter identified established warning signs (e.g., slurred speech, headache, blurred vision and double vision or loss of vision in an eye). The most common warning sign of stroke described was weakness of one-half of the body (identified by 138 (40.8%). One hundred and eighty-nine (55.9%) respondents correctly listed $\geq$1 established stroke factor, but only 148 (43.8%) respondents correctly listed $\geq$1 warning sign. Overall, there are considerable gaps in awareness with poorest levels evident in those aged over 70, and with no formal educational attainment.

Conclusion: This study suggests that many older Nigerian adults may not recognise early symptoms of stroke in themselves or others. Thus, they may lose vital time in presenting for medical attention. Level of knowledge surely differs among the six geo-political regions of Nigeria and within sub-groups. Local evidence is needed to best address knowledge deficits. Overall, lack of public awareness about stroke warning signs and risk factors must be addressed as one important contribution to reduce mortality and morbidity from stroke.

O100

Posterior circulation stroke and ataxia: clinical-MRI correlations

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Background: Ataxia is a neurological sign which indicates a lack of coordination in the gait (gait ataxia) or in the limbs (dysmetria or limb ataxia).
Ataxia is classically attributed to cerebellar hemispheric lesions, although lesions of the cerebellar peduncles in the brainstem may also cause this sign.
The differential role of the cerebellar cortex and nuclei in causing ataxia has been examined through the semi-quantitative International Cooperative Ataxia Rating Scale (ICARS) in hemispheric cerebellar stroke patients, showing that damage in cerebellar nuclei has a more lasting effect than cerebellar cortical lesions.
However ataxia related to damage in cerebellar peduncles has not yet been evaluated by ICARS.

Aim: to study functional localization of ataxia in the cerebellar system, including both its hemispheres and peduncles, in patients with posterior circulation (PC) strokes.

Methods: Seventy-five patients with an acute PC stroke were consecutively recruited in a multicentre setting at North Eastern Italian centres over a year. Axial T2 MRI and ICARS were performed.

Results: According to the clinical and MRI data, four patterns were identified:
Pattern 1 (20 pts). Hemispheric cerebellar infarct (posterior inferior cerebellar artery $\pm$ border zone): no limb ataxia; gait ataxia was present.
Pattern 2 (13 pts). Hemispheric cerebellar infarct (superior cerebellar artery): both limb and gait ataxia were present.
Pattern 3 (10 pts). Hemispheric cerebellar infarct and brainstem infarct involving the cerebellar peduncles: both limb and gait ataxia were present.

Pattern 4 (32 pts). Brainstem infarct involving the cerebellar peduncle: both limb and gait ataxia were present.
Pattern 5 (13 pts). Brainstem or thalamic infarct sparing cerebellar pathways: neither limb nor gait ataxia were present.
Limb ataxia was more frequent and severe in Pattern 2, 3 and 4 compared to Pattern 1 ($p < 0.05$), whereas gait ataxia was equally frequent in all the patterns. Gait ataxia was significantly more severe in Pattern 3 compared to Pattern 1 ($p < 0.008$) and to Pattern 4 ($p < 0.02$).

Conclusion: These cases indicate that gait ataxia is always present when the cerebellar system is damaged, regardless the site of the lesion (cerebellar hemispheres or peduncles). Instead, it appears that limb ataxia is more often associated with a damage in cerebellar peduncles rather than in the cerebellar hemispheres.

O101

High-risk of recurrent ischaemic events among patients with deferred endovascular treatment for symptomatic intracranial disease

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Background: Since intracranial angioplasty and stent placement remains to be proven as beneficial compared to medical treatment, patients are initiated on different antithrombotic medication combinations before resorting to this option.

Objective: To evaluate the outcome of patients angiographically diagnosed with intracranial stenosis >50% in whom intracranial angioplasty and stent placement was considered, but deferred for various reasons.

Methods: All the patients presenting to two academic hospitals with symptomatic intracranial disease between 2006 and 2008 who underwent catheter angiography were indentified. Patients with complete intracranial occlusion or less than 50% stenosis were excluded ($n = 14$). Demographic and clinical information collected from chart review. Angiographic images were reviewed to quantify the degree of stenosis.

Results: 31 patients included in the study. Median age was 60.5 years (range 35–85 years); 16 were men (51.6%). 16 (51.6%) patients were on antiplatelet medications at the time of the event and two patients were also on anticoagulation. No medication change was made in 11 (68.8%) patients, while antiplatelet agent was replaced or added in 5 (31.2%) patient. Six patients (19.3%) underwent intracranial angioplasty and/or stent placement with their initial diagnostic angiogram and in 25 patients endovascular treatment was deferred with best medical treatment in the interim period. Among patients who were kept on medical management 14 (56%) were readmitted with recurrent ischemic events in the vessel of distribution within a median of 27.6 days (range 1–243 days). Recurrent event happened within 1 week in 8 (57.1%), within 1 month in 12 (85%), and after 3 months in 1 (7.1%) patients. Recurrent ischemic events were observed in all the patients with basilar artery stenosis (see table). Of the 14 patients with recurrent ischemic events, nine subsequently underwent intracranial angioplasty and stent placement (64.2%). One patient died from brainstem infarct with his recurrent event.

Conclusion: A high rate of recurrent ischemic events was observed among patients in whom endovascular treatment was deferred, particularly those with basilar artery stenosis and those with high grade stenosis. This information would be beneficial in decision making for timing of the endovascular treatment among patients with symptomatic intracranial stenosis.

O102

Validation of a comfort/discomfort scale for stroke patients

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Objectives: Quality of life (QoL) is a commonly used concept, but it is often difficult to define operational objectives from QoL assessment. A more concrete but little used concept is that of comfort and discomfort (C/D). We aimed at creating and validating a C/D scale for stroke patients.

Methods: The scale is composed of two parts. The first one assesses comfort in 14 personal activities of daily living (pADL): food intake, cleaning and dressing the upper and lower parts of the body, urinary and faeces elimination, transfers, positioning in armchair and bed, sleeping, nurse care, use of wheelchair, walking, and sexual life. The C/D level is quantified on a visual analogue scale. The second part assesses personal and environmental factors promoting C/D, especially motor deficit, fatigue, spasticity and spasms, pain, sphincter problems, visual disorders, ataxia, depression, and mis-adaptation of the environment. Two independent observers conducted two successive interviews of 30 stroke patients and one interview of a close nurse. The average patient age was 59 years and the average FIM 85.9. The C/D level of patients was compared with that of 30 healthy subjects.

Results: Patients showed significant ($p < 0.05$) discomfort for all ADL items, except sleeping. Discomfort prevailed on food intake, toileting the upper and lower parts of the body, dressing the upper part, urine elimination, installation in chair. Main factors were motor deficit, stiffness, spasticity, and balance and communication disorders. We found fair inter-observers and test-retest reproducibility for both parts of the scale. Correlations between patient and caregiver perceptions were significant for dressing, urine and faeces elimination, and transfers. Global C/D level correlated with the FIM.

Conclusion: The C/D scale showed fair sensitivity in stroke patients, good reproducibility and good external validity. Nearly two-thirds of stroke patients have discomfort in pADL, which mainly results from 'motor' disorders. The scale helps defining most adapted treatments.

O103

Predictive factors of cerebral hyperperfusion syndrome before and immediately after carotid angioplasty and stent placement: diagnostic utility of single-photon emission computed tomography and transcranial colour-coded real-time sonography study

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Objectives: The purpose of our retrospective study was to find predictors of cerebral hyperperfusion syndrome (HPS) before and immediately after carotid angioplasty and stent placement (CAS) and to investigate the utility of single-photon emission computed tomography (SPECT) and transcranial color-coded real-time sonography (TCCS) as predictors.

Methods: Included for analysis were patients (1) who underwent elective CAS from July 2005 to March 2008, (2) with unilateral carotid stenosis, (3) who underwent SPECT study, (4) who underwent acetazolamide (ACZ) challenge test of SPECT study and (5) who underwent TCCS study. Regional cerebral blood flow (rCBF) and mean blood flow velocity (mBFV) in the middle cerebral artery (MCA) was examined. Asymmetry index (AI) = (rCBF in the

hemisphere with carotid stenosis/rCBF in the contralateral hemisphere), AI change, AI ratio = (AI change/AI before CAS), regional activity-to-cerebellar activity (R/CE) ratio = (rCBF in the hemisphere with carotid stenosis/rCBF in the ipsilateral cerebellum hemisphere), R/CE ratio-change, R/CE ratio-ratio = (R/CE ratio-change)/(R/CE before CAS), cerebral vasoreactivity (CVR) = (post-ACZ rCBF resting rCBF)/resting rCBF, MCA mBFV in the affected hemisphere and MCA mBFV ratio = (mBFV after CAS in the affected hemisphere/mBFV before CAS in the affected hemisphere) were assessed.

Results: Eighty consecutive patients underwent CAS and ten of them presented HPS after CAS. Between HPS and non-HPS groups, there were significant differences in severe carotid stenosis, CVR and MCA mBFV in the affected hemisphere ($p < 0.05$, Mann–Whitney U test) in the preoperative items, and significant differences in AI after CAS, AI change, AI ratio, R/CE ratio after CAS, R/CE ratio-change, R/CE ratio-ratio and MCA mBFV ratio ($p < 0.05$, Mann–Whitney U test) in the postoperative items. Logistic regression analysis showed that CVR ($p < 0.05$) was the significant predictor among the preoperative items, and that MCA mBFV ratio ($p < 0.05$) and R/CE ratio-change ($p < 0.05$) were the significant predictors among the postoperative items.

Conclusion: Significant predictors of HPS were CVR before CAS, and MCA mBFV ratio and R/CE ratio-change immediately after CAS. SPECT and TCCS studies are useful to predict HPS.

Oral session 15

General neurology 1

O104

fMRI "resting state" brain connectivity in vegetative state: clinical application of a novel automated quantification method

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Introduction: The aim of this study is to assess fMRI resting-state cerebral connectivity in vegetative state patients by means of a user-independent method. Resting baseline (or "default mode") activity is thought to be related to awareness of the internal world (i.e., mind wandering, daydreaming, mental imagery, inner speech etc) and encompasses posterior-cingulate/precuneal, anterior cingulate/mesiofrontal and temporoparietal junction cortices.

Methods: We here present a novel clinical application for a user-independent "default mode" network analysis. Resting state data were acquired on 12 vegetative state (age range 27–87 years) and 26 healthy subjects (21–60 years). Patients' diagnosis was based on Coma Recovery-Scale assessment prior and following scanning. Data were pre-processed and analyzed using independent component analysis ICA as implemented in Brain Voyager. Connectivity studies employed 13 target regions of interest ($10 \times 10 \times 10$ mm) defined on an average "default mode" map calculated in controls. Resting state connectivity was assessed by calculating the number of functional connections within the "default mode" map for each subject. Next, student T tests compared patients to controls at the group-level ($p < 0.05$).

Results: Compared to controls, vegetative patients showed a lower total number of edges (i.e., connections; 46 ± 15 and 24 ± 9, $p = 5 \times 10^{-6}$) and less functional connections with the precuneus (9 ± 2 and 4 ± 3; $p = 7 \times 10^{-4}$). The "default mode" network shows a reduced connectivity in vegetative patients as compared with controls mainly in posterior brain areas encompassing the precuneus and posterior parietal cortices.

Conclusions: The presented connectivity ICA method permits a user-independent identification of the "default mode" network connectivity in the vegetative state. Comparison with healthy control data emphasizes the importance of precuneal and posterior parietal functional disconnections in pathological loss of consciousness.

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O105

A multi-centre retrospective cohort study of miglustat in patients with Niemann-Pick disease type C

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Background and objectives: Niemann-Pick disease type C (NP-C) is an invariably progressive, lethal neurological disorder. Clinical trial OGT-918-007 indicated that miglustat can slow disease progression in patients with NP-C. Here we present final data from a multinational, retrospective cohort study assessing neurological disease progression in patients with NP-C on miglustat therapy.

Methods: All NP-C patients prescribed miglustat in 25 selected expert centres were included. Treating physicians completed a questionnaire on patient demographics, treatment history, disease progression and general health. A disease-specific disability scale was used to evaluate ambulation, manipulation, language articulation and swallowing at diagnosis and up to 4 follow up visits. Patient disability was evaluated using individual parameter scores as well as a composite score.

Results: 66 patients were included in a main cohort (mean ± SD age: 9.7 ± 7.6 years at diagnosis, 12.8 ± 9.5 years at miglustat initiation). A subset of 19 patients was also included in a natural history cohort (mean ± SD age: 13.6 ± 5.9 years at diagnosis, 18.7 ± 8.0 years at miglustat initiation). Median (range) treatment exposures in these groups were 1.46 (0.05–4.51) years and 1.2 (0.2–3.0) years, respectively. The mean ± SD periods between diagnosis and treatment initiation were 3.1 ± 3.4 years and 4.9 ± 4.1 years, respectively. In the main cohort, mean (95%CI) scores were 0.20 (0.16, 0.24) at diagnosis and 0.41 (0.35, 0.47) at treatment start.

Similar progression occurred in the natural history cohort; mean (95%CI) scores increased from 0.18 (0.13,0.23) at diagnosis to 0.48 (0.39, 0.57) at last pre-treatment visit. After miglustat treatment, mean (95%CI) scores were 0.45 (0.38, 0.52) in the main cohort and 0.44 (0.34, 0.35) in the natural history cohort, indicating stabilization. In the main cohort, the annual progression rate from diagnosis to treatment start was +0.11 units score and then decreased to −0.01 units score per year from start of treatment to last visit. Stabilization of neurological disease progression was seen in all age groups, but was greater in older patients.

Conclusions: Consistent with previous trial data, miglustat had clinically relevant beneficial effects on neurological disease progression in patients with NP-C. Age at disease onset had a notable influence on patients' response to therapy.

This research was supported by Actelion Pharmaceuticals Ltd.

O106

Full outline of unresponsiveness (four) compared to Glasgow Coma scale assessment in coma

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Objectives: The Glasgow coma scale (GCS) [1] is currently the "gold standard" in the standardized assessment of coma. It's major shortcomings, however, of are the failure to assess the verbal component in intubated patients, the lack of visual pursuit scoring and the absence of brainstem-reflex assessments. In 2005, Wijdicks et al. proposed a new coma scale, the full outline of unresponsiveness (FOUR) [2] which consists of four components (eye, motor, brainstem, and respiration), each component having a maximal score of 4. We here validated the French version of the FOUR as compared to the GCS in coma and related disorders of consciousness.

Methods: FOUR and GCS evaluations were performed in randomized order in 176 acutely brain injured patients (days from insult to randomization <1 month). Glasgow outcome scales were obtained three months after injury ($n = 63$). FOUR and GCS scores were compared using Spearman correlation and the distribution of total scores were assessed by means of Kolmogorov-Smirnov testing. A logistic regression analysis adjusted for age and etiology of coma was performed to assess the relation between the compared scores and outcome assessment.

Results: GCS and FOUR total scores showed a significant correlation ($r = 0.807$). A Gaussian distribution was observed for the FOUR total scores distribution (KS : 1.490, $p = 0.024$) but not for the GCS total scores (KS : 1.114, $p = 0.148$). GCS' verbal component was scored 1 in 146 patients, among these 131 were intubated. FOUR total scores (corrected for age) showed superior outcome prediction at 3 months (OR: 0.83; 95% CI: 0.70–0.98, $p = 0.03$) as compared to GCS total scores (OR: 0.85; 0.95% CI: 0.70–1.03, $p = 0.09$).

Conclusions: The FOUR score tests brainstem function and does not need a verbal response, thus allowing complete testing in intubated patients (in our sample 90% of patients showing GCS V1 score were intubated). As compared to the GCS, the FOUR scale here showed a better discrimination between good (i.e., recovery of independent living) and poor neurological outcome at 3 months.

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O107

Role of ion channel autoantibodies in NK-cell antibody-dependent anti-tumour immunity in patients with paraneoplastic Lambert-Eaton syndrome

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Lambert-Eaton Myasthenic Syndrome (LEMS) is caused by antibodies against presynaptic voltage-gated calcium channels (VGCC) and can be associated with small cell lung cancer (SCLC) as paraneoplastic LEMS. Patients with paraneoplastic LEMS and anti-VGCC antibodies show a better prognosis than patients with SCLC alone. We investigated whether antibody-dependent cell mediated cytotoxicity (ADCC) is increased in patients with paraneoplastic LEMS as compared to patients with non-paraneoplastic LEMS or SCLC alone.

ADCC was measured by LDH-release after incubation of N417 (small-cell lung cancer cell line) as target cells with patient's sera and peripheral blood mononucleated cells (PBMC) as effector cells. There was no significant difference in the ADCC between the different groups (LEMS with or without SCLC, SCLC alone or controls). However, incubation in sera from patients with SCLC induced a higher proliferation on N417 as compared with patients with LEMS or healthy controls.

Our study demonstrates that there is no difference in ADCC between patients with paraneoplastic LEMS or patients with non-paraneoplastic LEMS or SCLC alone. However, higher proliferation of SCLC-cells induced by sera from patients with SCLC, but not by sera from patients with paraneoplastic or non-paraneoplastic LEMS, might explain the better prognosis of patients with paraneoplastic LEMS.

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O108

Prospective neuropsychological assessment in medicine inpatients

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Objectives: Global prevalence of dementia is increasing. Hospitalisation for a transient somatic illness may represent a privileged opportunity to firstly detect cognitive impairment (CI). The aim of the present study was to determine frequency and severity of CI, as well as clinical-demographic factors associated with moderate to severe CI.

Patients and methods: In this prospective observational study, patients between 55–85 years hospitalised on a ward of internal medicine from Jan 2007 to Jul 2008 were included. Exclusion criteria were previously known CI, any somatic illness manifestly compromising cognitive functions, inability to undertake a complete neuropsychological examination, and previous institutionalisation. Clinical and demographic variables were recorded.
Two trained neuropsychologists administered a 60-min battery of six validated neuropsychological tests evaluating domains such as memory, language, attention, executive functions, visuo-spatials abilities, anxiety, and depression. In order to minimise influence of somatic illness, the neuropsychological evaluation was performed during the 3 days preceding discharge. mini-mental state (MMS) was performed to characterise the cohort, but not for CI classification.

Results: Out of a total of 73 patients, 70 completed the neuropsychological assessment. 57.1% of patients completing assessment were men. Mean age was 73.4 years (±8 years). 32.9% of patients presented severe CI, 37.1% moderate CI, 8.6% mild CI, and 21.4% normal cognition. Compared with patients with normal cognition or mild CI, patients with moderate to severe CI were older (75.2 years ± 7.2 vs. 69.2 years ± 8.4, $p < 0.01$), had less educational years (8.0 years ± 2.4 vs. 9.7 ± 2.4, $p < 0.01$), and presented more frequently a pathological MMS after correction for age and education (median 29, range 24–30 vs. 25, 12–30, $p < 0.001$).

Combination of advanced age (≥60 years) and low education (≤10 education years) had a positive predictive value of 79.6% for moderate to severe CI.

Discussion: Moderate to severe CI is common in medicine inpatients. Age, educational level, and MMS-score may provide information for selection of patients needing a complete neuropsychological evaluation. Further studies are needed to evaluate the accuracy of CI detected shortly before hospital discharge.

O109

Natural history of Niemann-Pick disease type C in a multi-centre observational retrospective cohort study

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Background and objectives: Niemann-Pick disease type C (NP-C) is a rare and devastating genetic disorder that features invariably progressive neurological deterioration and early mortality. We present the results from an observational retrospective cohort study conducted to assess neurological disease progression in patients with NP-C.

Methods: In an international, multicentre study, physicians managing patients with NP-C in clinical practice were asked to retrospectively assess disease progression using a disease-specific disability scale at diagnosis and up to 4 follow-up visits. All patients at 7 selected expert centres were included. The disability scale evaluated four neurological domains of NP-C (ambulation; manipulation; language articulation; swallowing) on a 4- to 5-point scale, with each parameter assigned scores from 0 (best) to 1 (worst), with equal weighting. Patient disability was evaluated using individual parameter scores as well as a composite score.

Results: Fifty-seven patients were included; mean ± SD age 10.7 ± 9.6 years at diagnosis and 16.2 ± 10.6 years at last visit. The mean ± SD observation period between the first and the last visit was 5.5 ± 4.8 years. Among patients with at least 1 year of follow-up, the majority (42/49; 86%) showed deterioration during the observation period; no patient showed spontaneous improvement. Between 43/56 (77%) and 51/57 (89%) of patients had disabilities in terms of ambulation, manipulation, language articulation and/or swallowing at last visit. Mean individual parameter scores showed three to sixfold increases; mean (95%CI) disability scale composite scores were 0.15 (0.11, 0.20) at diagnosis and 0.58 (0.50, 0.66) at last visit. The overall mean (95%CI) annual progression rate in composite score was 0.11 (0.08, 0.13) units/year. Progression rates of all parameters and the composite score were consistently higher among patients with the youngest age at diagnosis.

Conclusions: The disease-specific disability scale allowed us to quantitatively assess neurological disease in patients with NP-C, identifying continuous, unbroken progression. In line with previous data, neurological disease progression was dependent on age at disease onset.

This research was supported by Actelion Pharmaceuticals Ltd.

Oral session 16

Pain and headache

O110

Prevalence of patent foramen ovale and MRI white matter lesions in migraine with aura: a cross-sectional study

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Objectives: To evaluate in consecutive patients attending our headache clinic and suffering from Migraine with Aura (MA) the prevalence of a right-left shunt (R-Ls) by Contrast Transcranial Doppler Sonography (cTCD) and of MRI white matter lesions (WML) and infarcts and to search for possible correlations between R-Ls and MRI changes, and clinical features.

Methods: From 2006 to 2008, we enrolled 129 patients who attended our headache clinic with an ICHD-II diagnosis of MA (1.2.1). 50 patients had strictly visual auras, 79 had visual and sensory aura symptoms. There were 98 females and 31 males with a mean age of 34.32 y.o (±13.22) and the mean age of onset of attacks was 18.24 (±9.316). Mean attack frequency was 2.73/month (±3.76)
All were systematically screened for R-Ls by cTCD during rest and Valsalva maneuver (VM). R-Ls were graded according to the International 4-point scale: 0: no microbubbles; 1 :< 10; 2 ≥ 10; 3 = curtain.
Brain MRI was performed in 114 of these patients (T2-weighted and fluid-attenuated, inversion-recovery (FLAIR); matrix 256 × 160; 5 mm slices)

Results: cTCD detected a R-Ls in 60 MA patients (47%), in most of them (77%) even during normal breathing. Medium to large shunts occurred in 28% of MA patients. Prevalence of R-L shunt was equal in patients with strictly visual and those with visual and sensory auras (47%). There was no correlation between grade of R-L shunt and attack frequency/type, but the age at onset of attacks tended to be lower in patients with large R-L shunts (16.18 y.o compared to 19 y.o with no shunt, $p = 0.051$)
WMLs could be detected in 25 (22%) of MA patients. Prevalence of WMLs was not increased in the presence of a R-Ls but the number of WMLs tended to be higher in patients with large shunts (Mean 2.32 vs. 0.72 in patients with no shunt. $p = 0.136$). There was no correlation between WML load and attack frequency. None of our patients had a detectable infarct on MRI, neither in the anterior nor in the posterior circulation territories.

Conclusion: We confirm the high prevalence of R-Ls in a clinical sample of MA patients. In our sample R-Ls was not correlated with disease severity nor with prevalence of white matter lesions on MRI but the number of WMLs tends to be higher in patients with large shunts. Neither WMLs nor shunt grades were correlated with disease severity. These data suggest that R-L shunts, and thus PFO, do not play a major role in migraine pathophysiology and pathogenesis.

O111

Study of cerebral microcirculation during spontaneous migraine with aura by near-infrared spectroscopy

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Background: Migraine is a very common and debilitating disorder. In 20% of cases, the migraine headache is preceded by an aura. Leao first suggested a relationship between cortical spreading depression (CSD) and migraine aura, based on the uniquely slow spread of clinical and electrophysiological events. Some human neuroimaging studies performed by positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI), have indirectly suggested that CSD underlies migraine and cerebral hypoperfusion associated with spreading depression was a result of decreased metabolic demand. Innovative near-infrared spectroscopy (NIRS) can measure cerebral tissue oxygen saturation (StcO2) and the arterial pulse wave (APW) in cerebral microcirculation that reflect cerebral function and regional cerebral blood flow. During migraine with aura some studies performed by transcranial Doppler (TCD) showed a decrease in blood flow velocities and increase of the pulsatility index (PI) suggestive of hypoperfusion of cerebral microcirculation.

Objective: To study cerebral microcirculation during spontaneous prolonged migraine aura, to compare the results with headache-free periods, to identify mechanism of migraine aura.

Patient and methods: We studied 8 subjects (3 M and 5 F, range age 12–41) by innovative continuous-wave NIRS system (portable, 760 and 850 nm as source, 4 cm source-detector separation) and TCD during spontaneous prolonged aura of migraine attacks and after 2, 4, 6 h the end of aura.

Results: During aura of migraine attack NIRS showed significant decrease of amplitude APW (35%) $p < 0.002$, and increase of StcO2 (15%) $p < 0.008$ ipsilateral to the headache pain and contralateral to the symptoms of aura compared with headache-free periods, TCD showed a significant increase of PI (38%), $p < 0.001$ and decrease of diastolic velocity in the posterior and middle cerebral artery ipsilateral to the headache pain compared with headache-free periods.
NIRS and TCD parameters normalized only after 4–6 hours the end of migraine aura.

Conclusion: These findings suggest that hypoperfusion of cerebral microcirculation associated with spreading depression during migraine aura was a result of decreased metabolic demand rather than ischemic mechanism and normalized later the end of migraine aura; the presented method is capable to evaluate relative changes of hemodynamics in the cerebral microcirculation during migraine with aura.

O112

Processing visual stimuli in cluster headache: a combined functional and tractography study at 3 T

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Objective: Morphological and functional imaging studies have indicated that a primary hypothalamic dysfunction might be at work in the pathogenesis of cluster headache (CH). However, a few neurophysiological and metabolic studies have suggested a more global dysfunction of central modulation of peripheral stimuli in these patients. Aim of this study was to define the structural and functional magnetic resonance imaging (MRI) abnormalities of the visual network in patients with CH.

Methods: Using a 3 Tesla scanner, dual-echo, diffusion tensor (DT) and functional MRI (during visual stimulation with a 2 Hz checkerboard) were acquired from 18 patients with chronic CH and 18 sex- and age-matched controls. Using DT MRI tractography, probability maps for the major brain white matter (WM) fiber bundles were constructed from controls and applied to patients' data to calculate mean diffusivity (MD) and fractional anisotropy (FA) values. FMRI data were analysed using SPM2 software.

Results: No difference was found for any of the WM fiber bundles metrics analyzed between controls and CH patients. Compared to controls, CH patients showed a decreased activation of the right (R) middle occipital gyrus, the R dorsolateral prefrontal cortex (DLPFC) as well as an increased deactivation of the R postcentral gyrus ($p < 0.05$, corrected for multiple comparisons) (Figure). No correlation was found between fMRI changes and patients' clinical characteristics.

Conclusions: A central dysregulation of top-down modulation of antinociceptive system occurs in CH patients, as shown by the abnormal recruitment of the DLPFC and postcentral gyrus. Such an dysfunction tends to involve also other systems, including the visual one, and does not have corresponding structural abnormalities, measured using DT MRI. The lack of a correlation between fMRI changes and patients' clinical characteristics suggest that they might reflect congenital abnormalities.

O113

Epicrania fugax: six new cases and therapeutic results

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Objectives: Epicrania fugax (EF) is a novel syndrome recently proposed by Pareja et al in 10 patients presenting with ultrabrief shooting pain paroxysms, starting in posterior cephalic regions and spreading forward to the ipsilateral eye. The pain may be accompanied by ipsilateral lacrimation, rhinorrhoea or conjunctival injection. Painful episodes can be triggered by touching the trigger zone, and a slight painful sensation may remain in the stemming point. The number of paroxysms ranges between two attacks per month and countless attacks per day. In the first series anaesthetic blockades and carbamazepine were effective in two patients with frequent attacks. We report six new cases in which we have evaluated the therapeutic effects of several drugs.

Methods: Since the first description of EF in March 2008, six patients with this clinical picture have been attended at the neurology outpatient offices of our two centres. Four were female and two male. Mean age at onset was 56 years (SD: 19, range: 31–83).

Results: Cranial computed tomography or magnetic resonance Imaging were performed in all cases and did not show any abnormalities. Blood tests, including erythrocyte sedimentation rate, were also normal. No trigger was identified in any of our patients, while two of them suffered mild pain in the stemming area between the attacks. Apart from a stressful event in one patient, no particular event or trauma could be related to the onset of pain. One patient had a previous history of migraine without aura, but no relationship was described between both headaches. Interictal pain was responsive to acetaminophen. In two cases a preventive therapy was considered in order to avoid the paroxysms, and a third

patient received topiramate as a preventive of concurrent migraine. Gabapentin at a dose of 800 mg tid achieved a complete resolution of pain paroxysms in one patient. In the other patients gabapentin, amitriptyline and topiramate did not provide relief.

Conclusion: This description reinforces the proposal of EF as a new headache variant or a new headache syndrome. So far anaesthetic blockades, carbamazepine and gabapentin have been helpful for individual patients. Further observations and further therapeutic trials are needed.

O114

Clinical and somatosensory characteristics of pain in chemotherapy-induced neuropathy

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Chemotherapy-induced neuropathy (CIN) is a common negative side effect of antineoplastic therapies. Besides sensory loss, patients often report disabling pain. The range, however, of reported pain and clinical characteristics is wide: whereas some patients present with symptoms of neuropathic pain, others report exclusively exercise-induced pain which in combination with painful trigger points indicates myofascial pain. Based on the grading scheme for the assessment of neuropathic pain and clinical criteria we aimed at finding out sensory characteristics and mechanisms behind these pains using quantitative sensory testing (QST) and nerve conduction studies.

108 patients (f: 74; m: 34, mean age 57 years) with pain and/or neuropathy after antineoplastic chemotherapy were consecutively included. According to their pain characteristics patients were assigned to one of the following groups: no pain ($n = 66$), neuropathic ($n = 27$) and myofascial pain ($n = 15$). Patients with characteristics of both neuropathic and myofascial pain were excluded ($n = 20$). Clinical symptoms and signs were verified by nerve conduction studies of the right sural nerve. QST was performed on the right foot. It comprises 13 parameters including thermal and mechanical detection and pain thresholds, unmasks large- and small-fiber dysfunction and can detect hypo- as well as hyperphenomena (thermal or mechanical hyperalgesia). Additionally, questionnaires (HADS, McGill) were assessed. Statistical analyses comprised RM-ANOVAs.

Pain patients had higher anxiety (HADS: 8.3 vs. 6.4, $p < 0.05$) but not depression scores. There was no significant difference between the neuropathic and the myofascial pain group in respect of anxiety, depression and pain characteristics (McGill). Whereas nerve conduction studies indicated comparable sensory affection in all groups, QST detected an increased sensitivity for mechanical pain in the myofascial compared to the neuropathic pain group (z-score: +0.95 vs. -0.37, $p < 0.01$). All other QST parameters did not differ significantly between groups.

Although pain intensity is similar in both pain groups, different somatosensory characteristics may indicate different underlying pathophysiological mechanisms in these groups. The increased sensitivity for mechanical stimuli points to central sensitization as a somatosensory characteristic associated with myofascial pain. Our data encourage a careful diagnostic approach in pain patients which might allow a more stratified therapy.

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O115

Chronic pelvic pain due to pudendal and pelvic plexus neuropathy as neurological sequelae of anorectal surgery

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Objectives: Prevalence of pelvic postoperative Pudendal and Pelvic Plexus Neuropathy (PPPN) is not known.
While advances in minimally invasive technique in ano-rectal surgery (ARS) have recently gained world-wide success, the occurrence of proctological (fecal incontinence, obstructed defecation), urological (urinary urgency, incontinence), sexual post-surgical dysfunctions and chronic pelvic pain as well as neurological sequelae remain high.
Moreover pts who undergo subsequently pelvic surgery, with previously radiotherapy, known neurological disease or sacral/pelvic trauma are at major risk to develop a complication after ARS.
New attainment of neurophysiology and neuroanatomy of perineal and pelvic area, play essential role in avoiding and reducing co-morbidity.

Methods: From 2001 to 2008, 431 pts (244 female, 187 male, mean age 46,7 years) were addressed to our neurophysiology laboratory and underwent a thorough neurophysiological evaluation of pelvic floor to a suspected neurogenic chronic pelvic pain (CPP): for 299 pts (69.37%) CPP was the major post-ARS complaint.
Somatosensory evoked potentials of pudendal nerves (SEPs), sacral reflexes (SR), ElectroNeuroGraphy of Pudendal nerves (ENG), ElectroMyoGraphy of perineal muscles (EMG), sympathetic skin response (SSR), were assessed together with Visual Analogical Scale, McGill Pain Questionnaire and clinical evaluation.

Results: PPPN were found in 96% of pts as a sequelae of ARS, in 32 pts a Stapled Transanal Rectal Resection (STARR) was previouysly performed. PPPN was responsible for CPP, defecatory urgency, hypertonic perianal muscle contraction and hypersensitivity of perineal area.
Neurophysiological alterations showed a monolateral PPPN in 85% of pts, SEPs were pathological in 62%, EMG in 89%, ENG in 85%, RS in 75%, SSR in 92%.
Neurophysiological assessment was more sensitive rather than scores and clinical evaluation in revealing the pathophysiology of CPP.

Conclusions: Neurophysiological assessment of the pelvic floor is able to clarify the pathophysiology of post-operative CPP due to PPPN and to address to suitable therapy.
A better knowledge of the risk related to a iatrogenic neuropathy as a consequence of particular ARS is mandatory to a proper selection of patients and of the technical approach.

Oral session 17

Higher function disorders

O116

Gesture apraxia in patients with left, right or frontal lesion

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Objectives: Ideomotor apraxia classically results from a left hemisphere lesion of the parietal cortex. But controversies persist about the

role of right, left and frontal lesions on the occurrence of the different disorders which characterize apraxia, and the distinction with ideational apraxia. Here, we addressed disorders of recognition, knowledge, and production of simple and complex gestures, in a series of brain-injured patients.

Methods: We included 46 patients after a stroke (MCA left: 19, right: 15; ACA frontal: 6) or a traumatic brain injury (frontal: 6), and excluded those with severe perception disorders, aphasia or spatial neglect. The battery consisted of 13 subtests: imitation of finger and hand configurations, discrimination of meaningful/meaningless gestures, symbolic gestures (recognition, production on verbal command and imitation), pantomimes (recognition, production on verbal command, imitation, and with the object), then matching functional objects, recognition of objects by their function, production of complex sequential gestures, and knowledge of action sequences. Patients were compared with 50 matched control subjects (age, level of education).

Results: Left hemisphere lesions resulted in a deficit ($p < 0.05$) in all subtests, except discrimination of meaningful/meaningless gestures. This predominated on production subtests and when the command was verbal. Performing simple or complex gestures was similarly difficult. Right lesions impaired imitation of finger configuration, pantomimes (recognition and imitation), and action sequences. Frontal lesions discretely impaired pantomime imitation.

Conclusion: Left hemisphere lesions impair gesture production (classical ideomotor apraxia), but also gesture recognition, as well as performing sequential gestures (ideational apraxia). Right lesions disturb imitation of finger configuration and recognition and imitation of pantomimes, which could result from difficulties in the treatment of spatial information. Frontal lesions can have discrete consequences on pantomime imitation, and could be the consequence of attention disorders. This suggests that both hemispheres as well as frontal structures can participate in gesture information processing, depending on the quality of the task.

O117

Transient global amnesia: a genetic disease?

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The pathogenesis of transient global amnesia (TGA) is still unknown. We describe a family of eight siblings, with a clinical episode of transient global amnesia in four of them.

Cases: The oldest sister (67 years) planned to go to the beach by bike because she wanted to swim in the sea. She has amnesia for the whole trip by bike and her visit to the beach.

The brother (62 years) was gardening when he suddenly could not remember what he was doing. He didn't know why he was wearing working clothes. During this episode he repeatedly asked the same questions, within 24 h he completely recovered.

The second sister (58 years) arrived at the airport, confused and had an ongoing amnesia for hours. Five years later she had a similar episode of isolated transient amnesia.

The third sister (55 years) was in a health club and started to feel strange. She cannot remember what happened next, but friends witnessed she could not recall any new information.

The mother (75 years) of these children felt strange the day after her 75th birthday, and couldn't remember how she got all the flowers in her house. Next morning she was healthy.

Discussion: All cases in this family had a clinical episode of TGA. They had no relevant medical history and no other explanation of the transient amnesia was found. Incidence of TGA is 5 to 11 per 100.000 persons a year, with risk of recurrency of 3–26%. Therefore, it is unlikely this family all had a TGA by co-incidence. Pathogenesis of TGA is speculative. A Vasalva manoeuvre is suggested to cause venous congestion, which leads to temporary ischemia in the hippocampus. Indeed Vasalva manoeuvre like exercise, coughing, cold or emotions starts the TGA in more than half of all cases. If a Vasalva manoeuvre triggers a TGA the low rate of recurrency is surprising. Other possible mechanisms include an underlying cortical spreading depression, analogue of migraine.

Only a few case reports describe familiar TGA, i.e. in siblings. Our family suggests a genetic predisposition of TGA. TGA is relatively rare, the personal impact of a TGA is high, and we assume almost all people seek medical attention. We therefore belief this high TGA-frequency in one family is no coincidence. Further genetic research in TGA patients is warranted.

O118

Adult-onset leukodystrophy with neuroaxonal spheroids: a new family with new insights on the disease

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Background: Leukodystrophies are a diagnostic challenge, because of multiple forms with clinical overlap. Leukodystrophy with neuroaxonal spheroids is a rare form, with sporadic and hereditary cases, and unknown pathogenesis. Clinically, it is characterized by cognitive, behavioural and motor symptoms, and pathologically by loss of myelinated fibers in the centrum semiovale and axonal spheroids in the surrounding white matter. Brain magnetic resonance imaging (MRI) tends to show frontal predominance of the lesions. We report two siblings with clinical, imaging and pathological findings compatible with this entity.

Case report: A 33-year-old male, with a history of learning difficulties and aggressiveness at school, presented with a one-year history of apathy, impaired attention and memory, childish behaviour, inappropriate laughing and disinhibition. He subsequently developed aphasia, dysphagia and incontinence. Examination showed frontal release signs and global cognitive deficits. His 27 year-old sister had been admitted because of two years of progressive dementia and pyramidal signs. In hospital she developed mutism, dysphagia, spastic tetraparesis, seizures, and died 5 months later. MRI showed T2/FLAIR hyperintensities in the anterior subcortical white matter, corpus callosum, internal capsule and brain stem. Gradient echo and diffusion-weighted images showed a dark globus pallidus and substantia nigra in the first patient. Dorsal thalamus was involved in the second. Contrast enhancement was absent in the first patient and poor in the second. Brain biopsy in the first patient and autopsy in the second confirmed the diagnosis. Electron microscopy showed that spheroids were filled with degenerated small mitochondria, while in their proximal portions neurofilaments and neurotubules were prominent. Several nonswollen axons showed unusually large mitochondria with loss of cristae. No abnormal pigment was encountered. Five ballooned neurons were found in cortex under the involved white matter in the autopsy.

Discussion: This new family with hereditary leukodystrophy with neuroaxonal spheroids shows that this diagnosis must be considered in the presence of adult-onset white matter disease with frontal predominance. The lack of the pigment reported in most other cases suggests that it may be an epiphenomenon. The loss of myelin is probably secondary to axonal destruction. Axonal pathology in these cases is more widespread than is evident by light microscopy.

O119

Does cognitive impairment influence outcome in congestive heart failure? A systematic review

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Background: Awareness of the presence and impact of cognitive impairment in patients with chronic heart failure (CHF) has grown over the last years, but most data available in the literature focused on cognitive consequences of CHF. Patients with cognitive decline may be less well treated or less compliant leading to a worse cardiac outcome. However, the question of whether cognitive impairment negatively influences outcome in CHF patients has been less investigated.

Objective: To systematically review and critically appraise the published literature that evaluated the influence of cognitive impairment on mortality and readmission for acute decompensation in CHF patients.

Method: We performed a literature search based on medical subject heading (MeSH) terms for "heart failure, congestive", "ventricular dysfunction", "heart decompensation" and "heart transplantation", and for "cognitive impairment", "cognitive decline", "cognitive dysfunction" and "dementia". Studies were evaluated according to their methodology, characteristics of the study population, and cardiac parameters (baselines characteristics and outcome). We selected only studies where mortality and readmission were separately reported in patients with and without cognitive impairment and more than 3 months of follow-up

Results: Only three studies met selection criteria. They were all hospital-based. They included altogether 896 patients with CHF (516 with cognitive impairment at baseline, 57.6%) with a mean age around 79 years, of whom 608 patients (67.9%) were recruited in the same study published as a letter. Most cardiac characteristics, on-going therapies, and associated risk factors were not detailed. None of these studies included brain imaging. They studies showed that the mortality rate was higher in CHF patients with cognitive impairment at baseline. The 3 studies showed that the mortality rate was high in cognitively normal CHF patients, with rates of 17.9, 25.6 and 68.2% at 6, 12 and 60 months. The mortality rate was even much higher in CHF patients with cognitive impairment at baseline, with rates of 35.6, 40 and 96.3%.

Conclusion: There are data in the literature suggesting an increased mortality in CHF patients in case of associated cognitive decline but data are too scarce to identify whether this is just the result of an increased morbidity in patients with cognitive impairment or if there is a direct causal relationship via an undertreatment or poor compliance.

The study was funded by a research grant provided by ENS.

O120

Effect of high-altitude exposure on cognitive and psychological performance: data from the HighCARE project

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Objectives: Exposure to high altitude reduces oxygen supply to the central nervous system and may cause a variety of neuropsychological and psychological impairments (Wilson et al. 2009; Javier Virués-Ortega et al. 2004; Lowe et al. 2007, Fagenholz et al. 2007). Cognitive alterations following high altitude exposure have been variously described in literature for both ecological and simulated conditions (Pavlicek et al. 2005; Regard et al. 1991). The purpose of this study was to analyze neuropsychological and psychological profiles of normal subjects at sea level and when exposed to high and very high altitude (3,500 and 5,400 m), the latter conditions being considered as a model of cognition functioning in clinical conditions characterized by poor brain oxygen supply.

Methods: Forty-five normal subjects participating in the Himalaya's HIGHCARE expedition underwent an extensive neuropsychological and psychodiagnostic assessment in normoxia condition, at 3,500, 5,400 m and 3 month after expedition end. Different cognitive domains had been investigated with both traditional tools as well as computerized tests. Measures of reaction times and eye-movements (PVA test—Visuo-Attentional Performance Evaluation) were collected using an x50 eye-tracker. Also psychological and emotional status were investigated.

Results: Our data show quantitative and qualitative differences in cognitive performances between study conditions, with higher scores in normoxia and at 3,500 m than at 5,400 m. Significant differences and paradigmatic patterns of data emerge on different eye-movements/reaction times measures, while a general cognitive slowliness occurred at 5500 m condition. Subjects differed significantly for the presence of depressive/anxious symptoms. Data were correlated with cardiovascular and respiratory parameters.

Conclusion: High altitude exposure induces specific cognitive and psychological patterns, as well as peculiar alterations of eye-movements patterns. Computerized neuropsychological assessment seems more sensitive than usual tests to minimal changes observed in cognitive functions under hypoxia conditions. This assessment seem to be ideal in detecting small cognitive changes frequently observed in patients affected by mild vascular cognitive impairment (mVCI). Clinical implications for patients affected by diseases associated with hypoxemia will be discussed.

Oral session 18

Sleep disorders

O121

Restless legs and SCA2 are co-morbid phenotypes in ataxin 2 mutation carriers: common genotypes or modifiers?

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Objective To characterize the SCA2 phenotype was associated with sleep pathologies as periodic legs movement, cramps during sleep and other sleep disorders.

Methods: We analyzed 32 SCA2 patients with disease durations of 1–20 years, (CAG size 34–44), clinical scores, sleep interviews, and video-polysomnography recordings were scored.

Results: RLS was present at 48% in SCA2 patients compared to 11% in controls ($p = 0.00$). Strong correlation (R: 0.72, $p = 0.00$) was found among ataxia and RLS measured as SARA score and RLS index. Cramps and periodic legs movement were also close associated with SCA2 phenotype.

Conclusions: RLS movements are comorbid with ataxin two expansions perhaps proposing gene products interaction or trans-acting factors undescribed linked with nigro-striatal structures. RLS genetic locus could be rational modifiers of SCA2 amenable to target ataxin two toxicity. This is the first report showing a clear association among these very different entities. The comorbidity of RLS and SCA2 phenotype deserve special attention in the management and improvement of life quality of SCA2 patients.

O122

Restless legs syndrome in pregnancy: a prospective, systematic study

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Introduction: Three retrospective studies suggested a high frequency (11–26%) of restless legs syndrome (RLS) in pregnancy. None of these studies used standardized methods for assessment of RLS and sleep. Characteristics and determinants of RLS during pregnancy are poorly known.

Methods: Women during (from the second trimester, 1x/month) and after pregnancy (8 weeks post-partum) are prospectively studied. Assessment includes (1) interview about RLS-symptoms and sleep habits/disturbances: (2) standardized questionnaires (incl. the international RLS-scale (IRLSS), Epworth sleepiness scale (ESS), and Pittsburgh Sleep Quality Questionnaire (PSQI)); (3) blood tests (incl. hemoglobin, C-reactive protein and ferritin), (4) leg actigraphy (3rd trimester and post-partum).

Results: So far 340 women were screened. RLS was diagnosed in 35 women (10.3%), 24 participated in the study so far. 28% of them had a positive family history for RLS, 60% reported onset of RLS-symptoms before the 20th week, 60% had RLS-symptoms daily, 60% had an IRLSS>20, and 85% had a PSQI> 5. Anemia (defined as Hb <11 g/dl in pregnant women) was found in 10% of affected and unaffected women. Ferritin levels <50 were found in 88% of women. Women with (pRLS) and without RLS (nRLS) had similar values in hemoglobin CRP, and ferritin (mean Hb 11.8 mg/dl in pRLS, 12 mg/dl in nRLS; Ferritin 19.1 ìg/l in pRLS, 13.3 in nRLS).

Conclusion: Preliminary results of this ongoing study suggest that RLS in pregnancy: (1) is present in 10% of women; (2) frequently appears early in pregnancy; (3) is often severe/ frequent; (4) may not be related (only) to anemia/low ferritin levels; (5) has a significant impact on sleep quality.

O123

Early pathology in sleep studies of patients with familial Creutzfeldt-Jakob disease

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Objective: To assess sleep function by formal studies in patients with recent onset of familial Creutzfeldt-Jakob Disease (fCJD). The largest cluster of fCJD is in Jews of Libyan origin and linked to the PRNP E200 K mutation. The high index of suspicion in these patients often leads to early diagnosis with complaints of insomnia being a very common presenting symptom of disease. This is the first systematic polysomnographic investigation in this population.

Material and methods: The study included 10 consecutively examined fCJD patients diagnosed by clinical manifestations, MRI, elevated TAU protein the CSF and positive PRNP E200 K mutation. The patients were ambulatory and able to communicate. A standard polysomnography study (Embla® system by Flaga) was performed.

Results: All the patients presented a pathological sleep study in all scoring evaluation settings. The sleep stages were characterized by the disappearance of sleep spindles, outbursts of tri-phasic waves, and shallowing of the sleep with increased stage 2 and increased wake periods during the night. The average hypnogram included stage 1 2.3%, stage 2 68.8%, slow wave sleep 2.2 % and REM 6%. The respiratory channels demonstrated an irregular breathing with central and obstructive apneas and hypopneas.
The typical hypotonia during the night and the atonia during REM were replaced by hyperactive sleep in all the subjects with multiple jerks, movements and talking during the night.

Conclusions: Sleep studies are clearly universally pathological in early fCJD associated with the E200 K mutation. Specific disturbances such as central apnea and lack of atonia may serve as new diagnostic tools in the disease.

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O124

Nocturnal cerebral haemodynamics in obstructive sleep apnoea patients

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Objective: Near infrared spectroscopy (NIRS) non-invasively monitors brain tissue oxygen saturation (StO2) together with changes in concentration of oxyhemoglobin (O2Hb), deoxyhemoglobin (HHb) and total haemoglobin (tHb), and has proved the occurrence of cerebral hypoxia during episodes of nocturnal obstructive apneas in sleep disordered breathing (SDB) patients.

Aim of the present study was to investigate cerebral hemodynamic consequences of different types of nocturnal respiratory events (obstructive apneas and hypopneas) and of different disease severity (apnea- hypopnea index, AHI).

Methods: Nineteen patients with SDB of variable severity were investigated by nocturnal polysomnography coupled with cerebral NIRS: 7 snorers (AHI = 2 ± 2/h, range: 0.5–4.5); 7 mild SDB patients (AHI = 14 ± 8/h, range: 6.3–28.6); and 5 patients with severe obstructive sleep apnea syndrome (AHI = 79 ± 20/h, range: 39.6–92.9). NIRS data associated with different respiratory events were averaged and corresponding cerebral hemodynamic alterations were assessed.

Results: The relative changes of NIRS parameters were significantly larger in amplitude during obstructive apneas compared to hypopneas (mean HHb change of 0.72 ± 0.23 and 0.13 ± 0.08 micromol/l per sec, p value = 0.048), and in patients with severe SDB (as compared to mild SDB patients and simple snorers; mean HHb change of 0.84 ± 0.24, 0.02 ± 0.09 and 0.2 ± 0.08 micromol/l per s respectively, p value = 0.020). Moreover, NIRS and concomitant peripheral oxygen saturation changes correlated only during obstructive apneas and in severe SDB patients.

Conclusion: This study suggests that acute cerebral hemodynamic consequences of SDB lead to a failure of autoregulatory mechanisms with brain hypoxia only in the presence of frequent (AHI > 30) and obstructive respiratory events.

O125

Changes in middle cerebral artery flow by using continuous positive airway pressure in patients with sleep disordered breathing

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Background: Stroke represents the third leading cause of death and a major cause of serious long-term disability. Sleep disordered breathing (SDB) is found frequently in patients with acute stroke and after neurological recovery. Large fluctuations in cerebral blood flow during and after apnea were shown in several studies. For now, continuous positive airway pressure (CPAP) represents the treatment of choice in patients with SDB, especially in those patients with a high apnea-hypopnea index.

Objective: To observe, by using transcranial Doppler recording, the appearance of changes in the cerebral blood flows of the middle cerebral artery (MCA) in patients with SDB following the use of CPAP and assessing CPAP's possible effect in reducing the risk of stroke during sleep.

Materials and methods: A number of 6 patients (5 men and one woman) previously diagnosed in the sleep research laboratory with SDB were included in the study. Monitoring of the MCA by TCD was performed for two nights, one with and the next one without CPAP treatment. The mean cerebral velocity and the pulsatility index were continuously recorded by the TCD. For monitoring sleep parameters including the episodes of hypoxia we used the Watch PAT 100. The gap between the mean velocities and the pulsatility indexes of the MCA as recorded before and during the apneic episodes was compared.

Results: In patients with a high frequency of hypoxic events we observed a good statistical correlation between the mean velocities and the pulsatility indexes of the MCV in patients with SDB as related to and favoring the use of CPAP, showing that these cases seem to benefit more from the CPAP treatment than the milder cases. Therefore, we consider that CPAP represents a protective device in these patients during hypoxic episodes and for improvement of the cerebral blood flow. This effect might contribute in reducing the future risk for stroke in these patients.

O126

Dopaminergic treatment in restless legs syndrome: effects on vigilance

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Introduction: There is few information on excessive daytime sleepiness (EDS) in restless legs syndrome (RLS). We analysed data from the Swiss RLS study in order to assess frequency and characteristics of EDS and to evaluate effects of different RLS therapies concerning vigilance.

Methods: The Swiss RLS study was performed as a randomized, cross-over trial, conducted to compare treatment efficacy of the dopamine agonist pramipexole (PPX) versus levodopa/benserazide (L/B) in previously untreated, idiopathic restless legs syndrome (RLS) patients. Primary outcome measure of the present study was the change in subjective sleepiness (Epworth sleepiness scale [ESS] score). We analyzed data from thirty-seven patients (21 women), mean age was 56.6 (range 25–85), mean body-mass-index was 24.6 (±3.5 SD). Significant differences were estimated 3-way rANOVA. Pearson's product correlations were performed to identify correlations. Significance was determined as $p = >0.05$.

Results: EDS (as defined by ESS > 10), was found in 32% of the patients. Sleepy RLS patients were younger ($p < 0.001$) than non-sleepy. PPX and L/B both were effective in the treatment of RLS symptoms (IRLS score, $p < 0.001$ and $p = 0.002$). Overall ESS was reduced (main effect for "time", $p = 0.02$) independent from the dopaminergic substance. In sleepy patients ($n = 12$), PPX improved ESS ($p = 0.05$) from 14.3 (±2.3 SD) to 10.5 (±5.2), and L/B ($p = 0.1$) from 12.3 (±1.5) to 11 (±2.8) respectively. In 5/37 patients ESS deteriorated under treatment (PPX: $n = 3$, L/B: $n = 2$), no sleep attacks occurred.

Conclusion: Excessive daytime sleepiness is present in 1/3 of the patients. Short-term dopaminergic treatment usually promotes wakefulness, but infrequently leads to daytime sleepiness.

Oral session 19

Multiple sclerosis: treatment

O127

Functional connectivity changes of the motor network in patients with multiple sclerosis: a multi-centre fMRI study

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Objectives: Functional connectivity (FC) analysis is a powerful and straightforward approach to explore connections among remote, functionally-related brain regions and, contrary to effective connectivity, it does not require any a-priori selection of brain areas to be included in a model. Aim of this study was to characterize the spatial pattern of FC inside the motor network in a large group of MS patients.

Methods: Functional MRI scans during right hand movement were acquired in 61 right-handed patients with relapsing-remitting or secondary progressive MS without hand impairment and 74 age-matched, healthy subjects at eight European sites. FC was investigated by examination of the correlation between the left (L) sensorimotor cortex (SMC) and any other area in the brain. A seed reference time course was obtained by averaging the time courses within a spherical region of interest (with radius of 5 mm) centered at the most significantly activated voxel within the L SMC. Then, correlation analysis was carried out between the seed reference and the whole brain in a voxel-wise way. The cross correlation spatial maps obtained from each subject were transformed to z-scores by applying a Fisher's z-transform, and then entered in an ANOVA factorial analysis to assess the within-group strength of FC coefficients and to compare these strengths between controls and MS patients.

Results: Significant connectivity between L SMC and several brain areas was found both in healthy controls and in patients with MS ($p < 0.05$, corrected for multiple comparisons). In particular, the L SMC was significantly connected with the L and right (R) post-central gyrus, L and R precentral gyrus, L and R supplementary motor

area (SMA), L and R middle frontal gyrus, L and R insula, L and R SII, L and R thalamus and R cerebellum. Compared to controls, MS patients had increased connectivity between the left SMC and the R precentral gyrus, R middle frontal gyrus, the R insula and the R inferior parietal lobe.

Conclusions: Large multi-centre fMRI studies of FC changes in diseased people are feasible and can facilitate studies with sample size large enough for robust outcomes. Increased inter-hemispheric connectivity in MS for the simple motor task suggests local network modulation contributing to preservation of function.

O128

Thymic naive T-helper cells as immunologic marker of glatiramer acetate therapy in multiple sclerosis patients

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Objectives: As observed with other immunomodulatory treatments, Glatiramer acetate (GA) therapy is effective only in a percentage of multiple sclerosis (MS) patients, and it needs to be given for at least 6–12 months before any clinical response becomes apparent. Here, in order to investigate the immunological counterpart of these outcomes, we analyzed the extent of newly produced T cells in MS patients and verified if the quantification of this parameter could be used as an appropriate and precocious biomarker of immunological response.

Methods: The study population included: 89 MS patients treated with GA for more than one year, 84 therapy-free patients, and 31 patients who initiated the therapy at the time of the inclusion in the study and were followed up for 12 months; controls were 81 age-matched healthy donors. The production of new lymphocytes was measured by means of TRECs quantification and by determining the frequency of thymic naive T helper (Th) cells. T-cell repertoire was assessed by spectratyping.

Results: A thymopoietic pathway of T-cell regeneration appears to be activated in GA-treated patients because we found an increased frequency of thymic naive Th cells and a decreased frequency of effector memory T cells that led to overall modifications of the T-cell repertoire diversity. GA induces a differential effect on follow-up patients, as they could be divided in 2 groups, one in which thymic naive Th cells were unmodified by the therapy and one showing an increase of this subpopulation after 4 months of treatment. Furthermore, T-cell repertoire diversity was modulated only in patients showing an increased production of thymic naive Th cells lymphocytes, while those showing relapses all belonged to the group with unmodified thymic naive Th cells.

Conclusions: Data indicated that the assessment of thymic naive Th cells may allow an early identification of a subset of patients immunologically responsive to GA treatment. T-cell diversity changes can be due to the fact that the drug, acting as a mixture of conventional antigens, induces populations of new lymphocytes with T-cell receptors different to those observed before treatment. Therefore, GA may drive the T-cell response to non pathogenic epitopes, thus eliciting a reaction in the immune system that changes the composition of the peripheral T-cell pool and dilutes specific pathogenic autoreactive T cells.

O129

Transient down-regulation of the active subunit of interferon receptor in multiple sclerosis patients treated with interferon-β

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Objective: The study was aimed to investigate the modulation of the different subunits and isoforms of interferon (IFN) type I receptor (IFNAR) expression occurring in multiple sclerosis (MS) patients undergoing short-term IFN-β therapy (12 months), showing an heterogeneous pattern of response in terms of anti-IFN-β antibodies (Ab) production and MxA induction.

Methods: Blood samples were also obtained before therapy initiation (T0) and after 3 (T3), 6 (T6), and 12 (T12) months of therapy. Real-Time PCR was used for the quantification of mRNA for MxA, IFNAR1 and IFNAR2 subunits as well as for the IFNAR2.1 (inactive), IFNAR2.2 (active) and IFNAR2.3 (soluble) isoforms. Anti-IFN-β Ab were measured by radioimmunoprecipitation.

Results: When samples of MS patients obtained at T6 were analyzed altogether, IFNAR2.2 mRNA significantly decreased ($p < 0.05$) from T0, while IFNAR1 and IFNAR2 subunits and IFNAR2.1 and IFNAR2.3 were unchanged. Similarly, the mRNA for IFNAR2.2 diminished from T0 to T6 in the subgroup of samples that were MxA-induced at T12 or in those resulting anti-IFN-β Ab-positive. Finally, when samples were divided in 4 groups on the basis of a stable biological response to IFN-β [group A: constantly anti-IFN-β Ab negative/MxA-induced (50%), group B: permanently anti-IFN-β Ab positive/MxA-not induced (17%), group C: continuously anti-IFN-β Ab positive/MxA-induced (19%), and group D: temporarily B anti-IFN-β Ab negative and/or MxA-not induced (14%)] IFNAR2.2 isoforms showed a significant decrease from T0 to T6, but only in samples that were permanently anti-IFN-β Ab-negative/MxA-induced. In samples obtained at 12 months of IFN-β therapy no modulation of IFNAR forms were observed.

Conclusion: The interaction between IFN-β and IFNAR induced a transitory and mild down-modulation, at least at the mRNA level, of the active form of the receptor only in patients in whom an efficient IFN-β/IFNAR interaction is conserved, while the level of other IFNAR isoforms and subunits that did not change over time. These data indicate that a strong impact of IFNAR modulation on IFN-β therapy efficacy seems to be unlikely and argue against a role IFNAR subunits and isoforms as early markers of good biological responsiveness to systemically administered IFN-β.

The study was sponsored by Biogen Dompé.

O130

Atorvastatin does not interfere with interferon-β induced alterations of soluble CD95/ CD95L serum levels in multiple sclerosis: results from the Swiss Atorvastatin and Betaferon in Multiple Sclerosis (SWABIMS) Trial

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Objectives: The interaction of death receptors with their ligands including CD95 and CD95L are critical for inducing apoptosis and triggering immunoregulatory mechanisms in the pathogenesis of T cell-mediated autoimmune diseases such as multiple sclerosis (MS).

Recent studies indicate that the cholesterin-lowering statins possess immunomodulatory and anti-inflammatory properties that might be beneficial in the treatment of MS but may also interfere with favourable effects induced by Interferon (IFN)-β. In this study, we set out to determine the in-vivo effect of IFN-β and atorvastatin as add-on treatment on serum levels of soluble CD95 (sCD95) and soluble CD95L (sCD95L) in patients with relapsing-remitting MS (RR-MS).

Methods: Serum samples were obtained from the Swiss Atorvastatin and Bferon in Multiple Sclerosis (SWABIMS) Trial which aims to compare (1) a monotherapy of IFN-β 1b (250 mug every other day sc), with (2) IFN-β 1b plus atorvastatin as add-on therapy (40 mg per os per day). The treatment design consisted of a 3 month monotherapy with IFN-β and randomisation for continuation of mono- or change to add-on treatment after this period. Peripheral-venous blood was taken at timepoint 0, 3 and 6 months. The study included 24 RR-MS patients (mean age 31.6 years, range 18.9–47.7 years) and 8 age-matched healthy controls (mean age 34.0 years, range 22.1–54.4 years). Simultaneous measurement of sCD95 and sCD95L in serum samples was performed with the multiplex protein assay technology.

Results: In patients with MS, treatment with IFN-β increased serum levels of sCD95 and sCD95L significantly ($p < 0.01$ and 0.05, respectively). Addition of atorvastatin to IFN-β did not alter serum levels of sCD95 and sCD95L. Serum concentrations of sCD95 and sCD95L did not show any differences between MS and healthy control subjects.

Conclusions: In this study we provide further in-vivo evidence that IFN-β treatment by modifying serum levels of sCD95 and sCD95L may be involved in modification of peripheral T-cell survival and autoimmunity in MS. However, our study revealed that add-on treatment with atorvastatin, a promising drug for the treatment of MS which is assumed to attenuate IFN-β induced immunomodulation, is not associated with further alterations and accordingly does not interfere with IFN-β induced changes of sCD95/sCD95L serum levels.

Supported by Inselspital Bern and Swiss Multiple Sclerosis Society.

O131

Safety and utilisation update for natalizumab in patients with relapsing MS, including recent results from TOUCH™ and TYGRIS

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Objectives: Natalizumab (TYSABRI[R]), an α 4-integrin antagonist, has demonstrated a high level of efficacy in patients with relapsing multiples sclerosis (MS). In the pivotal, phase 3 AFFIRM study, natalizumab significantly reduced the annualised relapse rate by 68% and the risk of sustained disability progression by 42%-54% compared with placebo. The TYSABRI Outreach: Unified Commitment to Health (TOUCH[TM]) Prescribing Program and the TYSABRI Global ObseRvation Program In Safety (TYGRIS) are components of a global risk management programme that has been established to monitor the long-term safety of natalizumab.

Methods: Enrollment in the TOUCH[TM] Prescribing Program is required for all patients, physicians, and infusion centers involved in administration of natalizumab therapy in the United States. The goals of the TOUCH[TM] Prescribing Program are to ensure appropriate and informed use of natalizumab and to monitor patients for symptoms of opportunistic infections such as progressive multifocal leukoencephalopathy. TYGRIS is a worldwide, voluntary, observational study that evaluates the long-term safety of natalizumab in the clinical practice setting and is the largest long-term safety study of any MS therapy ever conducted. Details of patients' medical/MS history; prior natalizumab use; prior immunomodulatory, antineoplastic, or immunosuppressive agent use; and all serious adverse events are recorded in TYGRIS. The global risk management programme also collects postmarketing safety data from countries that do not participate in TOUCH[TM] or TYGRIS.

Results: As of the end of December 2008, approximately 37,600 patients worldwide were receiving natalizumab therapy. In the clinical study and postmarketing settings combined, more than 52,900 patients have been exposed to natalizumab. In the postmarketing setting only, approximately 4300 patients have received at least 24 months of natalizumab therapy. The most current exposure and safety data will be presented.

Conclusions: Natalizumab continues to have a favourable benefit–risk profile that supports its use in the treatment of patients with relapsing MS.

Studies supported by Biogen Idec, Inc. and Elan Pharmaceuticals, Inc.

O132

Magnetic resonance imaging (MRI) outcomes in patients with relapsing-remitting multiple sclerosis (RRMS) treated with cladribine tablets: results from the CLARITY study, a 96-week, phase III, double-blind, placebo-controlled trial

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Objectives: Cladribine tablets are in development for the treatment of multiple sclerosis. Cladribine is a pro-drug, and activation in specific cell types provides targeted and sustained immunomodulation, permitting the investigation of an oral short-course annual treatment. We evaluated the MRI outcomes of cladribine tablets vs. placebo for patients with RRMS, in a 96-week, randomised, double-blind, 3-arm, placebo-controlled, multicentre study: the CLARITY (CLAdRIbine tablets Treating multiple sclerosis orallY) study.

Methods: Patients with RRMS (McDonald criteria; Expanded Disability Status Scale [EDSS] score 0 to 5.5) were randomised to 2 dosing regimens of cladribine tablets (cumulative doses of 5.25 or 3.5 mg/kg), or matching placebo (1:1:1). Cladribine tablets were given as short courses (once daily for 4–5 days) in Weeks 1, 5, 9 and 13 (5.25 mg/kg arm) or Weeks 1 and 5 (3.5 mg/kg arm), and again in Weeks 48 and 52 (both arms). Prespecified secondary MRI endpoints over 96 weeks included number of T1 Gd+ lesions, number of active T2 lesions and number of combined unique lesions (CU)/patient/scan. MRI data were evaluated using a non-parametric analysis of covariance (ANCOVA) model adjusting for treatment, region and baseline lesion counts.

Results: In the ITT population, 456, 433 and 437 patients were randomised to 5.25 or 3.5 mg/kg cladribine tablets or placebo, respectively; groups were comparable for baseline characteristics, including number of T1 Gd+ lesions (mean 1.0, 1.0 and 0.8), and T2 lesion volume (mean 17.2, 14.8 and 14.3 mL, respectively). Cladribine-treated patients in 5.25 or 3.5 mg/kg groups had significantly less disease activity on neuroimaging assessment compared to placebo-treated patients, exemplified by 87.9 and 85.7% relative reductions in T1 Gd-enhancing lesions (mean 0.11 and 0.12 vs. 0.91), 76.9 and 73.4% relative reductions in active T2 lesions (mean 0.33 and 0.38 vs. 1.43), and 77.9 and 74.4% relative reductions in CU

lesions (mean 0.38 and 0.43 vs. 1.72 lesions per subject per scan), respectively; all $p < 0.001$ versus placebo. This highly significant cladribine-related treatment effect on MRI was evident at Weeks 24, 48 and 96 of study.

Conclusions: Brain MRI activity is greatly reduced by cladribine at both dosing regimens. The effects on MRI activity mirror the clinical benefits reported with cladribine tablets, supporting the key role of the drug in the treatment of RRMS

Study supported by: Merck Serono S.A., Geneva, Switzerland.

Oral session 20

Prognosis in cerebrovascular disorders

O133

Copeptin, the stable peptide of the vasopressin precursor is a good marker to predict 1-year outcome in patients with ischaemic cerebrovascular events

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Objectives: Costs of acute care account for about half of the total costs of stroke care. To better allocate our limited resources, accurate prediction of long-term outcome in stroke patients would be useful. Copeptin levels were found to predict 90 day functional outcome and mortality in stroke patients. This follow up study evaluated its predictive accuracy to predict 1-year outcome.

Methods: On admission ischemic stroke was assessed using the National Institute of Health Stroke Scale (NIHSS). Copeptin levels were compared to functional outcome one year after admission as assessed by a structured telephone interview. Outcome was classified according to the modified ranking scale (mRS) as favourable (0–2) or unfavourable (3–6). Secondary endpoints were death within one year from onset of stroke and patients' dependency on care after discharge (dependent versus independent).

Results: From 469 patients, 449 completed one-year follow-up and were included in this analysis. Median age was 75 (65–82) years, 40% were women. On admission, median NIHSS was 5 (IQR 2-10). Copeptin levels were higher in patients who died (28.10 pmol/l [IQR 13.20–60.88], in patients with a unfavourable functional outcome (19.30 pmol/l [IQR 9.60–36.98] and in patients living in nursing homes or at hospitals (16.50 pmol/l [IQR 9.12–28.90] compared to patients who survived (9.34 pmol/L [IQR 5.37–19.00], $p < 0.0001$), patients with a favourable outcome (8.12 pmol/l [IQR 4.58–14.65], $p < 0.0001$), and patients living at home (8.69 pmol/l [IQR 5.13-17-68], $p<0.001$). In a multivariate logistic regression analysis, copeptin on admission was a strong predictor for death (OR 2.7, 95%CI 1.2—5.7), functional outcome (OR 2.8, 95%CI 1.4–5.6) and dependency on care (OR 2.7, 95%CI 1.1–6.8), independent of age, and NIHSS. Copeptin had an area under the receiver operating curve (AUC) of 0.72 (95%CI 0.67–0.78) to predict functional outcome, 0.74 (95%CI 0.67–0.81) to predict death and 0.68 (95%CI 0.59–0.76) to predict dependency on care. Using copeptin levels in addition to NIHSS improved the AUC for functional outcome from 0.70 (95%CI 0.64-0.76) to 0.76 (95%CI 0.71–0.82, $p = 0.002$) and for mortality from 0.74 (95%CI 0.66–0.81) to 0.78 (95%CI 0.71–0.85), $p = 0.04$).

Conclusion: Copeptin levels predict poor functional outcome and dependency on care after one year of stroke. Copeptin is a useful and complementary tool to the NIHSS for early and post-discharge management of subjects suffering from acute ischemic stroke.

B.R.A.H.M.S AG, Biotechnology Centre, Henningsdorf-Berlin, DE manufactured the MR-proANP-assay, but did not fund this study, neither was funding obtained from commercial sources for this study.

O134

The visuo-spatial attention in neglect patients after acute ischaemic stroke

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Introduction: Neglect is considered to be a deficit of visuospatial attention, which typically occurs in acute stroke patients. The difference in functional state of attention system between acute stroke patients with neglect (NGL) and without neglect (non-NGL) is still unknown. We aimed to explore it using functional MRI.

Methods: We examined 26 healthy control subjects (30.3 ± 7.3 years) and 23 patients (67.23 ± 10.23 years, 13 with NGL and 10 non-NGL) 50.57 ± 31.22 h after ischemic stroke in the territory of the right middle cerebral artery. Non-NGL and NGL patients did not differ in age and time after stroke onset. All subjects were examined with fMRI while performing a task for visuospatial attention. Subjects were presented a central valid cue, and then the right/left targets (valid trials, in 66%) or no target (null event, 33%). Totally 64 right and 64 left targets were presented to each subject. We analyzed the fMRI activation between 3 groups: healthy subjects (HLTH), non-NGL, and NGL.

Results: HLTH, non-NGL and NGL subjects detected 64, 57.8 ± 10.7 and 21.6 ± 21.8 left targets correspondingly; and 64, 59.2 ± 10.4 and 51.6 ± 8.5 right targets correspondingly. In healthy subjects fMRI paradigm activated key attentional and visual areas in both hemispheres. In non-NGL patients, the pattern of activation was the same as in HLTH. In NGL patients, neither attention relevant nor visual areas were activated in the right hemisphere. Contrasting non-NGL vs. NGL showed difference of activation in all key attentional areas in the left hemisphere and post-Rolandic structures in the right hemisphere. In contrast, activation in the primary motor area, which was associated with the motor response, did not differ between non-NGL and NGL. This underlines that the BOLD response was the same both in NGL and non-NGL.

Discussion: In non-NGL, activation of key attention relevant areas was on the level of HLTH that enabled effective visuospatial processing. In contrast, NGL patients showed down-regulation in most of left and right attentional regions including undamaged right visual areas. Thus, though the structural lesion in non-NGL and NGL patients was similar, NGL patients had distinct functional state of their whole visuospatial attention system.

O135

Vascular event risk after small and large vessel ischaemic stroke

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Objectives: Small and large vessel disease (SVD and LVD) may have a different pathogenesis and prognosis but the risk of death and recurrent stroke appears to be similar in previous studies. Data on new cardiac events are scarce.

Methods: We included 887 patients with transient ischaemic attack or nondisabling ischaemic stroke of arterial origin, who were

referred to a university medical center in The Netherlands between 1995 and 2005 and followed them for the occurrence of ischaemic stroke, myocardial infarction or death. The primary outcome was a composite of death from all vascular causes, nonfatal ischaemic stroke, nonfatal myocardial infarction, whichever happened first. Two independent observers classified the cerebral ischaemia—both for baseline and recurrent events—as SVD or LVD. Classification was primarily based on brain imaging. Clinical features were used if brain imaging did not show an infarction or was not available.

Results: Overall survival after 1 month, 1 year and 5 years was 100, 98.5 and 89% respectively for SVD patients and 99.8, 97.6 and 86.6% for LVD patients. During a mean follow-up of 4.6 years new vascular events occurred in 39 of 266 SVD patients (annual event rate 3.2%) and in 96 of 621 LVD patients (annual event rate 3.4%). The corresponding age and sex adjusted hazard ratio (HR) for LVD versus SVD was 0.81, 95%-CI 0.56–1.18. Cardiac events (myocardial infarction and sudden death) occurred in 34 LVD patients (5.5%) and 10 SVD patients (3.8%); HR 1.05, 95%-CI 0.52–2.14. Ischaemic stroke recurred in 50 LVD patients (8.1%) and 23 SVD patients (8.6%); HR 0.75, 95%-CI 0.46–1.23. Recurrent stroke was classified LVD in 42 patients (84%) after LVD and was classified SVD in 15 patients (65%) after SVD.

Conclusion: Vascular event risk is similar after SVD and LVD, including the risk of cardiac events. Recurrent stroke subtypes after SVD and LVD tend to remain true to type.

O136

Endogenous thrombin potential is associated with carotid intima-media thickness in subjects younger than 45 years

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Background and aim: Thrombin is the essential enzyme product of the blood coagulation enzymatic cascade, and plays a role not only in thrombosis but also in the progression of atherosclerosis. We studied the relationship between thrombin generation (TG) and carotid intima-media thickness (IMT), an index of subclinical atherosclerosis.

Methods: We examined 150 asymptomatic middle-aged (mean age 61.7 years) subjects free of overt clinical atherosclerotic disease. Endogenous thrombin potential (ETP) was measured by calibrated automated thrombography (CAT). The thrombogram describes the concentration of thrombin in clotting plasma. It starts with the lag time in which no thrombin is formed. After a steep increase the thrombin generation curve arrives at its peak, the maximum concentration of thrombin. The ETP, the area under the curve represents the amount of thrombin built. In addition carotid intima media thickness (IMT) was determined by duplex ultrasonography of the common carotid arteries. We grouped the healthy donors into 3 age groups (younger than 45 years; 45 to 60 years; elder than 60 years). Statistical analyses were performed by the aid of SPSS. Correlations between IMT and thrombin generation values using CAT were calculated using Pearson′s correlation. p values less than 0.05 were considered to be significant.

Results: A significant positive correlation was seen between endogenous thrombin potential (ETP) ($p < 0.05$), lag time ($p < 0.001$), peak ($p < 0.05$) and carotid IMT in the age group <45a. and carotid IMT in the group healthy volunteers younger than 45 years . However, we could not determine any correlation between ETP and IMT in the groups of subjects elder than 45 years.

Conclusion: In a cohort of adults younger than 45 years without clinically overt atherosclerotic disease ETP, lag time and the peak of thrombin generation were significantly associated with carotid IMT. This might indicate a relationship between thrombin generation and the development of atherosclerosis. For the age groups older than 45 years there might be further factors influencing both thrombin generation and atherosclerosis such as co-morbidity with diabetes, hypertension, or hypercholesterinemia. These further factors might dilute the correlation of the blood clotting cascade and atherosclerosis generation in the elder population.

O137

Effect of stroke guidelines on inpatient stroke mortality and the subsequent 3 years

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Introduction: We present here the effect of stroke guidelines on mortality during admission and for the three years after discharge from hospital.

Methods: Data on all patients aged 18 years and over were collected for the years 1998, 2003 and 2005. The hospital has a 30 bedded stroke unit and stroke guidelines were first implemented in 1999. There is an integrated stroke care pathway for all patients admitted with stroke.

Results: Total number of stroke patients admitted were 369(1998), 349(2003) and 331(2005). The rate of brain imaging was 66% in 1998 and 95% in 2005($p<0.05$). The appropriate use of aspirin in ischemic stroke was 87%(156/179) in 1998 and 99%(260/262) in 2005($p<0.05$). The appropriate prescriptions for anticoagulation for AF in patients with ischemic stroke were 59%(22/37) in 1998 and 77%(24/31) in 2005($p > 0.05$). The number of patients who died during their admission with stroke was 40%(146/369) in 1998 and 29%(97/331) in 2005($p = 0.005$). The mortality rates for the years 1,2 and 3 following discharge were 17%(39/223), 8%(14/184) and 8%(14/170) for the year 1998 and 16%(38/234), 12%(22/176) and 6%(10/154) for the year 2005 respectively.

Conclusions: Our data show that rigorous implementation of stroke guidelines resulted in a significant improvement on overall stroke care and reduced inpatient stroke mortality but this benefit is not sustained following discharge. It is possible that there are other risk factors influencing mortality in stroke patients following discharge.

O138

Predictive factors and prognostic significance of early seizures in acute strokes

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Purpose: Despite common occurrence of early seizures (ES) in stroke, ES effect on prognosis was not well studied. Study was aiming to determine predictive factors of ES in stroke patients, and relationships between ES and stroke outcome.

Methods: 1,030 patients with acute stroke were prospectively and consecutively studied for number and type of seizures, initial stroke severity, mortality, and outcome in survivors. Stroke severity was assessed, clinically and by imaging. Multiple logistic and linear regression outcome analyses included age, gender, stroke severity, atrial fibrillation, ischemic heart disease, blood glucose level, claudication, hypertension, and seizure recurrence.

Results: 2.4% had seizures within 48 hours, and 4.36% had seizures within 14 days of the stroke. Seizures were significantly more frequent in hemorrhagic than in ischemic strokes ($p < 0.05$). Patients with seizures were significantly more likely to have confusional state, cortical involvement, and larger stroke than patients without seizures. In-hospital mortality rate was higher in seizure than in non-seizure group ($p < 0.005$). After multivariate analysis, cortical involvement (OR5.63) and acute agitated confusional state (OR3.92) were independent clinical factors for developing ES. In survivors, ES was related to a better outcome.

Conclusions: Cortical involvement in neuroimaging and agitated confusional state at the onset of stroke were independent predictive factors of early seizures in stroke patients. The efficacy of anticonvulsants in the prophylactic control of seizures should be assessed in prospective clinical trials conducted in the subgroup of highest risk patients.

Oral session 21

General neurology 2

O139

SPG11 is the major cause of autosomal recessive hereditary spastic paraplegia in Tunisia

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Background: Hereditary spastic paraplegias (HSP) constitute an heterogeneous group of neurodegenerative disorders characterized by progressive spasticity of the lower limbs. All inheritance modes are described and to date, more than 40 loci and 17 genes HSP were identified. Recently, the SPG11 gene that encodes spatacsin, was identified in AR-HSP. Objective: To estimate the frequency of SPG11 in a large series of HSP patients from Tunisia, to define the spectrum of the mutations in this gene and to describe the associated phenotypes.

Methods: We recruited and examined 88 subjects from 38 unrelated Tunisian AR-HSP families. We tested the included families for linkage to SPG11 loci using microsatellite markers from the candidate intervals, followed by direct sequencing of the SPG11/KIAA1840 gene in several linked families.

Results: We identified 14 SPG11 Tunisian families ($n = 14/38$ families, 36.8%), including 24 affected patients. Linkage to SPG11 loci was suggested by haplotype reconstruction and positive LOD score values. Patients in families TUN2, TUN3, TUN4 and TUN22 had partially similar haplotypes encompassing the SPG11 gene, suggesting inheritance of a common mutated ancestral chromosome. Similarly, families TUN9, TUN12 and TUN14 shared the same homozygous alleles for the whole SPG11 interval. In 9 families, the linkage results were validated through the identification of two recurrent truncating mutations (M245VfsX246 in 4 families and R2034X in 3 families) and the 2 new missense mutations (W1445C and K1013E) in the SPG11 gene. The clinical phenotype associated to SPG11 consisted of an early onset spastic paraplegia with mental impairment and severe disability, mostly associated with peripheral neuropathy, thin corpus callosum and white matter abnormalities.

Conclusions: We report the clinical and genetic results of 14 SPG11 Tunisian families including 24 patients, the largest group of North African patients of Arab origin investigated so far. SPG11 was originally described in Japanese patients then it has been found in many countries especially in North Africa and Italy. Complicated AR-HSP is the most frequent AR-HSP subtype in Tunisia, and SPG11 is the major gene for this entity (36.8%). Phenotype-genotype correlations suggest that testing for SPG11 in AR-HSP should be performed in complex forms when there is early onset spastic paraplegia with severe progression associated with mental deterioration especially when MRI shows thin corpus callosum.

O140

Loss of CAA interruption in large normal alleles atx2 is a risk factor to SCA2 gene instability: a haplotype and sequence-based study in large Cuban kindreds

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Objective: (1) To decipher the mechanism predisposing to SCA2 locus instability. (2) To identify other factor than CAG predisposing to SCA2.

Methods: We carried out haplotype studies in 13 SCA2 pedigrees and 89 controls ($n = 132$ chromosomes) using 6 microsatellite markers –STR- surrounding the mutant CAG.

Results: Strong linkage disequilibrium (LD) between SCA2 mutation and some STR alleles were found. CAG sequence analysis revealed new large alleles 30-31 CAG. These alleles were either pure or lacked the most proximal 5′ CAA interruption and were overrepresented respecting other alleles. We found strong association ($p = 0.0070$) between allele 4 at D12S1672 marker and 22 CAG allele lacking 5′CAA (configuration 13+8). Alleles with CAG different of 22 repeat, and lacked of CAA interspersion were strongly associated ($p = 0.0000$) with allele 4 of STR and the haplotype (3-3-4) ($p = 0.0013$). Further tests narrowed this group to the 29-31 CAG range, showing association ($p = 0.0063$) only with the haplotype 3-3-4 at D12S1332-D121672-D12S1333. Alleles with 29-31 CAG were unstable at somatic level (No. peaks = 3 ± 0.18 SEM, range 3–8 peaks) contrasting to stable chromosomes (No. peaks = 1 ± 0.18 SEM, range 1–2 peaks) in our kindreds. These findings were strengthened by the fact that a pedigree with SCA2 haplotype and pure large allele (30CAG), show that along with an intergenerational increase in repeat size there was a horizontal increase in repeat size with the birth order of the siblings indicating an important role for parental age in repeat instability during transmission.

Conclusion: Large alleles are the principal source of SCA2 expansion. Somatic mosaicism in normal large alleles is a valuable predictor to determine predisposition to genetic instabilities. This is the first work uncovering the mechanism driving to genetic unstability at SCA2 locus.

Supported by the Cuban Health Ministry.

O141

AFG3L2 mutations cause autosomal dominant ataxia SCA28 and reveal an essential role for the mitochondrial m-AAA protease complex in the cerebellum

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Objectives: Dominant spinocerebellar ataxias (SCA) are a heterogeneous group of neurological disorders characterized by cerebellar dysfunction mostly due to Purkinje cell degeneration. We previously mapped SCA type 28 to chr. 18p11 in an Italian family. Here, we report the identification of the gene causing SCA28.

Methods: Candidate genes within the SCA28 critical region were sequenced in a proband from the original family. Subsequent molecular screening was performed in a large sample of families ($n = 129$) and sporadic patients ($n = 150$) with spinocerebellar ataxia negative for mutations in known SCA genes. Functional studies were performed in a yeast cellular model. Expression studies were performed in human and rat central nervous system.

Results: We have found that AFG3L2 (ATPase family gene 3-like 2) is the disease-causing gene. Along with paraplegin, which causes recessive spastic paraparesis SPG7, AFG3L2 is a component of the mitochondrial m-AAA complex, an evolutionarily conserved protease involved in protein quality control. We have identified 4 heterozygous AFG3L2 missense mutations in the original kindred and in other 3/129 ($\sim$2%) unrelated SCA families. Interestingly, concurrent heterozygosity for a recessive paraplegin mutation negatively modulated the phenotype in one family. All the AFG3L2 mutations are located in the FtsH-like protease domain at highly conserved amino acids. Modeling on FtsH structure indicates that they may affect substrate interaction. AFG3L2 protein and transcript were found to be highly and selectively expressed in cerebellar Purkinje cells. Expression of normal and mutant AFG3L2 homocomplex in m-AAA-deficient yeast cells demonstrate that the mutations cause respiratory deficiency and proteolytic defect. Preliminary phenotypic analysis of the patients harbouring a mutation in the SCA28 gene showed a relatively uniform ADCA1-type clinical presentation characterized by slowly-progressive cerebellar ataxia with cerebellar atrophy and a frequent occurrence of oculomotor dysfunction and pyramidal signs.

Conclusion: This work identifies AFG3L2 as a novel cause of dominant neurodegenerative disease and indicates an essential role for the mitochondrial m-AAA protease complex in protecting the cerebellum against neurodegeneration.

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O142

Salvage therapy with bevacizumab and chemotherapy (irinotecan or fotemustine) in recurrent high-grade gliomas

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Background: Recurrent malignant gliomas have a poor prognosis with low response rates after salvage chemotherapy. Neoangiogenesis is a pathological characteristic of high grade gliomas. Malignant gliomas overexpress vascular endothelial factor (VEGF), that is an important negative prognostic factor. Bevacizumab is a monoclonal antibody that binds VEGF. Bevacizumab given in combination with irinotecan has been reported to be active with acceptable toxicity. We reported our experience with bevacizumab in combination with irinotecan and fotemustine in patients with recurrent high grade gliomas.

Objectives: To assess: efficacy and safety in a phase II study of bevacizumab in association with irinotecan or fotemustine in patients with recurrent high grade glioma after standard treatment (surgery, radiotherapy and concomitant/adjuvant temozolomide).

Methods: From November 2007 to January 2009 we treated 60 patients (25 females and 35 males) with bevacizumab, with a median age of 55 years (range: 19–70). Twenty-six patients were treated with bevacizumab plus irinotecan (group A) and 32 patients received bevacizumab plus fotemustine (group B). Two patients received bevacizumab alone because of persisting myelotoxicity from previous treatments. Those regimens were maintained until progression or unacceptable toxicity. Response on MRI was evaluated according to Macdonald criteria. Histological diagnosis was glioblastoma in 41/60 patients and anaplastic gliomas in 19/60.

Results: A significant clinical improvement in more than 50% of patients was seen in both groups, with steroid reduction in 50% of cases. The radiological median response rate was 38% in group A, 35% in group B. The median TTP was of 3 months (range: 1–11+). In group A, the PFS-6 was 24%; in group B the PFS-3 was 50% (not jet available at 6 months). Fatal adverse events were infrequent, and were a intratumoral hemorrhage in one patient and pulmonary embolism in another patient. Others side effects were fatigue, leukothrombocytopenia, asymptomatic intratumoral bleedings, thrombotic events.

Conclusions: Bevacizumab in combination with chemotherapy is a promising treatment for recurrent high grade gliomas with acceptable toxicity. The correlation of MGMT status and response and perfusion MRI data and response in these patients are ongoing.

O143

Adult medulloblastomas: neuropathology, resection, and 5-year survival

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Objectives: Almost 20 percent of medulloblastomas [MB] occur in adults. Behavior of adult MBs may differ from childhood MBs. We applied a novel pediatric classification system to adult MBs in anticipation that correlations could be established between histologic variables and outcome.

Methods: Retrospective study which related defined histologic variables [high cell density, balls, nodules, fine fibrillary stroma, necrosis, and prominent nucleoli] to 5-year survival in 10 adult MB patients. Ten pediatric MBs matched for tumour location, size and absence of metastases served as controls.

Results: At 5 years, 9 of 10 adults are alive. Adult MBs had high cell density [8/10]; absence of necrosis [8/10]; fine fibrillary stroma [5/10]; nodules and balls [3/10] and prominent nucleoli [4/10]. Recurrence rate was 40%. At 5 years, 2 of 10 children are alive. High cell density and fine fibrillary stroma were present in [7 of 10]; necrosis, balls, and nodules were absent in 9/10. Recurrence rate was 30%. Differences between adult and paediatric MBs in prevalence of histologic tumour variables are not significant.

Conclusion: Adults MB patients are more likely to survive longer than pediatric MB patients but are more likely to develop local recurrence or distal metastases. Survival differences between

adults and children are unlikely to be related to histology. Results of this pilot study indicate that the novel classification system for predicting outcome of pediatric MB has potential for use with adult MB.

O144

WHO Global Stroke Initiative: prospective population based stroke survey in Mumbai, India

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Background: We aimed to initiate a prospective community based stroke registry in Mumbai on subjects having "first ever stroke" (FES), and to collect data on annual incidence, stroke sub-types and case fatality at 28 days between January 2005, and December 2006.

Methods: A well-defined community with verifiable census data and representative of population structure of Mumbai was selected. Of 337,391 permanent residents, 156,861 people aged over 25 years who were eligible for survey were screened. WHO's STEPwise approach to stroke surveillance (Version 2) was the operational protocol.

Findings: 521 new cases of stroke (cerebrovascular disease) were identified; of these 456 (238 males and 218 females) had FES indicating an annual incidence of 145 per 100,000 people (95% CI: 120–170); age standardised rate (to 1996 world population by direct method of Segi): 152 FES per 100,000 people per year (CI 95% –172). Mean age was 66 yrs (SD± 13.60), women (mean age 68.9 years SD ± 13.12) were older than men (63.4 years SD ± 13.53).Stroke diagnosis was supported by CT in 407(89.2%) of 456 FES cases: 366(80.2%) had Ischaemic stroke, 81 (17.7%) had hemorrhagic stroke and 9(1%) were of unspecified category. Hypertension (blood pressure $>$ 140/90 mm Hg) alone or in various combinations was present in 378(82.8%) cases. By 28 days, 136 (29.8%) of 456 patients with FES died; 82 (17.9%) were stroke deaths, whereas 54(11.8%) deaths were related to comorbid disorders. Of 320 survivors 38.5% had moderate to severe disability (Modified Rankin score 3–5).

Interpretation: The results of Mumbai registry are similar to those reported from China and other industrialized cities such as Perth (Australia), Erlangen (Germany), and South London (UK). Similar studies from other regions of India will help in planning intervention and prevention strategies.

Funding: International Stroke Society and LKMM Trust Research Centre.

Oral session 22

Child neurology

O145

Clinical and laboratory findings in children with neuromyelitis optica: a long-term follow-up

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Neuromyelitis optica (NMO) is rarely seen in childhood.
We described clinical, radiological, cerebrospinal fluid findings, NMO-IgG results and prognosis in children with NMO.

There were 4 girls and one boy in this group. The ages of onset were 5, 7, 8, 9 and 11 years with the index event of bilateral ($n = 3$) and unilateral ($n = 2$) optic neuropathy. The second event occurred as transverse myelopathy in all the children with 6 months,1,2,3 and 7 years intervals between the first and the second index events. All the children had multiphasic course. Oligoclonal bands were positive in cerebrospinal fluid only one case; NMO-IgG detected in 4 children.Duration of follow-up were 6, 9, 12, 19 years. All the children had typical cervico-dorsal spinal cord lesions extended longer than 3 vertebra bodies and only three cases developed atypical cerebral lesions during follow-up period.

Final etiologic diagnoses were made only two children as systemic vasculitis and biopsy-proven inflammatory demyelinating disorder consistent with multiple sclerosis.

All the children responded to corticosteroids and azathioprine in the early stages of clinical picture, but two cases developed severe relapses in spite of PLEX and Rituximab in the later period of disorder. EDSS scores of the cases at January 2009 were 3.0, 3.5, 4.0, 7.5 and 8.5.

This study revealed that NMO was complex and heterogenous disorder in the spectrum of inflammatory demyelinating disorders and childhood-onset cases were very similar to adult-onset cases in terms of clinical and laboratory aspects.

O146

Neuromyelitis optica: disease onset in relationship with infections and vaccinations

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Objectives: Neuromyelitis optica (NMO) is an uncommon but life-threatening demyelinating disorder. With the discovery of the NMO antibody in 2004, diagnostic criteria have been revised. Relationships with preceding infections and/or immunizations have been well studied in other demyelinating disorders with positive correlation with acute disseminated encephalomyelitis and negative correlation with multiple sclerosis (MS). There have been several case reports only linking specific vaccinations or infections as a precipitating factor for NMO, but this correlation has not been systematically studied in children.

Methods: Charts were retrospectively reviewed for patients under 21 years old who presented to Cleveland Clinic in 2004 or after and were subsequently diagnosed with MS or NMO based on McDonald and Wingerchuk revised diagnostic criteria, respectively. Data collection included general demographics, clinical presentation, MRI, CSF, serum NMO antibody (NMOAb), treatment, and immunization record. Descriptive data, Fisher's exact, and Wilcoxon sum rank test were used as appropriate. All tests were two-tailed and performed at a significance level of 0.05. SAS 9.2 software (SAS Institute, Cary, NC) was used for all analyses.

Results: Nine NMO patients were identified with complete vaccination records obtained on six. Five were NMO antibody positive. Twelve control MS patients were matched for age and gender with no statistical difference between the groups. Symptom onset ranged from 7 to 16 years old in the NMO group (range 7 to 13.9 years for NMOAb positive and 9.5 to 15.8 years for NMOAb negative group). There was a predominance of females (7:2) and African-Americans (7:2). All NMO patients were treated with steroids, 4/9 with IVIG, and 6/9 (including all five NMOAb positive) were started on azathioprine. There was no correlation with disease onset and any vaccinations (hepatitis B, haemophilus influenzae type B, polio virus, diphtheria, tetanus, pertussis, pneumococcus, mumps, measles, or rubella). Six of 9 had preceding infections within one week of onset although statistical significance was not reached ($p = 0.08$).

Conclusion: Although sample size is small, our study suggests that there may be a correlation between NMO onset and preceding infections. There is no evidence of any childhood vaccinations as a precipitating factor for NMO. As the fundamental cause of the presumed autoimmunity in NMO remains elusive, further studies with larger sample size are needed.

O147

Locked-in syndrome in children: report of 5 cases and review of the clinical and ethical challenges

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Objectives: The development of intensive care has considerably increased the number of children surviving acute brainstem damage. Some children may awaken from their coma being nearly completely paralyzed and only able to communicate via small eye movements. This condition, coined locked-in syndrome (LIS) [1], is defined by (1) the presence of sustained eye opening; (2) preserved awareness; (3) aphonia or hypophonia; (4) quadriplegia or quadriparesis; and (5) a primary mode of communication that uses vertical or lateral eye movement or blinking. The rarity of LIS in children causes the diagnosis to be oftentimes missed or delayed [2]. Additionally, there is not much literature informing neurologists and and medical professionals about the management of LIS in children.

Methods: We here report five cases of LIS in children and adolescents and review the literature on this very challenging medical condition.

Results: Our case series and review of the literature shows that the most common etiology in children is ventral pontine stroke (20 out of 33 published cases including our 5 patients; i.e., 61%), most frequently caused by a vertebrobasilar artery thrombosis or occlusion. Concerning prognosis, two of our reported cases died (3 months and 2.5 years after onset; the former after treatment withholding) and 3 survived (one up to 11 years post-insult) remaining with a severely handicapped motricity but meaningful self-scored quality of life. We also observed that most pediatric LIS patients show some motor recovery (11 out of 31; 35%) while in 26% "good recovery" was reported (16% remained quadriplegic and anarthric and 23% died).

Conclusion: We here summarized our experience concerning the problem of caring for LIS in children. Due to the rarity of this condition at young age, its diagnosis may be missed and patients may wrongly be considered as being in a coma, vegetative state or akinetic mutism. The reported and reviewed data stress the need for physicians to carefully interpret signs and symptoms of LIS.

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O148

Mitocondriopathies: a paediatric series

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Introduction: Mitocondriopathies are the metabolic diseases most frequent in children and result from the deficit of respiratory chain enzymes. They have a varied phenotypic presentation and commonly involve nervous system. No association was found between the type of enzyme deficit and the clinical manifestations, however there are no data regarding the severity of the deficit and the clinical presentation.

Objectives: Determine the frequency and type of neurological manifestations and its association with the enzyme deficit severity in a series of pediatric patients with mitochondrial pathology.

Methods: Retrospective study in which clinical files of all patients with mitochondrial pathology admitted in the Neuropediatrics and Metabolic Diseases Unit of the Department of Paedriatrics of Hospital de Santa Maria between 1998 and 2008 were reviewed. SPSS 14.00 was used to analyze the data.

Results: Forty eight files were reviewed with the inclusion of 29 patients in the data analysis with probable or definitive diagnosis of mitochondrial pathology. Sixteen patients were female with a mean age of 3.2 years. Twenty five patients presented nervous system symptoms being delayed psycho-motor development and epilepsy the most frequent ones. Twenty four patients presented enzymatic deficit which severity did not correlate with neurological presentation.

Conclusions: In our series clinical manifestations of mitochondrial pathology have association neither with the type nor with enzymatic deficit severity.

O149

6-month US phase 3 clinical study of SNT-MC17/ idebenone in the treatment of children with Friedreich's ataxia: interim safety results

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Objectives: Idebenone is a ubiquinone analogue that serves both as a potent antioxidant and as an electron carrier that facilitates electron transport across the mitochondrial respiratory chain. A phase 3 study in the US is currently being conducted to evaluate the efficacy and safety of idebenone in US children with Friedreich's ataxia (FRDA).

Methods: This is an ongoing, double-blind, placebo-controlled, 2-centre US study (IONIA; NCT00537680). Eligible participants are 8- to 17-year-old ambulatory patients with genetically confirmed FRDA and mild-to-moderate neurological impairment. Patients were randomised to receive placebo or 1 of 2 body weight-adjusted doses of idebenone. Patients weighing less than or equal to 45 kg received 450 or 1,350 mg idebenone daily (~10–20 mg/kg), whereas those weighing more than 45 kg received 900 or 2,250 mg daily (~30–50 mg/kg). Safety was evaluated through adverse events (AEs) reporting, electrocardiograms (ECGs), standard clinical assessments, and laboratory tests of urine and blood samples.

Results: The study has completed enrollment of 70 patients and blinded interim safety data are presented. Of the first 46 patients providing data at interim, none have discontinued treatment. Median age was 12 years. Gastrointestinal disorders were the most frequent class of AE (24 [19%] of 127 events reported). The vast majority of AEs (88%) were mild. The only 2 serious AEs reported, chest pain and idiopathic thrombocytopenic purpura, were considered unrelated to the study drug and occurred in 2 patients who had histories of these events before the study was begun. No patients experienced clinically significant changes in ECGs, vital signs, or laboratory test results.

Conclusions: Interim safety data suggest that idebenone is safe and generally well tolerated in paediatric patients with FRDA.

This study was funded by Santhera Pharmaceuticals.

O150

Virtual reality visual feedback cues for gait improvement in children with gait disorders due to cerebral palsy

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Objectives: To study the effects of gait training with visual feedback cues on the walking abilities of children with gait disorders due to CP.

Methods: A wearable virtual reality (VR) device was used to create visual feedback cues in the form of checkerboard black and white tile arrangement responding dynamically to the patient's motion. Ten randomly selected children of average age 13.3 ± 6.2 years with gait disorders due to CP participated in the study. Baseline performance (walking speed and stride length along a 10 m straight track) was measured before device use. Following 20 min training with the device and 10 min rest, performance without the device was measured again and compared to the baseline performance.

Results: The average improvement in walking speed was 21.70 ± 36.06%. For participants with baseline walking speed below the median improvement was 35.75 ± −47.76% and for participants with baseline walking speed above the median improvement was 7.65 ± 12.85%. Average improvement in stride length was 8.72 ± 9.47%. For participants with baseline stride length below the median improvement was 12.78 ± 12.13% and for participants with baseline stride length above the median improvement was 4.67 ± 3.69%. For participants with age below the median improvement in walking speed was 9.59 ± 23.06% while for participants with age above median improvement was 33.81%±44.96%. For participants with age below the median improvement in stride length was 9.41 ± 11.97% while for participants with age above the median improvement was 8.03 ± 7.57%.

Conclusion: VR visual-feedback cues can improve gait parameters in children with gait disorders due to CP. Baseline walking speed and stride length are good predictors of improvement, with higher improvement associated with lower baseline performance. Age is a good predictor of improvement in walking speed, but not in stride length, with significantly higher improvement in walking speed found in children of older age.

Oral session 23

Dementia

O151

Diffusion tensor MRI assessment of white-matter fibre changes in Alzheimer's disease and mild cognitive impairment

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Objective: White matter (WM) changes have been reported by several histopathological studies in Alzheimer's disease (AD). These changes are heterogeneous, ranging from mild myelin attenuation to marked axonal loss and reactive gliosis. Diffusion tensor (DT) MRI, which is sensitive to WM tissue changes in vivo, may provide specifc markers for regional changes in WM. Here we wished to assess the integrity of the normal appearing WM in the major fiber bundles in subjects with AD and mild cognitive impairment (MCI).

Methods: Twenty-one AD patients (age: 75 + 8 SD, women: 9, MMSE: 19 + 6), eleven amnesic MCI (age: 69 + 8 SD, women: 5, MMSE: 26 + 1) and fifteen healthy controls (age: 70 + 6SD, women: 9, MMSE: 29 + 2) underwent a clinical and neuropsychological evaluation, and brain conventional and DT-MRI on a 1.5T scanner. Subjects with major vascular damage were not included into the study. Mean diffusivity (MD), fractional anisotropy (FA), as well as parallel and radial diffusivities were measured in the normal-appearing WM of eight major fiber bundles (corpus callosum, cingulum, fornix, corona radiata, arcuate, uncinate, inferior longitudinal and inferior fronto-occipital fasciculi), using an atlas-based automated technique.

Results: Compared to controls, MCI and AD patients showed cognitive deficits in all the domains investigated ($p < 0.02$, ANOVA with Bonferroni correction). MD was significantly increased in AD patients compared to controls in the corpus callosum, cingulum, arcuate, inferior longitudinal fasciculus, and corona radiata ($p < 0.05$, ANOVA with Bonferroni correction). FA values did not differ between AD patients and controls ($p > 0.17$); this pattern was likely due to an increased axial diffusivity ($p < 0.007$) coupled with a non-significant increase in radial diffusivity ($p > 0.08$). Diffusivity and FA values from MCI patients did not differ from those of AD patients and controls ($p > 0.05$). However, a trend for progressively increasing MD from normal aging to AD was detected in all the tracts (p (trend) <.05), except for the fornix ($p = 0.43$).

Conclusions: The major brain WM fiber bundles show diffusivity alterations which followed the trajectory normal aging/MCI/AD. These changes are likely to be secondary to Wallerian degeneration of WM fiber tracts following neuronal injury.

O152

Diffusion tensor-based tractography of language networks in semantic dementia

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Objective: Cognitive deficits in semantic dementia (SemD) have been typically attributed to anterior temporal lobe (ATL) grey matter (GM) damage. However, certain aspects of the syndrome could be related to altered connectivity between language pathways involving the temporal lobe. In this study we investigated the principal language-related cerebral pathways in SemD using diffusion tensor imaging (DTI)-based tractography and combine the findings with cortical anatomical and functional MRI data.

Methods: We used DTI-based tractography in five SemD patients and eight controls to investigate the left superior longitudinal (SLF), inferior longitudinal (ILF) and uncinate fasciculi. From each tract, mean diffusivity (MD), fractional anisotropy (FA), and parallel and transverse diffusivity were obtained. Voxel-based morphometry (VBM) was used to assess GM and white matter (WM) atrophy and functional MRI (fMRI) to investigate the neural correlates of reading in the same patients.

Results: SemD patients had significantly higher MD, and parallel and transverse diffusivity in the ILF and uncinate fasciculi. In the SLF, the arcuate component showed significantly higher MD, and parallel and transverse diffusivity, while the fronto-parietal component was relatively spared, with a significant difference observed only for radial diffusivity. Compared with controls, SemD patients also demonstrated significantly lower FA in all tracts except for ILF. The distribution of MD values showed that damage was more severe in the anterior portion of ILF and the portion of the uncinate fasciculus in the temporal pole. The left parietal cortex did not show significant volume changes on VBM and demonstrated normal fMRI activation in response to phonologically-based reading.

Conclusions: SemD is associated with anatomical damage to the major superior and inferior temporal WM connections of the left

hemisphere, with relative sparing of the fronto-parietal component of the SLF. These findings may contribute to explain the dissociation between marked single-word and object knowledge deficits, and sparing of phonology and fluency in patients with SemD.

O153

Self-perceived memory impairment predict Alzheimer's disease but not vascular dementia in independent elderly with white matter changes. Results of the LADIS study

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Objective: To ascertain if self-perceived memory impairment in independent elderly with white matter changes (WMC) is predictor of dementia.

Methods: The LADIS (Leukoaraiosis and Disability) is a prospective European study that evaluates the impact of WMC on the transition of independent elderly into disability. Patients with WMC were enrolled because of minor neurological, cognitive or motor complaints, or incidental findings on cranial imaging, without impact in daily living activities. Subjects were evaluated at baseline and yearly during 3 years with a comprehensive clinical and functional protocol, including a neuropsychological battery (MMSE, ADAS-Cog, VADAS-Cog extension, Trail-making and Stroop tests) and evaluation of depression (DSM-IV criteria and the geriatric depression scale (GDS)). Irrespectively of the referral cause, a question about memory complaints was done in all patients. In each follow-up visit, patient cognitive status was classified as demented, cognitive impairment not demented and no cognitive impairment, according to usual clinical criteria, and then classified according to dementia subtypes. MRI was performed at entry and at the end of the study. WMC severity was rated according to the Fazekas scale. To assess predictors of dementia and dementia subtypes we used survival Cox regression analysis.

Results: 639 subjects were included (74.1 $\pm$ 5 years old, 55% women, 9.6 $\pm$ 3.8 years of schooling). 168 patients (26%) were enrolled due to minor cognitive complaints without any impact in independency. From the total sample, 63% (399 patients) had complaints from memory at baseline. 89% (568), 78.4% (501), and 75% (480) of the patients from the initial sample were followed-up in clinical visit at year 1, 2 and 3. At the end of the study 90 patients were demented (Alzheimer dementia with vascular component, 34; Vascular dementia, 54; Fronto-temporal dementia, 2) and 147 patients had cognitive impairment not dementia. Using survival Cox regression we found self-perceived memory impairment at baseline as independent predictor of dementia in last follow-up. Considering dementia subtype, self-perceived memory impairment was predictor of AD with vascular component, independently of age, education, WMC severity, GDS score, temporal atrophy and cognitive measures at baseline, but not predictor of Vascular dementia.

Conclusion: Self-perceived memory impairment predicts Alzheimer dementia but not Vascular dementia in independent elderly with WMC.

O154

rs5848 variant influences GRN mRNA levels in brain and peripheral mononuclear cells from patients with Alzheimer's disease

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Objective: To test the effect of progranulin gene (GRN) variants on susceptibility to Alzheimer's disease (AD) and on expression levels in brain tissues, Peripheral Mononuclear Cells (PBMC) and cells isolated from cerebrospinal fluid (CSF).

Methods: An association study of rs9897526 and rs5848 was carried out by allelic discrimination in an Italian population of 355 patients with AD and 401 controls and in a replication population of 355 European American cases and 343 controls. Expression analysis was carried out in parietal lobe of 68 neuropathologically-confirmed AD, as well as in PBMC and in cells isolated from CSF by Real-Time PCR, to test the influence of such variants on GRN expression.

Results: None of the variants tested likely acts as a susceptibility factor. rs9897526 anticipated the onset of the disease. GRN expression in the parietal lobe of AD cases showed a 0.76-fold decrease over controls (1.31 $\pm$ 0.07 vs. 1.73 $\pm$ 0.12, $p = 0.0025$). Patients carrying the rs5848 TT genotype presented the lowest GRN expression levels (0.96 $\pm$ 0.12, $p = 0.014$). Despite no significant differences were found in the relative PBMC and CSF GRN expression between patients and controls, stratifying patients according to the presence of rs5848 T allele, a statistically significant 0.57-fold decrease in GRN mRNA levels over C carriers was found in PBMC (0.70 $\pm$ 0.12 vs. 1.22 $\pm$ 0.23, $p = 0.04$). This effect was dose-dependent, as patients carrying the TT genotype showed lowest GRN mRNA levels in PBMC (TT = 0.46 $\pm$ 0.14; CC = 1.22 $\pm$ 0.23, $p = 0.013$).

Conclusions: GRN is not a risk factor for sporadic AD but likely acts as disease-modifying gene.

O155

Role of amygdala in odour identification: diagnostic contribution for Alzheimer's disease

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Objectives: Impairment of olfactory functions in Alzheimer's disease (AD) is well known; it starts already in the early stage of mild cognitive impairment (MCI) with a deficit of odor identification. This is attributed to early involvement of mesiotemporal lobe structures in neurodegenerative process in AD; however the role of each single structure is still uncertain.

Methods: 10 AD patients according to NINCDS-ADRDA criteria, 28 MCI patients subdivided into amnestic MCI (aMCI, $n = 19$) and non-amnestic MCI (naMCI, $n = 9$) according to Petersen's

criteria and a control group ($n = 10$) underwent a smell identification assessment using the University of Pennsylvania Smell Identification Test (UPSIT) and a smell identification test developed at our Memory Clinic—the Motol Hospital Smell Test (MHST). Volume of left and right amygdala was measured in all subjects using magnetic resonance imaging.

Results: The volume of both left and right amygdalas was significantly reduced in AD and aMCI patients compared to the control group ($p < 0.05$); reduction in naMCI group was not statistically significant ($p > 0.05$). Scores achieved in smell identification tests correlated with the volume of left and right amygdala ($p < 0.01$).

Conclusion: Reduced volume of both amygdalas in AD patients corresponds with previous studies and anatomical-pathological basis of AD. Amygdalar volume was reduced as well in aMCI and intact in naMCI group which supports hypothesis that aMCI converts to AD, whereas naMCI into non-AD dementias. High correlation between odor identification performance and amygdalar volumes suggests that amygdala plays a significant role in this olfactory process and its atrophy conduces to odor identification deficit in AD patients.

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Oral session 24

Infection

O156

Comparative gene expression analysis in VZV-infected versus noninfected human dorsal root ganglia neurons

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The most common neurological disease caused by any of the herpesviruses is zoster, which is a result of reactivation of latent varicella zoster virus (VZV) from sensory neurons. The spectrum of neurological disorders caused by VZV infections has expanded over the last few decades, but hardly any knowledge has emerged about the biology of VZV-host interactions, especially during viral latency. In the present study we explored the transcriptional profile in VZV latently infected human dorsal root ganglia (DRG) by whole genome microarrays.

Eighteen DRG from 6 individuals were first screened for the occurence of a latent VZV-infection using VZV62-immunohistochemistry. RNA from these DRGs was tested for its integrity and RNA samples with good RNA quality were selected for cDNA microarrays. We used 3 VZV-negative and 5 VZV-positive DRGs from two individuals. The microarray analysis was performed with the Affymetrix GeneChip technology. For statistical analysis all VZV-negative versus all VZV-positive DRG (comparison 1) as well as the VZV-positive and VZV-negative DRGs from the same individual (comparison 2) were compared. A more than 1.5-fold change was found in 67 transcripts (comp. 1) and in 119 transcripts (comp. 2).

In particular a downregulation of the transcription factors EGR1/2 (early growth response 1/2) and cFOS/FosB (v-fos FBJ murine osteosarcoma viral oncogene homolog), and the chemokine CCL2 was noticed in both comparisons. To verify these transcriptional changes a quantitative RT-PCR was performed with RNA from 21 VZV positive and 7 VZV negative DRGs. A significant downregulation of EGR1 by a factor of 2.7 could be detected in VZV positive DRGs ($p < 0.05$). In addition, FosB was downregulated by a factor of 39 in VZV positive DRGs ($p < 0.05$). To further substantiate a relation of VZV latency and the expression of cellular transcription factors we correlated the VZV DNA copy number in the DRGs with the transcript level of EGR1. EGR1 negatively correlated with the VZV DNA amount in the ganglia ($p < 0.005$).

During VZV latency certain cellular transcription factors are downregulated. It is known that lytic VZV replication is in part dependent on cellular transcription factors like AP-1. We hypothesize that VZV downregulates cellular transcription factors during latency to prevent transactivation of viral genes that would lead to lytic reactivation. Our work provides a first indication of how VZV latency could be maintained in human sensory neurons.

O157

An audit report of 75 cases of tetanus from a Nigerian tertiary health care facility

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Tetanus is now a rare disease in the developed world. However, it remains an important cause of death, and is associated with a high case mortality in the developing world.

Objective: All patients who were hospitalized at the State Specialist Hospital, Maiduguri from 1995 to 2009, with a final diagnosis of tetanus were retrospectively studied.

Methods: There were 44 males (mean age 30.2 years, median age 29) and 31 females (mean age 29.4 years, median age 29 years). The yearly number of patients with tetanus varied from none to ten, with a mean of five.

Results: Most of the patients belong to lower socio-economic status (SES) with low educational attainment. Eighteen had a history of a recent wound or had wound at the time of admission. In most patients, the portal of entry could not be assessed. Those with higher educational attainment had medical wound care, and received tetanus immunoglobulin. Three patients with lower SES had medical wound care, but none received tetanus immunoglobulin despite absence of childhood immunization. Most patients (81.3%) had the generalized type of disease. A mild or localized type was seen in 14 patients. No cephalic type was recorded. Wound cultures were not taken in all patients at the time of admission. The wounds were located on the lower limb or foot in 14 patients and on the finger or hand in 4 patients bitten by snakes. Most of the wounds were acquired while farming or walking through bushes. Sixteen patients had an incubation period of less than one week and eleven of them suffered from severe disease. The classical symptoms of trismus, dysphagia and muscular rigidity were present in all patients with generalized disease, while abdominal pain was seen in localized disease. The mean duration of admission was 7.3 days (range 3–23 days). Thirty-four patients had atelectasis, 16 autonomic dysfunction and 4 renal impairment. Treatment consisted of nursing in dark quiet room, wound management, administration of immunoglobulin, antibiotics, treatment of muscle spasm and instability of the autonomic nervous system and supportive care. Overall mortality was 33.3% (25 out of 75).

Conclusion: Tetanus remains a major health problem and a difficult-to-treat disease with a substantial morbidity and mortality rate. A national vaccine promotion campaign and enhanced effort to educate the public against the so-called western propaganda particularly in northern Nigeria where this study was carried out seems warranted.

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The presence of antiautonomic membrane receptor antibodies do not correlate with the brain white-matter lesions in Chagas' disease

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Introduction: Chagas' disease is endemic in Brazil and autonomic dysfunction occurs since its early phases. We previously demonstrated correlation between parasympathetic dysfunction and brain white matter lesions.

Objective: To correlate the presence of serum functional circulating antibodies with β adrenergic (Ab-β), muscarinic (Ab-M) or muscarinic and β adrenergic (Ab-Mβ) activity, the autonomic system function and brain white matter lesions in chronic chagasic patients.

Methods: In fifteen consecutive chronic chagasic patients, the autonomic nervous system was evaluated using the sinus arrhythmia test, and brain magnetic resonance imaging (MRI) was performed to detect white matter hyperintense lesions. The sera of all patients were tested to the presence of circulating functional Ab-β, Ab-M or Ab-Mβ activity, evaluating changes in cardiac rate of isolated rabbit hearts electrocardiogram.

Results: Sera from 11 of 15 chronic chagasic patients had some cardiac activity (Ab-β: 7; Ab-M: 1; Ab-Mβ: 3); however, there was no significant correlation between the presence of antibodies and the autonomic system function or the presence of hyperintensities in MRI.

Conclusion: The mechanism involved in the genesis of hyperintense lesions seen in brain MRI of chronic chagasic patients is still unresolved, although apparently related to parasympathetic dysfunction. More studies are needed to understand lesion's physiopathology.

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Atypical presentation of isolated intradural extramedullary spinal neurocysticercosis

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Background: Cysticercosis represents the most common parasitic disease affecting the central nervous system (CNS), caused by T. Solium, where humans are the intermediate host. CNS is involved in 60-90% of the cases, whereas isolated spinal cysticercosis is very uncommon.The clinical manifestations of the subarachnoid cysticercosis are due to direct compression and inflammatory reaction causing myelopathy or multiradiculopathy.

Case report: A 49 year-old man, otherwise healthy, was referred to our department for a 5 year history of recurrent atypical headache (according to IHS criteria) associated to neck stiffness. These symptoms progressively decreased in frequency but the patient later complained of a progressive severe back pain and left foot drop. He was treated with low dose steroids with only partial remission. Neurological examination showed a bilateral weakness in foot dorsiflexion (particularly in the left side, MRC 2-3) associated to lower limb hyporeflexia and hypotrophy, as well as tactile hypoesthesia with L5-S1 distribution and mild impairment of pallesthesia in the lower limbs. He underwent brain and spinal MRI which showed the presence of multiple, well-circumscribed lesions in the subarachnoid space, with cerebrospinal fluid (CSF) signal intensity, constricting thoracic spinal cord and dislocating the cauda roots. After Gd administration, cystic lesions showed peripheral enhancement suggestive of arachnoid scarring. Brain scan was normal. Blood tests were normal. CSF analysis demonstrated a mild lymphocyte pleocytosis, increased protein, and low glucose level. EMG revealed a chronic motor multiradiculopathy particularly of left L5 root and both S1 roots. A surgical procedure with T4-T5 laminectomy and biopsy was performed for resection of pathologic mass and diagnosis. After opening the dura, a firm yellowish tissue wrapping the roots was found. The pathological analysis confirmed the diagnosis of neurocysticercosis. Thus, the patient was treated with albendazole and desamethasone for 4 weeks. He recovered apart from mild weakness in the left foot dorsiflexion, while the MRI findings were stable at 2 months-follow-up.

Conclusion: We present a rare case of neurocysticercosis heralded by atypical headache presentation and primary spinal localization, successfully treated with albendazole and surgery. Cysticercosis should be always taken into consideration in the differential diagnosis of atypical headache and chronic meningitis.

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The difference by ultrasonography between ulnar neuropathy at the elbow in Brazil: entrapment or leprosy?

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The isolated lesion of the superficial ulnar nerve by leprosy is commonly seen in Brazil. Sometimes it is difficult to make the difference between entrapment and leprosy, as both can cause ulnar nerve enlargement at the elbow. Ultrasonography (US) is an accurate and easily applied test for the diagnosis of ulnar enlargement at the elbow. We compare the cross-sectional area by US of the ulnar nerve at the elbow (CSA-M) and approximately 2 cm proximal to this point (CSA-I), to try differentiate ulnar palsy due to entrapment at the elbow (UNE) and ulnar palsy due to leprosy (UNL).

The CSM-A and the CSM-I of the ulnar nerve were measured in 13 patients with UNE and 4 with UNL. Ulnar sensory and motor nerve conduction studies were performed. In all patients we performed a biopsy of the dorsal sensory branch of the ulnar nerve in the hand to confirm the diagnosis of leprosy. Reference values were obtained in 47 healthy volunteers.

The mean age of the patients was 45.17 years. In the controls the mean CSA-M and CSA—I was 6,75 and 6.14 mm^2, respectively. In UNE the mean CSA-M was 14.6 and the mean CSA-I was 6.14. In UNL the mean CSM-M was 13.5 and CSM-I was 12.5 mm^2.

In UNL the nerve was enlarged at the elbow and above it and in UNE there was no thickness above the elbow, We conclude that US of the ulnar nerve at the elbow and 2 cm above it is an accurate and easily applied test to differentiate UNE from UNL.

POSTER SESSIONS

Poster session 1

Cerebrovascular disorders: mechanisms and treatment

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Ischaemic stroke after Takotsubo cardiomyopathy

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Background: Takotsubo cardiomyopathy or 'stress cardiomyopathy' is a rare syndrome, that looks like an acute coronary syndrome with, ECG changes, elevated troponin and a left ventricular dysfunction which is seen as the typical reversible 'apical ballooning' in the ventriculography, without any signs of coronary heart disease in the coronary angiography. It affects mostly elderly women with previous emotional, psychological or physical stress, and generally carries an excellent prognosis.

Cases reports: We report two cases of female patients, with 68 and 89 years old, who suffered an ischemic stroke during the first week after hospital admission by an acute coronary syndrome diagnosed as Takotsubo cardiomyopathy. In the first case, patient presented with sudden right upper limb weakness and parestesia, recovering a few days over. CT scan showed and acute ischemic lesion in the left rolandic area. The second one developed a right total anterior circulation infarction, with neglect, left homonymous hemianopsia and hemiparesis due to an infarction in the area supplied by the inferior division of the right middle cerebral artery. Both patients had hypercholesterolemia. The second one was also hypertensive and experienced an lacunar stroke with right hemisensory defect six months earlier, recovered with no sequela. Further etiological work-up was negative in both patients for any other cardioembolic and for carotid stenosis in the first one. The second patient was lost for follow-up and not submitted to any other vascular investigation.

Discussion: There are only a few case reports found in the literature of ischemic stroke or TIA occurred in closed temporal relationship with Takotsubo cardiomyopathy. Considering the potential cardioembolic mechanism of acute left ventricular dysfunction, those address an etiological role for this syndrome in the context of stroke and TIA. Even we could not prove the absence of an alternative atherosclerotic mechanism for stroke in the second patient, our cases might add further support on the relevance of Takotsubo cardiomyopathy as a cause of ischemic stroke and TIA.

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Cardioembolic stroke and functional outcome after IV thrombolysis

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Background: It has been suggested that an embolus obstructing a cerebral artery may be more susceptible to lysis if it is due to embolism from the heart rather than from a lesion in the extracranial arteries. A dramatic improvement of symptoms within the first hours to days is regularly encountered in acute ischemic stroke. The underlying mechanism is presumed to be rapid migration of an embolus lodged in a large cerebral artery to its distal branches. This is particularly seen in cardioembolic and not in atherothrombotic stroke.

Objective: To investigate if cardioembolic stroke is more susceptible to thrombolysis than atherothrombotic stroke.

Methods: We investigated the relation between cardiogenic embolism and functional outcome in a hospital based consecutive patient registry comprising 300 ischemic stroke patients treated with rtPA. Functional outcome of patients with and without cardioembolic stroke was compared. Favourable outcome was defined as a modified Rankin Scale (mRS) score 0–2 at 3 months.

Results: 110 patients (37%) had cardioembolic stroke; atrial fibrillation ($n = 102$), acute myocardial infarction ($n = 2$), myxoma ($n = 1$), thrombus ($n = 3$), prosthetic heart valve ($n = 1$), and patent foramen ovale combined with atrial septal defect ($n = 1$). Baseline characteristics and mean NIHSS scores at admittance were not different between the two groups. 45% of patients with cardioembolic stroke had a favourable outcome after thrombolysis versus 55% of non-cardioembolic stroke patients. Cortical infarcts caused by embolism from the heart ($n = 98$) had a good outcome in 43% of patients versus 49% in atherothrombotic stroke ($n = 147$). In patients with lacunar infarcts this was 64 versus 77%. 56% of patients with symptomatic carotid stenosis ($n = 40$) had a favourable outcome.

Conclusion: The prevalence of cardioembolic stroke in our rtPA treated patient cohort was higher than we expected considering that embolism from the heart causes about one-fifth of all ischemic strokes. The suggestion that cardioembolic stroke is more susceptible to rtPA treatment could not be confirmed in our population.

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Reversible postpartum angiopathy: all is well when it ends well

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Introduction: Reversible cerebral vasoconstriction syndromes (RCVS) encompass a group of disorders characterized by prolonged but reversible multifocal vasoconstriction of cerebral arteries, often without an identifiable cause. RCVS have been reported to occur in various clinical settings, namely during pregnancy or in the postpartum period—postpartum angiopathy (PA). The later is typically characterized by acute-onset, severe, recurrent headaches, with or without additional neurological signs and symptoms, with onset within days after uncomplicated labor and delivery.

Clinical case: A previously healthy 28-year-old woman underwent a caesarean delivery, in the 39th week of an uncomplicated pregnancy. On the fourth postpartum day, the patient developed complaints of severe and recurrent holocranial headache, persisting in the following days. A week later, acute-onset of dysarthria and right brachiofacial hemiparesis occurred. Blood and cerebrospinal fluid testing results were unremarkable. Brain-MRI confirmed the presence of several multifocal ischemic lesions. Transcranial triplex scan demonstrated bilateral moderate vasoconstriction of middle cerebral arteries. Empirical symptomatic treatment with calcium channel-blocker (nimodipine) was initiated, determining clinical improvement. Subsequent evaluation with transcranial triplex scan and conventional brain angiography showed no features of vasoconstriction. Neurological deficits gradually disappeared within weeks. The follow-up at 3 and 6 months confirms full neurological recovery.

Conclusion: In the postpartum setting the differential diagnosis of new onset headaches is quite extensive, comprising eclampsia, dural sinus thrombosis, intracranial bleeding and postpartum angiopathy. The authors present a case which underlines the clinical and imagiological hallmarks of Postpartum Angiopathy. Although its pathophysiology is still unclear and the treatment remains empirical, the prognosis tends to be very favourable.

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The role of jugular vein valve incompetence in defining transient global amnesia aetiology

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Objective: Different etiologies have been proposed for transient global amnesia (TGA), such as venous congestion and microvascular damage. Jugular vein valve incompetence (JVI) is commonly described in TGA patients, but its contributing role in TGA pathogenesis is still unknown. In the present study, we investigated the possible relationship between JVI and pathogenetic mechanisms in TGA.

Methods: Two-hundred forty-three TGA patients underwent clinical and neurological assessment. Demographic characteristics, TGA precipitating factors and vascular comorbidities were carefully recorded. In each patient, JVI was assessed by Doppler ultrasonography.

Results: TGA patients were grouped according to the presence ($n = 171, 70.4\%$) or the absence ($n = 72, 29.6\%$) of JVI. TGA patients with JVI showed a higher presence of precipitating factors, namely Valsalva-like manoeuvre (JVI+ vs. JVI-, 35.8 vs. 17.1%, $p = 0.004$) and emotional stress (36.6 vs. 21.4%, $p = 0.023$); whilst these patients had less vascular comorbidities, namely hypertension (37.2 vs. 51.4%, $p = 0.047$) and carotid arteriosclerosis (20.5 vs. 31.9%, $p = 0.050$).

Conclusions: These findings argue for at least two different TGA-associated mechanisms, defined by JVI. On one hand, JVI associated with Valsalva-like manoeuvre and emotional stress supported the venous blood congestion hypothesis; on the other, the absence of JVI and the higher frequency of vascular comorbidities claimed for the microvascular damage hypothesis.

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Glutamate and inflammatory cytokines in focal cerebral ischaemia: a translational study

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Introduction: Glutamate and cytokines are involved in the pathophysiology of cerebral ischemic damage. It is not clear if glutamate is a specific biomarker of brain damage or can be increased in other pathological conditions. Aim: to evaluate the glutamate and cytokines (IL-6,TNFa) plasma levels in 3 groups: (1) acute cerebral infarct (CI) humans, (2) rat model of focal cerebral ischemia, (3) rat model of tissular stress.

Methods: Groups: humans (G1): Prospective case-control study. Cases ($n = 58$):acute CI patients;Controls ($n = 19$):acute non-neurological diseases. Variables: glutamate, TNF receptor 1 (TNF-R1) and IL-6 within first 12 h after symptoms onset and at 72 h; stroke severity (NIHSS), disease severity (APACHE); CI volume; 3-months functional status (mRS). Embolic stroke model (G2): Long-Evans(LE) rats. Subjects($n = 5$): internal carotid artery embolization with autologous clot. Tissular stress model (G3): LE rats ($n = 5$) subjected to muscle compression in back paw during 180 m. Variables (rats): glutamate, TNFa and IL-6 at 3 and 72 h (G2 and G3); volume of ischemic lesion (H&E) and neuronal death (TUNEL) (G2).

Results: Human: glutamate and cytokines were increased over time. However, they did not correlate with infarction size and tended to be higher in non-neurological damage. A positive correlation was found between IL-6 at 72 h and stroke severity ($r = 0.543, p < 0.0001$) as well as 3-months mRS ($r = 0.401$; $p = 0.004$) in cases; and between IL-6 and APACHE score on admission in controls ($r = 0.497$; $p = 0.036$). Glutamate levels did not correlate with disease severity. Rat: Glutamate and cytokines were increased over time, but did not correlate with infarct size and neuronal death. There were no differences between subjects and sham-operated rats. Moreover, G3 showed higher glutamate levels at 3 h($p = 0.08$) and 72 h ($p = 0.028$) than G2.

Conclusion: Plasma glutamate and cytokines are elevated in brain infarction. However, they are even more elevated in other tissues damage, both in human and animal models.

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The role of inflammatory markers in carotid artery stenosis aetiology

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Background: The main role of internal carotid artery stenosis in the pathogenetic mechanism of ischemic stroke is distal embolisation originating from unstable carotid plaque. Plaque morphology obtained by Carotid Duplex Sonography has been considered to define the plaque at risk for cerebrovascular events. The aim of this study is to find a correlation of several inflammatory markers with symptomatic carotid stenosis and signs of unstable carotid plaques in Carotid Color Coded Duplex Sonography.

Material and method: We investigated 65 patients (mean age: 66.29 ± 7.77; 45 men) with internal carotid artery stenosis. 39 patients were symptomatic (26 stroke, 3 RIND, 8 TIA, 2 amaurosis fugax). With carotid duplex sonography we evaluated the degree of stenosis (we divided it in three categories: <60, 60–80, >80%), surface and plaque morphology. Serum levels of white blood cells (WBC), monocyte count, erythrocyte sedimentation rate, fibrinogen and CRP were measured.

Results: The mean values of white blood cells and monocytes were significantly higher in symptomatic versus asymptomatic group (WBC: 7.70 vs. 6,36 $p = 0.001$; monocyte count: 0.66 vs. 0.52 $p = 0.02$). Patients with severe stenosis (>80%) or ulcareted plaque surface had the highest values if inflammatory markers,but the results were statistically significant only for WBC. Patients with echolucent carotid plaques had significantly higher mean values of some inflammatory markers than patients with echogenic carotid plaques (WBC: 7.77 vs. 6.54; $p = 0.01$; monocyte count: 0.67 vs. 0.53, $p = 0.04$)

Conclusions: Inflammatory markers can be usefull in detection of patients with carotid plaques at high risk of destabilization. The degree of inflammatory process in carotid plaque can be measured with standard inflammatory markers. Echolucent carotid plaques are correlated with inflammation in the plaque.

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The role of echocardiography in the investigation of stroke: a case report of myxoma and cardioembolic stoke in a young female

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Introduction: Myxomas are primary neoplasms of the heart found mainly in the left atrium, in young individuals and in women. There's an overall incidence of 0.001–0.3% found occasionally in autopsies1. Myxoma material or its thrombotic complications might embolize to the encephalon though rare cases have been described. As a cause of cardioembolic stroke, the incidence ranges between 1:250 in young individuals and 1:750 in the elder.
Echocardiogram is gold standard for its diagnosis, being the transesophageal (TEE) the most accurate1.

Case presentation: We present a 38-years-old female with a past history of ischemic stroke six moths before, admitted and investigated in another hospital, no cause being found. As a part of the investigation she performed a transthoracic echocardiogram (TTE) which was negative for cardiac embolism. She also reported an important weight loss in the past year with iron-deficiency anaemia.
The patient presented in our emergency department with complaints of disarthria and a left hemiparesis. The MRI showed an infarct on the right frontal subcortical white matter. During the investigation in our unit, a TTE was preformed and a mass lesion was found on the left atrium, with a length of 24 × 18 mm. On the TEE the mass was reported to have a larger diameter of 27 × 28 mm.
She was submitted to cardiac surgery with extraction of the mass. On the pathological studies this mass had histological features that confirmed it as a myxoma. On the lab work-up, anticardiolipin antibodies were found to be positive.

Discussion: The particular interest of this case is that myxomas are a very rare cause of stroke, being 0.5% of all cardioembolic strokes. TTE although presenting a high sensitivity for intracardiac mass lesions, it might be confusing or equivocal, especially in obese patients. In this patient the first TTE was negative and the second misjudged the size of the mass. Only the TEE was able to identify and characterize the myxoma. Echocardiography is a technique that largely depends on the experience and accuracy of the technician, fact that can alter significantly its sensitivity.
There are some authors that describe an immune reaction secondarily to myxomas, which may explain, in part, the positivity for anticardiolipin antibodies in this patient.

Conclusion: This case illustrates the importance of echocardiography in the investigation of stroke, especially in young patients, when cardioembolic source is suspected

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Improving the outcome of cardioembolic stroke with early antioxidant therapy

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Background: Oxidative stress has a major role in the pathogenesis of cerebral ischaemia/reperfusion injuries. Since cardioembolic strokes have a high rate of spontaneous recanalisation, antioxidants should have good results in this subtype. In our study we evaluated the effect of antioxidant treatment with α-lipoic acid (LA) started in the first 24 h after stroke onset on the outcome of cardioembolic (CE) stroke.

Method: CEs were selected from 2 consecutive series of acute ischaemic stroke patients admitted to our hospital according to the TOAST criteria. Each patient had demographic data recorded, the NIHSS score and the Barthel index (BI) evaluated at admittance and discharge. Oxidative stress was assessed by measuring the serum malondialdehyde (MDA) levels with the tiobarbituric acid method at admittance and on days 3 and 7. The control group received treatment according to current guidelines, while the second group received in addition 600 mg of LA intravenously for 7 days. The two-tailed independent-samples T test was used for comparison of the two groups, and statistical significance was set at $p < 0.05$.

Results: The 34 patients in the LA-treated group, although slightly older and in worse condition on admittance than the 18 cases of the control group (mean NIHSS score 10.8 vs. 9.1; mean BI 68.5 vs. 76.1; $p < 0.05$), were discharged in a similar neurological and functional status (mean NIHSS score 4.1 vs. 4.5, mean BI 88.2 vs. 85.9; $p > 0.05$) after a significantly ($p < 0.02$) shorter hospitalization (10.7 vs. 14.9 days). Successive measurements showed a steady increase of MDA in CEs during the first 7 days. LA attenuated this incremental trend. While similar at stroke onset, the serum MDA levels were significantly lower in the LA-treated group both on day 3 ($p < 0.01$) and 7 ($p < 0.001$).

Conclusions: Our results indicate that LA administered early after stroke onset diminishes lipid peroxidation, as demonstrated by the decreased levels of MDA in the sera of patients who received antioxidant treatment. We ascribe the significant improve in clinical outcome to the diminution of oxidative stress in cardioembolisms. Similarly, antioxidant treatment started before or soon after reperfusion therapy could further improve the outcome of thrombolysed ischaemic stroke patients.

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Vasomotor reactivity in proximal and distal segments of middle cerebral artery and optimising test duration

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Introduction: Cerebral vasomotor reactivity (VMR) is known as the vasodilatation capacity of cerebral arterioles to perfusion changes.

Objectives: (1) To determine the difference in VMR between the proximal and distal segments of middle cerebral artery (MCA) with breath holding index (BHI) in healthy subjects, (2) To determine the optimal test period by establishing BHI modifications when the breath holding periods and the periods measuring the MCA basal velocity at rest are changed.

Methods: Ten healthy volunteer who were acquainted about the study were included in the study. Transcranial doppler (TCD) recordings were made simultaneously from ipsilateral MCA with TCD 2 Hz probe in two different depths. Mean velocity measurements at rest at 180-120-60 and 30 s were accepted as the basal values. Maximal velocity (*V*max) values were determined after breath holding sequentially 10-15-20 and maximum seconds. In both depths BHI was calculated as indicated in literature for 4 different basal values and for 4 different breath holding times and statistical significance was researched for all parameters.

Results: (1) When same basal velocity determining times and same breath holding times compared with depth; BHIs which obtained from proximal were higher than distal BHIs (for each $p < 0.05$, Wilcoxon sign test) (2) There was no statistical significance when BHIs were compared with each other in different basal times and different breath holding periods (Friedman test, $p < 0.05$ and Wilcoxon signed-ranks test, $p < 0.012$).

Conclusion: (1) BHI results between the proximal and distal segments of the MCA were statistical significant, VMR capacity of the distal segment was lower than the proximal segment. (2) When 4 different basal value times and 4 different breath holding periods were compared there was no significant difference. It is not possible to suggest that distal arteries have more risks about ischemic stroke because they have small calibration and low VMR capacity because VMR is an indirect indicator of precapillery vasculature. Different basal value times and breath holding periods were used in VMR measurement in different studies in the literature. Because of the patient's adaptation and shortness of the test time, mean velocity measurement at rest at 30 s and breath holding period for 10 s is sufficient and optimal for the BHI measurement because there are no statistically differences between the different groups.

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Vasomotor reactivity in the ophthalmic artery

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Objectives: Ophthalmic artery is the first and middle cerebral artery is the last intracranial branch of the internal carotid artery. In order to

evaluate vascular reserve proximal and distal branches of internal carotid artery, this study was planned.

Methods: Breath holding index (BHI) was assessed via bilateral transtemporal insonation of the middle cerebral artery and transorbital insonation of the ophthalmic artery in fifteen healthy individuals using transcranial doppler.

Results: Breath holding index (BHI) of the right middle cerebral artery and ophthalmic artery were found 1.65 ± 0.53 and 1.04 ± 0.59 and the left middle cerebral artery and ophthalmic artery were found 1.57 ± 0.50 and 1.15 ± 0.68 respectively. BHI of the ophthalmic artery was decreased than BHI of the middle cerebral artery on the both sides ($p < 0.05$).

Conclusion: Our findings suggest that the vascular reserve of ophthalmic artery is different and low from cerebrovascular reserve of the basal cerebral arteries. Ophthalmic artery can not response as well as intracerebral vessels to systemic vasodilatator stimulus. When we correlated this finding with clinic data, existing of amorosis before hemispheric findings in the internal carotid artery stenosis or occlusion may be related with inadequate vasomotor reactivity of the ophthalmic artery compared to intracerebral basal arteries.

P171
Dysfibrinogenaemia as a cause of arterial ischaemic stroke

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Background: Once the established causes of ischemic stroke are absent, hypercoagulable states should be considered in young adults. Dysfibrinogenemia is a rare cause of stroke. We report a stroke patient with dysfibrinogenemia.

Case presentation: A 27 year-old man admitted to our department with a sudden loss of consciousness and right hemiparesia. In his medical history he had developed multiple episodes of arterial and venous thrombosis (digital artery, pulmonary artery, subclavian artery, lower limb veins). Molecular studies had showed homozygous afibrinogenemia. Neurological examination revealed lethargy, sensorimotor aphasia, right hemiparesia and the right central facial paralysis. Magnetic resonance imaging showed an infarction in the territory of the left middle cerebral artery (MCA). Angiography showed lack of flow in the left MCA and the A2 segment of the left anterior cerebral artery and a decrease of flow in the left vertebral artery. Fresh frozen plasma (FFP) and low-molecular-weight heparin treatment was initiated and warfarin was used for maintaining treatment.

Conclusion: The last step in coagulation cascade is the conversion of fibrinogen into fibrin polymer. Fibrin polymer is essential for stabilization of the platelet plug. The fibrin polymer is digested by the fibrinolytic system. Dysfibrinogenemia is the abnormality of fibrinogen function and may be congenital and acquired. Also it is becoming increasingly clear that afibrinogenemia should be considered as a subset of dysfibrinogenemia. Fibrinogen takes a part in both procoagulant and fibrinolytic pathways, therefore dysfibrinogenemia may be associated with both hemorrhagic and thrombotic disorders. The mechanism of the thrombosis associated with dysfibrinogenemia is unclear. An abnormal fibrinogen may lead to thrombosis through either increased clot formation or defective fibrinolysis.

Congenital dysfibrinogenemia usually causes mild to moderate hemorrhage. Thrombosis occurs in only 10% of patients and is mostly venous. Dysfibrinogenemic patients manifesting as arterial ischemic stroke is very rare in the literature. Congenital afibrinogenemia is a very rare disease and its treatment consists of fibrinogen replacement with FFP and anticoagulation. It should be considered as a risk factor in young patients with ischemic stroke and needs careful monitoring of treatment because of the potentiality of appearance of hemorrhagic and thrombotic states simultaneously.

P172
Infarction of the anterior cerebral artery associated with acute Lyme neuroborreliosis

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Introduction: It is reported that anterior cerebral artery stroke accounts for approximately 2% of all strokes. Anterior cerebral artery stroke presents with crural paresis, less with arm paresis and frontal signs. Cerebral vasculitis is a rare complication of Lyme neuroborreliosis. Usually it is difficult to prove the role of borrelia infections in the causality of stroke, particularly in the elderly, when other potential causes exist. We describe a case of an infarction of the anterior cerebral artery associated with an acute Lyme neuroborreliosis.

Case report: An 88-year-old woman was admitted due to an abulia. In the last days the patient had suffered for dizziness and a moderate headache. She had a history of hypertension, but no diabetes mellitus, coronary heart disease, atrial fibrillation or prior stroke. The neurological examination revealed an abulia, but no paresis. The cerebrospinal fluid was analysed and exhibited slight pleocytosis, disruption of the blood–brain barrier and positive antibodies against borrelia. Immunoblot was also positive (IgG and IgM). One day later the patient developed a marked paresis of the right leg with Babinski sign and a mild paresis of the arm without sensory deficits. Brain computed tomography and diffusion-weighted MRI revealed an infarction of the left anterior cerebral territory. Follow-up examination of the cerebrospinal fluid showed a marked pleocytosis. Upon antibiotics, the short-term outcome was excellent. After 6 months there had been a marked recovery of motor deficits and the patient resumed her everyday activities.

Conclusion: This case shows that an acute neuroborreliosis can be associated with focal cerebral vasculitis and stroke. Our case is unusual for several reasons. The initial complaint of the patient was suggestive for encephalitis rather than of stroke. The clue to vascular pathology was the hemiparesis occurring later. The probable mechanism of stroke was obstruction of the anterior cerebral artery by borrelia induced vasculitis of the arterial wall, although ultrasound studies and MR angiography were normal. Borrelia induced cerebral vasculitis should be considered in unusual strokes. To our knowledge, this is the first description of borrelia associated infarction of the anterior cerebral artery.

P173
Measurement of vasomotor reactivity in MCA stenosis

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Objectives: Cerebral vasomotor reactivity (VMR) represents autoregulatory capacity of arterioles, which may be reduced in large-artery stenosis. We try to measure VMR in patients with MCA stenosis with a novel method.

Methods: Consecutive patients with MCA stenosis on MRA were included. Patients with ipsilateral ICA stenosis or advanced small vessel disease were excluded. Degree of stenosis was graded as mild, moderate and severe by MRA criteria. VMR was measured by CO2 retention achieved by rebreathing in 6-liter reservoir bag with monitoring of end-tidal CO2 (ETCO2) level. TCD measured the change of mean flow velocity (MFV) of MCA before and

after rebreathing, and VMR was calculated as percent change of MFV.

Results: 44 patients (32 men, 61 years) and 19 controls (10 men, 61 years) were included. 58 MCA segments with stenosis were compared with 38 without stenosis. Mean VMR was reduced in stenosis group ($41.6 \pm 19.94\%$ vs. $57.1 \pm 9.84\%$, $p < 0.001$). Reduction of VMR was well correlated with the severity of stenosis ($p < 0.001$). Multivariate logistic regression model revealed stenosis as the independent determinant of reduced VMR ($p < 0.001$). Sensitivity and specificity for the prediction of stenosis were 79.2 and 77.8% with the cut-off value of VMR less than 45%. Bed-side measurement of VMR is feasible and VMR is reduced in MCA stenosis. TCD measurement of VMR is useful for the diagnosis of MCA stenosis and prediction of hemodynamic impairment.

P174

Carotid-cavernous fistula – Endovascular stent-graft therapy

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Objectives: The carotid cavernous fistulae (CCF) are commonly treated by endovascular methods such as deployment of a detachable balloon into the cavernous sinus (transarterial or transvenous approach), the embolization with spirals (in case of failure of the baloon treatment) and the angioplasty with stent-graft. There are few reports describing revisions using constructive, transarterial approaches when these techniques fails. The purpose of our work is to underline the importance of the endovascular stent-graft therapy since in Romania the present treatment for CCF is the carotid artery ligature.

Methods: We present four cases, females, aged 31–66 years, diagnosed in the period July 2006 to February 2008 in the Neurology Clinic of the Emergency University Hospital, by clinical, cerebral MRI and "4-vessels" angiographic exam with either traumatic or spontaneous CCF (two patients presented left CCF and two patients presented bilateral CCF). The treatment of choice was angioplasty with stent-graft followed by post-dilatation with a 4×12 mm baloon. The procedure was performed via transfemoral approach under general anesthesia. All patients received intravenously systemic heparinization at the beginning of the procedure followed by enoxaparine for 24–48 h and double-antiplatelet therapy (aspirine and clopidogrel).

Results: Final angiograms at the end of the procedure confirmed total exclusion of the fistula and normal aspect of the internal carotid artery (ICA) in three of our patients while in one case important residual filling of the cavernous sinus from the ICA persisted, a second stent-graft being placed on the site. No thromboembolic complications occurred in any patients. The 6-month and 1-year follow-up examinations revealed no changes in the angiographic features and a normal neurological exam in all patients.

Conclusion: Covered stent grafts can sometimes be used as a valid alternative in the treatment of CCF, when more standard treatments fail and the anatomy of the ICA is favorable. As there are reports showing that endovascular treatments with balloons alone are unable to obtain complete and permanent occlusion of the CCF, the placement of an endovascular stent-graft before applying the balloon could be needed.

Our results and follow-up should encourage the further use of the stent-grafts. The procedure needs caution both because of possible periprocedural complications (arterial spasm) and of little understanding of long-term follow-up.

P175

Recurrent stroke as the initial manifestation of an occult lung adenocarcinoma

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Objectives: Cerebrovascular accidents are a relatively common neurological complication among patients with systemic cancer (15%). Their pathogenetic mechanisms include atherosclerosis, non-bacterial thrombotic endocarditis (NBTE), disseminated intravascular coagulation, septic or neoplastic cell embolism, and venous sinus thrombosis. Typically, stroke complicates advanced disease; however rarely it may constitute the initial manifestation of an underlying tumor. We present a patient with relapsing strokes, due to NTBE associated with an occult lung adenocarcinoma.

Case-history: A 55-year old male, with a 2-week history of left hemispheric stroke, was admitted to our department with severe left hemiparesis. Cranial MRI revealed multiple bilateral ischaemic lesions of frontal and parietal lobes. On cerebral angiography a moderate stenosis of the left middle cerebral artery was found, with no other abnormalities. A transoesophageal echocardiogram was unremarkable. Laboratory examinations showed marked elevation of inflammation markers, D-dimers and CA 15-3. CSF was normal as were repeated blood cultures. Thorough screening for neoplasia, including axial computed tomography and gastrointestinal endoscopy was negative. Despite treatment with low molecular weight heparin, the patient's condition deteriorated and two weeks following admission he presented signs of brainstem ischemia and ataxia of the left limbs. A repeat brain MRI showed multiple acute subcortical infarcts as well as a massive infarct of the left cerebellar hemisphere. Laboratory tests demonstrated frank disseminated intravascular coagulation, while a new transesophageal echocardiogram revealed a large vegetative lesion in the aortic valve. Ten days later, the patient developed respiratory insufficiency and was intubated. A repeat chest CT scan showed left pleural and pericardial effusion. Cytological examination was consistent with the presence of pulmonary adenocarcinoma. The patient was submitted to chemotherapy and cardiac surgery was considered. However he subsequently developed arterial embolism of the right inferior limb and died due to multiorgan failure.

Conclusion: An occult malignancy should always be considered in patients with embolic stroke of unclear etiology, especially if there is laboratory evidence of a hypercoaguable state. In such cases, a thorough investigation for possible NBTE should be performed with repeated transephophageal echocardiograms.

P176

Tight adjustment of blood glucose level by intensive insulin therapy significantly reduces intracranial hypertension in patients with vascular or infectious disorders of the central nervous system

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Objectives: Several large, randomized, controlled trials revealed that intensive insulin therapy (IIT) could improve the outcome in critically ill patients. Furthermore, it was suggested that IIT is able to decrease intracranial hypertension in patients with traumatic brain injury.

Objective of our study was to test, whether tight adjustment of blood glucose level (target 80–140 mg/dl) versus standard blood glucose management (target 80-180 mg/dl) could reduce intracranial hypertension in patients with severe vascular or infectious disorders of the central nervous system (CNS).

Methods: 64 patients with elevated intracranial pressure (ICP), who were continuously monitored by an external ventricular drainage (EVD), were studied retrospectively before (group 1, $n = 32$) and after (group 2, $n = 32$) implementation of IIT as a standard of care in our neurologic intensive care unit (ICU). Blood glucose targets were 80–180 mg/dl in group 1 and 80–140 mg/dl in group 2. Both groups were analyzed with regard to differences of ICP within the first 14 days. Furthermore the groups were compared respecting the clinical course and follow-up (days on mechanical ventilation, days in ICU/hospital, rate of complications like ventriculitis or hypoglycaemia, mortality, and outcome measured by the modified rankin scale (mRS)).

Results: Patients in the IIT group had significantly lower mean (12 ± 4 vs. 16 ± 5 mmHg, $p < 0.001$) and maximal (18 ± 7 mmHg vs. 25 ± 11 mmHg, $p<0.001$) ICP values starting from day 8. Furthermore, IIT significantly reduced the need for mechanical ventilation (11 ± 13 days vs. 17 ± 15 days, $p < 0.05$) and the mRS at discharge from ICU (4 ± 2 vs. 5 ± 1, $p < 0.05$). Additionally, there was a trend (but no statistical significance) towards a shortened necessity of EVD, decreased dependency on sedatives, fewer days in ICU and hospital, and reduced rate of infectious complications like pneumonia, urinary tract infection, and sepsis in the IIT group. The rate of hypoglycaemia did not differ between both groups.

Conclusions: In patients with elevated ICP due to severe vascular or infectious CNS disorders, tight control of blood glucose level (80–140 vs. 80–180 mg/dl) could be helpful in the management of intracranial hypertension and seems to be a safe and feasible procedure. If IIT decreases morbidity or mortality, or improves the outcome in this patient population has to be analyzed in further prospective studies.

P177

Usefulness of transcranial motor evoked potentials monitoring during surgical clipping for unruptured aneurysms

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Objective: The aim of this study is to evaluate the usefulness of transcranial motor evoked potentials (MEPs) monitoring and its impact on the morbidity after surgical clipping for unruptured aneurysms.

Methods: The study period was from January 2007 to December 2008. After the first implication of transcranial MEPs monitoring together with somatosensory evoked potentials (SSEPs) in mid-December 2007, it routinely has been done for aneurysm surgery. Before that time, the blood flow insufficiency could be verified by Doppler ultrasonography only. A more than 50% decrement compared with baseline recordings or a loss of MEPs was regarded as a warning sign and promptly notified to the neurosurgeon. Surgical outcomes focused on the motor status and CT findings were compared before and after the application of MEPs monitoring during one year, respectively.

Results: Before the application of MEPs monitoring, 66 consecutive patients underwent direct clipping for unruptured aneurysms (ICA:14, ACA:26, MCA:33). After that, aneurysm clipping under intraoperative MEPs and SSEPs monitoring was performed in 99 consecutive patients(ICA:19, ACA:36, MCA:64). In the former group, a new motor deficit was developed in 3 of 66 patients (4.5%). However, in the latter group, no new motor deficit was found except for one patient who showed delayed hemiparesis after 24 h due to venous infarction. MEPs changes were found in 11 patients which were related to both temporary clipping (7 patients) and permanent clipping (4 patients), and recovered in all after prompt clip removal or readjustment. At the same time, SSEPs changes were noticeable in only 4 patients.

Conclusions: Transcranial MEPs monitoring is a simple and reliable tool for the prediction of postoperative motor function. The ischemic complications can be reduced via prompt corrective responses under MEPs monitoring.

Neuro-epidemiology

P178

Stroke subtypes in hospital, Porto Alegre, Brazil

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Introduction: Stroke is a leading cause of mortality and disability in Brazil and racial differences in stroke subtypes have been documented. Few data of prevalence of stroke subtypes in Latin America are available in literature.

Objectives: The objective of this study is describe the prevalence of stroke risk factors in Porto Alegre-Brazil, and determine the patterns of stroke subtypes in a population in the patients in São Lucas Hospital.

Methods: We analyzed data from 250 patients with acute ischemic stroke (58.1% women, aged 61.2 mean years) who were enrolled in stroke data bank. Standardized data assessment and stroke subtype classification were used in Excel.

Results: A total of 250 patients with ischemic stroke, 243 (58.1%) women and 175 (41.9%) men aged mean 61.2 years. Large-artery atherosclerosis was the most common cause of stroke (*n*: 102, 40.8%), followed by cardioembolism (*n*:76, 30.4%), microangiopathy (*n*:28, 11.2%), unknown (*n*:24, 9.6%) and other etiology (*n*:20, 8%).

The prevalence of hypertension was 74%; the prevalence of diabetes was 19.2%; the prevalence of dyslipidemia was 42.8% and the prevalence of smoking was 20.4%. These results showed variations among the stroke subtypes. The presence of stroke before the admission was 26.3% in the cardioembolism; 25.4% in the large-artery atherosclerosis and 21.4% in the microangiopathy.

Conclusion: In summary the stroke subtypes showed difference in the prevalence of the main risk factors. In this study, hypertension and dyslipidemia were the most prevalence risk factors. Because of this, the knowledge of the physiopathology is important for the correct diagnosis and treatment of the patients.

P179

Mumbai Stroke Registry Quality of Life in Stroke Survivors

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Background: We initiated prospective community based stroke registry in Mumbai, in subjects having first-ever-stroke (FES), to collect data on stroke epidemiology and disability status in stroke survivors from Jan 2005 to Dec 2006.

Methods: A well-defined community (H-ward) with verifiable census data was selected, 156,861 people aged over 25 years who were eligible were screened. WHO STEPwise approach to stroke surveillance Version 2 was operational protocol. Neurological deficit on admission was recorded by National Institute of Health Stroke Scale (NIHSS) and disability status at 28 days by modified rankin scale (MRS).

Findings: 456 FES subjects were identified. By 28 days, of 131subjects with mild neurological deficit at onset (NIHSS < 5 at onset) 87 made good recovery (MRS 0–2) and 3 died (2.2%). Of 149 subjects with moderate deficit (NIHSS 6–15), 34 showed good recovery (MRS 0–2), 97 (65.1%) had moderate to severe disability (MRS 3–5) and 15 (10%) died. Whereas in 70 subjects with severe neurological deficit (NIHSS 16–42), 19 (27.1%) had moderate to severe disability (MRS 3–5) and 48 (68.5%) died. In 103 subjects where NIHSS score at onset was not verifiable, by 28 days 23 remained moderate to severely disabled (MRS 3–5) and 67 (65%) died. In the latter group CT confirmation of stroke diagnosis was available in 67 of 103(65%) cases; and in majority (82 cases) ischemic stroke was major sub-type.

Interpretation: In MSR mild neurological deficit at onset was associated with good recovery whereas those with severe neurological deficit at onset had poor prognosis in terms of outcome (disability status). In developing countries like India there are difficulties in implementing intensive and immediate treatment on account of: lack of public awareness on warning symptoms, poorly organized ambulance services, non-availability of acute care beds, leave aside cost of modern drugs (e.g. TPA). To reduce post-stroke disability, immediate treatment will have to be initiated by general medical practitioners trained in intensive stroke care.

The study was supported by unrestricted grant from the Global Stroke Fund of International Stroke Society.

P180

Impact of cerebrovascular diseases in a neurology emergency department

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Background: Recent developments in acute stroke care demanded implementation of pathways to guarantee immediate access of patients to a stroke care unit. Characterization of patients who attend neurology emergency department (NED) is fundamental to organize acute stroke care minimizing time loss and maximizing available resources. Our NEDs' reference area is 600,000 inhabitants for general neurology and 1,000,000 for stroke fast track (SFT). Patients may come directly to the emergency department (ED) and be referred to neurologists by general practitioners working in the ED, or may be directly sent to Neurology from primary care units and smaller hospitals.

Objective: To quantify and characterize patients attending NED.

Methods: Prospective registry of all patients attending NED. Selection of the first complete entries of each month of the year 2007. Statistical analysis.

Results: Data regarding 541 patients and 24 days were analysed. The average affluence to NED was 23 patients/day. Significantly higher affluence was recorded in winter months (average 28). Mondays and Fridays were the top days of the week. Average age was 56 years old (minimum 6 months; maximum 97 years) and a similar sex distribution was observed. Most patients were referred to the neurologist by general practitioners (40%), 25% were sent from primary care units and the same number came from smaller hospitals. The main reason for referral was transient conscience loss (21%) followed by motor deficit (17%) and headache (13%). SFT patients represented 5% of patients observed daily in NED. Complementary exams were demanded in 75% of patients, mainly brain CT scan (51%) and blood tests (31%). Cerebrovascular diseases were the main diagnosis (29%), with ischemic stroke representing 70% of these. Epileptic seizures represented 13%, and primary headache 9% of patients. An important number of patients did not have neurological disease (29%). Half the patients were discharged home, 25% were sent to observation by a different speciality, and 10% were admitted to our neurology department. Posterior neurological consultation was scheduled in 15% of patients.

Conclusion: Ischemic stroke was responsible for ¼ of the consultations in our NED. The knowledge of patterns of affluence and reference allowed us to reorganize NED reference criteria, and proper administration of acute stroke care. This analysis could be useful to other centres organizing their SFT.

P181

Familial multiple sclerosis in Northern Greece: a population-based study

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Background: The aetiology of multiple sclerosis (MS) is unknown. MS is thought to be a complex trait determined by genetic and environmental factors with increasing incidence among families.

Objectives: To perform a population based prevalence study on the rate of familial MS and recurrence risk amongst defined categories of first degree relatives in Thessaloniki (Northern Greece) and to obtain 9 year (between 1999 and 2007) clinical follow up data.

Methods: In a Greek population-based sample of 1,280 definite MS patients, 2,560 parents, 3.156 relatives, 79 familial MS were identified from the patients' records. A semi-structured questionnaire has been developed to collect data. By interview, we elicited information on family structure and illness in first-degree relatives (parents, brothers or sisters, aunt/uncle-niece/nephew, first and second cousins). All patients were followed for 9 years using the expanded disability status scale (EDSS).

Results: The mean disease duration of MS was 16.3 ± 7.2 years (42% relapsing remitting MS, 9% primary progressive MS and 49% secondary progressive MS). EDSS was 4.74 ± 1.2. The overall frequency of familial MS was 6.3% for first-degree relatives. We revealed a significantly higher number of maternal families compared to paternal families ($p = 0.041$). Rates for siblings were 5.1% for female and 4.1% for males. The highest risk was observed in sisters of female patients (7%). Female-to-male sex ratios were higher among affected nieces/nephews, when compared to the sex ratio for aunts/uncles ($p = 0.037$).

Conclusions: Our data suggest: 1. The frequency of familial MS in Northern Greece in first-degree relatives is low. 2. Our findings confirm previous studies for a maternal effect in MS susceptibility.

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Prevalence and incidence of multiple sclerosis in the Province of Kavala and Thassos, north-eastern Greece

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To ascertain MS Prevalence and Incidence rates for the region of Kavala and its neighboring island of Thassos for which no previous data exist an electronic MS registry was established and patients were collected on the basis of the cross-checked principle from a variety of independent data sources. Prevalent and incident cases were considered all those who satisfied combined Poser's and McDonald's criteria for clinically definite MS. Laboratory supported probable cases were also included.

Crude prevalence rate was 38.6 per 100,000. Sex specific prevalence was 44.9/100,000 in women and 32.1/100,000 in men giving a sex ratio 1:1.43 men to women. Mean total prevalence rate by age was greater for the group aged 40–44(103) and 45–49(77). We are concerned with progressive increase in incidence from 0.65 during 1953 to 3.45 mean annual incidence rate the last decade. Age specific incidence was greatest for the group aged 15–25 giving a sex ratio 2:1women to men.

The study confirms high prevalence and incidence rates in the North-Eastern Province of Kavala and Thassos with a total population of 145,054. In accordance with most recent surveys conducted in Greece we support the view that these are areas of high risk for MS according to Kurtzke. Better diagnostic tools and the variation in risk factors may be responsible for this.

P183

Survival rate of patients with Wilson's disease

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Introduction: Wilson's disease (WD) is inherited autosomal recessive disorder of copper metabolism, leading to its accumulation in various organs including liver, brain, cornea, kidneys and heart, with resulting chronic degenerative changes. Objective: To investigate survival rates, prognostic factors and causes of patients death in a large database of national study on WD.

Patients and methods: We performed a retrospective analysis of 142 patients with clinically verified WD from several specialized institutions in Belgrade and Novi Sad. The data collection process scroll off continuously from 1980 to 2008. All data were calculated by life table method, Cox proportional hazard model and Standardized Mortality ratio.

Results: The average age at onset of our patients was 23.5 ± 9.0 years, while the average duration of the treatment was 10.2 ± 8.6 years. The cumulative probability of survival in a fifteen-year' period for whole group was $76.7 \pm 4.9\%$. WD patients who treated more than 11 years had statistically significantly better survival than those who treated 10 years and shorter (49.4 ± 13.6 vs. $92.3 \pm 4.3\%$). The univariant Cox regression analysis also confirmed that significantly poorer outcome of WD in our population was related to duration of treatment (HR $= 0.1$, 95%CI 0.01–0.2, $p = 0.001$) The most frequent reasons of death in our patient's population were liver cirrhosis (five patients, 16.6%), haemorrhage due to oesophageal varices (four patients, 13.3%) and suicide (four patients, 13.3%), while in three cases cause of death was unknown.

Conclusion: Better prognosis of WD was associated with male sex, younger age at onset, neurological clinical profile, and treatment continuity.

P184

An integrative characterisation of SCA2 in Cuba: epidemiological, genetic neurochemical and electrophysiological findings in 7926 Cuban carriers

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Objective: To evaluate the clinical epidemiology, electrophysiological, molecular and neurochemical biomarkers of SCA2.

Methods: Availability of a high number of SCA2 carriers enables us to asses Clinical epidemiology, molecular, neurochemical and neurophysiological studies were done in all Cuban SCA2 families.

Results: The highest frequency of SCA2 mutation was observed in Holguín province, where the prevalence rate is 163.18 per 100 000 inhabitants, but there are regions within where the prevalence reaches up to 503 per 100,000 people. The genetic anticipation was observed in the 80% of transmissions and the expansions were presented in 89.02%. The neurochemical analyses demonstrated a significant decrease of serum and CSF levels of Zn, Cu and Fe in patients. The neurophysiological studies showed the involvement of nervous structures since presymptomatic stages, specially the sensitive amplitudes and N20 and P40 components of the SSEPs. The progression of these abormalities was correlated with disease duration, polyglutamine expansion size and ataxia score. The polysomnographic recording showed the severe REM pathology with insufficient muscle atonia and periodic legs movements (PLMs) occurs in several cases. The electronystagmographical studies showed a significant reduction of maximal saccade velocity (MSV) in patients and presimptomatic. MSV was negatively correlated with the polyglutamine expansion in both groups.

Conclusions: Hereditary ataxias in Cuba make up the highest prevalence in the world. Electrophysiological abnormalities of peripheral nerves and somatosensory pathways reflect an early and progressive axonal damage. REM pathology can be associated with the pons, nigrostriatal and thalamic degeneration and PLMs may be related with a dysfunction of dopaminergic pathways. MSV is the most important electrophysiological biomarker for genetic researches of SCA2. Neurochemical results indicate an impairment of the microelements homeostasis in SCA2. These evidences support the application of new strategies for treating this disease.

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Dementia/Higher function disorders

P185

Difference of progression in subjects with mild cognitive impairment and Alzheimer's disease according to the white matter lesions: a pilot study

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Objectives: Alzheimer's disease (AD) has a history of stroke and white matter lesions(WMLs) as a risk factor. The elderly who is not demented has also them as an aging process. We investigated the difference of progression between the subjects with mild cognitive impairment(MCI) and AD according to the WMLs and the previous stroke.

Methods: nine patients with MCI and 28 patients with AD were enrolled and followed up. Their WMLs on MRI were classified as 3 groups according to the severity. After follow-up, the changes of K-MMSE and CDR scores were compared according to the history of previous stroke, the presence of lacune on MRI, and the severity of WMLs separately in the patients with MCI and AD.

Results: For the MCI patients, the changes of K-MMSE scores were more severe in the patients with the severe WMLs. However, those changes of the patients with AD were reversed. The AD patients with mild WMLS and no stroke history had a better progress. The presence of lacune on MRI showed worse results both patients with MCI and AD.

Conclusion: The history of stroke, presence of lacune on MRI, and the severe WMLs are bad prognostic factors in MCI patients. However, the stroke history and severe WMLs do not further have prognostic, rather protective or compensatory, effects in AD. We hypothesize that the other cause might be a result of ChEIs. The presence of lacune on MRI has continuously deleterious effects in the progress of MCI and AD.

P186

Recognition of facial expressions of emotions in Alzheimer's disease and frontotemporal dementia

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Objectives: The comprehension of different facial expressions of emotions is fundamental for social behavior. Darwin argued that certain emotional expressions are innate. Neurodegenerative disorders, such as Alzheimer disease (AD) and fronto-temporal dementia (FTD) are characterized by behavioral disorders that suggest abnormalities in emotional processing. The aim of this study is to investigate recognition of facial expressions of emotions in patients with AD and FTD as compared to healthy individuals (HC) matched for age and gender.

Methods: Consecutive outpatients with AD or FTD have been assessed with the Mini Mental State Examination, the Clinical Dementia Rating Scale, the Global Deterioration Scale, the Cornell Scale for Depression and the Neuropsychiatry Inventory. Recognition of facial expressions of emotions have been evaluated, in both patients and HC, using a standardized task with 30 pictures from Ekman and Friesen's series representing the six primary emotions (happiness, sadness, anger, surprise, fear and disgust).

Results: Patients with AD ($n = 11$) and FTD ($n = 9$) showed a significant impairment in the recognition of anger (FTD< HC $Z = -2{,}604$ $p = 0.009$), surprise (AD < HC $Z = -4{,}941$ $p < 0.001$; FTD < HC $Z = -3{,}805$ $p < 0.001$) and disgust (AD < HC $Z = -4.052$ $p < 0.001$; FTD < HC $Z = -3.132$ $p = 0.002$). There was no association with severity of dementia or the presence of depression.

Conclusions: Patients with dementia, both AD and FTD, showed a significant impairment in the recognition of facial expressions of emotions. Our study brings further evidence on the need to investigate targeted brain areas and to identify specific clinical endophenotypes.

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Mapping the progression of atrophy in early and late onset sporadic Alzheimer's disease: a tensor-based morphometry study

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Objectives: Early (<65 years, EO-AD) and late (>65 years, LO-AD) age-of-onset Alzheimer's disease present as different clinical syndromes. An early multidomain cognitive impairment is typical of EO-AD, whereas a progressive memory deficit is more characteristic of LO-AD. Neuroimaging studies have shown greater neocortical involvement in EO-AD, and more prominent medial temporal lobe atrophy in LO-AD. Patterns of longitudinal atrophy changes in EO-AD and LO-AD have not yet been compared. Our objective was to map the progression of regional gray matter (GM) atrophy in EO-AD and LO-AD.

Design/methods: T1-weighted MRI scans were obtained at presentation and at one-year follow-up from 15 EO-AD (mean age: 56, standard deviation [SD]: 5), 14 LO-AD (mean age: 78, SD: 5), and 41 age-matched control subjects ($21 < 65$; $20 > 65$ years). Tensor-based morphometry (TBM), implemented in Statistical Parametric Mapping software (SPM2), was used to map progression of GM atrophy over time. Age, gender and follow-up duration were considered as confounding variables. A level of significance of $p < 0.05$ corrected for multiple comparisons was accepted.

Results: Over one year, all patients versus controls showed a large area of GM contraction in bilateral parietal, posterior cingulate, precuneus, hippocampus, and medial frontal regions. When we considered patients as two separate groups on the basis of age-at-onset, greater GM contraction was found in the medial frontal areas for EO-AD, and in the medial temporal regions for LO-AD. Both patient groups showed GM loss over time in the precuneus and posterior cingulate.

Conclusions: EO-AD and LO-AD are associated with a relatively different pattern of progression of GM atrophy over the first year after diagnosis. These results suggest that age at onset influences the way AD pathology, not only begins but also progresses. In the future, TBM may be helpful in identifying factors that oppose or accelerate the disease process.

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Non-linear dependency between EEG channels in Alzheimer's disease

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Background and aims: In this study we propose a novel algorithm for detecting of the non-linear communication between EEG channels in Alzheimer's disease (AD). Objective of this study is to look for the most sensitive measure of the communication among brain neurons in AD. The most frequent measure of EEG signals similarity is coherence and correlation, including similar methods. All those methods reflect only linear dependency and don't reflect time evolution. There were also applied methods derived from chaotic system theory such as

mutual information entropy and correlation dimension. The problem is, that they suppose presence of deterministic chaos in EEG. However it was not proved. What's more simulation shows, that correlation dimension reflect mainly linear correlation between EEG channels and is not sensitive to a non-linear dependencies. Similar objectives are against Kolgomorov entropy and largest Lyapunov exponent.

Methods: In study 25 AD patients was examined. In control group there was 25 age matched healthy subjects. Their EEG data was processed by the same manner as in AD patients. EEG signal (sampling frequency 200 Hz, 19 channels according to the standard 10/20, duration 20 min) was filtered by a standard manner (0.5–60 Hz, adaptive notch filter). Blinking, eye moving artefacts and was removed by independent component analysis. Muscle artefacts were manually removed. For non-linear dependency estimation modified source derivation (to remove linear dependencies) was used. Among all channels the parameters of communication by the correlation, coherence, mutual information entropy, largest Lyapunov exponent and non-linear modelling on logarithmic and quadratic AR model and radial network was computed. Time evolution of those parameters was also followed up. The methods were applied to a free-artefact data set after denoising and manual artefact elimination.

Results: The best results for ROC curve in AD patients demonstrated logarithmic AR and radial network modelling after elimination linear dependencies between EEG channels. Changes of similarity measure in time bring another independent parameter of communication between channels.

Conclusions: Removing linear dependencies between EEG channels improves sensitivity of methods estimating non-linear dependencies in AD. The best models for those dependencies are logarithmic AR model and radial network.

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Chlamydia infection and sporadic Alzheimer's disease: shedding light on the link between neurodegenerative and vascular brain disorders?

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Background: Chlamydia pneumoniae (CP) is a quite diffuse microorganism, commonly causing respiratory tract involvement followed by lifelong infection. Interestingly, recent preliminary reports indicate that CP might be involved in Alzheimer's disease (AD) pathogenesis facilitating β-amyloid deposition. (1) CP has also been detected in AD post-mortem brain tissue. (2) However, more rigorous studies investigating the possible role played by CP in AD pathogenesis are currently lacking.

Objectives: To assess if CP infection might be a risk factor for sporadic AD.

Methods: We have currently enrolled 40 cognitively-spared controls and 40 mild-to-moderate probable sporadic AD. Serum antibody titers against CP, Chlamydia trachomatis and Chlamydia psittaci were assessed by immunofluorescence and ELISA. Moreover, brain CT scan and carotid ultrasonography were obtained from all AD patients.

Results: CP seropositivity was found in 55% of AD versus 14% of controls (chi-square 9.4, $p < 0.003$; OR 7.6, 95% CI 1.63–38.8). Seropositivity was at low titre in all cases, suggesting a previous infection. By contrast, serum titres for the other two Chlamydia species were negative in all subjects. Post hoc analysis of AD patients, according to the vascular load at the brain CT scan, resulted in a skewed profile: 37% of CP seropositive vs. 0% of CP seronegative AD patients displayed minor non-strategic vascular lesions. Stratification according to the presence of atherosclerotic plaques at the carotid ultrasonography (stenosis < 20%, ECST) allowed to separate 60% CP seropositive versus 25% CP seronegative AD patients.

Conclusion: We found a significant increase in CP seropositivity in AD patients, when compared to age-matched controls. CP might contribute to AD pathogenesis through two different, potentially coexisting, mechanisms: first, by accessing directly into the CNS through one of its target cells, i.e. granulocytes (Trojan horse hypothesis), and inducing a chronic inflammatory process leading to, or associated to, AD. Second, CP might be involved in determining microvascular damage, possibly adding a vascular component to the pathogenesis of AD. This latter hypothesis is supported by the evidence that CP is considered a putative risk factor for vascular diseases, and that, in our sample, post hoc analysis suggests a skewed profile in relation to the vascular load of AD patients.

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P190

Relationship between serum cortisol and dehydroepiandrosterone sulphate levels and degree of cognitive impairment in patients with Alzheimer's disease and vascular dementia

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Objective: The objective of the present work is to study the relationship between serum cortisol and dehydroepiandrosterone sulphate (DEHEAS) levels and degree of cognitive impairment in patients with Alzheimer's disease and vascular dementia.

Methods: The present study included thirty demented patients selected randomly from the outpatient clinic of Alexandria university hospitals. Their ages ranged from 52–85 years old with a mean of 68.5 years. They were 13 males and 17 females. Fifteen patients had probable Alzheimer's disease (AD) and the other fifteen had vascular dementia (VD).In addition, fifteen elderly healthy volunteers, age and sex matched with no evidence of dementia served as control group. Both the patients and control groups were subjected to morning collection of blood samples for determination of the plasma cortisol and DEHEAS levels and the 30 points Mini Mental State Examination (MMSE) to assess cognition.

Results: The results of the present study showed that the mean serum cortisol level increase while the mean serum DEHEAS level decrease progressively with age. The mean serum cortisol level in AD and VD patients (21.82, 33.57 respectively) were significantly higher than that of the control group (16.9). On the other hand the mean serum DEHEAS level in AD and VD patients (27.84, 47.24 respectively), were significantly lower than that of the control group (177.8). There was also a significant correlation between the serum cortisol and DEHEAS levels and degree of cognitive impairement in patients with AD and VD.

Conclusion: The present study showed an evidence of possible relationship between the serum cortisol and DEHEAS levels and the presence and severity of cognitive impairment in elderly patients with probale Alzheimer's disease and vascular dementia.

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Electroencephalogram background activity characterisation with novel detrended approximate entropy in Alzheimer's disease patients

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Objectives: Clinical evaluation of the severity of Alzheimer's disorder (AD) depends largely on neuropsychiatric tests, such as mini-mental status examination (MMSE) and clinical dementia rating (CDR), though they are not absolutely objective. The Fourier based quantitative-electroencephalogram (EEG) provides a route for evaluation of late stage AD objectively, but is limited in early stage due to improper linear signal modeling. On the other hand, the approximate entropy (ApEn) attempts to quantify the complex information embedded in EEG time series nonlinearly, which complies the fact that EEG originates from nonlinear interaction, but a technical issue has been ignored by most of the researchers: the signal should be stationary. In this study, we tried to determine the relationship between embedded complex information and MMSE for not only the early and moderate AD patients but also after treatments by improved ApEn.

Methods: Eleven fulfilled criteria AD patients (5M/6F; mean age 71.1 $\pm$ 7.4 years) participated from the neurological outpatient department. The initial MMSE was 20.1 $\pm$ 4.1. All patients received the first resting awake 30-minute EEG before the therapy (acetylcholinesterase inhibitor or MNDA receptor antagonist). Five of them received follow-up resting awake EEG and MMSE with the interval of 6 months after the therapy. Instead of using the original ApEn, the 30-s EEG data without artifacts were selected and analyzed with a new proposed method, "Detrended-ApEn" to attenuate the influence of intrinsic nonstationarity.

Results: The Detrended-ApEn for five patients with follow-up EEG showed compatible results with the clinical syndromes and MMSE. The correlation factors in 11 AD patients showed moderate correlation (0.52–0.64, $p < 0.05$) between MMSE scales and Detrended-ApEn in Fp1, F3, T3, P3, P4 and O1, where are compatible with AD pathology.

Conclusion: The dynamic complexity in EEG fluctuations will be degraded by pathology degeneration, and Detrended-ApEn provided an objective, non-invasive and non-expensive tool for evaluating and following the AD patients.

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Clinical and electrophysiological assessment of dysautonomia in Alzheimer's disease

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Autonomic system involvement in different degenerative diseases has been frequently discussed. It is well established that pronounced autonomic failure appears early in multiple system atrophy (MSA), whereas it is moderate or mild in Alzhemier's disease (AD).

The aims of the study were: to assess clinical dysautonomia in AD (mostly to evaluate the presence and pattern of ANS involvement), to perform the electrophysiological assessment of dysautonomia in AD, using noninvasive electrophysiological tests: the sympathetic skin response (SSR) and R-R interval variation test (RRIV), as well as to analyze the relationship between clinical and electrophysiological abnormalities in this disorder.

The clinical and electrophysiological assessment of dysautonomia was performed in 54 patients with AD in comparison to 37 healthy controls matched for age and sex. The clinical evaluation of dysautonomia was performed using Autonomic Symptoms Questionnaire (Low 1997). To assess the paraclinical dysautonomia in neurodegenerative disorders two noninvasive electrophysiological tests were used: the sympathetic skin response (SSR) and R-R interval variation test (RRIV).

In Alzheimer's disease clinical dysautonomia was observed in 66% of patients; SSR was abnormal in 27% of patients whereas RRIV test was abnormal in 88% of cases.

According to our clinical tests results the autonomic nervous system may be damaged in Alzheimer's disease. The abnormal sympathetic skin response was rarely seen in Alzheimer's disease whereas the abnormal R-R interval variation test was observed in the majority of patients with AD. If the autonomic electrophysiolgical tests were within normal limits there was no clinical evidence of dysautonomia in the studied patients group. This fact is suggestive of significant sensibility of electrophysiological tests being used.

The abnormal eletrophysiological tests results were frequently found in the absence of clinical dysautonomia which support the hypothesis that these tests are useful in the assessment of subclinical dysautonomia. This observation points out the complementary role of autonomic tests and clinical evaluation.

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Oxidative stress in patients with mild cognitive impairment and depression: a possible factor for increasing the risk of developing dementia?

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Objective: Mild cognitive impairment (MCI) has been defined as a transitional state between regular aging and dementia. Still, not all patients with mild cognitive impairment develop dementia. It has been proved that patients with depression and mild cognitive impairment present a doubled risk of developing dementia of Alzheimer type as those with MCI only. Considering the importance of oxidative stress in MCI and Alzheimer disease, our current objective was to determine the level of oxidative stress in MCI patients with depression, compared with non-depressed MCI patients.

Methods: The patients were selected using Petersen criteria for mild cognitive impairment. The cognitive performance was assessed using mini mental state examination (MMSE), Alzheimer's disease assessment scale- cognitive subscale (ADAS-cog), clock drawing test and verbal fluency test. Psychiatric examination for depression was based on structured interview and diagnostic and statistical manual of mental disorder, fourth edition criteria.

We assessed the levels of some enzymatic antioxidant defences like superoxide dismutase (SOD) and glutathione peroxidase (GPX), as well as lipid oxidation makers like MDA (malondialdehyde), using chemiluminometric and spectrophotometric methods.

The results were compared to an aged-matched non-depressed MCI control group.

Results: A decrease in the specific activity of SOD and GPX was found in MCI patients with depression compared with non-depressed MCI patients. Also, the concentration of serum MDA was increase in MCI patients with depression. We also observed a correlation between the cognitive alteration and the levels of oxidative stress in depressed patients with MCI.

Conclusions: We conclude that patients with MCI and depression have an increased level of oxidative stress, compared with non-

depressed MCI patients. This could explain the increased risk of patients with depression and mild cognitive impairment of developing dementia-Alzheimer type.

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Oxidative stress in mild cognitive impairment – A signal for Alzheimer's disease?

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Objective: Mild cognitive impairment (MCI) is a transitional stage between normal cognitive aging and mild dementia or clinically probable Alzheimer's disease (AD). There is a great interest in the relationship between MCI and the progression to Alzheimer's disease (AD). Several studies show the importance of oxidative stress in the pathogenesis of AD. The aim of this study was to determine the oxidative stress status in MCI and AD patients.

Methods: The patients were selected using Petersen criteria for MCI and NINCDS ADRDA criteria for AD. The cognitive performance was assessed using mini mental state examination (MMSE), Alzheimer's disease assessment scale- cognitive subscaleADAS-cog (ADAS-cog), clock drawing test and verbal fluency test. We assessed the levels of some enzymatic antioxidant defences like superoxid dismutase (SOD) and glutathione peroxidase (GPX), as well as lipid oxidation makers like MDA (malondialdehyde), using chemiluminometric and spectrophotometric methods. The results were compared to an aged-matched control group.

Results: Alterations in the activity of the antioxidant enzymes (SOD and GPX) were found in MCI and AD peripheral blood compared to age-matched controls. Also, MDA levels were significantly increased in the AD and MCI patients, comparative with the control group. Moreover, in MCI patients, cognitive function positively correlates with antioxidant levels.

Conclusions: These results support the hypothesis that oxidative damage is an important event in the pathogenesis of neurodegenerative diseases. Also, it seems that some peripheral markers of oxidative stress appear in MCI with a similar pattern to that observed in AD, which suggest that oxidative stress might represent a signal of the AD pathology.

P195

Increased levels of Helicobacter pylori IgG antibodies in cerebrospinal fluid of patients with Alzheimer's disease

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Objectives: Recent evidence suggests that the possible presence of antineuronal antibodies and autoimmune mechanisms may be responsible for eliciting neuronal cell death in Alzheimer's disease (AD). To determine whether *Helicobacter pylori* (*H. pylori*) plays a role in AD, a prospective, non-randomized, comparative study was carried out to examine the levels of anti-H. pylori-specific IgG antibodies in the cerebrospinal fluid (CSF) and serum of patients with AD, compared with those of age-matched cognitively normal controls.

Methods: CSF was aspirated from 27 patients with AD and 27 age-matched cognitively normal patients with prostate hyperplasia or long-bone fractures necessitating surgery after epidural anesthesia. Serum samples were obtained from AD patients and the day before surgery from control participants. Anti-H. pylori IgG concentrations in the CSF and the serum were measured by means of an enzyme-linked immunosorbent assay.

Results: The mean concentration of anti-H. pylori-specific IgG was significantly greater in: a) the CSF of AD patients (10.53 ± 12.54 U/mL) than in controls (8.63 ± 8.01 U/mL, $p = 0.047$), and b) the serum of AD patients (30.44 ± 33.94 U/mL) than in controls (16.24 ± 5.77 U/mL, $p = 0.041$). CSF anti-H. pylori IgG antibodies correlated with the degree of severity of the disease.

Conclusion: H. pylori specific IgG antibody levels are significantly increased in CSF and serum of AD. Moreover, the titer of anti-H. pylori antibody in CSF might reflect the severity of AD, thereby supporting a role for this common infection in the pathobiology of the disease. Further research, however, is required to elucidate the hypothesis of the infectious link related to H. pylori and AD pathophysiology.

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Effect of eradication of Helicobacter pylori infection in Alzheimer's disease patients

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Objectives: Alzheimer's disease (AD) is by far the most common cause of dementia of aging. The disease is characterised by progressive impairment in memory, visuospatial skills, complex cognition, language, and personality in its earlier stages. Infectious agents have been proposed as potential causes of AD. Recently we documented a high prevalence of Helicobacter pylori (Hp) infection in patients with AD. We aim to access the effect of Hp eradication on the AD cognitive (MMSE: mini mental state examination and CAMCOG: Cambridge Cognitive Examination for the elderly) and functional (FRSSD: functional rating scale for symptoms of dementia) status parameters.

Methods: In the first part of the study, a total of 50 consecutive patients with AD and 30 age-matched anaemic controls underwent upper gastrointestinal endoscopies and gastric mucosal biopsies to detect the presence of Hp infection by histologic analysis and rapid urease test. Serum anti-Hp-specific IgG was analyzed by enzyme-linked immunosorbent assay. In the second part, Hp-positive AD patients received triple eradication regimen (omeprazole, clarithromycin and amoxicillin) and all patients were observed followed-up for 2 years while under the same treatment with cholinesterase inhibitors.

Results: Hp was detected in 88% of AD patients and in 46.7% of controls ($p < 0.001$). Hp eradication was successful in 84.8% of treated patients. At the 2-year clinical endpoint, a significant improvement was found in cognitive and functional patients' status parameters in the subgroup of patients where Hp eradication was successful ($p < 0.001$ and $p = 0.049$ for MMSE and CAMCOG respectively; $p < 0.001$ for FRSSD), compared with baseline readings. In contrast, the same parameters deteriorated from baseline to 2-year follow-up in the subgroup of patients for whom eradication of Hp failed, they refused and/or were noncompliant with their eradication therapy. AD parameters did not differ or slightly deteriorated (not statistically significant) from baseline to 2-year follow-up values in Hp negative patients at baseline.

Conclusion: Hp eradication may positively influence AD manifestations, suggesting a possible common link between Hp and AD. Longer-term follow-up, however, is required to validate the beneficial effect of Hp eradication therapy.

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Neurochemical and neuroimaging characteristics in patients with mild cognitive impairment

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Objectives: To investigate the possible associations of cerebrospinal fluid (CSF) biomarker levels (P-tau181 and Aβ42) with neuropsychological and neuroimaging characteristics in patients with MCI-executive (MCI-ex) and MCI-amnestic single domain deficit (MCI-a). To evaluate the influence of treatment with NMDA-receptor antagonist memantine on CSF biomarker levels.

Methods: 27 MCI-a and 20 MCI-ex patients underwent neuropsychological assessment, brain MRI and lumbar puncture (LP). Ventricular indices (AHI, CVI 1 and 2, VBI), mean thickness of medial temporal convolution, inter-uncus distance, presence of leucoareosis and ischemic lesions were calculated. CSF biomarkers were measured in duplicates with commercially available ELISAs. 5 patients with MCI-a underwent 2 measurements of CSF biomarker levels before and after treatment with NMDA-receptor antagonist memantine.

Results: MCI-a group showed lower score in the modified Grober and Buschke (GB) test versus MCI-ex group ($p < 0.0001$). MCI-ex group had lower score in the Frontal Assessment Battery (FAB) ($p = 0.017$). MCI-a versus MCI-ex patients had higher AHI ($p = 0.028$), CVI 2 ($p = 0.016$) and inter-uncus distance ($p = 0.032$), as well as lower CVI 1 ($p = 0.029$). Leucoareosis and ischemic lesions were more frequent in MCI-ex group ($p = 0.014$; $p = 0.017$). P-tau181 level was higher in MCI-a versus MCI-ex and Aβ42 level was lower in MCI-a vs. MCI-ex group ($p < 0.0001$ each). Aβ42 level correlated with CVI 1 ($r = 0.498$, $p = 0.006$) and AHI ($r = -0.393$, $p = 0.02$). We found correlations of P-tau181 and Aβ42 levels with FAB ($r = 0.321$, $p = 0.028$; $r = -0.328$, $p = 0.024$, correspondingly) and GB test scores ($r = -0.551$, $r = 0.625$; $p < 0.0001$ each). In patients with MCI-a after treatment with NMDA-receptor antagonist memantine the level of Aβ42 significantly increased (420 $\pm$ 106 pg/ml in LP2 vs. 351 $\pm$ 87 pg/ml in LP1, $p = 0.02$).

Conclusions: Poor memory test results in MCI-a patients are associated with higher levels of P-tau181 and lower levels of Aβ42 in CSF as well as with more pronounced brain atrophy on MRI. Treatment with NMDA-receptor antagonist memantine can possibly influence the neurodegenerative process.

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Moderate olfactory deficits predicts development of dementia within two years in mild cognitive impairment subjects

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Objective: recently, severe olfactory deficits have been underlined in Alzheimer's disease (AD). It has been found that also individuals with MCI have a low olfactory performances. Therefore, purpose of the present study was to analyse the relationship between smelling and cognitive functions in a sample of MCI subjects and the predictive role of smell deficits in the conversion toward dementia.

Methods: Eighty-eight outpatients fulfilling criteria for MCI were enrolled. Each patient underwent a wide multidimensional and neuropsychological assessment. Subjects were assessed about their olfactory function (threshold, odor identification and memory) by means of a psychometric evaluation. Odor identification was detected by a culturally adapted (CA) and validated version of the University of Pennsylvania Smell Identification Test (UP-SIT), the CA-SIT. The main end point was the development of dementia within two years from the enrolment. Forty-six (46) healthy subjects, matched for age, were recruited as control group and underwent the same multidimensional and olfactory assessment.

Results: thirty-five MCI subjects showed a good smell identification performance (CA-SIT $\geq$ 24/34; mean 26.3 $\pm$ 2.2; MCIS-) similar to controls (mean 26.9 + 3.1), whereas 53 had a moderate olfaction deficit (CA-SIT $<$ 24/34; mean 16.7 + 3.9; MCIS+). MCI+ scored worse in episodic memory than MCIS$-$ ($p < 0.001$), differences in other cognitive domains were not significant. Eighty-four MCI patients were followed-up at 2 years; 27 were converted to dementia (26/27 were AD). The percentage of conversion among MCIS+ and MCIS$-$ were 47 and 11,4% respectively (p 0.000). In a logistic regression model adjusted for age, functional status (IADL, BADL) and cognitive performances (MMSE, Short story, Raven's coloured matrices, Trail Making Test B, Rey's figure recall), low olfaction score (CA-SIT $<$ 24) predicted development of dementia (OR 5.13, C.I. 11.2–22.6, p 0.03).

Conclusion: smell identification deficit (CA-SIT $<$ 24) represents a strong predictor of dementia, among MCI subjects. Smell identification test would consider a useful tool, beside neuropsychological examination, to better characterize different entities among subjects with referred cognitive complaints.

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Clinical correlates of executive dysfunctions in mild cognitive impairment

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Objective: Cross-sectional studies have so far suggested a gradual decline across the adult life span of executive functions, although it is unclear whether these effects are due to age-associated response slowing or to a genuine impairment. Whether preservation of executive function relates to factors such as level of education, vascular risk factors or emotional status needs to be clarified. Purpose of the present study was to investigate these issues in a population of elderly subjects affected by Mild Cognitive Impairment (MCI).

Methods: One hundred-sixty-eight MCI outpatients were investigated. The main end point was the analysis of the socio-demographic, clinical and neuropsychiatric characteristics of two groups of MCI classified on the basis of their performance on two cognitive test: Trail Making Test (TMT) A and TMT B. Subjects with a poor score ($\geq$1.5 SD below age and education adjusted norms on standard neuropsychological tests) in one or both tests were ordered as Executive Functions impaired (EF impaired).

Results: Eighty subjects (47.6%) resulted EF impaired. The main significant (T test, $p \leq 0.05$) features that differed EF impaired from EF not impaired MCI subjects were: older age, lower education, a greater number of somatic diseases and of chronically drugs intake, greater functional (IADL functions lost) and motor disabilities (Tinetti scale), recurrent presence of more than one vascular risk factors, poorer global cognitive performance measures (MMSE, ADAS-Cog and CDR sum of boxes) and more severe anxiety symptoms at the Neuropsychiatry Inventory. The two groups were comparable as

regards measures of memory retrieval. A logistic regression model revealed that among these socio-demographic and clinical features, old age (≥80 years; OR = 4.42; $p = 0.02$) and low education (≤5 years; OR = 3.01; $p = 0.003$) were the only two variables independently correlate with the presence of impaired executive functions among MCI subjects.

Conclusions: We observed a strong association between poor performance on TMT and low educational level, suggesting that preservation of executive function correlates strictly to level of education and to age rather than to other clinical or socio-demographic features. In light of the present data the "cognitive reserve" theory, proposing that people with higher education show clinical symptoms of dementia later than those with less education, should be revised and restricted to executive functions.

P200

Inflammatory markers and oxidative status in patients with Alzheimer's disease treated with cholinesterase inhibitors

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Objectives: Alzheimer's disease (AD) is the most frequent neurodegenerative disorder associated to dementia in the elderly, and at present no effective therapy exists. Both inflammation and oxidative stress are thought to play a role in AD pathogenesis and progression, and assessment of the effects of pharmacological treatments on such mechanisms is therefore of great importance. The aim of the present study was to investigate plasma oxidative status and polymorphonuclear leukocyte (PMN) oxidative metabolism in a group of AD patients and to assess the possibile correlations with anticholinesterase (AChE) treatments.

Methods: The study included 19 patients with possible or probable AD according to NINCDS–ADRDA criteria (age = 75.4 ± 6.1 years; F/M = 17/2) treated with either donepezil (12) or rivastigmine (7) at currently recommended doses. Patients were studied twice, at enrollement and after six weeks. At each visit, a blood sample was obtained by venipuncture to investigate plasma antioxidant capacity (assessed by the Ferric Reducing Ability of Plasma—FRAP method), and PMN production of reactive oxygen species (ROS, assessed by a standard spectrofluorimetric assay and expressed as fluorescence intensity in arbitrary units—AU).

Results: There was no significant difference in any of the parameters under study between the first and the second visit, and individual patient's data were therefore pooled together in subsequent analysis. Mean ± SD FRAP values were 1.24 ± 0.38 microM in donepezil-treated patients and 1.49 ± 0.51 microM in rivastigmine-treated patients ($p > 0.05$). Production of ROS by PMN stimulated with fMLP 0.1 microM was 155.2 ± 96.7 AU in donepezil-treated patients and 331.6 ± 250.5 AU in rivastigmine-treated patients ($p < 0.05$). Reference values obtained by retrospective analysis of historical data from a large cohort of healthy subject were [mean (95% CI)] 1,40 (0.96-1.84) microM for FRAP and 366,1 (260.7–471.5) AU for ROS production from fMLP-stimulated PMN.

Conclusions: The present results indicate that in AD patients treatment with donepezil may be associated with lower oxidative burst of circulating PMNs, thus supporting the proposed antinflammatory and immunomodulating profile of some drugs used in AD. Whether such properties contribute to the clinical effects of pharmacotherapies needs however careful assessment in ad hoc studies.

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Effects of memantine on behavioural symptoms in moderate-to-severe Alzheimer's disease patients: a post-marketing surveillance study

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Objective: To evaluate memantine effectiveness on behavioural and psychological symptoms of dementia (BPSD) in the clinical practice and to identify variables that may predict the effects of the therapy.

Methods: The effects of memantine on behaviour were analysed in the database of a post-marketing surveillance (PMS) study promoted by the Lombardy Region Health Office, involving 43 Alzheimer's Disease (AD) Units. From July to December 2005, 399 moderate-to-severe AD patients free of cholinergic medications were enrolled, treated with memantine (standard titration to 10 mg bid) and followed-up for 6 months (1). BPSD were assessed in a subgroup of 297 patients (mean age 77 ± 8 years; 73% female; mean neuropsychiatric inventory (NPI) score 28 ± 24) for whom NPI subscores (12 behavioural symptoms) at baseline, at third and at sixth month were available. The 12 BPSD were clustered as follow: affect, physical behaviour, psychosis and hypomania. The main outcome measure was the proportion of each cluster responders at 6 months of therapy. The patients who showed the improvement in baseline score on at least one cluster symptom and no worsening in all the other cluster symptoms were considered as responders. Patients who discontinued treatment prematurely were considered as non-responders.

Results: The prevalence of each BPSD cluster at baseline was as follow: 79% affect, 79% physical behaviour, 50% psychosis, 36% hypomania. The proportion of responders was: 30% affect, 24% physical behaviour, 29% psychosis, 27% hypomania. Memantine stable dosage was associated with a higher probability of having a response (affect OR 9; 95% CI 3.75–21.63; physical behaviour OR 17.78; 95% CI 5.91–53.51; psychosis OR 23.66; 95% CI 5.05–110.85). A response after 3 months of therapy was associated with a greater probability of response after 6 months of treatment (affect OR 10.51; 95% CI 4.92–22.48; physical behaviour OR 10.75; 95% CI 4.57–25.33; psychosis OR 25.48; 95% CI 7.26–89.35).

Conclusion: he main limit of this PMS study is the difficulty to assess BPSD changes due both to the natural history of the disease and to changes in other CNS active drugs.

In the clinical practice for moderate-to-severe AD patients treated with memantine, the main predictive variables of a 6 months BPSD improvement were stable dosage of memantine and an early response to therapy at 3 months.

Reference

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Epilepsy

P202

Occipital lobe epilepsy, myoclonus, refractory status epilepticus, ataxia and polyneuropathy represent the core features of a syndrome caused by POLG1 mutations

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Objectives: Mutations in the mitochondrial DNA polymerase γ (POLG1) cause various heterogeneous neurological phenotypes. Recent studies report a syndrome characterized by epilepsy and spinocerebellar ataxia due to POLG1 mutations. We here describe clinical and genetic data of 4 new patients with this syndrome.

Methods: In this retrospective study we selected 4 unrelated Belgian patients with confirmed pathogenic mutations in POLG1 and reviewed their clinical, radiological and electrophysiological data.

Results: Two patients harboured a homozygous A467T mutation, one patient a homozygous W748S mutation and one patient was compound heterozygote for these two changes. Only one individual had a family history of mitochondrial disease.
The age of disease onset ranged from 12 to 26 years. All patients suffered from refractory epilepsy. In all but one, the epileptic syndrome had initial features of occipital lobe epilepsy (OLE), often associated with migraine. Cerebral imaging revealed a progressive occipital lobe lesion in all cases, with electroclinical evidence of occipital lobe epileptic activity, often during end-stage refractory status epilepticus (RSE). Simple partial motor seizures and myoclonus were present in all. One patient presented with progressive myoclonic epilepsy and another had an episode of myoclonic status epilepticus. The disease course in all patients was complicated by the occurrence of RSE. Additional clinical manifestations in three patients included progressive ataxia, sensory neuropathy and in a single case progressive external ophtalmoplegia, dysartria and minor cognitive decline. Death occurred on average 7 years after disease onset (range 7 months to 15 years), in three patients related to RSE and in one due to hepatic failure precipitated by sodium valproate treatment.

Conclusion: This study confirms that mutations in POLG1 cause a clinical distinctive syndrome, which is recognisable early in its course. POLG1 mutations should be considered in any young person presenting with a combination of OLE, RSE, myoclonus, ataxia, sensory polyneuropathy, external ophtalmoplegia or progressive myoclonic epilepsy. Treatment of seizures with sodium valproate should be avoided in view of the risk of fulminant hepatic failure.

P203

Early memory improvement after temporal lobe epilepsy surgery

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Objectives: Questions are still open as to which memory mechanisms change after temporal lobe epilepsy (TLE) surgery and which factors may predict a positive outcome. The objective of this study was to compare the short and long-term changes of material-specific memory and learning after surgery for drug-resistant TLE.

Methods: Twenty-eight adult patients with drug-resistant left or right TLE were evaluated before and six months and one year after surgery. The surgical resections involved, to different extent, the anterior lateral and mesial temporal lobe structures. Rey's figure, the Short story, and Word list and Corsi's blocks learning were used to assess verbal and visuospatial long-term memory and learning. Separate non-parametric Wilcoxon and Mann-Witney tests were used for statistical analysis.

Results: After surgery, both left and right TLE patients reported complete seizure remission except for three cases with sporadic attacks. With respect to the postoperative evaluation, at the 6-month follow-up, the verbal and visuospatial test scores were lower in the left and right TLE patients, respectively, but the changes were not significant. By contrast, the left TLE patients showed significant improvement in visuospatial memory, while the right TLE patients showed significant improvement in verbal learning. One year after surgery, further cognitive improvements were observed but not significantly so. Between-group comparisons did not show any difference except for higher verbal learning scores in the right TLE patients at the 6-month follow-up.

Conclusions: Material-specific memory and learning supported by the non-operated temporal lobe may significantly improve a few months after TLE surgery. This suggests that specific cognitive improvement may be an early consequence of successful operations for TLE. In selected patients, taylored surgery and seizure control may predict some gain in memory and learning.

P204

Propagation of activity within the dentate gyrus

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Objectives: To investigate the spread of excitation in the dentate gyrus with stimulation of stratum granulosum at different sites.

Methods: Data were sampled from fluorescence changes of the voltage-sensitive dye RH 795 incorporated into cellular membranes after electric stimulation and recorded with a 464-photodiode array in a neuronal network in vitro. The decrease of fluorescence of the sensitive dye depends on the level of cell-excitation.

Results: The experiments showed that stimulation of the crest of the stratum granulosum evoked activity in this entire layer and in the hilus. The inner edge of the ectal limb adjacent to the presubiculum was omitted. Propagation of activity to the ectal limb and the hilus was twice (6.3 ms) as fast as to the endal limb (12.6 ms). The longer latency to the endal limb showed the involvement of multisynaptic processes indicating neural computation of activity.
If the point of stimulation was set in the stratum granulosum of the ectal limb the entire layer in the endal limb was activated whereas only the end of the stratum granulosum within the ectal limb and a small region adjacent to the prosubiculum of the entorhinal cortex were included.
Stimulation of the endal limb showed higher levels of activity within the dentate gyrus compared to other stimulation sites. The pattern of propagation, however, was similar to that evoked by stimulation of the stratum granulosum in the ectal limb. Activity from the endal limb reached the area around the crest within 3.78 ms, i.e. that the time of information exchange and communication between these two regions was unusually fast. Propagation of activity to the stratum pyrimadale was nearly exclusively via the endal limb.
Throughout the different stimulation sites stratum granulosum of both limbs communicated with the hilus indicating the importance of this region.

Conclusion: In conclusion, the pattern of activity in the hilus, at both ends of the stratum granulosum and in the region adjacent to the prosubiculum was always the same independent of position and

amplitude of the stimulus. The region adjacent to the presubiculum was always omitted. In spite of the macroscopic similar organization of both limbs the endal limb takes a more significant position regarding the propagation of activity.
According to the known course of the mossy fibres activity is primarily propagated to the stratum lucidum in the suprapyramidal zone and from there to the stratum pyramidale of the hippocampus proper.

P205

Temporal lobe epilepsy with amygdalar enlargement: a morphologic and functional study

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Objectives: The recent advent of high-resolution magnetic resonance imaging (MRI) has shed light on temporal lobe epilepsy with non-tumoural amygdalar enlargement (TLE-AE) as a possible, poorly recognized etiology (Bower et al; JNNP 2003; Mitsueda-Ono et al. Clin Neurophysiol 2006, Suppl 1). However, the anatomical and functional characteristics of this entity have not been elucidated thus far. The present study aimed to clarify the morphologic and functional characteristics of TLE-AE by using MRI and [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET).

Methods: By using 3T MRI and FDG-PET, we compared cerebral grey matter volume and glucose metabolism in 8 patients with TLE-AE and healthy subjects. Voxel-wise statistical analyses were performed using SPM5, and the grey matter volume was assessed using voxel-based morphometry (VBM).

Results: In the TLE-AE patients, a significant increase in the grey matter volume and a significant decrease in glucose metabolism were detected in the ipsilateral amygdala and thalamus. In contrast, no significant decrease in the grey matter volume was found in the TLE-AE patients at all.

Conclusion: The patterns of increase/decrease in the grey matter volume and glucose hypometabolism in patients with TLE-AE were different from those in patients with mesial temporal sclerosis (TLE-MTS) that have been reported in the previous studies. This leads us to the hypothesis that TLE-AE is a clinicopathologic entity distinct from TLE-MTS, although TLE-AE might contain heterogeneous pathological substrates.

P206

Spectrum of epileptic disorders in limbic encephalitis

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Objectives: Clinical manifestations of limbic encephalitis are composed of psychiatric dysfunctions, cognitive impairments and a variety of epileptic seizures. Here, we describe the clinical spectrum of epileptic disorders in the patients with limbic encephalitis.

Methods: We encountered seventeen patients who meet the diagnostic criteria of limbic encephalitis. None of them were due to para-neoplastic in etiology. The semiology of the seizures, clinical courses and neuro-imaging findings were analyzed and categorized.

Results: The median age of enrolled patients was 50 years old. Female patients were six (35.3%) and eleven male (64.7%). Twelve patients presented with status epilepticus as their initial symptoms of the illness. All of these patients experienced complex partial seizures of temporal origin and secondarily generalized tonic-clonic seizures. Among them, seven patients required management for refractory status epilepticus during which additional multifocal partial motor seizures often occurred. Three patients presented with pilomotor seizures and one of them had two episode of generalized tonic-clonic seizures. Two patients had complex partial seizures only. On MRI, four patients (23.5%) showed unilateral limbic lesion and thirteen patients (76.5%) had bilateral limbic involvement. None of the patients with unilateral involvement experienced status epilepticus. All of three cases of pilomotor seizures had unilateral lesion. Among thirteen cases with bilateral limbic lesion, twelve developed the status epilepticus. Mortality was two out of seventeen patients (11.8%) due to sepsis. Two factors attributed to the poor prognosis. The first was the extra-limbic extension of the lesion in follow-up MR images, particularly the bilateral pulvinar involvement. The second was the duration of refractory seizures and subsequent prolonged immune suppression.

Conclusion: Epileptic disorders associated with limbic encephalitis showed a broad clinical spectrum from pilomotor seizure to fatal refractory status epilepticus. Complex partial seizures with secondary generalization is the most common epileptic manifestation of limbic encephalitis. MRI findings appeared to be valuable in predicting clinical courses and prognosis.

P207

Evaluation of seizure and sleep characteristics of patients with pure nocturnal seizures

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Objectives: Many authors are interested in different aspects of the relationship between sleep and epilepsy, but the seizures occurring only during sleep have not been investigated in detail. The aim of this study was to describe the clinical features of the patients who had only nocturnal seizures and to evaluate their sleep characteristics.

Methods: We included epileptic patients seen in a study period of one year, who had been followed up by our epilepsy outpatient clinics at least for two years, and had only nocturnal seizures (more than 3). Their clinical, semiological, EEG and MRI findings were investigated from their files and their syndromes were defined accordingly. We also applied the Medical Outcomes Study-Sleep Scale (MOS-SS) after their informed consent.

Results: Among a total of 1401 patients, only 38 (2.7%) have met these criteria and reported pure nocturnal seizures. The mean age was 32 ± 13, with a follow-up period of $7 \pm 4{,}4$ years and 20 were female. According to the International League Against Epilepsy (ILAE) criteria, 24 (63.1%) had cryptogenic partial, 5 had symptomatic partial, one had idiopathic partial and only 3 had idiopathic generalized epilepsy. EEGs were normal or nonspecific in 5 subjects whose syndromes remained undetermined. The MRI lesions of symptomatic partial cases showed various etiologies such as occipital dysplasia, mesial temporal sclerosis, glial tumor, encephalomalacia and multiple sclerosis plaques. Monotherapy was found to be effective in 24/38 of the patients.
Twenty-two patients agreed to participate in our MOS-SS study. They were divided into two groups; 17 patients had less than one seizure per month and 5 patients had ΓëÑ 1 seizures per month. We compared the sleep problems index II scores (9 of 12 items of the MOS-SS); however we found no significant differences between these two groups.

Conclusion: The patients presenting with only nocturnal seizures had mostly cryptogenic partial epilepsy. Their nocturnal seizures usually have good prognosis and monotherapy achieves seizure control in most of cases. Frequent seizures seem not to affect the sleep quality in this population.

P208

First diagnosis and treatment of patients with juvenile myoclonic epilepsy and time period to the final diagnosis and treatment

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Objectives: Juvenile myoclonic epilepsy (JME) is one of the most common types of epilepsy. It affects approximately 7-10% of adolescents and adults with epilepsy. JME is characterized by myoclonic jerks alone (3–5% of cases) or in combination with generalized tonic-clonic seizure (80% of cases) or absense seizure (20% of cases). JME has always a myoclonic component and myoclonic seizures should be present in order to establish the diagnosis of JME.

Methods: In the present study we analyzed clinical and EEG data of JME patients who were referred to our Epilepsy Departemnt in the period between 2004–2009. We evaluated 105 patients with JME and the following parameters were assessed - age at onset of seizures, age at first diagnosis of epilepsy and type of present epileptic treatment, as well as age at which the diagnosis of JME was established and an adequate antiepileptic treatment was started.

Results: Our results reveal that in many cases the correct epileptic syndrome was determined with a time delay (from 1 to 56 years) thus leading to an inadequate drug choice and a false impression of treatment resistance.We found out that the main factors responsible for the misdiagnosis were failure in eliciting a history of myoclonic jerks and misinterpretation of the EEG finding.

Conclusions: A correct JME diagnosis is strictly dependent on the ability of the interviewer to look for myoclonic jerks in the history and on the main diagnostic tool—the EEG.

P209

Electronic database for epilepsy clinics: experience of over one year

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Objectives: In order to have an electronic management of the clinical data of our patients we created a database .MDB (Microsoft DataBase) for our Epilepsy Unit. This electronic tool allows to make specific analyses, such as dividing patients into epileptic syndromes and relative aetiology. This approach, other than allowing a comparison with similar data (i.e. other Epilepsy Centres or literature), gives the opportunity to reconsider critically the diagnostic process. We can also evaluate how an electronic tool ameliorates the diagnostic definition.

Methods: We analyzed clinical data of all patients attending our Epilepsy Clinics between December 2006 and March 2008. For all patients we revaluate the medical history. Data have been organized and saved in an epilepsy database (updated at 1.2c-.MDB format), group through SQL queries.

Results: Our sample encompasses 615 adult patients (M = 300; F = 315; age range = 17–96 years). We identified 321 with "Partilal Epilepsy", 75 with "Generalized Epilepsy", 15 with "not determined if partial or generalizedΓ", 5 with "special syndromes". In 85 patients the syndrome was not specified or "not epileptic manifestations". A total of 114 patients were still in the diagnostic process. Analyzing the specific aetiology of patients with partial symptomatic epilepsy syndromes ($N = 155$): 29% were diagnosed cerebrovascular disease, 18% traumatic brain injury, 15% primary or secondary brain tumors, 12% congenital/perinatal encephalopathy, 11% malformations, 8% brain infections, 3% degenerative disorders and 4% of unknown origin.

Conclusions: Our electronic database has definitely improved quality of medical record collection and rapidity of analysis. The easily understandable format and the fully comprehensive data collection allowed a rational evaluation of the diagnostic process. A correct definition, in terms of syndrome and specific aetiology, is the essential basis for a rational and correct treatment.

P210

Adult case of Rasmussen encephalitis initially presented with stroke-like episodes

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Objectives: Rasmussen Encephalitis is a rare but severe immune-mediated brain disorder leading to unilateral hemispheric atrophy, associated progressive neurological dysfunction and intractable seizures. We report a case of RE with initial manifestation of stroke like episodes. The diagnosis was supported on the European consensus statement about pathogenesis, diagnosis and treatment of Adult Rasmussen encephalitis published in Brain medical magazine(2005; 128:454–471).

Methods: A 49 years-old woman was admitted to our clinic due to several episodes of partial numbness of the right extremities and kinetic aphasia with mean duration of 1 minute. Right hemiparesis was added. Epilepsia partialis continua was expressed as clonic movements of the right arm. Her course was stabilised after 9 months of progressive deterioration.

Results: The brain magnetic imaging showed a left lesion, simulating an ischaemic damage in the left temporal lobe and atrophy of the head of the caudate nucleus and the frontal lobe ipsilaterally. Her electroencephalogram revealed polymorphic delta waves and epileptiform activity over the affected lobes and contralateral asynchronous slow waves. Cerebrospinal fluid and laboratory examinations were unremarkable. The brain biopsy revealed necrosis of gyral segment and abundant perivascular round cells. SPECT examination revealed decreased hematosis of the left parietal-frontal-temporal lobes. The magnetic resonance spectroscopy showed decreased N-acetyl-asparate-choline ratio. She was treated with oxcarbazepine and levetiracetam with mild control of the episodes. Corticosteroids and IVIG administration were not helpful for the treatment management of the patient.

Conclusions: The diagnosis of RE rests on clinical, electrophysiological and morphological studies as the consensus statement proposes. After disease duration of 1 year, differential diagnoses are few. The challenge is the early recognition of the disease in order to avoid or retard the progressive hemiatrophy and the neuronal loss.

P211

Glutamate content in the brain in normally developing children and in children with seizure disorders: 1H in-vivo MRS study

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Objectives: We propose the quantitative indicators for the characteristics of regional and age peculiarities of the brain metabolism in normally developing children and in children with seizure disorders using primary spectral parameters of glutamate signal (Glu).

Methods: 42 children are examined by 1H MRS using 1.5T Signa EXCITE HD (GE). All subjects are divided into two groups. The 1st group (NG) consists of 10 healthy children (in the age from 1 month to 16 years). The 2nd group (PG) includes 32 developmentally delayed children with seizure disorders (in the age from 2 weeks to 16 years). The subjects of both groups are divided into 5 age group: less than 1 month, from 1 month to 1 year, from 1 to 3 years, from 3 to 8 years, and older than 8 years. For some children the monitoring of brain maturation in uterus and then in early newborn age is provided. Spectral matrixes in supraventricular region parallel to the canthomeatal line are obtained. 2DCSI 1H spectra are recorded with- and without water saturation: TR/TE = 1,500/144 ms. All spectra are recorder. The water signal intensity, corrected for age dependent changes, used as an internal standard for calculation of Glu content.

Results: In each voxel of the spectral matrix we introduce two indicators: the metabolite content AM as the peak area and the metabolite concentration CM as the ratio of the peak area to the sum of all the peak areas S: CM = AM/S. We analyzed the temporal alterations of the Glu content during neurodevelopment. In white matter (WM) in the NG in the age from 1 to 3 months the Glu content increase rapidly, reach maximum in 6 months, and thereafter decreased moderately to adults level for the age 1 year. In gray matter (GM) in the NG in the age from 1 to 3 months the Glu content increase rapidly before values, characteristic for adult level. In children with the events of neurological disorders (PG) in all ageing groups the Glu content is higher than in NG, and in both regions (WM, GM) of the brain no plateau is observed.

Conclusion: MRS investigation of the fetal, neonatal and adolescent human brain gives us a unique possibility for monitoring of the neurodevelopment and provide a baseline for age related differences in the normal human brain and in the brain under pathology.Our quantitative approach gives us information about excitotoxic influence of glutamate on the developing brain.

P212

Topiramate-induced reversible visual hallucinations: report of two cases

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The incidence of psychotic symptoms during clinical trials of topiramate was not significantly different from the rate for placebo or reported rates of psychosis in patients with refractory epilepsy. Furthermore, acute visual hallucinations after the use of topiramate is unusual manifestation.

Two patients with refractory complex partial seizure who had no psychiatric history developed symptoms visual hallucinations after the use of topiramate.

After reduction of topiramate dosage in both patients, a full remission of the visual hallucinations was obtained without the need of neuroleptic drugs.

We report on two epileptic patients who developed reversible visual hallucinations after the use of topiramate.

P213

High serum tau protein in patients with therapy-resistant intractable epilepsy under a baseline

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Objective: Tau protein is a neuronal microtubule-associated protein; a novel class of axonally-derived phosphor-proteins that appears to function in the formation and maintenance of axon by influencing microtubule organization. Tau is more heavily phosphorylated in fetal than in adult brain, and is also hyperphosphorylated in Alzheimer's disease where it forms the major component of paired helical filaments. Tau has been identified as a diagnostic agent for detecting axonal damage in brain trauma. One clinical state associated with axonal damage could be epileptic seizure which is a severe neurological condition. Attempts, to identify biomarkers of axonal damage are of a great significance, prompted us to examine pathological heat tau protein in epilepsy.

The aim of this study was to determine serum tau protein concentrations in patients with therapy-resistant intractable epilepsy under a baseline.

Method: Tau was measured by immunofluorescent method using monoclonal anti-mouse IgG FITC conjugated and monoclonal anti-TAU-2 antibodies (Sigma); and detecting the bound tau protein at immunofluorescent microcopy. Results were expressed as optical density units of FITC-labelled binding sites. Protein that was useful in the present study has an apparent molecular weight ranged between 55 and 62 kDa being in phosphorylated or non-phosphorylated forms.

Results: Ten patients with intractable temporal lobe epilepsy (mean age $\pm$ SD; 31.32 ± 7.53 years) and 10 controls (31.6 ± 5.36) were investigated. Tau protein levels in sera were measured under a baseline condition: 48 hours seizure-free and consisted of a 48-h period with no seizure. Patients had long-standing intractable drug-resistant epilepsy: 4 ± 3.6 seizures per month with mean seizure onset $\pm$ SD: 9.95 ± 7.68 years and mean disease duration $\pm$ SD: 20.68 ± 9.46. Serum tau concentrations in therapy-resistant epilepsy under baseline conditions were higher compare with controls (0.34 ± 0.02 vs. 0.04; $p < 0.05$) that could reflect severity of epilepsy either its long duration or high seizure frequency; tau may be a useful diagnostic marker of slightly axonal damage in epilepsy demonstrating degree of severe course. Fundamental clinical and experimental researches are needed to clarify the role of tau protein as a biomarker of axonal damage at epilepsy.

Conclusion: Serum tau protein levels were elevated in patients with long-standing intractable therapy-resistant epilepsy under a baseline.

P214

Characteristics and proposed aetiologies of epilepsy in multiply handicapped children

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Objective: To describe the characteristics, proposed etiology and prevalence of epilepsy in patients with multiple handicaps in a specialized center.

Methods: A total of 200 consecutive multiply handicapped patients were retrospectively studied. Criteria for inclusion were follow-up period for at least 2 years. Types and prevalence of epilepsy were correlated with the different forms of disabilities. Other factors associated with epilepsy such as age of first seizure, neonatal seizures and family history of epilepsy were also analyzed.

Results: Follow-up ranged between 24 and 148 months (mean 54 months). The overall prevalence of epilepsy was 29% in the total group. It was 59.7% in Cerebral palsy; 24.5% in mental retardation; 61% in sensory deficits group; and 42% in other behavioral disturbances group. First seizure occurred during the first year of life in 74.2% of patients with epilepsy. Generalized and partial were the predominant types of epilepsy (62 and 38%, respectively). Neonatal seizures and family history of epilepsy were associated with a higher incidence of epilepsy. The proposed etiologies in the group were: Perinatal injury; Remote central nervous system infection; Trauma; Developmental and genetic brain disorders.

Conclusions: epilepsy in multiply handicapped children is a major problem. It can be predicted if seizures occur in the first year of life, in neonatal period and if there is family history of epilepsy.

P215

Complementary therapy use among epileptic patients in tertiary care hospitals in north-eastern Nigeria

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Objectives: Epilepsy is the most prevalent neurological disorder requiring long-term treatment and compliance. In Nigeria, it is generally perceived as a manifestation of super natural forces; thus many patients use complementary therapies. This study determined the pattern of use of these complementary therapies among epileptic patients.

Methods: Five hundred adult patients with epilepsy visiting the outpatient clinics of three tertiary health centres in north-eastern Nigeria were interviewed regarding use of complementary therapies. The type of complimentary therapy used, persons who recommended the therapy and the reasons for trying these therapies was noted in these patients.

Results: Eighty five percent of the patients interviewed had used one form of complementary therapy or another. Most patients (74%) sought these therapies first before seeking the services of a doctor in hospital. Prayer sessions in various forms administered by clergy men were used by 92% among whom 46% used additional herbal preparations and concoctions. Use of complimentary therapies was seen among patients at all educational level although use of herbal preparations and concoctions was more frequent among the lower educational class. Influence of family and friends (68%) and media (19%) were the common reason for trying these therapies. The most frequent reason for this therapy was the perceived super natural cause of epilepsy.

Conclusions: The use of complementary therapy was found to very high and some of the herbal preparations and concoctions may be proconvulsant, contain toxins or affect liver enzymes. Patients should be enlightened on these possible adverse effects.

Motor neuron diseases

P216

A multidisciplinary approach improves quality of life perception in patients with amyotrophic lateral sclerosis

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Objectives: A multidisciplinary approach, including physical therapy assisted programs, in neuromuscular disease patients has proven to improve quality of life (QoL) in Amyotrophic Lateral Sclerosis (ALS) patients. The effects of physical exercise in patients with ALS are controversial but there are indications that QoL improves. The general objective of our study is to verify whether management in a multidisciplinary center improves perception of quality of life in patients with ALS. More specifically, we wish to determine whether an individualized physical exercise program improves QoL as perceived by the patients.

Methods: 15 patients (8 male, 7 females, age range 51-76, mean 61.57 ± 8.38) with diagnosis of ALS were subjected to: (1) MMT; (2) ALS-FRS-r; (3) FVC; (4) Therapeutic exercise (i.e. active assisted and passive mobilization, and stretching); (5) McGill QoL Single-Item Scale (MQoL-SIS) before access to the multidisciplinary clinical center and at discharge after the physical program.

Results: When the patients were asked about their symptoms, physical symptoms subscore was better after the recovery than on admission (respectively 16.50 ± 6.69 and 21.43 ± 5.93, $p = 0.017$). Moreover, the subscore about existential well-being showed a significant improvement at the discharge compared to admission (respectively 45.93 ± 7.16 and 41.57 ± 9.29, $p = 0.019$). The other subscores (psychological symptoms and support domains) did not show any significant change.

Conclusions: A multidisciplinary approach, including an individualized physical exercise program, appears to provide an improvement of the physical symptoms and existential well-being a perceived by ALS patients. These results emphasize the necessity of a coordinated multidisciplinary care between specialist and therapists for ALS patients. We wish to further explore quality of life perception in patients with neuromuscular disorders as a result of a physical exercise program in a multidisciplinary context using INQoL, an individualized QoL scale, specifically constructed for patients with neuromuscular diseases. This scale will possibly allow us to better correlate aspects of QoL related to the muscle condition, which may have been underscored by the more generic measure of QoL.

P217

Caregiver burden and disease progression in amyotrophic lateral sclerosis

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Objectives: Studying caregiver burden in amyotrophic lateral sclerosis (ALS) is an extremely relevant topic, due to the impact that such a dreadful disease has on the whole family. Moreover, psychological intervention on caregivers could be extremely important not only for them, but also for ALS patients. Aim of this study was the assessment

of caregiver burden in relation with disease progression, taking into account types of patient-caregiver relationships.

Methods: We gave 49 ALS patients' caregivers, subdivided into Group 1, Gp1 (36 partners) and Group 2, Gp2 (13 siblings), the Caregiver Burden Inventory (CBI) evaluating five dimensions of caregiver burden: Time-Dependence Burden (T/dep-B), Developmental Burden (Dev-B), Physical Burden (Phys-B), Social Burden (Soc-B) and Emotional Burden (Emot-B). We correlated single dimension scores and total scores with disease progression (measured by the ALS Functional Rating Scale-Revisited, ALSFRS-R) assessing patients' motor functions in bulbar, limb and breathing domains).

Results: In Gp1, total and T/dep-B scores were significantly ($p < 0.01$) correlated with disease progression (ALSFRS-R total and single domain scores).

In Gp2, we did not find a significant correlation between total burden scores and disease progression. We found a correlation between T/dep-B and total scores on ALSFRS-R, but not with the single domain scores.

In both groups, severe bulbar symptoms appeared to be related with higher caregivers' Phys-B. In Gp1, Emot-B scores were significantly correlated with the ALSFRS-R bulbar domain; Dev-B scores with severe impairment in ALSFRS-R limb and breathing domains.

Conclusions: This study represents a first step in the evaluation of different aspects of caregiver burden, by considering both caregiver- and patient-related variables, such as caregiver age and sex/gender differences, type of patient-caregiver relationship, and patient's physical impairment.

We plan to extend our preliminary work to a larger sample of subjects.

P218

Effects of lithium administration on oxidative stress markers in amyotrophic lateral sclerosis patients

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Objectives: Amyotrophic lateral sclerosis (ALS) is a neurological disease characterized by a selective degeneration and death of upper and lower motor neurons, initiating in mid adult life and almost invariably progressing to paralysis and death over a 1–5 year time course. The causes of motorneurons loss are still unknown, but accumulating evidences indicate that oxidative stress is involved in the pathogenesis of this disease. The only treatment actually approved for this disease is Riluzole, an antiglutamatergic drug, that prolongs survival in ALS patients by about two months. Recently it has been proposed a possible role of lithium salts on the treatment of this disease. Lithium, a well known mood-stabilizing drug used for the treatment of bipolar affective disorders, at the same time is increasingly recognized as neuroprotectant agent mainly by its effects on cellular mechanisms linked to autophagy and mitochondriogenesis.

Methods: We tested the effect of lithium carbonate (plasma levels ranging from 0.4 to 0.8 mEq/l) on 20 ALS patients (mean age $\pm$ SD: 64.3 years $\pm$ 7.0). In all enrolled patients, before beginning treatment, we assessed peripheral oxidative stress markers, in particularly advanced oxidation protein products (AOPP), ferric reducing ability of plasma (FRAP), total glutathione, and disease progression clinical signs quantified by ALSFRS-r and MRC scale. These evaluations were performed, during add-on to riluzole treatment, at the acquisition of the targeted plasma lithium level in plasma and at 6 months after starting lithium treatment.

Results: We evidenced that, at lithium range of 0.4–0.8 mEq/l, the patients presented, compared to baseline values, significant reduction of AOPP ($p < 0.005$), increase of FRAP but not significantly ($p = 0.08$) and significant increase of total glutathione ($p < 0.002$).

Conclusion: We conclude that lithium therapy is able to reduce circulating levels of blood oxidative stress markers in ALS patients. ALSFRS-r and MRC did not change after this short course treatment. Whether or not the modification of oxidative stress markers and anti-oxidant defence is related to a direct effect of this drug on pathogenic mechanism and time course of the disease is still an open question, to be addressed with long term studies in conjunction with clinical efficacy assessment.

P219

Epidemiology of amyotrophic lateral sclerosis in Isfahan, Iran

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Background: Few studies are carried out on the epidemiology of amyotrophic lateral sclerosis (ALS) in Middle East with no reports from Iran.

Objective: To determine the epidemiological and clinical features of ALS among the Iranian population living in Isfahan, Iran.

Methods: Medical records of all hospitals with a neurology department and outpatient neurology clinics in Isfahan province from 2002 to 2006 were reviewed and all cases with the diagnosis of ALS according to El Escorial diagnostic criteria were extracted and related demographic and clinical data were gathered and analyzed.

Results: We found 98 new cases (66 men and 32 women) with definite, probable, or possible ALS. The average annual incidence was 0.42/100,000, with the highest incidence rate among those aged 70-74 years. On 21 March 2006, the crude prevalence was 1.57/100,000. Median survival from onset was 48 months (95% confidence interval 34–61) and survival rates for one, three, and five years after the onset were 94, 66, and 32%, respectively.

Conclusions: The incidence and prevalence of ALS in the Iranian population seems to be lower compared to other populations. The survival of our patients was longer than previously reported.

P220

Novel homozygous mutation in SOD1 gene in a patient with familial amyotrophic lateral sclerosis

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Objective: Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disorder characterized by degeneration of motor neurons determining progressive muscular atrophy, weakness and death from respiratory failure.

Approximately 10% of ALS cases are familial (FALS) and 20% of them are due to several mutations in the Cu/Zn superoxide dismutase (SOD1).

Until now all the SOD1 mutations are autosomal dominantly inherited with the exception of D90A which is the only variation reported to be causative of ALS both in heterozygous and homozygous state.

Here we report a novel homozygous mutation in SOD1 gene in a patient affected by motor neuron disease and with multiple affected family members.

Case report: The proband is a 45-years-old man, born from non consanguineous parents coming from the same village in Syria. One

brother and two sisters died before age of 50 due to respiratory failure after complaining marked hypotonic inferior limbs. A 50-years-old proband's cousin is also affected by ALS. Proband's clinical history was unremarkable, with the exception of recurrent low back and lower leg pain, since a minor trauma at 40 years. He was first seen at the age of 45 reportedly for the same symptoms. At the neurological examination, he presented a lower limb weakness and decreased muscle bulk, with paretic foot dorsiflexion. Serum creatine kinase level was elevated (626 U.I; n.v.: < 180), while other blood and cerebrospinal examination was normal. EMG showed active and neurogenic signs at the left L5, left and right S1, as well paraspinal myomers, Motor Evoked Potentials showed a decreased left central conduction time.

Results: Sequence analysis of the SOD1 exons from the proband's DNA revealed a novel homozygous nucleotide substitution within exon 4 (c.352C > G), resulting in an aminoacid substitution from leucine to valine in codon 117 (L117 V). The mutation was absent in 120 Italian controls and has never been reported worldwide.

Conclusion: This is the second homozygous mutation in SOD1 gene in FALS. The clinical presentation of a preparetic phase with lower back, hip, or knee pain, muscle cramps, and stiffness in the legs for months or even years, followed by insidious onset of paresis in one leg that progresses slowly to involve the other limbs is very similar to that of D90A. However disease duration seems to be shorter. Further studies are needed to address the autosomal recessive or dominant nature of this mutation and its pathogenetic mechanisms.

P221

Amyotrophic lateral sclerosis presenting during pregnancy: report of clinical and genetic features of three cases

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Objectives: A few previous reports have described patients with ALS presenting during pregnancy, but the association is rare and pathogenic relationship is still to be demonstrated. In this study we wished to evaluate the frequency, clinical and genetic aspects of ALS cases, associated with pregnancy, in a cohort of patients attending our neuromuscular centre.

Methods: We retrospectively analysed charts from female patients with a diagnosis of ALS attending the Muscle Clinics at Nemo Center and at IRCCS Policlinico San Donato during the year 2008. Of 76 female patients, 3 had the diagnosis of ALS during the first pregnancy (4%).

Results: Case 1: a previously healthy 33-year-old woman presented with subacute, severe, left lower limb pain after delivery, followed by progressive weakness and wasting of the left leg, mimicking a lumbo-sacral radiculopathy. Electrophysiological studies showed widespread denervation involving more than one district. Genetic studies demonstrated an aspartate for glycine substitution at position 93 (G93D) in the Cu/Zn superoxide dismutase 1 (SOD1).

Case 2: A 43-year-old woman started complaining of diffuse fasciculations in the right leg, followed by progressive weakness and wasting, immediately after delivery. Family history and electrophysiological studies confirmed the diagnosis of ALS. Genetic studies demonstrated a phenilalanine for leucine substitution at position 84 (L84F) in the SOD1.

Case 3: A 32-year-old pregnant woman presented with progressive weakness and oedema of the left hand during her first pregnancy (at 6-months). A cesarean delivery at week 43 was performed because of gestosis. Weakness rapidly got worse and progressed to the 4 limbs. Severe muscle atrophy and widespread fasciculations became evident in the months following delivery. Electrophysiological studies showed fasciculation and denervation in several districts. Genetic studies ruled out mutations in the SOD1 gene.

Conclusion: Our data confirm that, although rare, pregnancy may reveal an already present but not yet clinically overt ALS through pathological mechanisms yet to be determined. Further studies are needed to explore the possibility that, amongst others, hormonal modifications during pregnancy may increase the susceptibility to oxidative stress related, for instance, to mutations in SOD1.

P222

Assessment of sensory peripheral nerves conduction parameters in patients with ALS

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Objectives: To evaluate the frequency and type abnormality of sensory peripheral nerves in patients with definite and probable amyotrophic lateral sclerosis (ALS), according to El Escorial diagnostic criteria.

Methods: Material consisted of 80 patients (36 F, 44 M) aged 22–83 years, with 18 months of the mean disease duration. Motor and sensory conduction velocity, distal latency, F wave latency and amplitude of evoked potentials in ulnar, median, peroneal and sural nerves were estimated.

Results: On neurological examination the diminished superficial sensation in distal parts of the limbs was present in 10% of ALS patients. In ENG prolonged mean value of distal latency and conduction velocity in motor peripheral nerves were noted in ALS group, however diminished amplitude of evoked potentials was observed the most frequently (85% of the cases). Abnormal parameters of sensory peripheral nerves conduction was found in 73% of ALS patients. Slow conduction velocity in all examined sensory peripheral nerves was present in more than 20% of patients (mainly in median nerve 29%). The most frequent changes were observed in sural nerve as diminished amplitude values (37% of the cases).

Conclusion: Our electrophysiological studies revealed that abnormal nerve parameters are present in majority of ALS patients. These abnormalities may reflect axonal degeneration of sensory peripheral nerves in the course of motor neuron disease.

P223

Neurophysiological and neuropsychological markers of early cognitive impairment in motor neuron diseases

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Objective: We aimed to assess the presence of cognitive dysfunction in amyotrophic lateral sclerosis (ALS) and lower motor neuron disease (LMND) by means of event-related potentials (ERPs) and neuropsychological (NP) tests, and to investigate the differences in ERP and NP parameters between ALS and LMND.

Methods: N1, Mismatch Negativity (MMN), and novelty P300 (P3a) were recorded using a Passive Oddball Paradigm in 16 ALS patients (pts), 7 LMND pts and 20 age- and education-matched healthy controls. Clinical features and behavioural and cognitive status were investigated by means of standardized scales and tests.

Results: Concerning NP tests, ALS pts had lower performances in tests of short-term recall ($p = 0.034$), short-term verbal memory ($p = 0.013$), reasoning ($p = 0.008$), semantic ($p = 0.014$) and phonological ($p = 0.049$) fluency in comparison to controls. ALS pts had also lower scores than LMND pts in a cognitive estimation test ($p = 0.029$). In contrast, LMND pts were impaired only in the phonological fluency task ($p = 0.009$).
ERP recordings revealed reductions of N1 ($p = 0.017$) and P3a ($p = 0.037$) amplitudes over frontal sites in ALS group compared to controls. The P3a of a central site (Cz) was of lower amplitude in ALS than in LMND patients($p = 0.019$). Conversely, LMND patients did not differ from healthy controls in any of the ERP responses.
MMN latencies were significantly longer in ALS group than in controls and in the LMND group. Only ALS patients with impaired ERPs (38%) had a larger number of pathological scores in NP tests than controls ($p = 0.002$).
A correlation was found between MMN latencies and the percentage of pathological NP test scores irrespective of motor dysfunctions only in ALS patients.
Moreover, MMN latency over frontal (F3; $p = 0.046$) and central (Cz; $p = 0.050$) sites was delayed in LMND pts (43%) who evolved to ALS compared to LMND pts who have not evolved to SLA.

Conclusion: Our ERP and NP findings confirm the hypothesis of the presence of sub-clinical cognitive impairment, concerning short-term memory, attention and executive functions, in ALS and not in LMND. The MMN latency and P3a amplitude appear to be neurophysiological parameters which can support the clinical distinction between ALS and LMND. Only MMN latency seems to be a sensitive measure to detect sub-clinical cognitive dysfunction. MMN could assume clinical relevance in following the progression of the disease.

P224

Disabling parkinsonism following brief exposure to lithium carbonate in a patient with amyotrophic lateral sclerosis

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Several cases of Parkinsonian syndrome induced by lithium have been described, mainly related to high serum level exceeding the therapeutic range. We report a case occurring at a very low lithium blood value in a 46 years old male patient affected by amyotrophic lateral sclerosis (ALS). The patient was diagnosed as bulbar ALS 6 years before and at the time of our first visit, 4 years later, he was classified as probable laboratory supported ALS according to the El Escorial criteria. Before starting lithium assumption (300 mg/day) for compassionate use he showed anarthria and mild dysphagia, slight lower limbs hypostenia and rare diffused fasciculations. Muscular tone was normal in all limbs. Functional status was good (ALS functional rating scale 34/40). Renal, hepatic, thyroid and parathyroid function were normal.

Associated medications, unchanged for several months, were riluzole (100 mg/day), α-tocopherol (900 mg/day), trihexyphenidyle (4 mg/day) and atropine (0.25 mg/day, for sialorrhea). Lithium blood level, tested every week, was always at lower therapeutic range (0.3 mEq/L).

Three months later he developed severe parkinsonism with stiffness, positive cogwheel phenomenon, bradykinesia and festinating gait. Lithium value was 0.31 mEq/L, blood count, electrolytes, renal and thyroid function were normal. Lithium and atropine were immediately discontinued but extrapyramidal symptoms persisted. Brain CT scan and MRI were normal. DAT scan examination showed normal dopaminergic function in the basal ganglia. A therapeutic attempt with L-dopa (400 mg/day) didn't improve parkinsonian symptoms. In the same period the patient developed a progressive spastic hypertone both at the upper and lower limbs.

Eight months after lithium discontinuation the extrapyramidal features significantly improved, persisting only festinating gait, but functional status severely worsened because of spasticity (ALS-FRS 20/40).

This is a very rare case of lithium neurotoxicity not associated to high serum level. We can hypothesize that the imbalance between dopamine and acetylcholine neurotransmission may be responsible for both the parkinsonism and the worsening of spasticity.

Moreover our case suggests many caution in the prescription of drugs in ALS patients. Also drugs commonly available for other disease should be tested in clinical trial before being used in ALS because of the different tolerability and high sensibility to side effects of this kind of patient.

P225

Decline of ALS-FRS and Norris scale scores in a group of patients affected by ALS and treated with lithium

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Objectives: Recent evidence suggests that daily doses of lithium, leading to plasma levels ranging from 0.4 to 0.8 mEq/L, may delay disease progression in human patients affected by ALS. Lithium also showed an effect for neuroprotection in vitro and in vivo experiments. The objective of this study was to determine the effect of lithium on disease progression in patients with amyotrophic lateral sclerosis (ALS).

Methods: We evaluated outpatients followed-up at the Motor Neuron (MN) disease centre of the Hospital Policlinico of Milan. We enrolled a group of ALS patients from February 2008, assessing them at entry and every 3 months, mean follow-up time was 7.8 months. Primary outcome measures were survival, time to death, tracheostomy or permanent assisted ventilation. Secondary outcome measures were the rate of deterioration of function assessed by the Norris scale and the ALS Functional Rating Scale 40. Patients were treated according to our protocol with daily doses of lithium, leading to plasma levels ranging from 0.4 to 0.8 mEq/L.

Results: Seventeen patients were evaluated for the study but 5 were excluded due to contraindications to lithium therapy. The remaining 12 patients (66.67% males) were treated, their mean age was 60.67 years old (y.o.; C.I. 6.07, $p < 0.05$).
One patient had mostly upper MN signs, 5 mostly lower MN signs and 6 had the classic ALS form. Mean age of onset was 55.5 y.o. (CI 6.29, $p < 0.05$). Mean disease duration was 5.17 years (CI 1.77, $p < 0.05$).
Mean ALS-FRS-40 score at the start of the study was 30.83 (CI 2.55, $p < 0.05$), mean Norris Scale score was 80.5 (CI 4.76, $p < 0.05$).
Mean ALS-FRS-40 score at the end of the study was 25.42 (CI 3.16, $p < 0.05$), mean Norris Scale score was 71 (CI 6.17, $p < 0.05$).
Mean progression rate for ALS-FRS-40 score was 0.9/month (CI 0.5, $p < 0.05$), for Norris scale score 1.18/month (CI 0.54, $p < 0.05$).
No patient died during the study, neither anyone needed tracheostomy or full-time assisted ventilation.
Only the patient with mostly first MN signs had no worsening of the ALS-FRS-40 (27, from start to end).
No severe adverse events was recorded during the study.

Conclusion: Treatment of ALS with lithium does not appear to effectively and significantly delay disease progression in a small cohort of patients. A major difference with the previous observational study is the longer disease duration at the beginning of the treatment, that may have contributed to the lack of disease stabilization.

P226

Study of corticospinal tract in amyotrophic lateral sclerosis using diffusion tensor MRI

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Background and objectives: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with a progressive degeneration of upper and lower motor neurons. Diffusion tensor (DT) MRI imaging allows the measurement of quantities reflecting the size, such as the apparent diffusion coefficient (ADC) and orientation such as fractional anisotropy—FA of water-filled spaces in biological tissues.The aim was to determine water diffusion changes along pyramidal tracts in patients with amyotrophic lateral sclerosis and to assess whether diffusion tensor (DT) MRI findings correlated with patients's disability .

Methods: Patients with a diagnosis of ALS and controls underwent a diffusion tensor imaging examination. Disease severity was determined by means of the ALS Functional Rating Scale-Revised (ALSFRS-R). DTI-EPI data were acquired on a 3.0 Tesla GE along 15 nonparallel directions. The diffusion tensor Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA), were computed from data and compared between groups on a voxel-by-voxel basis after normalization to MNI space. Regions of interest (ROIs) were manually drawn in the left and right pyramidal tracts. All statistical analysis have been performed with $p < 0.01$. Correlation analyses of diffusion parameters and disease severity were performed using linear regression.

Results: Several brain areas showed changes on ADC and/or FA measures. Compared to controls, ALS patients had significantly lower FA ($p < 0.01$) in both posterior limb of internal capsule and both cerebral peduncle. Mean ADC values of ALS patients were significantly higher than those of controls in the same areas. Finally, a significantly correlation was found between FA values and the ALS-FRS-R.

Conclusion: Brain DT MRI in ALS patients allows to detect structural degeneration of the CST and corticobulbar tract. The correlation found between disability and FA values suggests that DT MRI may be useful adjunctive tool to monitor ALS evolution.

P227

Moto neuron transplantation rescues the phenotype of spinal muscular atrophy with respiratory distress type 1

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Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a fatal form of infantile motor neuron disease caused by a mutation in the IGHMBP2 gene. There is currently no effective treatment or cure, although motoneuron replacement is a possible therapeutic strategy for SMARD1 and other motor neuron diseases.

We transplanted motoneurons (from transgenic mouse expressing GFP only in motoneurons (HB9-GFP)) that were selected for p75NTR antigen expression into the spinal cord of nmd mice, an animal model of SMARD1. We also administered a cAMP analogue and a phosphodiesterase type 4 inhibitor in order to overcome myelin-mediated repulsion of neurite outgrowth, as well as GDNF to attract axons toward their skeletal muscle targets. At the end stage of the disease, donor-derived motoneurons were detected in the nmd anterior horns: axons extended into the ventral roots and formed new neuromuscular junctions. Furthermore, treated nmd mice had improved neuromuscular function and increased life spans; this correlated with the number of newly formed motor units and the preservation of endogenous neurons. The neuroprotective effect was associated with a reduction of chemokines and proinflammatory molecules in treated spinal cords, as demonstrated by Luminex MultiAnalyte cytokine profiling.

This is the first report that functional restoration of motor units with transplanted motoneurons is feasible in an animal model of a human motoneuron disease, opening up new possibilities for therapeutic intervention.

P228

TARDBP gene mutations in 314 individuals with familial and sporadic ALS

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Objectives: Increasing evidence suggests a direct role of the TAR DNA-binding protein 43 in neurodegeneration. Mutations in the TARDBP gene, which codes for TDP-43 protein, have been recently reported in individuals with familial and sporadic amyotrophic lateral sclerosis (ALS). To further define the spectrum and frequency of TARDBP mutations, we present genetic analysis data on TARDBP in a cohort of 314 probands, including 16 subjects with non-SOD1 familial ALS.

Methods: All patients (60.7% males; mean age at onset: 58.3 years; 21.4% bulbar onset) were consecutively recruited for this cross-sectional study from the Department of Neurology, Policlinico Hospital-Milan, the Department of Neurosciences Institute-University of Padua and the Neurological Institute-University of Pisa, between January 2001 and June 2008. All subjects fulfilled the El Escorial criteria for probable or definite ALS. The probands included 308 Italian patients, five Greeks, and one Belgian. In all FALS cases, mutations in SOD1, ANG and VAPB were excluded before their inclusion in the study. The five coding exons and splicing sites of TARDBP gene were amplified by PCR and directly sequenced.

Results: We identified four different heterozygous missense mutations, within exon 6, in five unrelated ALS patients (1.6%). Two of these mutations (p.G348C, p.A382T) were detected in carriers who belong to families with a clear autosomal dominant transmission. One of these pedigrees showed several affected members within five generations and with variable clinical features: age at disease onset ranged from 36 to 70 years; disease duration varied from 36 to 60 months. Furthermore, we report two novel mutations (p.G294 V and p.G295S) which were identified in two sporadic cases. All of the mutations were absent in 300 healthy subjects and located in a highly conserved region of TDP-43.

Conclusion: The identification of five ALS patients carrying TARDBP alterations extends the spectrum of TARDBP mutations

and supports the pathological role of TDP-43 in motor neuron disease. Our findings provide evidence that TARDBP mutations represent a rare cause of disease in Italian sporadic ALS forms (1%); however, combined with the literature, our data further support TARDBP mutations as a relevant cause of familial ALS (12.5%). The accumulating data on clinical and molecular epidemiology associated with TARDBP mutations may serve to define genotype-phenotype correlations, and help genetic counselling in affected families.

P229

Study of emotional reactivity in patients with amyotrophic lateral sclerosis

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Objectives: Seldom described as depressed, ALS patients seem to cope efficiently about their diagnosis. It thus appears important to identify the elements at the origin of this state.
The objective is to show the existence of a fundamental emotional dysfunction in ALS. Are the emotions perceived more positively, more intensely? Are positive informations memorized better?

Methods: 10 ALS patients, 7 men and 3 women (62.7 years $\pm$ 9.6), with one mean duration of 28 month ($\pm$13), an average score of 36.6 to the ALSFRS, and 10 subjects controls, 7 men and 3 women (62.5 years $\pm$ 10.3) were evaluated with, an anxiety scale (STAI), a depression scale (BDI-II), a normalized corpus of "emotional words" of valence and intensity variables (Syssau and Font 2005), a battery of executive tests (Miyake et al. 2000).

Results: ALS patients pointed out more positive words that negative ones from the normalized corpus of "emotional words", with the two recalls (recall 1 : $p = 0.0117$; recall 2 : $p = 0.0051$). Only the negative words were significantly better recalled by the group controls with recall 1($p = 0.0284$) and 2 ($p = 0.0022$). In addition, ALS patients did not have higher depressive intensity ($p = 0.7317$) compared with controls, but they had a higher anxiety ($p = 0.0233$).

Conclusion: The main results support that ALS patients memorize more positive informations, this tendency being accentuated with time. No correlation having been able to be highlighted, it thus appears that these data can not be related to a dementia, a major executive dysfunction, an anxious and/or depressive symptomatology. It is then possible to consider that in ALS an adaptative mechanism aiming at improving the capacity of adaptation and to even maintain a positive image is a characteristic of the patients.

P230

Immunohistochemical studies of brain-derived neurotrophic factor in skin of patients with sporadic amyotrophic lateral sclerosis

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Objectives: To elucidate whether brain-derived neurotrophic factor (BDNF) is increased in the skin of patients with sporadic amyotrophic lateral sclerosis (ALS).

Background: Studies of ALS skin have shown unique pathological and biochemical abnormalities. The lack of bedesore formation in ALS patients is considered characteristic. BDNF promotes motor neuron survival in animal models of motor neuron and peripheral nerve damage. BDNF synthesized in peripheral tissues is likely to play an important role in regeneration of motor neurons. Furthermore, axotomized adult motor neurons respond to BDNF, and exogeneous BDNF administration retards motor deterioration in the wobbler mouse, an animal model of motor neuron disease (MND). These findings suggest that BDNF could be of therapeutic benefit in MND including ALS. Although several studies of BDNF in ALS have been reported, little is known concerning the skin of ALS.

Methods: We examined BDNF immunoreactivity of biopsy speciments of skin overlying the left biceps from 15 ALS patients (mean age 59.7 years) and 15 control subjects with other neurologic disorders (mean age 59.4 years). A densitometric analysis was performed using an image analysis program.

Results: BDNF immunoreactivity was markedly positive in the epidermis and moderately positive in some dermal blood vessels and glands in ALS patients. These findings became more conspicuous as ALS progressed. On the other hand, the epidermis, dermal blood vessels and glands and the dermis in control subjects, and the dermis in ALS patients showed a weak positive reaction even after repeated antigen-retrieval trials. The optical densities for BDNF immunoreactivity of the epidermis in ALS patients (2.88 $\pm$ 1.10) were significantly higher ($p < 0.001$) than in control subjects (1.45 $\pm$ 0.18). In addition, there was an appreciable positive correlation ($r = 0.78$, $p < 0.001$) in ALS patients between the densities for BDNF immunoreactivity and duration of illness, but there was no such correlation in control subjects. There was no significant difference in the optical density for BDNF immunoreactivity of the dermis between ALS patients (1.23 $\pm$ 0.52) and control subjects (1.51 $\pm$ 0.37).

Conclusion: BDNF was found to be siginificantly up-regulated in skin samples from ALS patients. Since BDNF is known to promote motoneuron survival, BDNF may have a trophic role in skin of ALS patients and may help to explain why decubitus formation is rare in ALS.

P231

Glide-symmetric visual feedback for gait improvement in patients with multiple sclerosis

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Objectives: To compare the effects of gait training with distinctly symmetric visual feedback cues, adapted to the "glide symmetry" of human locomotion, to the effects of training with visual feedback cues without distinct symmetry, on the walking abilities of patients with multiple sclerosis (MS).

Methods: A wearable virtual reality (VR) device was used to create visual feedback cues, responding dynamically to the patient's motion in a feedback fashion, so that they appear to be fixed in space. The device was capable of producing one of two repetitive patterns, the first comprising equally spaced transverse lines (no distinct symmetry), and the second squared black and white tiles in checkerboard arrangement (distinct symmetry, called "glide reflection"). The side-length of the tiles in the second arrangement was equal to the spacing between the transverse lines in the first.
Two disjoint groups of randomly selected patients with gait disorders due to MS were each trained with visual feedback cues consisting of

one of the two patterns. Ten patients used the transverse lines arrangement while eleven patients used the checkerboard tile arrangement. Patients in the two respective groups were instructed to step between the transverse lines or within alternating black and white tiles. Baseline performance (walking speed and stride length along a 10 m straight track) was measured before device use. Following 20 min training with the device and 10 min rest, performance without the device was measured again and compared to the baseline performance.

Results: The average improvement in the group using the visual cue of transverse lines was $7.79 \pm 4.24\%$ in walking speed and $7.20 \pm 3.92\%$ in stride length. The average improvement in the group using the visual cue of checkerboard tile arrangement was $21.09 \pm 18.39\%$ in walking speed and $12.99 \pm 11.72\%$ in stride length.

Conclusion: Patients with gait disorders due to multiple sclerosis, training with a glide-symmetric visual feedback cue, showed a significantly higher improvement in their gait than patients training with a visual feedback cue without distinct symmetry.

P232

ALS multidisciplinary unit: respiratory cares

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Introduction: Amyotrophic lateral sclerosis (ALS) needs very complex multidisciplinary cares. The development of Multidisciplinary Units might organize and achieve a better assistance to patients.The aim of this study is to evaluate the results of the early neumological intervention during the first two years of an ALS Unit.

Methods: Observational study of the patients attended in the ALS Unit during the period from March, 2006 to December, 2007. The following information has been recorded: age, gender, ALS initial form (bulbar or spinal), months of evolution up to non-invasive ventilation (NVI), adjustment to NIV, type of ventilator, tolerance to the ventilation and tracheostomies done.

Results:45 patients diagnosed of ALS were checked, 24 men and 21 women, middle age of 65,88 years old (ranging from 41 to 91 years old). The mortality was 37.8 %. 3 patients were lost in the follow-up. According to the initial form of ALS, 30 patients were spinal (66.7%) and 14 bulbar (31%), with a major mortality in the spinal group (46%) versus bulbar (21.42%). 20 patients were adapted to NIV (44.4 %), with a major use of the volumetric ventilators (60%), than pressure ventilators (40%), leaving BIPAP for the patients who needed an orofacial mask. 53.33% of spinal ALS were adapted to NIV (37.5% to BIPAP and 62.5 % to volumetric ventilator) and 28.57 % of bulbar ALS to NIV (50% to BIPAP and 50% to volumetric ventilator). The evolution of the disease up to the beginning of NIV was very variable (35,88 months of average), which shows the variability of the disease. The tolerance to the NIV was good at 66.7% of the cases. Tracheostomies were done on 5 patients (4 spinal ones and 1 bulbar), with survival up to the current moment of 3 of them.

Conclusions: During the first two years of ALS Unit, the spinal ALS group was more numerous than the bulbar group, with a major adaptation to VNI. Volumetric ventilators were used more frequently and its tolerance was good. Tracheostomy was practised in more spinal than in bulbar patients.

P233

Decreased level of 5-methyltetrahydrofolate: a potential biomarker for pre-symptomatic amyotrophic lateral sclerosis

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Objective: To determine whether homocysteine (Hcy), folic acid and 5-methyltetrahydrofolate (5-MTHF), an important transmethylation metabolite of the methionine-homocysteine transmethylation cycle, are sensitive biomarkers to the early amyotrophic lateral sclerosis (ALS), a neurodegenerative disease without special biomarkers for early diagnosis.

Methods: SOD1G93A transgenic mice of ALS were used for this study. The mice were divided into four groups according to the disease progression. The age-matched wild-type littermates are used as the controls. We use LC/MS-MS to analyze the concentrations of Hcy, folic acid and 5-MTHF in the plasma, spinal cord and cortex of the mice.

Results: The level of 5-MTHF is significantly decreased in the plasma, spinal cord and cortex at the early stages of pre-symptomatic ALS transgenic SOD1G93A mice while folic acid is decreased at the middle to late stages of the disease. Furthermore, we found that the level of Hcy is markedly elevated after the motor symptom onset in the ALS mice.

Conclusions: Our study suggests that 5-MTHF may be a potential biomarker for ALS.

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P234

Pathological role of autophagy in motor neuron degeneration in SOD1G93A mouse model of amyotrophic lateral sclerosis

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Objective: Aberrant protein misfolding is thought to contribute to the pathogenesis of amyotrophic lateral sclerosis (ALS) but the detailed mechanisms are largely unknown. The objective of this study is to determine the pathological role of autophagy, a major protein degradation system, in motor neurons (MN) degeneration associated with ALS.

Method: SOD1G93A mouse model of ALS was used in this study. We systematically investigated the specificity of the autophagic alteration and its association with MN degeneration in the spinal cord of ALS mice at different stages of disease by electron microscopy (EM) examination of autophagosomes and autophagic vacuoles (AVs), immunostaining and immunoblotting assays of the autophagic protein marker microtubule-associated protein 1 light chain 3-II (LC3-II), beclin-1 and mammalian target of rapamycin (p-mTOR). MN dentrites and axons were labeled with against MAP2 and tubulin, respectively; and protein aggregations in MN were detected with ubiquitin immunostaining.

Results: We found that LC3-II is markedly and specifically increased in the spinal cord MN of ALS mice. EM and immunochemistry show that AVs are significantly accumulated in the

dystrophic axons of spinal cord MN. Furthermore, beclin-1 and p-mTOR are also significantly altered in the spinal cord of ALS mice. All these changes appear in the ALS mice at the age of 90 d and progressively deteriorated which are in parallel with the loss of spinal cord MN.

Conclusion: Our results indicate that the autophagic pathway is altered when the ALS mice are at the early stage of disease. The alteration in autophagy is closely correlated with the progression of disease and MN degeneration, indicating that autophagy might be actively involved in the pathogenesis of the disease. It is worthwhile in the future to investigate whether autophagy is an early sign of the disease in patients with ALS and whether autophagy is a potential therapeutic target for this devastating disease.

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Multiple sclerosis

P235

Prognosis of primary progressive multiple sclerosis: do cerebrospinal fluid oligoclonal IgM bands play a role?

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Primary progressive multiple sclerosis (PPMS) accounts for 10–15% of all MS cases and it is characterized by a steady progressive deterioration of neurological functions over months or years. Although neuroaxonal degeneration seems to underlie PPMS, the pathogenesis and the extent to which immune-mediated mechanisms operate is unclear and no distinct immunological profile has yet been defined for this disease form. The presence of cerebrospinal fluid (CSF) oligoclonal IgM bands (OCIgM) at diagnosis was previously reported to predict a more severe course in relapsing-remitting (RR) MS. Conversely, very few data exist on OCIgM in PPMS, which frequently shows a very disabling course.

The aim of this study was to investigate the immunological CSF profile, in particular the presence of OCIgM, in PPMS patients, compared to RR and secondary progressive (SP) forms and to search for early clinical and biological factors with a possible prognostic role in PP forms.

One hundred and forty-nine MS patients with at least 5 years of follow-up were included: 45 with PPMS, and 104 with an acute onset. Clinical and demographic details were assessed. CSF collected at diagnosis was examined for the presence of OCIgG and OCIgM, detected by isoelectric focusing and immunoblotting. The prognostic role of various clinical and immunological factors, with respect to the EDSS at 5 years, was evaluated through multivariate analysis.

CSF OCIgM were found less frequently in PPMS (7/45; 15%) versus MS with an acute onset (47/104; 45%) ($p < 0.001$). In particular, they were found in 36.7% of RRMS and in 61% of SPMS patients.

Multivariate analysis showed that only the presence of OCIgM influenced the probability of reaching EDSS scores greater than 3, 3.5 and 4 at 5 years in PPMS ($p < 0.03$; $p < 0.04$: $p < 0.09$), and an EDSS score greater than 4 in patients with an acute onset ($p < 0.067$).

OCIgM are less frequently found in the CSF from PPMS compared to other disease forms. Our results suggest a minor role of inflammation/autoimmunity in PP-MS pathogenesis or a strict compartimentalization of these processes within the central nervous system.

The present results confirm that the presence at diagnosis of CSF OCIgM in RR and SPMS patients predicts a more severe form of disease, as previously reported. Although tested on a small number of PPMS patients, their presence seems to maintain a prognostic role also in this MS form.

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Correlations between cognitive performance and peripheral blood mononuclear cell production of inflammatory and neurotrophic factors in multiple sclerosis patients

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Background: Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system, frequently associated with impairment of cognitive functions.

Disruption of cortico-cortical and cortico-subcortical signalling pathways by demyelination has been suggested to underlie the cognitive dysfunction in MS. However there is an increasing interest in understanding the molecular bases of MS-related cognitive deficit.

Objective: The aim of this study is to evaluate the role of inflammatory and neurotrophic factors in the development of cognitive dysfunctions in MS.

Methods: We studied 30 patients with relapsing-remitting MS, matched for age, education, disease duration, type of immunomodulating therapy, degree of disability and overall cognitive status and 30 age, sex, education matched healty controls.

We correlated peripheral blood mononuclear cells (PBMCs) production of brain derived neurotrophic factor (BDNF), IL10, tumor necrosis factor (TNF) α and IL6, with performances on specific neuropsychological tasks.

Spontaneous neurotrophin and cytokine production was measured in duplicate by enzyme-linked immunoadsorbeant assay in supernatants of unstimulated PBMCs.

Results: In our patients we found that low BDNF levels were correlated with decreased performances on test of constructive praxis and increased time of execution on task of divided attention and visual scanning both in men and women. Moreover in men we observed a negative correlation between TNF α and many cognitive domains, such as memory, executive functions, linguistic and visuo-motor tracking, while IL6 levels correlated negatively only with memory, executive functions. In women high IL10 levels correlated with good performances on memory and linguistic tasks

There were no correlations between neurotrophin, cytokine levels and cognitive performances in healthy controls.

Conclusions: We observed a correlation between cognitive performances and BDNF, TNF α, IL6 and IL10 production by PBMC in MS patients. Our results suggest that BDNF may have a neuroprotective effect on cognitive performances both in women and men, IL10 may have a positive effect on cognitive function only in women whereas TNF α and IL6 seem to favour cognitive impairment only in men.

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CMV seropositivity in multiple sclerosis Persian patients

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Infection with Cytomegalovirus is considered one of the possible key environmental factors in the aetiology of multiple sclerosis (MS). Its

role as a underlying factor in Ms remains controversy this study was done to determine relation between CMV seroposivity and MS in Persian patients.

Method: This cohort study was conducted in Isfahan, the second greatest city of Iran, situated in the Asia. 82 serum samples were collected from relapsing-Remitting or secondary-Relapsing MS patients and 38 serum samples from sex and age matched healthy subjects. In both groups, antibody positivity and titer for CMV IgM and CMV IgG were determined by the enzyme linked immunosorbent assay (ELISA). The CMV antibody levels (including IgM and IgG) were compared in two groups by *t* student test.

Results: Total 82 MS patients (64 females and 18 males) and 38 controls (29 females and 9 males) were included ($p > 0.05$). The mean (SD) titer of CMV IgM in MS group was 6.73 (12.63) versus 8.71 (23.61) in control group ($p > 0.05$); likewise, the mean (SD) titer of CMV IgG in MS patients was 15.59 (9.11) versus 12.64 (14.46) in control group ($p > 0.05$).

Conclusion: Our findings suggested that CMV infection does not play a significant role in MS.

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TREM-2 and TREM-1 expression in the central nervous system and possible function in modulating inflammation during MS

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Triggering receptor expressed on myeloid cells (TREM)-2 and TREM-1 are innate immune receptors on myeloid cells that appear to modulate inflammatory cell responses in opposite directions. TREM-2 is expressed by microglia and macrophages. Its engagement in mice reduces inflammatory responses and, in microglial cells, promotes phagocytosis. Evidence in humans and animal models suggests a neuroprotective role for TREM-2 in the central nervous system (CNS). Blockade of TREM-2 worsens murine EAE. The biology of TREM-2 is still not fully understood, and its natural ligand is unknown. TREM-1 is expressed on monocytes/macrophages and neutrophils where it serves as a critical amplifier of inflammatory signaling. Its possible role in EAE/MS has never been investigated.

Immunohistochemistry for TREM-2 and TREM-1 was performed on frozen sections of CNS tissues from MS and non-MS autopsies. TREM-2 and TREM-1 expression on cerebrospinal fluid (CSF) and peripheral blood leukocytes was investigated by flow cytometry in MS and non-MS subjects. ELISAs to detect soluble TREM-2 and TREM-1 were performed on CSF of subjects with relapsing-remitting MS, primary progressive MS, other inflammatory neurological diseases (OIND) or non-inflammatory neurological disorders (NIND). Myelin laden human macrophages were obtained in vitro from blood monocytes after culturing with M-CSF and human myelin: chemokines levels were measured in cell culture supernatants by using cytometric bead array flex sets.

TREM-2 was expressed on a subset of CSF monocytes and was highly expressed on myelin-laden macrophages in active demyelinating MS lesions. Soluble TREM-2 was elevated in the CSF of MS and OIND subjects. Soluble TREM-2 levels in blood did not differ among groups. Activation of TREM-2 on myelin laden macrophages obtained in vitro led to a reduced production of MCP-1, MIP1β and MIP1α. TREM-1 was expressed by macrophages in active demyelinating MS lesion, on CSF monocytes and soluble TREM-1 was detectable in CSF.

TREM-2 receptor and its soluble counterpart might be implicated in modulating inflammatory responses in the CNS during MS. Preliminary results showed also TREM-1 expression on monocyte/macrophages in the CNS and suggest that it may amplify inflammation during MS.

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P239

Evaluation of the peripheral intranodal sodium channels in multiple sclerosis

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Objectives: Multipl sclerosis (MS) is primarily a disease of the central nervous system. It is accepted that MS does not affect peripheral nervous system (PNS) except optic nerve. Although there is no published evidence for involvement of PNS in MS except a few brief reports, this issue is still controversial. On the other hand sodium channels may play a critical role in axonal injury in MS. There are some axonal excitability studies for peripheral nevre sodium channels. Strength-duration time constant (SDTC) is a measure of axonal excitability that depends on the biophysical properties of the axonal membrane at the node of Ranvier and can provide some information about sodium channel function. In this study, we aimed to investigate the possible influences of MS on SDTC.

Methods: The strength-duration time constant (SDTC), which partly depends on persistent sodium conductance active at the resting membrane potential, was measured in median motor axons of 20 MS patients and 20 age-matched healthy persons. The strength-duration time constant (SDTC) values were compared statistically.

Results: We found that there was no difference in SDTC values between the study (0.4158 ± 0.07) and control (0.4382 ± 0.15) groups ($p = 0.563$).

Conclusion: There is a few case reports and brief reports in literature suggesting that MS may also influence PNS. Contrarily to these reports, our data suggests that there is no significant difference between MS patients and healthy persons with regard to functions of sodium channels in peripheral nerves. Since the number of patients are small in our study, our data should be confirmed in studies with larger number of patients.

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IL-17 and IL-22 producing increased in multiple sclerosis relapses are MBP-specific. A multi-centre longitudinal study

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Objective: Longitudinal evaluation of Th17 and Th1 peripheral blood(PB)lymphocyte percentage, cytokine and chemokine production, and antigen specificity in multiple sclerosis(MS) patients.

Methods: Outpatients with relapsing-remitting MS free from any treatment and age-and gender-matched healthy subjects(HS). Serial PB samples. Active MS(AMS) had a clinically documented exacerbation within the last 10 days; inactive MS(IMS) had no exacerbations in the last 3 months and no new PD/T2 or gadolinium-enhancing lesions on two subsequent MRI, 3 months apart. Intracellular cytokine and surface type I interferon(IFN) receptor chain1(IFN-αR1) expression by cytofluorometry, interleukin(IL)-17-producing myelin basic protein(MBP)- or PPD-stimulated PB lymphocytes by ELISPOT. In addition, with or without increasing doses of IFN-βin vitro, the signal transducer and activator of transcription(STAT)1 phosphorylation by Western Blot, and the apoptosis of anti-CD3 monoclonal antibody-stimulated PB lymphocytes by propidium iodide staining and annexin V and 7-amino-actinomycin D dual color cytofluorometry.

Results: We analyzed 36 HS and 83 MS patients(41 AMS and 42 IMS)(18 prospectively followed up for 6–15 months) from six MS centers. Th17 cell percentage, low in HS and IMS, increased by about 7-fold in AMS. In contrast, Th1 cell percentage was not significantly increased in AMS or IMS. Th17 percentage closely matched the changes in disease activity being always higher in AMS, lower or undetectable in IMS, and high again during a subsequent relapse. Th1 percentage changed randomly and independently of disease status. Percent IL-22-producing T CD4 + cells, low in HS and IMS, increased 5-fold in AMS. We found two distinct CD4 subsets expanded in AMS producing either IL-17 and IL-22 or only IL-22. IL-17- or IL-22-producing cells detected in MBP-stimulated PBMC was very low in HS, whereas it was significantly increased in AMS. IFN-αR1 expression, IFN-β-induced STAT1 activation and apoptosis were significantly greater in Th17 than in Th1 cells. IFN-αR1 expression and IFN-β-dependent STAT1 activation progressively increased during in vitro Th17 polarizing differentiation with a highly significant positive correlation and not during Th1 polarizing differentiation.

Conclusions: Th17, increased in MS relapses, might be self-reactive or bystander cells participating to the MS lesions. Their specificity for a myelin antigen suggest that they are encephalitogenic.

P241

Anti-interferon antibody production and MxA induction in multiple sclerosis patients treated for one year with interferon-β

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Objective: To investigate the response to interferon (IFN)-β treatment in terms of anti-IFN antibodies (anti-IFN Ab) production and MxA induction in the first year of therapy, and the relationship between these two parameters.

Methods: One hundred-eighteen MS patients that initiated IFN-β therapy at the time of the inclusion in the study were enrolled. They were followed-up for one year and blood samples were obtained at 3, 6, and 12 months after therapy initiation. Anti-IFN Ab were quantified by radioimmunoprecipitation after radiolabelling of IFN-β with 125I iodide by the chloramine-T method. MxA was measured by Real-Time PCR in samples obtained at 12 hours after IFN-β injection.

Results: At 12 months of IFN-β therapy, 52.5% of the patients were anti-IFN Ab negative/MxA-induced and 7.5% were anti-IFN Ab positive/MxA-not induced patients. However, there were also anti-IFN Ab positive/MxA-induced and Anti-IFN Ab negative/MxA-not induced patients. In some patients, the progression of anti-IFN Ab increase and MxA decrease was time-related, in others this condition became suddenly evident very early. Furthermore, anti-IFN Ab induction may precede of several months or be concomitant with the lack of MxA induction. Most patients were permanently anti-IFN Ab positive/MxA-non induced or anti-IFN Ab negative/MxA-induced, others showed these conditions only at one point of the analysis; in some patients only one of the two parameters changed over time. Sporadic evidences of isolated MxA-negative samples in the absence of anti-IFN Ab were likely to be related to blood drawing not performed at 12 hours after the last IFN-βinjection as recommended. Finally, up to now, there has been no evidence for an association between therapy drop-outs and anti-IFN Ab production or lack of MxA induction.

Conclusion: Our data indicated that the early response to IFN-βtreatment in terms of anti-IFN Ab and MxA induction is highly variable and there are different and individual patterns of reaction, at all the times of the analysis. However, the identification of several samples that became permanently anti-IFN Ab positive/MxA-not induced early after therapy initiation, suggests the utility to evaluate IFN response long before than two years after therapy beginning, as previously suggested for neutralizing antibody determination. This may prove helpful especially in view of the recent introduction of alternative therapeutic approaches.

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Increased expression of Kv1.3 channels in peripheral blood T-lymphocytes of patients with multiple sclerosis

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Objectives: Multiple sclerosis is a chronic demyelinating disorder, characterized by immune alterations in the central nervous system as well as in the peripheral blood. Recently, Kv1.3 channels, which play a key role in T-lymphocyte activation, were found to be highly expressed in inflammatory infiltrates from MS brains, whereas their blockade was shown to ameliorate animal models of MS. Herein, we studied the electrophysiological properties of Kv1.3 channels and the levels of their expression in peripheral blood T-lymphocytes of MS patients, compared to healthy individuals.

Methods: Twenty patients with MS (10 with relapsing-remitting and 10 with secondary progressive disease) and an equal number of healthy individuals were included in the study. T-lymphocytes were separated from peripheral blood by ficoll density gradient centrifugation and Kv1.3 currents were recorded in the whole-cell configuration of the patch-clamp technique. Additionally, in order to assess the expression of Kv1.3 mRNA transcripts, total RNA was isolated from T-lymphocytes from both groups and specific primers for Kv1.3 and glyceraldehyde 3-phosphate dehydrogenase as reference, were used for semi-quantitative RT-PCR.

Results: The intrinsic gating and kinetic properties of Kv1.3 currents in patients with MS were similar to control individuals. However the average peak Kv1.3 currents elicited at +40 mV were significantly higher in MS patients, being 756 ± 37 pA, compared to 390 ± 40 pA in the control group ($p < 0.01$). Measurement of cell capacitance to normalize currents for cell size also gave significantly higher current densities in the patient group, indicating an increased number of Kv1.3 channels per cell in MS T-lymphocytes. The above finding was also supported by data from RT-PCR: in T-lymphocytes

of MS patients, the relative expression of Kv1.3 mRNA was significantly increased (1.15 ± 0.3), compared to cells from control individuals (0.75 ± 0.15, $p < 0.001$).

Conclusion: Overall, our findings support a higher Kv1.3 channel expression and increased Kv1.3 current responses in T-lymphocytes of patients with MS. Given the key role of Kv1.3 channels in T-lymphocyte physiology, this up-regulation could significantly contribute to the T-cell hyperactivity that has been reported in MS. Studies to further elucidate the possible pathogenetic role of this abnormality, may also lead to the development of new immunomodulatory treatments for this disorder.

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Infectious diseases, related vaccinations, and risk of multiple sclerosis later in life: a case-control study

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Introduction: Whether infectious diseases or vaccination is a contributing factor to later multiple sclerosis (MS) development is a serious matter of controversy so far. We have conducted a retrospective controlled study in which gender and age were exactly-matched to assess possible correlation between MS and past history of some prominent infections which might rarely be misdiagnosed or misrecalled. We have also assessed if related vaccinations are etiological factors for MS.

Methods: A multi central case-control study was designed and data was collected from March 2006 to December 2008, Iran. Cases were included if a definite diagnosis of MS was documented by an expert neurologist and the patient was accordingly registered to an Iranian local MS society. Controls were selected from normal society afterward if there was no history of any symptom that might suggest undiagnosed MS. Pertusis, Chicken pox, mumps, measles, and viral hepatitis were selected to be studied as their natural history, changes in appearance, and severity rarely remains the patient undiagnosed. Subjects were interviewed in person and asked of lifetime incidence of abovementioned infectious diseases and history of the related vaccinations. Data was analyzed if both vaccination and infection were taken place before the onset of the MS or similar period in matched control.

Results: The data was collected from 927 MS patients with a mean age of 32.5 ± 8.7 and F/M ratio of 3.6. Of the total 927 patients we could match 343 cases to same gender and age controls so far (mean age $= 30.7 \pm 8.6$; F/M ratio $= 2.2$). Among studied infectious diseases, only history of mumps increased the risk of the later MS (OR $= 1.5$, 95%CI 1.0, 2.2; $p = 0.03$). On the contrary, vaccination for mumps (OR $= 6.9$, 95%CI 2.9, 16.9; $p < 0.001$), varicella zoster virus (OR $= 5.5$, 95%CI 2.5, 12.7; $p < 0.001$), and pertusis (OR $= 3.7$, 95%CI 1.8, 7.7; $p = 0.002$) reduced the risk of the MS respectively.

Conclusion: Present data does not support those studies which mentioned immunization as a risk factor for MS. Our findings suggest that mumps might associate with increased risk of MS and mumps vaccination could possibly prevent MS later in life. This strong association might be a result of common pathophiysiological pathways or the role of the earlier oversensitization in consequent autoimmune disease. Moreover, immunization against both chicken pox and pertusis may reduce the risk of later MS development.

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Nicotinic acetylcholine receptors in cerebral white matter: PET study using 2-[F-18]-F-A85380 in multiple sclerosis

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Background: Positron emission tomography (PET) has demonstrated specific binding in human cerebral white matter (WM) of tracers targeting the $\alpha4\beta2$* subunits of the nicotinic acetylcholine receptors ($\alpha4\beta2$*-nAChR). We explored this binding in patients with multiple sclerosis (MS), and hypothesized that $\alpha4\beta2$*-nAChR binding yields additional information on WM lesions defined by anatomic (MR) imaging.

Methods: Cranial MRI and PET using 2-[F-18]-F-A85380 (2-FA) were performed in eleven patients with MS (three smokers) and eleven healthy subjects (HS) matched for age, gender and smoking habits. Volumes of interest (VOIs) were defined: in patients, T2 hyperintense or/and T1 hypointense "lesions" ($n = 286$); corresponding VOIs mirrored to the opposite hemisphere ("control" in normal appearing white matter, NAWM, $n = 286$); in healthy subjects, representative WM volumes in areas typically affected by MS lesions ("pseudo-lesions", $n = 265$), and corresponding "pseudo-controls" in the opposite hemisphere ($n = 265$). 2-FA PET was performed up to 7 h following i.v. application of the radiotracer. Parametric images of the distribution volume were calculated using the Logan Plot, and the arterial input function was corrected for individual plasma protein binding and metabolites of 2-FA. Distribution volumes were determined, and distribution volume ratios (2-FA-DVRs, a measure of specific nAChR binding) using the corpus callosum as reference region.

Results: In non-smoking or smoking healthy controls, pseudo-lesions and their respective contralateral VOIs displayed the same 2-FA-DV and were therefore combined. Smoking status did not significantly affect 2-FA-DV in HS. MS patients displayed slightly higher 2-FA-DV values in both lesions and "control" NAWM VOIs as compared to pseudo-lesions ($p < 0.05$, ANOVA). Smoking MS patients had higher 2-FA-DVRs than non-smoking MS patients. These results were confirmed when restricting analyses to lesions at least $5 \times 5 \times 5$ mm in size. MRI-defined lesions did not show distinct distribution patterns of 2-FA-DVR suggestive of histological heterogeneity detectable by 2-[F-18]-F-A85380 PET.

Conclusion: MS is associated with an increase in white matter $\alpha4\beta2$*-nAChR availability which is further increased by chronic smoking. The increase in NAWM suggests that 2-[F-18]-F-A85380 PET can complement MR imaging, refining the characterization of white matter pathology.

P245

Pro- and mature-brain derived neurotrophic factor in patients with multiple sclerosis

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that may lead to severe neurological deficits. Pathological and non-conventional MRI studies have shown that, in patients with MS, the permanent disability correlates with axonal loss and brain atrophy rather than

with inflammation. Recently the neuroprotective aspect of inflammation has been documented and it is thought that this effect is induced by neurotrophins, specially brain derived neurotrophic factor (BDNF). There is clear evidence that mRNA of BDNF is readily detectable in peripheral blood mononuclear cells of MS patients and that its level is increased in MS patients compared with patients with other neurological diseases or healthy controls; it is considerably increased in the acute phase and in case of complete or partial recovery from new symptoms; furthermore, lower BDNF values are found in patients with secondary-progressive (SP) MS in comparison with controls. These studies strongly suggest that serum levels of BDNF are significantly correlated with the clinical outcome in MS.

We carried out a case-control study to investigate the role of pro and mature BDNF in MS and possible correlation of total BDNF serum levels with clinical variables such as disability (EDSS score), disease course disease duration, number of relapses. Inclusion criteria was clinically define MS according with McDonald criteria and a relapsing-remitting form of MS. Exclusion criteria was disease's modifying therapy, corticosteroid therapy or in the last 2 months, relapse in the last 4 weeks and any inflammatory disease in the last 4 weeks. We used Western Blotting to determined the serum levels of the 2 forms of BDNF

We studied 20 patients (16 female and 4 male) with and 20 healthy control. Mean age of MS group was 40 (min 30, max 55, DS 8,324), mean disease duration was 5.3 years(min 1, max 13, DS 3,672), mean number of relapse was 1.95 (min 1, max 3, DS 0,795), mean EDSS was 1.9 (min 1, max 6, DS 1,15). We found a statistically significant difference in means level of proBDNF that was 15738,32 UA (DS 5075,14) in MS group and 22677,575 UA (DS 10899,53) in healthy subjects. We did not find any correlation between BDNF levels and clinical variables.

Our results suggest a different role of pro- and mature-BDNF in the natural history of MS.

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Comparison of the degenerative and inflammatory markers in cerebrospinal fluid in multiple sclerosis patients with relapsing-remitting course of disease and after clinical isolated syndrome

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Objective: Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system (CNS) leading to demyelination and axonal loss. Cerebrospinal fluid (CSF) evaluation is the basic method to considerate inflammation activity and degree of degeneration in CNS. We tried to find differences among inflammatory and degenerative markers in patients with relapsing-remitting course of MS (RRMS) and after clinical isolated syndrome (CIS).

Method: We evaluated 149 patients −66 MS patients (46 RRMS and 20 CIS) and 83 controls with other non-inflammatory diseases. We assessed markers of integrity of blood-brain barriere (BBB): albumin quotient and prealbumin, inflammatory markers: CRP, transferin, C3, C4 complement factors, haptoglobin, β-2-microglobulin, orosomucoid, α-1-antitrypsin, markers of tissue destruction: APO-AI, APO-B, cystatin C, neuron-specific enolase, tau-protein and β-amyloid. Intrathecal synthesis was considered according to the number of oligoclonal IgG bands(OCB)in alkaline fraction in IEF and IgG quotient(IgG).

Results: We found increase of values of some inflammatory and degenerative markers in patients even after CIS. Intrathecal synthesis (QIgG) was higher in RRMS then in CIS, but number of OCB was higher after CIS. We evidenced statisticaly significant lower values of cystatin C in CSF in RRMS compared with CIS. Chi-square test demonstrated significant lower share of patients with normal values of β-amyloid by RRMS patients(80%patients) beside controls(normal 95.2% patients).

Conclusion: We did not found differences in values of inflammatory and degenerative markers in CSF patients with RRMS and after CIS. Only decrease of cystatin C in CSF seems to be demyelination level indicator.

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Common genetic variants and risk of multiple sclerosis in Volga-Ural populations

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Multiple sclerosis (MS) is a severe autoimmune disease of central nervous system, leading to demyelination and affecting mostly young people (from 16 to 35 years). Genetic predisposition to MS has been well established, but, in spite of recent advances in the investigation of aetiopathogenesis of MS, little is known about the molecular basis of the disease.

We conducted the gender- and ethnicity-dependent association study of TNFA, TNFB, TNFR1, IL1B, IL1R1, IL6, IL10, IL12, FAS, APOE genetic markers with MS and its clinical variants. TNFA, TNFB, IL1B, FAS, APOE allelic variants were associated with MS in Tatar ethnic group. Increased risk of MS was marked by TNFA(-308)*AG, FAS(-670)*AG and IL1B(-511)*TT genotypes (MS with optic neuritis at the disease onset), TNFB(252)*AG and APOE*2/4 (in women), whereas TNFA (-308)*GG, FAS(-670)*AA, TNFA(252)*AG (in women) were found to be protective. IL1B, IL1R1, IL6 polymorphic variants were associated with susceptibility to MS in Russian population. Carriers of IL1R1 (3653)*TT, IL1B (-511)*CC genotypes had increased risk of MS with ataxia at the disease onset, and IL1R1 (3653)*CC, IL1B (-511)*TC genotypes were protective.

Our findings provide new evidence regarding the participation of certain cytokine and apoptosis genes in the pathogenesis of MS in Tatar and Russian population of Volga-Ural region. These data are important for better understanding of the molecular basis of the disease.

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Acute haemorrhagic leukoencephalitis in old age with severe brainstem and spinal cord involvement. Clinico-pathological case report

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Background: Acute hemorrhagic leukoencephalitis (AHLE) is characterized by an acute, rapidly progressive, and frequently fulminant inflammatory hemorrhagic demyelination of CNS white matter, usually postinfectious and associated with death or severe morbidity within few days. We report a clinicopathological case of AHLE in a 70-years-old patient.

Case Report: A 70-year-old male developed abdominal pain and low fever a week earlier of becoming progressively lethargic and tetraparetic. He was admitted in respiratory arrest, requiring intubation and mechanical ventilation. Examination revealed a non responsive coma, with small, symmetric and reactive pupils, absent oculocephalic and right corneal reflexes, flaccid tetraplegia and no meningeal signs. He had no fever or leucocytosis. MR imaging showed disperse hemispheric white matter, basal ganglia and predominantly brainstem and spinal cord lesions. CSF showed 267 white cells/μL (76% neutophils), 400 red cells/μL, increased protein level (2,40 g/L) and normal glucose. Acute disseminated encephalomyelinatis (ADEM) was the first diagnosis established and high-dose steroids (1 g/day) started. Polymerase chain reaction for herpes group, CSF serology and microbiology tests were all negative. On the third day, immunoglobulin treatment was started. MR imaging on the eight day revealed extension of the lesions and CSF analysis markedly increase of proteins reflecting spinal block due to brainstem and cervical spine massive edema. Patient had progressive worsening of his condition and died 9 days after admission. Macroscopic neuropathological examination showed diffuse brain edema, with multiple necrotic and hemorrhagic lesions in the white matter, internal capsule, brainstem and spinal cord. Histopathology was characterized by multiple foci of perivascular demyelination, necrotizing vessels and predominantly macrophagic and few lymphocytic perivascular infiltrates. The diagnosis of AHLE was established.

Discussion: AHLE in elderly patients and massive involvement of brain stem and spinal cord are rare. We believe that the immunological trigger in this patient was related to a probable previous abdominal viral illness. Some findings should have pointed to this particular aggressive ADEM variant, such as neutrophilic pleocytosis and foci of hemorrhage in the MR imaging. AHLE usually has a fulminating course with coma and death in days. Early diagnosis is crucial for the institution of potential live-saving treatment.

P249

Assessment of fatigue, sleep disorders and depression in multiple sclerosis patients: correlation to disability

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Objectives: Literature data suggest that fatigue, sleep disturbances and depression are frequent in multiple sclerosis (MS) and that a possible correlation exists among these symptoms.
We assessed these symptoms and evaluated their frequency comparing these data with those of healthy controls.

Methods: Fatigue, sleep disorders and depression were assessed respectively by: the modified Fatigue Impact Scale (mFIS), the Pittsburgh Sleep Quality Index (PSQI) and the Beck Depression Inventory (BDI).
These three self-reported questionnaires were administered to 50 consecutive MS outpatients (33 females), aged 19-63 years (mean 38.4 ± 9.6), with neurological disability evaluated by the expanded disability status scale (EDSS) ranging 0-7 (mean 2.6 ± 1.9) and 50 healthy controls (37 females), aged 20–54 years(mean 35.9 ± 7.6).

Results: The mean scores for each scale in MS patients and in healthy controls were respectively: mFIS 38.9 ± 25.3 vs 25.8 ± 18.9 (not significant). PSQI 6.3 ± 4.3 vs 5.3 ± 3.3 (not significant); BDI 6.9 ± 5.9 vs 5.5 ± 5.2 (not significant).
Patients were divided in two subgroups according to their disability: 38 with EDSS $\leq$ 3.5 (mean 1.6 ± 0.9) and 12 with EDSS $\geq$ 4 (mean 5.5 ± 0.9). The results in the two groups were significantly different: mFIS 33.6 ± 22.8 versus 55.7 ± 27.2($p < 0.00$); PSQI 5.5 ± 4.2 versus 8.8 ± 3.7($p < 0.00$); BDI 5.9 ± 5 versus 10.2 ± 7.8 ($p < 0.00$).

Conclusions: Fatigue, sleep disturbances and depression seem to have similar frequencies in MS patients and healthy controls. These results are surprising: first, because estimated prevalence of depression in MS patients is about 50%; second, a higher PSQI score in MS patients was expected, due to symptoms like bladder disturbances, neuralgic pain, spasticity and restless legs syndrome, that commonly afflicts these patients. Only after division in two subgroups, based on their EDSS score, results change significantly revealing mild depression, mild sleep disturbances and moderate fatigue in MS patients with higher disability.

P250

Psychopathological symptoms in relatives of multiple sclerosis patients in Greece

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Objectives: To evaluate the psychopathological symptoms of Multiple Sclerosis (MS) patients' relatives in Greece by using a self-report questionnaire.

Methods: The General Health Questionnaire (GHQ-28) was administered to 25 caregivers (males = 15, mean age = 44.7 ± 13.15 years) of MS patients, who were currently admitted to the hospital, due to a relapse of their disease. Demographic and additional information was also recorded. GHQ and its four subscales were scored according to the binary method.

Results: Using the 4/5 cut-off score, based on the Greek GHQ norming study, almost half of the relatives (12/25) reported symptoms indicating some degree of psychopathology.

The participants scored higher on the Somatic concern (2.00) and Anxiety and insomnia (2.12) subscales and much lower on the social dysfunction (0.93) and depression (0.76) ones. Women had higher levels of self-reported symptoms in all subscales, reaching statistical significance in the Somatic ($t(23) = 2.38$, $p = 0.026$) and anxiety ones ($t(23) = 2.10$, $p = 0.047$). Age and type of relationship were not associated with GHQ scores, while educational level showed a mild negative correlation (r approximately -0.3).

Conclusion: Taking into account the strong bonds, characteristic of Greek families, there is evidence that the burden of care of an MS patient may cause their relatives to experience anxiety and somatic symptoms in levels that cause psychological distress.

General neurology

P251

Designing a disease registry for Niemann-Pick disease type C

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Background and objectives: Niemann-Pick disease type C (NP-C) is a rare and fatal progressive neurological disease. Efforts to study this condition are hampered by its extreme variability in terms of symptom profile and time-course, and the still limited information on the natural history and disease course. Here we report the initiation of a disease registry designed by an international scientific committee of experts, to evaluate long-term disease natural history in patients with NP-C, both untreated and treated with miglustat, the first available treatment for NP-C.

Methods: This registry forms a multicentre, prospective, observational project. For inclusion, all patients must have a confirmed diagnosis of NP-C; both untreated patients and those treated with miglustat are eligible for entry. Centres worldwide are encouraged to report data from NP-C patients attending their routine in- and/or outpatient visits. Patients and/or a legal guardian are required to provide written, informed consent. Demographic, diagnostic, treatment history and most relevant disease-specific data are collected. Patients' disability status is evaluated and followed using a disability scale that evaluates ambulation, manipulation, language and swallowing. For miglustat-treated patients, safety-related events and physicians' reports on adherence to drug labelling recommendations are recorded.

Results/data analysis: The total number of patients to be included in the registry will be open. Reporting of summary data from included patients, including exploratory statistical analyses, will be undertaken on a yearly basis. Kaplan–Meier estimates of the proportion of patients without disability worsening (individual and combined disability scores) at different time points will be computed with two-sided 95% confidence limits. Cox modelling and multivariable logistic regression will be used to explore the relationship between potential prognostic factors, treatment and outcomes.

Conclusion: This first international registry for patients with NP-C will provide further, valuable insight into the nature and progression of NP-C over time, and important further information on patient outcomes from the use of miglustat as a therapy for patients with NP-C.

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P252

Magnetic resonance and fundoscopy imaging of cerebral fat embolism: a case report

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Objectives: Fat embolism syndrome (FES) is an uncommon but serious complication of long bone fractures and is frequently diagnostically challenging. FES is characterized by a classic triad of hypoxemia, neurologic dysfunction and petechial rash. We present a new case of FES with characteristic findings in magnetic resonance imaging (MRI) and eye fundoscopy.

Methods: Previously health 25-year-old man with bilateral femoral fractures due to a bike accident; no evidence of cranial traumatism. At emergency department Glasgow score of 15 and no focal neurological deficits. He underwent fractures traction. 24 h later he developed respiratory failure and decreased consciousness, requiring ventilatory support. Bilateral alveolar consolidation in chest computed tomography (CT). Eye fundoscopy showed exudation and bilateral macular oedema. On brain MRI, conventional T2-weighted and FLAIR sequences revealed diffuse white matter and periventricular bilateral hiperintense foci, with areas of restricted diffusion in diffusion-weighted images. On a gradient-recalled echo (GRE) sequence, white matter punctate hypointensities, consistent with haemorrhages in corpus callosum, deep and subcortical white matter, internal capsula and cerebellar hemispheres. Patent foramen ovale was excluded by transesophagic echocardiography. No skin lesions were observed. The patient was discharged from the hospital two months after admission with significant recovery of his neurological condition.

Results: FES may be due to fat emboli through a lung or heart right-left shunting, or to releasing of free fatty acids that damage capillary endothelium producing oedema and punctuate haemorrhages. FES neurological symptoms can vary from altered level of consciousness, focal deficits, seizures, coma, and rarely death. Diagnosis of FES is clinical, but brain MRI allows for the diagnosis and characterization of acute cerebral lesions, ruling out other aetiologies.

Conclusion: In the presence of neurological symptoms hours after a trauma, a FES should be suspected. MRI and fundoscopy findings are a help to establish diagnosis. Despite extensive MRI lesions, outcome, as in our patient, may be favourable.

P253

1H MR spectroscopy of grey and white matter in carbon monoxide intoxication

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Carbon monoxide (CO) intoxication leads to acute and chronic neurological deficits, but little is known about the specific noxious mechanisms. 1H magnetic resonance spectroscopy (MRS) may allow insight into the pathophysiology of CO poisoning by monitoring neurochemical disturbances. Yet the literature on MRS in CO poisoning is still very limited. To further examine the short-term and long-term effects of CO on the central nervous system, we describe seven patients with CO poisoning assessed by gray and white matter MRS, magnetic resonance imaging (MRI) and neuropsychological testing. Five patients suffered from acute high-dose CO intoxication and were in coma for one to six days. In these patients, MRI revealed hyperintensities of the white matter and globus pallidus. MRS showed increased choline (Cho) and decreased N-acetyl-aspartate (NAA) ratios to creatine (Cr) predominantly in the white matter. Lactate peaks were detected in two patients during the early phase of high-dose CO poisoning. Two patients with chronic low-dose CO exposure and without loss of consciousness had normal MRI and MRS. On follow-up five of our seven patients had long-lasting intellectual impairment including one individual with low-dose CO exposure. MRS showed persisting biochemical alterations despite normalization of morphological changes on MRI. In conclusion, MRS was normal in chronic low-dose CO exposure. Yet in patients with high dose exposure abnormal gray and white matter levels of NAA/Cr, Cho/Cr and lactate detected by 1H MRS suggest disturbances of neuronal function,

membrane metabolism and anerobic energy metabolism, respectively. Early increases of Cho/Cr and decreases of NAA/Cr may be related to poor long-term outcome, but confirmation by future studies is needed.

P254

Reversible metronidazole-induced cerebellar toxicity in a multiple transplant recipient

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Objectives and Method: Case study and review of literature.

Results: A 61 year old with type 1 diabetes and a renal transplant received a pancreatic transplant, rendering him insulin-independent. The wound became infected with resistant Klebsiella and was treated with meropenem and linezolid. The linezolid was later replaced with oral metronidazole and amikacin was substituted for meropenem once antibiotic sensitivities were known. He received six weeks of amikacin and eleven weeks of metronidazole. Towards the end of his admission, he became progressively ataxic over 1 day and was unable to walk unaided. On examination there were upper and lower limb cerebellar signs with severe truncal and gait ataxia. Eye movements were full with no nystagmus. The remaining neurological examination was normal. An MRI brain showed increased T2-signal intensity in the dentate nuclei bilaterally. Within 24 h of discontinuation of metronidazole he was able to mobilise with a frame. He was discharged 6 days after the onset of ataxia and 3 days after the cessation of metronidazole. There was a mild residual gait ataxia but he was able to walk with the aid of a stick.

Metronidazole is known to cause neurological side effects at both toxic and therapeutic levels. Seventeen cases of reversible metronidazole-induced CNS disturbance have been reported in the English language literature. It appears to be associated with specific MRI changes of increased signal intensity of the dentate nuclei bilaterally, most notably seen on FLAIR sequences. The predominant symptom is ataxia but the co-occurrence of encephalopathy and/or peripheral neuropathy associated with more extensive MRI abnormalities seems to be more common than the pure cerebellar syndrome. The duration of metronidazole therapy required to induce symptoms is variable but is usually prolonged and/or at high doses. The average daily dose of reported cases was 1.6 g (median 1.5 g) with an average duration of 79 days (median 28 days). An isolated cerebellar syndrome has only been reported in four cases, three of these had dysarthria. All showed reversibility of both the MRI changes (where performed) and the symptoms and signs of ataxia within days to weeks of cessation of treatment (mean 20 days).

Conclusions: Metronidazole-induced ataxia is a rare reversible cause of cerebellar ataxia which specifically affects the dentate nuclei, from which a full recovery can be expected.

P255

Spontaneous spinal intradural haematoma associated with cranial subarachnoid haemorrhage: a case report

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Objectives: Spontaneous spinal hematoma is an uncommon condition, especially when the location is intradural. It is rarely associated to intracranial hemorrhage. We report a case of spontaneous and simultaneous subarachnoid cranial hemorrhage and intradural spinal hematoma. We discuss the possible pathogenic mechanism for this unusual association

Methods: A 74-year-old woman with a background of hypertension, paroxysmal atrial fibrillation and biological mitral an aortic valve replacement. She was taking acenocoumarol. Admitted due to an acute cervical back pain, paraplegia and urinary retention. On examination slight decrease of awareness, paraplegia, low thoracic sensory level and meningeal irritation were found. Spinal magnetic resonance Imaging (MRI) revealed an extensive spinal intradural hematoma. Cranial computed tomography (CT) showed diffuse subarachnoid hemorrhage. The patient was treated conservatively with steroids and anticoagulation reversal. There was no functional improvement and she died due to a respiratory infection.

Results: Most cases of spinal hematoma have multifactorial etilogy. Following idiopathic ones, cases related to anticoagulant therapy and vascular malformations represent the most common categories. Anticoagulant therapy alone probably does not trigger spinal hemorrhage. It is likely that there must additionally be a locus minoris resistentiae to predispose the hemorrhage. Migration of extramedullary bleeding has been occasionally described, mainly when subarachnoid location. We consider that spinal bleeding was the initial lesion in this case and it was favoured by the anticoagulant therapy. Subarachnoid hemorrhage could be due to cranial migration of spinal bleeding. We propose the large size of spinal hematoma, and supine posture adopted during first hours after admission as the predisposing factors of cranial migration of the bleeding through subarachnoid space.

Conclusion: It should be considered the possibility of a craneal extension in large spinal hematomas, especially when predisposing factors as anticoagulant therapy are present.

P256

Stabbing tapeworm headache. A case report

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Objectives: Headache as the sole manifestation of neurocysticercosis (NC) has been uncommonly reported, and, when noticed, most cases are migraine-like headaches. We report a patient with stabbing headache as the sole presenting feature of a subarachnoid cyst.

Methods: A 27-year-old woman, borned in Bolivia with no significant past history. She complaint of frequent short stabs during the last 18 months, severe in intensity, affecting only right frontal scalp. No autonomic or vegetative accompanying symptoms. Neurological examination was unremarkable. Cranial Magnetic Resonance Imaging (MRI) revealed a 2 cm cystic lesion, located right frontal subarachnoid, rounded and well-defined, and slightly ring contrast enhancing. Scolex was visualized within the cyst as a bright nodule producing the typical described imaging, which is the typical image of a cyst in the vesicular phase. In addition, there were four more cysts; two of them in right frontal convexity, one left parasagittal, and the last on left frontal pole. Patient was treated with albendazole (2 weeks) and prednisone (4 weeks), with complete resolution of stabbing headache. A repeat MRI performed 3 months later revealed some calcified dots and disappearance of the cysts.

Results: NC is the most common parasitic disease of the central nervous system worldwide and is especially frequent in many countries of Latin America. It presents usually with seizures, but has pleomorphic manifestations. A high proportion of individuals harbouring parasites in the central nervous system remain free of symptoms for years. Headache is not an uncommon symptom of NC, either alone or associated with seizures or increased intracranial pressure. However, it is unusual as the sole, presenting form of NC. Migraine-like is the most common NC related headache, and may be preceded by aura which characteristics are related to cyst localization. In our patient the unique location of stabs made us to suspect an

organic origin. Coincidence of the main lesion and stabs location, and the complete pain relief after anticysticercal therapy suggests a causal relationship between NC and headache.

Conclusion: NC diagnosis should be considered in patients from endemic regions who complain of atypical headache.

P257

Sjögren's syndrome suspected and diagnosed as of neuromuscular disease

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Objectives: Sjögren's syndrome is an autoimmune disease in which the exocrine glands are primarily attacked. 85% of patients present with sicca symptoms; the remaining 15% depend on a physician's suspicion. The peripheral nervous system is an important site of extraglandular attack, even without the typical sicca symptoms. We report 6 cases of neuromuscular presentation of this syndrome in patients who have not consulted for sicca symptoms.

Material: 6 patients who consulted about neuromuscular symptoms during the period 2007-2008 are reported, without sicca symptoms as an initial complaint. They underwent neuromuscular examination, electrophysiologic examinations, dry eyes studies, syalometry, and minor salivary gland biopsy.

Results: Two patients presented with small and large fiber neuropathy; one patient presented with bilateral vestibulochoclear disease; one patient with V nerve neuralgia; two patients, with autonomic and vestibular neuropathy. All patients met diagnostic criteria of Sjögren's disease.

Conclusions: Neuromuscular disease secondary to Sjögren's syndrome is rather frequent in those patients referred to a neuromuscular consultation. The challenge is that of suspecting this syndrome in those patients who consult about neuromuscular symptoms without complaining of sicca symptoms as a first complaint: they only mention these symptoms if induced. It is vital for neurologists to take this treatable differential diagnosis into account, since 15% of patients suffering of this syndrome do not complain of dry eyes or mouth.

P258

Brachial plexopathy secondary to mycotic axillary artery aneurism

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Objectives: Aneurism of the axilary artery is a rare disease most frequently caused by penetrating injuries that result in false aneurisms. True aneurisms are caused by atherosclerosis, syphillis, thoracic outlet obstruction, shoulder trauma and medial cystic necrosis. Due to their anatomical relationships, they can damage the brachial plexus. There is only one report of a rapidly progressive plexopathy due to a mycotic subclavian and axillary aneurism. We report a new case of such impairment.

Methods: A 44-year-old woman was admitted for 10 kg weight loss, malaise, chronic fever and chills over a four-month period, associated to a rapidly progressive paresis, pain and wasting of the left upper limb. She underwent physical examination, fundoscopy, laboratory tests, echocardiogram, angiogra, and neurophysiologic studies for a diagnostic plan.

Results: A conjuntival petechia, and one at fundoscopy were detected, and a three-centimeter pulsatile mass was palpated at left axilla. No adenopathies were found. Left radial pulse was attenuated, and proximal and distal muscles of the left upper limb were wasted. Eritrosedimentation rate was elevated, and kidney function was impaired, compatible with glomerulonephritis. A completed blood count disclosed an anemia and a deep plachetopenia. A systolic murmur of mitral insufficiency was found, and a doppler echocardiogram revealed mitral insufficiency with vegetations on the surface of the anterior mitral valve. Neuromuscular examnination revealed weakness and wasting of proximal and distal muscles of the upper limb, with arreflexia. Neurophysiologic testing confirmed the diagnosis of brachial plexopathy. Blood cultures were positive for Haemophillus parainfluenzae. Angiogram visualised a five-centimeter aneurism. The patient was treated with antibiotics (ampicillin), and vascular surgery, with mild improvement of motor function.

Conclusion: Mycotic aneurisms arise from septic emboli to the vasa vasorum or atherosclerotic plaques. They develop rapidly and are associated with neurological deficits. To our knowledge, this is the second report of a rapidly progressive brachial plexopathy due to a mycotic axillary aneurism.

P259

Potential complications of lumbar puncture: 3 case reports

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Objectives: Lumbar puncture (LP) is a frequently practised procedure as part of investigations of neurological disorders. The procedure can commonly cause headache or it may lead to infection. However, there are rare complications associated with LP, which are the source of great concerns for the neurologists.

Methods: Three different cases admitted to hospital with indications for cerebrospinal fluid examination is discussed. The clinical details, investigations and imaging in each case reveal the subsequent complications after perfroming diagnostic lumbar punctures.

Results/discussion: Pneumoencephalus is recognized to complicate epidural anaesthesia as well as cranial or sinus operations. To our knowledge, there is no previous report of pneumoencephalus complicating a diagnostic LP. Accidental dural rupture causing pneumoencephalus can result in catastrophic consequences. Our case, however, made a full recovery with taking conservative measures.
The second case presents a patient who underwent a diagnostic LP whilst being on anticoagulation therapy. In this case, subdural haematoma following the procedure, performed by the general medical team, caused fatality.
Last but not the least; meningeal enhancement was the consequence of yet another diagnostic LP in a patient who was admitted to hospital and treated with a chain of investigations.

Conclusion: A more rational approach to the absolute indications of daily practice of LP in acute medical wards is necessary. The rate of post-LP complications can be minimized through strict attention to contraindications and technique.

P260

Differential diagnosis and utility of AQP4-antibody assays in an insidious case of longitudinally extensive transverse myelitis

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Introduction: Longitudinally extensive transverse myelitis (LETM) is considered part of the Neuromyelitis Optica (NMO) clinical

spectrum. An early diagnosis and treatment can reduce the disability related to this severe condition. NMO-IgG or Aquaporin 4-antibodies (AQP4-Abs) are specific markers of NMO and related disorders and are generally detected by indirect immunofluorescence (IIF).

Here we report an insidious case of extensive myelopathy which presented differential diagnosis issues, and in which only a spinal cord biopsy and recently established assays for AQP4-Abs led to a diagnosis of NMO-related disorder.

Case report: A 29-year-old Nigerian woman presented with persistent nausea associated with behavioral changes and depression which was initially attributed to gastric paresis and subsequently to a psychiatric disorder. Over the next weeks, the patient developed motor and sensitive deficits of the four limbs and bladder dysfunction. An MRI of the spinal cord revealed a gadolinium-enhancing lesion extending from the medulla oblongata to T4 which was biopsied to rule out a possible neoplastic or infectious origin. The pathological analysis revealed perivascular lymphocytic infiltration suggesting an inflammatory lesion. The patient underwent high-dose intravenous steroid treatment with marked improvement but three months later presented with a relapse of myelitis characterized by persistent hiccups, which also benefited from steroids. A sample of serum was tested by IIF but did not show the typical immunostaining pattern for NMO-IgG. A cell-based assay for AQP4 (AQP4-CBA) and a Fluorescent Immunoprecipitation assay (FIPA) performed in Oxford were positive, leading to a diagnosis of NMO spectrum-related LETMS, and more systematic immunosuppressive treatment.

Discussion: LETM can be a challenging diagnosis in cases in which the clinical criteria for NMO are not satisfied, and intractable hiccups or nausea are not recognized as characteristic of NMO. Although this patient had an inflammatory spinal cord biopsy, IIF for NMO-IgG proved negative as it is in a proportion of cases. However, with the higher sensitivity of recently developed cell-based and FIPA tests, the diagnosis was made with improved prospects for the patient.

P261

The importance of transcranial Doppler in diagnosis for syncope

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Objectives: Syncope is a common cause in patient with transient loss of consciousness (TLOC) and cerebral syncope is not truly rare.

Methods: We evaluated the incidence of cerebral syncope by transcranial doppler(TCD) with head up-right tilt table test (HUTT) to patient with transient loss of consciousness between March 2004 and January 2009.

Results: We performed TCD with HUTT in 180 patients with TLOC. Patients were divided into three groups on the response to both tests. Positive response to both TCD and HUTT in 97(53.9%) patients, negative response to both tests in 64(35.6%) patients. In 19(10.5%) patients, positive response on TCD but negative response on HUTT. The positive response of TCD means that reduction of mean blood volume of middle cerebral artery to below 50% of baseline level volume. This patient which positive response to only TCD is cerebral syncope. In 6(31.6%) of 19 patients, meaningful reduction of middle cerebral artery volume was presented in only diastolic volume on TCD.

Conclusions: Cerebral syncope which positive response to only TCD is not rare. We must perform TCD associated with HUTT in patient with TLOC for diagnosis of cerebral syncope.

P262

Cobalt neurotoxicity: a lesson from hip arthroplasty

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Objectives: To investigate the effects of metal ions released by hip arthroprotheses, in particular cobalt ions, on human nervous system.

The role of cobalt or cobalt-chromium alloy on human tissues has not been definitively established. Cobalt can produce different well known toxicological effects: local respiratory symptoms due to the inhalation exposure to cobalt-containing dusts, and systemic effects; on the other hand neurological toxicity has been only occasionally reported and never described in reviews.

Methods: We have studied the case of a 58-year-old woman with neurological disturbances (blindness, nerve deafness and polyneuropathy) caused by cobalt release after revision of her left hip arthroplasty. At the time of admission we performed a neurological examination, several laboratory investigations and an instrumental diagnostic work-up. The case was then referred to the Toxicology Department to investigate an undisclosed intoxication performing the determination of metal ions concentration in different biological samples.

Results: The neurological examination at admission showed a selective II and VIII bilateral cranial nerves impairment and mild distal sensory-motor disturbances. Laboratory investigations revealed only a slight increase of inflammatory markers. Brain MRI revealed the hyperintensity of optic nerves and traits, EMG/NC showed mild lower limbs nerve amplitude reduction, acoustic and visual evoked potentials were positive for bilateral absence of brainstem acoustic responses and irregular cortical visual responses.

Cobalt concentrations in the biological samples resulted dramatically higher than reference values: cobalt concentrations were 1187, 549, 90 and 11.4 μg/l in urine, blood, plasma and liquor respectively (reference values: 0.1–1.5, 0.05–2.7, 0.1–0.6 and 0.05–0.15 μg/l).

Conclusions: The hereby presented case underlines the potential serious consequences of cobalt ions on human nervous system. Other studies are now required to reveal the biochemical bases of cobalt neurotoxicity. An important feature of cobalt is its ability to induce an hypoxia-like effect; some in vitro studies have suggested that mitochondria could be a specific target of the metal toxicity. The fact that the neurological syndrome (including polyneuropathy, deafness and blindness) seen in our patient is the same seen in some mitochondrial cytopathies, underlines the central role of mitochondria in the neurotoxicity of cobalt.

P263

Refractory neurosarcoidosis responding to infliximab

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Objective: To describe 2 cases of refractory neurosarcoidosis responding to infliximab, a monoclonal antibody directed against tumour necrosis factor-α(TNF-α). Neurosarcoidosis is an uncommon complication of systemic sarcoidosis and tends to be associated with greater resistance to therapy and worse outcome. The mainstay of treatment is steroids, often combined with other immunosuppressants. There is accumulating evidence that suggests that TNF-α may play a pivotal role in the inflammatory cascade.

Design/methods: We describe the clinical and radiological features of two cases of neurosarcoidosis refractory to steroids and first line immunosuppressants who subsequently received infliximab and showed sustained clinical improvement.

Results: Patient 1 presented with a three week history of headaches, fatigue, concentration difficulties associated with visual and sleep disturbance. Examination revealed obesity and hemianopia. Cerebrospinal fluid (CSF) protein level was raised and investigations revealed panhypopituitarism and hypothalamic dysfunction. Brain magnetic resonance (MR) imaging showed a hypothalamic dural-based mass extending into the thalamus, optic chiasm and lateral ventricular area, biopsy of which confirmed sarcoid. Despite steroids and pulse cyclophosphamide therapy his disease continued to progress. Latent tuberculosis was excluded and he was commenced on infliximab. He had a prompt and clinical and radiological response to infliximab sustained over 3 infusions.

Patient 2 presented with a four year history of early morning nausea, headaches and left sided numbness. Examination revealed mild ataxia. CSF showed lymphocytic pleocytosis and brain MR imaging showed obstructive hydrocephalus and diffuse leptomeningeal enhancement. Brain biopsy was consistent with chronic inflammatory changes. There was an initial response to steroids but he developed considerable toxicity. He declined cyclophosphamide and disease progression continued whilst on methotrexate. He was commenced on infliximab with dramatic improvement following the first infusion. He remains well after his third infusion

Conclusion: Infliximab is a promising agent in neurosarcoidosis refractory to other immunosuppressant agents. TNF-α blockers are not without possible side-effects, thus careful monitoring of patients is essential. Large randomized controlled trials are needed to further elucidate the role infliximab in the treatment of neurosarcoidosis.

P264

Pharmaco-resistant epilepsy as paraneoplastic presentation of unknown malignancy in the adult

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We report two patients with seizures resistant to antiepileptic drugs, who finally were diagnosed of paraneoplastic limbic encephalitis (LE), leading to detect a malignancy.

Case 1: A 46 year-old man with repeated tonic-clonic seizures was admitted to the intensive care unit, requiring high doses of three antiepileptic drugs. Behaviour disorder, disorientation, severe amnesia and brainstem signs appeared. After adding intravenous methylprednisolone there was a gradual recovery in two weeks, although the memory deficit persisted.

Case 2: A 61-year-old man developed recurrent stereotyped episodes of head turning, facial automatisms, consciousness clouding without postictal confusion, compatible with frontal status epilepticus. Neurological exam intercrisis was normal. He was treated with increasing doses of antiepileptic drugs in successive combinations, improving finally with phenytoin, pregabaline and levetiracetam.

Wide blood and CSF analysis including tumour markers, thyroid tests, and antineuronal antibodies (Ab) (anti Hu,Yo, Ri, amphiphysin) were negative. In case 1, CSF showed increased proteins and oligoclonal bands. EEG revealed generalised slowing of the background activity, without focal or epileptiform anomalies. Cranial MRI was normal, except FLAIR-increased signal in cyngular cortex in case 2.

In case 1, posterior mediastinal masses were found on tomography, with hypercaptation on γgraphy, identified as undifferentiated carcinoma after biopsy.

Total body tomography was normal in case 2, but a small cell lung carcinoma was diagnosed 18 months after the initial presentation.

Paraneoplastic LE is a rare disorder characterized by behaviour changes, seizures (often partial), and memory loss, developed in days or weeks. Most are associated with small cell lung cancer. The presence of symptoms beyond the limbic system as in the case 1, highly suggests a paraneoplastic origin. Cycles of methylprednisolone are recommended. Therapeutic response is excellent in idiopathic LE and may be good in LE with anti-Ma2 or without antineuronal Ab, in contrast with LE related to anti-Hu.

Several Ab have been recently described in patients with LE such as antipotassium channels, unexplored in our cases. The test of these Ab is useful for diagnosis, prognosis and therapy decisions. However, even with normal EEG, MRI and immunologic study, LE must be suspected in adults with refractory seizures, leading to the search of an occult tumour during a long follow-up.

P265

Subarachnoid haemorrhage and leukaemic meningoencephalitis in an adult patient with acute lymphoblastic leukaemia

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Objectives: The acute lymphocytic leukaemia (ALL) is one of the most common malignancies in patients younger than 15 years. The incidence rate in adult is 1/100,000 persons/year and represents 20% of adult leukemia. Adult patients with ALL are at risk of developing central nervous system (CNS) involvement during the course of the disease. The purpose of our paper is to underline the importance of the neurological complications at those patients since and treatment and prognosis are influenced by this complication.

Methods: We present the case of a 44 years old female patient diagnosed in May 2007 with pro-B acute lymphoblastic leukemia, CALLA+ with hyperleucocytosis. The hematological treatment included CNS prophylaxis with cytosine arabinosid (ARA-C), methotrexate (MTX) and dexamethasone. During the course of the disease multiple complications occurred such as primary fibrinolysis syndrome, marked depression and confusional state. Three months after the onset the patient was hospitalized in the Neurology Clinic of the Emergency University Hospital for intense cervical spine pain and decreased muscle strength in the right limbs.

Results: On admission lumbar puncture was performed revealing a CSF suggestive of subarachnoid hemorrhage. The angiographic exam and the head CT scan were normal. The cerebral MRI showed focal thickening of the meningeum with gadolinium enhancement, suggesting neoplazic meningoenkefalitis. The final diagnoses were subarachnoid hemorrhage and leukemic meningoencephalitis. The patient received systemic antiedematous drugs, cerebral vasodilator (nimodipine) and steroids as well as intrathecal/systemic chemotherapy and radiotherapy. Four months later a bone marrow biopsy revealed hematological remission, the control lumbar puncture revealed a normal aspect of the CSF and the remission of the neurological symptoms was complete.

Conclusion: The particularity of the case consists in the age of the debut of the leukemia, the uncommon evolution of the simptomatology with primarily fibrinolysis and the precocious involvement of the CNS (the first three month after diagnoses of the hematological disease). The two neurological manifestations, subarachnoid hemorrhage and leukemic meningoencephalitis, could be explained by the involvement of the walls of pial vessels, the extension of the leukemic

infiltrate to the deep perivascular spaces and the diffuse inflammation of the vessel wall.

P266

Neurological eponyms of perpetrators, victims and bystanders in the Nazi era

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In the 1920s the neurosciences in Germany were world-class. Then came the Hitler regime and with it two distinct changes happened to the research milieus in Berlin and elsewhere.

First, the persecution of Jews and others deprived Germany of many of its most outstanding scientists.
Second, numerous German and Austrian physicians became active in NS-euthanasia programs.

In recent years the medical community has become more aware of the ethical burden associated with eponyms derived from scientists of the Third Reich. Yet a list of these eponyms with emphasis on clinical neurology is still missing. The author therefore presents 31 neurological eponyms derived from 30 physicians who lived in the Nazi era. Among them are victims, forced out of the country or murdered in concentration camps; protestors, who risked their academic careers and often their lives; beneficiaries, who published on brains from "euthanized" children; and aggressors, directly involved in the planning and execution of NS-euthanasia programs.

P267

A brief history of MRI

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Objectives: The use of magnetic resonance imaging (MRI) has now become widespread in the diagnosis and management of neurological conditions. It has been developed by numerous scientists over a period of seven decades from principles first discovered in the 1930s. This poster presents a historical view of the development of clinical MRI with reference to the original papers and scientists involved in this work.

Methods: Using textbooks and reviews, the historical development of MRI was traced from the 1930 s to the present and the original papers describing each development were obtained.

Results: The fundamentals of nuclear magnetic resonance were discovered in the 1930s and 1940s by Isidor Rabi, Felix Bloch and Edward Purcell. These findings were developed into NMR spectroscopy for chemical and physical molecular analysis in the 1950s and 1960s. In the 1970s, knowledge from the development of CT by Peter Hounsfield coupled with the work of numerous other scientists enabled the first human MRI scanner to be built in 1977 by Richard Damadian. In the 1980s, new techniques such as magnetisation transfer imaging, diffusion-weighted imaging, gradient-echo imaging, echo-planar imaging, MR angiography were developed. These were followed by functional MRI and diffusion tensor imaging in the 1990s. The latter technique has been developed over the last decade to enable non-invasive visualisation of white matter tracts using diffusion tensor tractography.

Conclusions: The development of MRI for clinical is based on discoveries initially made 70 years ago, which have been successively built upon by several generations of scientists. Magnetic resonance imaging thus owes its existence to many talented scientists, and indeed four Nobel Prizes have been awarded over this period.

P268

Neurological diseases in Gilles de Corbeil's medical poetry

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Objectives: Gilles de Corbeil was one of the most prominent physicians of the Middle Ages. A student of medicine in the famous School of Salerno, he was the initiator of the scientific teaching of medicine in Paris during first years of 13th century.

Methods: Medieval medical texts written in verse are not unusual. Poetry increases clarity and concision, provides students a mnemonic aid, and pretends to preserve future integrity of the text. We review translation from Latin of four texts attributed to Gilles de Corbeil and consider references to neurological diseases. Liber de urinis (LU) constitutes a compendium of uroscopy and shows, in more than 500 verses, a urine analysis specifying its different colours, substances and components. Apart from urine, pulse is the main diagnostic tool available to physicians of the time; so in De pulsibus (DP) Corbeil analyses different kinds of pulse and their significances in 380 verses. De virtutibus et laudibus compositorum medicaminum (DVLCM) versifies in four books and over 4.500 verses, Antidotarium nicolai, the most famous medieval treatise on pharmacology and antidotes. Finally, De signis et symptomatibus aegritudinum (DSSA) exposes, following the usual medieval pattern a capite ad calcem (from head to toe) common symptoms of diverse diseases.

Results: LU and mainly DSSA classify headaches, accordingly to their cause and duration, depending on the colour of patient's urine. In the medioevo headache is explained by the humoral theory, and urine colour changes depending on the disbalanced humour. Previously Salernitan Masters had defined migraine as the pain that afflicts only half of the head. DSSA considers, for instance, two holocranial headaches; one of them, rapidly reversible, due to gastric affections, and other more prolonged related to a systemic disease. DP connects spasms to a type of pulsing, and explains stuttering based on the existence of a rapid pulse. LU describes as humours changes lead to spasms, whose prognosis depend on the characteristics of the urine. Finally DSSA suggests an origin for tinnitus and carries out a detailed description of symptoms related to stroke, including motor, sensitive, language or perception impairment.

Conclusion: Analysis of Gilles de Corbeil' medical poetry gives us an interesting view of how medieval European physician understand neurological diseases, mainly based on cultural heritage from ancient times.

Poster session 2

Cerebrovascular disorders: diagnosis and imaging

P269

Moyamoya syndrome: the importance of considering rare causes in differential diagnosis of ischaemic stroke

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Introduction: Moyamoya syndrome is a clinical identity characterized by the presence of progressive and chronic occlusive disease of intracranial vessels, secondary to a known etiology and with the same

angiographic features of Moyamoya disease. It affects mainly young adults, manifesting most frequently with recurrent ischemic strokes.

Case report: Male, 44 years old, with a past medical history of hypertension, diabetes, hypercholesterolemia and smoking. Admitted to our hospital with dysarthria and left paresthesia of sudden onset. Neurologic examination revealed dysarthria and a mild left hemiparesis (grade 4+). Brain CT and MRI revealed a right cortico-subcortical frontal ischemic lesion. There was no evidence of significant carotid stenosis in the Doppler ultrasound study. At discharge he had a modified Ranking Scale (mRS) of 1. One week later he was admitted again with worsening of the previous left hemiparesis. Brain MRI revealed a new ischemic lesion in the territory of right middle cerebral artery. Angio-CT demonstrated a bilateral moyamoya pattern, more severe at the right arteries of the anterior circulation, which was confirmed by conventional angiography. No thrombophilic or autoimmune diseases were found. He was discharged with a mRS of 3, taking aspirin, and was purposed to a surgical revascularization procedure.

Conclusion: This case illustrates the importance of considering this syndrome in the differential diagnosis of ischemic stroke, mainly in young patients and even in the presence of classic vascular risk factors. The correct diagnosis of this clinical identity allows implementing the recommended treatment (revascularization surgery and treatment of the underlying cause), which decreases the incidence of new strokes in this patients and improves the functional and neurologic outcome in most of them.

P270

Double traumatic intracranial and extra cranial carotid artery dissection: a case report

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Background: Cervicocephalic artery dissection of two or more segments occurs preferentially in woman,is rare and moreover in the same patient. The classical triad of an extra cranial ICA dissection presentation is ipsilateral headache,facial or neck pain and parzial Horner's syndrome;intracranial ICA dissection is rarer, occurs in a younger age group (mean age of 25 years)and a less favourable clinical outcome with a mortality rate of 75%; it is also less common, almost exclusively spontaneous and symptoms are associated with a subarachnoid haemorrhage (SAH).

Methods: We report a case of traumatic double carotid artery dissection (CAD) in a previously healthy 35-year-old man who, 3 days after a car accident, had had a gradual onset of chest pain and incomplete Horner's syndrome.

Results: Brain computed tomography (CT) showed no abnormality. Carotid duplex ultrasonography showed significantly decreased flow in the right ICA without evidence of plaquing. Brain and cervical area magnetic resonance imaging/angiography (MRI/MRA) showed loss of flow in the intrapetrous segment of right ICA without infarcts and the diagnosis was dissection. He started anticoagulant oral therapy (TAO).One month later, he performed a clinical follow-up: he did not complain about new symptoms or trauma; he presented a progressive neurological recovery and INR ratio was in range. He underwent a new MRI/MRA that showed a partial resolution of right ICA dissection (70% stenosis) and the new occlusion of the cervical (C1-C2) segment of left ICA as a dissection consequence.

Conclusion: This case confirms that multiple CAD are preceded by a minor trauma and can have a favourable clinical outcome in most patients but, on the contrast, shows a different clinical presentation way for intra and extra cranial ICA dissection; moreover this report shows neurological resolution in an intrapetrous ICA dissection.

Discussion: This case is important because confirms that multiple CAD are not so rare, can be asymptomatic and well detected by MRI/MRA; on the other hand TAO seems to be suboptimal in this case. In our department, in the next 4 months, we have had 4 new cases of intracranial carotid artery dissection, on the level of intrapetrous segment. Could be a common risk factor? Maybe climatic? Others?

P271

Primary angiitis of the central nervous system with a stroke-like presentation

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Objectives: Primary angiitis of the central nervous system (PACNS) is a rare idiopathic disorder, in which vasculitic lesions are confined to small and medium-sized vessels of the brain and/or spinal cord, without evidence of systemic involvement. Its clinical features are variable and include headache, seizures, confusion, cranial neuropathies as well as ischaemic or haemorrhagic cerebrovascular events. According to the existing literature, in the vast majority of cases, stroke is not the presenting clinical manifestation. We report a patient with recurrent multifocal strokes that was subsequently diagnosed with histologically-proven PACNS.

Case history: A 63-year old male, was admitted to our department with dysarthria and a moderate left hemiparesis. Brain MRI revealed multiple acute ischaemic infarcts in the right centrum semiovale. Laboratory studies showed markedly increased erythrocyte sedimentation rate and elevated C-reactive protein, with no evidence of infection. Digital angiography revealed segmental narrowing of multiple intracranial vessels, including both internal carotids, left anterior cerebral artery and both vertebral arteries. One week following admission, the patient developed left hemiplegia. A repeat MRI demonstrated additional infarcts in the right frontoparietal cortex with gyral enhancement, as well as in the left frontal lobe. A vasculitic syndrome was suspected; however serum autoantibody testing was negative as were temporal artery and skin biopsies. CSF analysis revealed a mild pleocytosis with increased protein content. Over the following days, the patient's condition deteriorated further and he developed left hemianopia, confusion and impaired consciousness. A stereotactic brain biopsy revealed a lymphocytic vasculitis. Diagnosis of PACNS was established and the patient was put on prednizolone and on monthly trials of intravenous cyclophosphamide, with gradual improvement of his neurological condition. At the end of the treatment period he was fully oriented and presented a moderate left hemiparesis.

Conclusion: The clinical presentation of PACNS may mimic a wide variety of disorders. Early suspicion and diagnosis is essential, given that otherwise the outcome can be fatal. In patients presenting relapsing strokes and an unexplained clinical deterioration, brain biopsy should be considered, especially when MRI findings, inflammation markers and CSF analysis are compatible with vasculitis.

P272

No spontaneous recanalisation in complete occlusion of the carotid artery

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Objectives: To examine whether recanalization takes place in complete occlusion of the carotid artery.

Background: The natural history of complete carotid artery occlusion is uncertain. Several anecdotal reports and retrospective studies suggested that in a small number of patients, spontaneous recanalization may take place. This possib il ity has prognostic and therapeutic consequences since recanalization might carry an increased risk of stroke in the respective territory as well as implying the need for close follow up of patients with a chance of recanalization in order to devise conservative or surgical therapy.

Materials and methods: We retrospectively evaluated DUPLEX data obtained from patients referred to our vascular diagnostic laboratory within a 6 year period: between January 2001 and December 2006.

Results: 8,449 patients underwent DUPLEX examination within this period. In 280 patients (3.3%) there was ultrasonic evidence for complete carotid artery occlusion. 183/280 patients (65%) had a repeated examination at least one year following the initial examination. In none was there evidence for re-canalization.

Conclusions: In our cohort there is no evidence for spontaneous recanalization of complete occluded carotid arteries. These findings differ from two other studies that identified recanalization in smaller group of patients. A prospective study is warranted to verify our findings.

P273

Cerebral haemodynamics in Behcet's disease: a transcranial Doppler study

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Objectives: Transcranial doppler ultrasonography permits the noninvasive measurement of blood flow velocities. Breath holding index (BHI) is a vasodilatory stimuli and can be used to measure the changes in these velocities like CO2 inhalation and acetazolamide administration. We aimed to investigate the reserve capacity of cerebral circulation in patients with Behcet's disease without neurological involvement both in anterior and posterior.

Methods: 12 patients with Behçet's disease without neurological involvement followed up by rheumatology clinics and 20 healthy people as control group were included in our study. Breath holding indexes were computed by transcranial doppler sonography monitorization through middle cerebral arteries (MCA) and posterior cerebral arteries (PCA) bilaterally to assess anterior and posterior cerebral circulation hemodynamics.

Results: Mean BHI in Behçet group in left MCA was 1.84 ± 0.51, in right MCA 1.87 ± 0.51, in left PCA 1.56 ± 0.59 and in right PCA 1.59 ± 0.65. In control group mean BHI values were 1.42 ± 0.20, 1.43 ± 0.24, 1.53 ± 0.29, 1.51 ± 0.24 respectively. While differences in BHI values between Behçet and control groups in left MCA ($p = 0.002$) and right MCA ($p = 0.002$) were statistically significant, differences between two groups in both PCA's ($p > 0.05$) were statistically insignificant.

Conclusion: In patients with Behcet's disease despite arterial system is affected rare than venous system, symptom and signs of involvements of posterior circulation territories, brainstem and cerebellum, are clinically dominant. MRI and SPECT studies support these data. As a result of our study, it may be possible to say that, anterior circulation increases its cerebrovascular reserve probable with an adaptation mechanism for an ischemic accident due to vasculitis in patients with Behcet's disease even without any neurological involvement, but posterior circulation can not show these adaptability.

P274

Atheroma plaques echogenicity in acute stroke standarised by grey scale median

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Introduction: Echogenicity of atheroma carotid plaques is related with higher risk of stroke. To date clinical and subjetive ultrasonografical criteria are used to identify the symptomatic plaques but the standadized gray scale median (GSM) value could be an useful objetive tool for this diagnosis. Our aim is to analyze the utility of the assessment of echogenicity of the atheroma carotid plaques by means of the GSM system, comparing the symptomatic carotid with the asymptomatic one in the same patient.

Methods: Observational prospective study with inclusion of acute non-cardioembolic anterior cerebral circulation ischemic stroke patients (February–December 2007). Only patients with bilateral plaques in both carotid bifurcation and/or internal carotid artery were included. Echogenicity of plaques was measured by a digital and standardized gray scale system in carotid ultrasound B-mode (longitudinal proyection) conducted within the first week after admission.

Results: 72 patients were included (51 aterothrombotic and 21 lacunar infarction) with a total of 175 plaques examined. Plaques located in symptomatic-side had less echogenicity than those in the silent side (25.0 vs. 30.0; $p = 0.038$). Symptomatic plaques were less echogenic than asymptomatic ones (19.5 vs. 30.0; $p < 0.0001$). In the group of aterothrombotic stroke, symptomatic plaques had less echogenicity than asymptomatic ones regardless the degree of carotid stenosis (18.0 vs. 30.0;$p = 0.002$). Stenotic plaques (>70%) showed lower ecogenicity than those with lower degree of stenosis (17.5 vs. 28.0; $p = 0.002$). A receiver operation curve (ROC) analysis point to GSM value of 24.5 as the point associated to higher sensitivity (67%) and specificity (76%) to identify a plaque as symptomatic.

Conclusions: Symptomatic atheroma plaques and plaques located in carotid symptomatic-side have lower echogenicity than non symptomatic ones. The point of 24.5 GSM value could be used at cut off to identify which plaque is symptomatic.

P275

Diagnostic value of D-Dimer measurement in patients with suspected cerebral venous sinus thrombosis

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Background: Cerebral venous sinus thrombosis (CVST) can be presented with headache, seizures, and focal neurological deficit. Brain CT scan may be normal in up to 30% of cases, and MRI may not be available. D-dimer (DD) which is increased in other thromboembolic situations could be a useful test in CVST as well

Method: We conducted a prospective study of 104 consecutive patients with headache or unusual ischemic stroke (infarction in brain CT, but not compatible with any brunch of cerebral arteries), suggesting CVST. D-dimer test determined for all patients in the

emergency ward within the first 24 h. Titers above 500 ng/ml were regarded as positive test. MRI and MRV were performed as a diagnostic gold standard for CVST.

Results: From a total 104 patients, 21 cases (20.2%) were confirmed (by MRI and/or MRV) to have CVST, 20 of whom had positive DD test. so sensitivity of the test was 95.2 (CI 95%: 74.1–99.8). In the remainder 83 (without CVST) it was increased in only 14(16.8). Specificity, negative and positive predictive values of DD test were 83.1 (CI 95%: 73–90.1), 98.6 (CI 95%: 91.2–99.9) and 58.8% CI 95%: 40.8–74.9) respectively. CVST was associated with oral contraceptive pills consumption in female ($p = 0.001$), but not with sex ($p = 0.24$) or age ($p = 0.20$).

Conclusion: Application of D-dimer test would be useful when CVST is considered as a differential diagnosis.

P276

The lesion location on diffusion MRI in acute pontine infarction influences the early neurological deterioration

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Objectives: The etiopathomechnism involved in early neurological deterioration of acute pontine infarcts is not well understood, although progressive motor deficit is a common problem in pontine infarcts. We attempt to identify the frequency and the prognosis as well as predictors of early neurological progression in acute pontine infarcts.

Methods: Consecutive patients with acute pontine infarcts within 24 hours after symptom onset for a year were included. A standard protocol of brain MRI and MR angiography(MRA) were performed on admission and 1 week later. Epidemiologic data, including vascular risk factors and baseline inflammatory markers, such as high sensitivity C-reactive protein(hsCRP), D-dimer, fibrinogen, leukocyte count, were collected. An early neurological progression was defined as one or more point worsening of NIHSS between admission and seven days later.

Results: Thirty five patients(mean age 65) were included. Twenty-five had paramedian pontine infarcts (71.4%) and 10 had the others (28.6%). The most frequent stroke subtype was large artery atherosclerosis (51.4%), followed by undetermined etiology(22.9%), lacune (11.4%), cardioembolism (8.6%), and stroke of other determined etiology (5.7%)($p < 0.05$). Fifteen patients (42.9%) revealed the stenosis of the basilar artery. The lesion extension on the follow-up MRI was present in 15 patients (42.9%). Progressing stroke occurred in 9 patients (25.7%) and non-progressing stroke in 15 (74.3%) ($p < 0.001$). Among progressing stroke and non-progressing stroke, there were no statically significant differences in the known vascular risk factors and inflammatory markers. Early neurological progression was significantly associated with the paramedian pontine infarcts (OR, 1.62; CI, 1.19–2.20). Although early recanalization of the occluded vertebra-basilar artery on the follow-up MRA did not prove the significant difference, the lesion extension on the follow-up MRI revealed the significant association with progressing stroke (OR, 7.87; CI, 1.33–46.66). Two patients (22.2%) in progressing stroke and 7 patients (26.9%) in non-progressing stroke present a good prognosis (mRS,T1) after 3 months($p > 0.05$).

Conclusion: The paramedian pontine infarcts and lesion extension on the follow-up MRI in patients with acute pontine infarcts were associated with early neurological progression. The characteristic findings on the initial MRI may guide early intensive treatment for the prevention of early neurological deterioration.

P277

Isolated vertigo and possibility of brain ischaemia: evaluation by diffusion-weighted magnetic resonance imaging

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Objectives: In isolated vertigo, we cannot definitely distinguish between central and peripheral vertigo by using history and physical examination. Some central cause of isolated vertigo such as cerebellar stroke can be life-threatening and may require intervention. Brain infarction can be detected shortly after the onset of clinical symptoms by using diffused weighted MRI (DWI). We conducted this study to identify isolated vertigo patients with higher probability of brain infarction to perform DWI.

Methods: Fifty five consecutive patients with isolated vertigo who had at least one cardiovascular risk factor were enrolled. A questionnaire, consisted of cardiovascular risk factors was completed and DWI was performed for each patient. We used chi-square method to analysis the association of cardiovascular risk factors with infarction identified by DWI in isolated vertigo patients.

Results: Using DWI, 5 (9.1%) patients had an acute ischemic stroke. Among cardiovascular risk factors, Chi-square analysis showed significant relationship between diabetes mellitus (DM) and infarction.

Conclusion: Isolated vertigo may happen due to occlusion of a small artery in the territory of posterior inferior cerebellar artery. DM causes atherosclerosis in small arteries. According to our results DWI can be recommended in diabetic patients with isolated vertigo.

P278

Biological effect of 1-hour continuous Doppler monitoring using a diagnostic transcranial probe

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Objectives: Since the 1970s, in vitro and animal models studies demonstrated an acceleration of thrombus dissolution when using an ultrasound beam. The aim of the study was to monitor the changes in haemocoagulation parameters in acute stroke patients and healthy volunteers after a 1-h continuous Doppler monitoring (CDM) using a standard diagnostic 1–4 MHz duplex transcranial probe with maximal diagnostic energy (MI 1.4).

Methods: Thirty-two acute stroke patients (19 males; age 50–84, mean 68.5 ± 9.0 years) were randomized for standard treatment (ST) (16 patients) and for ST with CDM of the middle cerebral artery (MCA) (16 patients). Thirty-two healthy volunteers (16 males; age 50–70, mean 55.7 ± 3.8 years) underwent a 1-hour CDM of the MCA using a standard diagnostic 1–4 MHz transcranial probe. Two weeks later, they underwent a CDM of the radial artery (RA) and, 4 weeks thereafter, a standard neurosonological examination (NSE). Plasma levels of tissue plasminogen activator (tPA), α-2-antiplasmin (AP), plasminogen (Pg) and plasminogen activator inhibitor-1 (PAI-1) were examined before, at the end and 24 hours after a CDM or

NSE. Student's t-test and Wilcoxon signed ranks test were used for statistical evaluation.

Results: In stroke patients, a significant decrease of PAI-1, Pg and AP activity by a mean of 60, 32 and 24% resp., and an increase of tPA antigen by a mean of 56% was found after a CDM of the MCA when compared to ST group and the healthy volunteers after the MCA CDM ($p < 0.05$ in all cases). In healthy volunteers, PAI-1, AP activity and tPA antigen significantly decreased after a CDM of the MCA by a mean of 27, 5, and 8% respectively ($p < 0.05$ in all cases), with values normalization within 24 hours. After a CDM of the RA in healthy volunteers, only a significant decrease in PAI-1 and AP activity by a mean of 17 and 3% was found ($p < 0.05$). Standard NSE did not affect any of the measured factors. No adverse events were recorded.

Conclusion: Continuous Doppler monitoring using a diagnostic 1–4 MHz duplex transcranial probe may affect the fibrinolytic system in humans.

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Correlation between trancranial colour-coded sonography, CT angiography and digital subtraction angiography in stroke patients

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Objectives: Atherosclerotic affection of cervical and cerebral arteries is one of the most common causes of ischemic stroke. Various neuroimaging methods could be used for vascular pathology detection. The aim of the study was to compare intracranial vessel findings in stroke patients performed with three different examination methods—transcranial color-coded sonography (TCCS), CT angiography (CTA) and digital subtraction angiography (DSA) within 2 months.

Methods: An uni-center, retrospective study was performed. Thirty-five patients, who fulfilled the inclusion criteria, were involved in the study (25 males, age 23–79, mean 59.65 ± 12.33 years). All patients were hospitalized during the 12 months (January 2007 to December 2007) and all of them underwent TCCS, CTA and DSA angiography within 2 months. Internal carotid artery, M1 section of middle cerebral artery (M1), A1 section of anterior cerebral artery and P1 section of posterior cerebral artery (P1) on both sides were examined. Findings were divided into four groups: normal, stenosis <50%, stenosis 50–99% and occlusion. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values and Cohen's kappa were statistically evaluated for comparison of all three methods.

Results: Due to technical circumstances or insufficient temporal bone window 226 of together 280 vessels were evaluable. Sensitivity, specificity, PPV, NPV of CTA and TCCS in comparison with gold standard DSA were 75, 98.6, 80, 98.1 and 81.3, 96.2, 61.9, 98.5% resp. CTA and DSA findings were in concordance in 96.02% vessels, Cohen's kappa = 0.694. TCCS and DSA findings were in concordance in 94.25% vessels, Cohen's kappa = 0.628. CTA and TCCS findings were in concordance in 94.25% vessels, Cohen's kappa = 0.619.

Conclusion: A substantial agreement was found between all three methods. Two of evaluated methods are sufficient for diagnosis when consenting, when not the third method should be implemented.

P280

Clinical-imaging study and therapeutic aspects in the cardioembolic stroke

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Objectives: evaluation of frequency of the cardioembolic stroke in contrast with other ischemic strokes, the specification of major sources of embolism, imaging and therapeutic aspects, as well as the estimation of some evolutionary aspects on the ground of neurological factors and comorbidity.

Methods: we have studied 522 patients, interned to the Clinical Neurology nr. 1 in Targu Mures in the 1 June 2007 to 30 May 2008 period, with the diagnosis of ischemic stroke. Based on the clinical and neuroimaging data, we have observed the following types of ischemic strokes: atherothrombotic ischemic stroke 71.64%; cardioembolic ischemic stroke 25.28%; stroke with undefined mechanism 3.08%.There have been defined patients having cardioembolic stroke who have met the following conditions: (1) they presented potential sources of cardioembolism; (2) neurological deficit with sudden entrance; (3) the absence of suggestive clinical and neuroimaging data referring to a significant cervicocranial occlusive disease.

Results: We have found cardioembolic stroke at 132 patients (26.08%) out of which there were 50.76% female and 49.24% male. The primary sources of cardio emboli we met, were the atrial fibrillation 75.75%, myocardial infarction 25.75% and in smaller percentage valvular heart disease, dilated cardiomyopathy, patent foramen ovale a.s.o. The primary risk factor was the high blood pressure (91.7%), followed by hypercholesterolemia (37.1%), dyslipidemia (27.27%), ischemic stroke in the history (15.9%), obesity (10.6%). Based on the data we obtained from exploring the CT at the moment of internation 43.53% of the patients didn't have recent lesions. The most of the lesions were found in the territory of vascularization of the left middle cerebral artery (12.1%). During the extra- and transcranial ultrasound Doppler examination 11.36% of the patients did not show any signs of atheroma and 88.63% had insignificant wounds lesions. 46.84% of the patients had antiplatelet and anticoagulant treatment, and 45.04% were without any treatment. A number of 21 patients (15.9%) have shown recidivated cardioembolic stroke.

Conclusions: The cardioembolic stroke has a significant percentage regarding cerebrovascular illnesses, and the clinical-neurological and non-invasive examination is very important at the diagnosis.

Clinical neurophysiology

P281

The protective effect of vitamin E on locus coeruleus in early model of Parkinson's disease in rat: immunoreactivity evidence

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Objective: Free radical formation and oxidative stress might play an important role in the pathogenesis of Parkinson's disease (PD). In vitro data indicate that neuromelanin (NM) pigment is formed the excess cytosolic catecholamine that is not accumulated intosynaptic vesicles via the vesicular monoamine transporter 2 (VMAT 2). We

designed this study to investigate the neuroprotective effects of vitamin E in the early model of PD.

Methods: Male rats ($n = 40$) with unbiased rotational behavior were randomly divided into five groups: sham operated group (SH, $n = 8$), vehicle-treated SH group (SH + V, $n = 8$), vitamin E-treated SH group (SH + E, $n = 8$), vehicle-treated lesion group (L + V, $n = 8$) and vitamin E-treated lesion group (L + E, $n = 8$). Unilateral intrastriatal 6-hydroxydopamine (12.5 μl) lesioned rats were treated intramuscularly with α-tocopherol acid succinate (24 I.U/kg, intramuscular [i.m.]) 1 h before surgery and three times per week for 2 month post-surgery. To evaluate the vitamin E pretreatment efficacy, tyrosine hydroxylase (TH) immunoreactivity and immunostaining intensity (ISI) for monoamine transporter 2 were used.

Results: TH immunohistochemical analyses showed a reduction of 20% in locus coeruleus (LC) cell number of vitamin E pretreated lesioned group but the cell number dropped to 60% in the lesioned group. The ISI of the cells was measured for VMAT2 in LC.
Lesioned groups:

1. had the lowest VMAT2 ISI of all neurons;
2. There was an inverse relationship between VMAT2 ISI and NM pigment in the locus and
3. Neurons with the highest VMAT2 ISI also had high TH ISI.

Conclusion: The data support the hypothesis that repeated i.m. administration of vitamin E exerts a protective effect on the LC neurons in the early model of PD.
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P282

Addressing the predictivity of electrophysiological biomarkers in SCA2: 20-year long-term follow-up study

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Objectives: (1) To delineate the degenerative pattern in peripheral nerves in SCA2. (2) To asses the predictive value of Electrophysiological parameters as progression markers. (3) To identify early alterations in non-symptomatic first degree with SCA2 mutation.

Methods: 202 patients from 56 families with SCA2 and Fifty five non-symptomatic first-degree relatives of SCA2 patients were studied 6 times during 20 years by motor and sensitive nerve conduction studies and multimodal evoked potentials as well.

Results: The most consistent findings were the reduction in amplitude or absent in sensitive potentials and the increase in absolute latency of P40 component. Our data shown the structures of the nervous system are involved before any clinical symptom and/or sign appear. This allows us defining four stages in the evolution of this disease: first: normal electrophysiological parameters. Second: decrease in the amplitude of the sensitive potentials, increase in the absolute and interpeak latencies in the SSEPs, and abnormal morphology in the BSAEPs. Third: increase electrophysiological abnormalities, which correspond with the first clinical manifestation of the disease and fourth: both, peripheral and central afferent conduction blocks appear, expressed by absence of the response in sensory conduction nerve studies and in SSEPs. This classification of the disease in different stages allows to know the degenerative process during the evolution of the disease of the afferent and efferent systems. Also, the existence of electrophysiological abnormalities in non-symptomatic subjects permits to choose the optimal moment for the evaluation of a specific therapeutic treatments

Conclusion: Our electrophysiological results agree with the loss of ganglion cells in the dorsal root ganglia. This study have point out to a close association among CAG mutation and electrophysiological alterations, ending with a total blockade of the afferent conduction as a sign of severe neurodegeneration. The molecular substrate is linked with increase of ataxin-2 toxicity accounting for more neuronal neuronal loss in the Peripheral and Central Nervous System.

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P283

The endophenotype versus genotype damage: saccade latency assessing the toxicity of polyQ after neurocognitive rehabilitation in SCA2

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Objective: To evaluate the efficacy of rehabilitative therapies by using the endophenotype (Saccade Latency).

Methods: Availability of a large cohort of 90 patients were rehabilitated in our specialized ataxia clinic during 6 months. After and before evaluation was performed by using ataxia rating scales (SARA, ICARS) and Saccade Latency was recorded using Ottoscreen apparatus.

Results: A large follow up assesment—6 months—of neurocognitive rehabilitation showed the qualititative and quantitative improvement of saccade in SCA2 mutation carriers debuting with ataxia and the principal markers of SCA2. Saccade Latency improvement was dependent of SCA2 modifiers.

Conclusions: Future restorative strategies addressing cognition improvement in SCAs with subtle changes on cognition must appreciate the usefulness of endophenotype due to sensibility and the link with targeted SNC structures. Rehabilitative medicine in presymptomatic stages must be assessed by using endophenotype.

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P285

Mirror movement and ipsilateral motor evoked potentials to transcranial magnetic stimulation in a stroke patient: a case report

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Objective: To investigate the physiopathology of mirror movements (MMs) using focal transcranial magnetic stimulation (TMS) in a stroke patient.

Methods: A 67-year old patient affected by a right sylvian stroke, with no history of MMs underwent clinical (MRC, Nine Hole Peg Test-NHPT; Martin's Vigorimeter) and neurophysiological examination one week (T0) at one month (T1) after standard neurorehabilitation treatment. Bilateral TMS cortical mapping, with simultaneous recording from three upper limb muscles (abductor pollicis brevis, APB; abductor digiti minimi, ADM; extensor carpi radialis, ECR) was performed, with MEPs amplitude (MA) and number of responsive sites (RS) measurement. Mirrors to isometric contraction of the same muscles of both sides were measured using surface EMG.

Results: MMs were observed to voluntary movement of both the unaffected and affected hand. MMs were greater to movement of the

non paretic side, both at T0 and T1. Left hand function improved over time (MRC: 4½ vs. 5; NHPT: 41″ vs. 30″, Vigorimeter: 0.4 vs. 0.5) while right hand function resulted unchanged. At T0, MT was 65% of maximal stimulator output bilaterally. At stimulation intensity, contralateral-MEPs (cMEPs) were evoked in all three muscles during stimulation of unaffected (UH) (RS:11.4 + 4.1; MA:236.4 + 77.8) and affected hemisphere (AH) (RS:9 ± 2; MA:217.4 ± 54.6). iMEPs were evoked in ECR (RS:6.0; MA:98.5) to UH stimulation and in ADM (RS:6.0; MA:106.5) and ECR (RS:1.0; MA:51.0) during AH stimulation. At T1, even with 5% MT reduction on UH, cortical representation of the three cMEP (RS:10 ± 1.7; MA:395.6 ± 125.4) and of ECR iMEPs (RS:10; MA: 342) increased. Instead, stimulation of the AH at the same SI than T0 showed reduced cMEPs (SR:2; MA:55) and iMEPs (ADM RS:2; MA: 62).

Conclusion: iMEPs in stroke patients have been reported, often to high stimulation intensities or with background muscle contraction, often associated with poor clinical outcome. In the present case, iMEPs over UH increased over time together with functional improvement of the affected limb. Moreover, MMs were more evident to movement of the unaffected limb compared with the affected. We can hypothesize that the stroke was associated to increased excitability of the ipsilateral corticospinal pathway, increasing with clinical improvement. It can be hypothesized that reduced excitability of the AH at follow-up could be related to increased transcallosal inhibition from the expanded UH.

P286

Correlation between simple movement performance and cortical activation in healthy ageing

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Objectives: Normal aging is associated with several modifications in the cerebral motor system whose effect has been widely investigated with fMRI, PET and EEG. Age related differences, detected particularly when similar performance is achieved or when movement were more complex, reflect into an increased and more bilateral activation in elderly subjects. In addition, several studies reported a significant slowing in motor execution in the elderly subjects. Aim of this study is to identify areas and periods showing age-related cortical activation changes and to correlate them with movement performance.

Methods: Twelve young and nine elderly healthy right-handed subjects performed a self-initiated brisk right thumb extension during 32-channel EEG recording. The aging-effect over cortical generators of movement-related-cortical-potentials (MRCP), reconstructed using cortical current density (CCD) on a realistic volume conductor, was evaluated in five different periods and in mesial and lateral motor-related areas. Pearson partial correlations among age, CCD and movement initiation and termination were performed.

Results: Two mechanisms of activation increase emerged. All subjects increased their mean activity passing from late preparation to execution. Elderly subjects, consistently with neuroimaging studies, also recruited new sub-regions inside the same area. Their over-activation mainly occurred during late preparation in those areas related to simple movements (caudal mesial areas and both sensorimotor cortices) and in contralateral sensorimotor cortex during the movement evoked phase. During the latter, rostral mesial areas were less activated in elderly compared with young subjects. After removing the age effect, positive Pearson partial correlations were found between movement initiation and cortical activity in caudal mesial areas and ipsilateral sensorimotor cortex. Conversely, negative partial correlation was found between movement termination and pre-SMA activity.

Conclusion: The elderly over-activation within areas involved in control of simple movement, together with reduced movement performance, is more likely related to their reduced selectivity in activating the motor cortex, rather than to a compensatory mechanism aimed at optimizing performance. The correlation between a longer movement duration and pre-SMA activity suggests its involvement in movement termination.

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Reduced integration of cortical representation of hand muscles with ageing: a TMS study

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Objectives: To evaluate effects of aging on motor cortical representation using focal transcranial magnetic stimulation (TMS) mapping.

Methods: We studied a group of 30 right-handed healthy volunteers subdivided into two groups: 14 younger (aged 25.5 ± 1.8) and 16 older (aged 61.3 ± 5) by transcranial magnetic stimulation. We performed cortical mapping of three hand muscles (abductor pollicis brevis, abductor digiti minimi and extensor carpi radialis). We analyzed: (a) the number of responsive sites (RS) for each muscles; (b) the whole hand area (WHA) as the topographic surface *covered* by the three maps; (c) the degree of overlap measured as the ratio between (b) and the average of (a). Motor performance was evaluated using the Nine Hole Peg Test (NHPT).

Results: Both groups had a greater RS in the dominant hemisphere (DH) than in non-dominant one ($p = 0.007$ in younger and $p < 0.001$ in older; paired t test) but no WHA difference was found in between the two sides. On superimposed map representations of the three muscles we found in both groups a significantly greater degree of overlap in DH compared to nDH ($p = 0.03$ in both groups, paired t test). However, overlap was less evident for DH of older group compared to the younger one ($p = 0.03$, unpaired t test). At NHPT, the right hand was faster than the left in both groups ($p = 0.001$, paired t test) and younger performed the motor task better than older with both hands. The degree of overlap of the non dominant hemisphere in the whole group was correlated to NHPT performance ($r = 0.6$, $p = 0.001$; Pearson correlation).

Conclusions: In our findings, hand dominance and hand performance is associated to a higher degree of overlap within the hand muscle representation, possibly resulting from simultaneous integrated activation during skilled movements. In healthy aging, even with preserved hemispheric dominance of hand representation, the ability to integrate the representation of single muscles is reduced.

P288

Vestibular evoked myogenic potentials in patients with cerebellar infarction

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Vestibular evoked myogenic potentials (VEMP) have been known to useful in documenting abnormality in patients with various vestibular disorders but the studies of VEMP in cerebellar

infarction patients are rare. We recorded VEMP in eighteen patients with acute ischemic stroke in the cerebellum. The main outcome measures of VEMP were recorded in all subjects and findings in patients group were compared with our normal laboratory data. VEMP abnormalities were found in 72%(13/18) of acute cerebellar infarction patients. In ten patients, abnormalities were recorded on ipsilateral side of lesion and recorded on contralateral side in three patients. Sorting by vascular territory, abnormalities were found in 83%(10/12) of PICA territory infarction, 50%(2/4) in AICA territory, 50%(1/2) in SCA territory. Follow up studies which were performed three months later revealed recovery of waves in 69%(9/13) of patients. VEMP would be considered a useful complementary neurophysiological tool for the evaluation of vestibular-cerebellar circuit in cerebellar infarction patients

Pain and headache

P289

Call-Fleming syndrome secondary to simultaneous intake of sibutramine and fluoxetine

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Objectives: To report the clinical case of a patient who developed diffuse reversible segmental cerebral arteries constriction as a consequence of concomitant intake of two vasoconstrictive drugs and, in that way, alert for the risk of associating drugs with vasoactive effects.

Methods: We reviewed the clinical files of a patient with Call-Fleming Syndrome secondary to the association of Sibutramine to chronic treatment with Fluoxetine.

Results: A 48 year-old woman with no previously known vascular risk factors or personal history of migraine was admitted in the Emergency Room for holocranial headache of sudden onset, continuous, with severe intensity, associated with motor aphasia and diplopia. A cranial computerized tomography was performed showing various hypointense lesions of the white matter, predominantly in the left, compatible with vascular or demyelinating lesions. A posterior cranioencephalic magnetic resonance imaging showed multiple paraventricular and pontine lesions with increased T2 signal, normal or decreased T1 signal, not enhancing after gadolinium injection. Biochemical, serologic, auto-immune and cytological work up including screening for oligoclonal bands in the cerebral spinal fluid were performed and results were all negative/normal. Visual evoked potentials were normal. Cerebral angiography and cervical MRI performed later, while asymptomatic, did not show any changes.
The patient's medical background was positive for a chronic depressive syndrome for which she was treated with Fluoxetine. In the last 2 years she reported intermittent intake of Sibutramine and recurrent headaches. Considering the possibility of iatrogenic cerebral vasospasm, both drugs were suspended with marked clinical and imagiologic improvement.

Conclusion: Several reports showed that vasoactive medications can lead to Call-Fleming Syndrome. In this case, the simultaneous intake of these drugs led to a potentiation synergism, resulting in cerebral vasoconstriction. The normal angiographic study allowed to exclude large or medium vessel pathology. Considering the widespread use of antidepressive drugs, the vigilance of the patients' full medical treatments gains importance to avoid potentially hazardous interactions.

P290

Spontaneous intracranial hypotension: clinical and imaging spectra

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Background: Spontaneous intracranial hypotension (SIH) is an uncommon, but increasingly recognized, syndrome. It can be spontaneous or symptomatic, being the former rare. According to Monro-Kellie doctrine, the reduction of CSF volume causes distortion of pain sensitive vascular structures, a phenomena increased by gravity when assuming the upright position. Typical imaging findings consist of subdural fluid collections, pachymeningeal enhancement, pituitary hyperaemia and brain sagging.

Objectives: To describe clinical and imaging characteristics, treatment and follow-up of SIH patients.

Methods: Clinical revision of all SIH patients observed at our hospital. All secondary SIH cases were excluded. All patients had brain/spinal imaging exams.

Results: There were three patients with spontaneous SIH criteria: two men and one woman, with 37, 44 and 47 yo. They presented with orthostatic headache that relieved with supine position. There was previous minor head trauma. On neurological examination, one presented with left sixth nerve paresis and neck rigidity. CT was abnormal on patient 1 and 2, and normal on the third. MRI showed bilateral subdural hemorrhage and tonsilar descendent into the foramen magnum (1 and 2) and diffuse thickening of intracranial dura, with gadolinium enhancing (2). On patient 3 there was only meningeal enhancement.
All patients had abnormal spine MRI: patient (1) thickening of dural sac, more prominent on dorsal portion, with epidural film. Patient (2) diffuse thickening of spinal dura, without obvious CSF leak. Patient 3 had at C2-C3 level intradural and extradural enhancing, reflecting epidural venous plexus engorgement. Patients were treated with prolonged supine position, abundant oral fluid intake, caffeine and indomethacin. There was clinical improvement, without invasive measures.

Comments: If the symptoms are typical MRI should be done. Patients 1 and 3 had indirect signs of CSF spinal leak, on spinal MRI, that agrees with what is described in the literature, being the most frequent cause of spontaneous SIH. All patients had a benign course despite conservative treatment.

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Lifetime anxiety symptoms in migrainous vertigo

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Objective: To investigate the correlation between balance tests and lifetime panic agoraphobic spectrum scale in patients with migranous vertigo.

Background: Recent studies suggest that there is a link between vestibular and anxiety disorders.

Method: Balance tests and panic attack and agoraphobic scales were evaluated in 26 migrainous vertigo patients recently seen in our neurotology outpatient and compared with control group. There were 22 women and 6 men in the patient group. All patients had migraine diagnosis according to the International Classification of Headache Disorders II. All of them were referred to neurootology outpatient clinic with vertigo, dizziness and imbalance complaints. After neurootological examination 19 had vestibulopathy.

There were 6 women and 6 men in the control group. Balance tests were Berg balance scale (BBC), dizziness handicap inventory (DHI), activities specific balance confidence scale (ABC), SF 12 health quality scale, functional reach test, timed up and go test, five times sit to stand test, falls efficacy scale (FES), dynamic gait index (DGI), functional gait assessment (FGA). Lifetime panic agorophobic spectrum scale were given to both patients and controls.

Results:

1. There were not a significant difference between ages of patients and controls.
2. Patients and controls were significantly different in balance tests and lifetime panic agoraphobic spectrum scale.
3. There was a significant difference in correlation between lifetime panic agoraphobic spectrum scale and DHI, ABC and SF 12 health quality scale.

Conclusion: Our results show that migrainous vertigo patients have more self-perceived balance problems which are correlated with the lifetime panic agoraphobic spectrum scale.

P292

You may lie during quantitative sensory testing, but your skin won't!

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Objectives: Quantitative sensory testing (QST) reflects subjective appraisal of thermal sensation, but does not provide objective documentation of physiological changes. We examined how fluctuations in sudomotor autonomic activity correlate with warm and heat pain perception.

Methods: In 22 healthy volunteers, we applied various protocols of thermal stimuli and recorded the electronic visual analog scale (VAS) and the sudomotor activity by means of surface electrodes attached to the hand. We considered two measures: the mean level of electrodermal activity (meanEDA) and the sympathetic skin response (SSR). For the analysis of EDA, we considered four different VAS-based phases according to the segments defined by relevant psychophysical marks.

Results: In all stimuli paradigms, SSRs appeared at a mean delay of 1.6 s after subjects marked either warm or pain sensations. There was an association of low amplitude predominantly negative SSR with warm stimuli, and of large amplitude predominantly positive SSR with heat pain stimuli (chi-square; $p < 0.05$). MeanEDA was significantly higher during the pain phase in comparison with pre-perception, warm and post-perception phases.

Conclusion: Thermoalgesic stimuli induce reflex changes in sudomotor activity that are well correlated with subjective perception of warm and heat pain sensations. This association brings additional information on physiological consequences of the stimuli, which could offer interesting possibilities for clinical practice.

P293

A migraine survey in the informatics sector

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Objectives: Migraine attacks have been reported to be induced by elementary and complex light stimuli.Moreover light stimuli may not only be a migraine trigger but also an overloading factor for a sensitive migraine brain.Among the eye strain factors induced by light, computer screens gain importance every other day.

Methods: We conducted a questionnaire in collaboration with Turkish Informatics Association and Statisticians Association among the employees of the informatics sector.The three item ID MigraineTM screener test which has been accepted with a 91.8% sensitivity and 63.4% specificity in migraine diagnosis was asked to participants besides their sex, occupation, years passed in informatics sector, total time computer used in a day and monitor properties.

Results: 216 participants' answers were eligible for data entry and analysis.65% was male and 35% was female.37.5% of informatics sector employees (44.4% female and 55.6% male) have been diagnosed as having migraine on the basis of their answers in ID MigraineTM screener test.The prevalence of migraine diagnosis among women was 47.36% and among men was 32.14% ($p = 0.027$).They have been working in informatics sector a mean of 11.69 ± 0.77 years and have been using computer actively a mean of 9.23 ± 0.3 h a day.Desktop computer has been used by 36.1% and laptop by 39.2% of the migraineurs.Their monitor types were TFT-LCD (Thin Film Transistor Liquid Crystal Display) in 38.2% and CRT (Cathode Ray Tube) in 33.3%. Migraine was diagnosed mostly in more stressful occupations in the sector such as project manager (14.8%), sales manager (14.8%), software developer (12.3%) and hardware and database expert (11.1%) and others.

Conclusion: In our study both the migraine prevalence rates in the informatics sector and among male and females employees were higher than normal population.As classically females suffered from migraine more than males in this sector also.Migraine prevalence among males was strikingly high.It has been observed that computer type (laptop/desktop, $p = 0.65$) and monitor type (TFT-LCD/CRT, $p = 0.61$) were not triggers of migraine.Different occupations in the informatics sector have different migraine prevalences but there is not a statistically meaningful difference between them.In our questionnaire migraine diagnosis has been made according to the ID MigraineTM screening test.With our results we aim to put forward the high prevalence of migraine in informatics sector.

The survey has been conducted in association with Turkish Informatics Association and Statisticians Association.

P294

Effect of lamotrigine in the rat cortical spreading depression model of migraine with aura: correlation between electrophysiological data and FOS immunoreactivity

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Background: In 20% of migraine patients the attack is preceded by an aura, which is likely due to Leao's cortical spreading depression (CSD). There is some evidence that lamotrigine (LTG) is an effective preventive treatment for migraine with aura, but not for migraine without aura.

Objectives: To compare in the rat model of KCl-induced CSD the effect of LTG on occurrence of CSDs and Fos expression in the cortex.

Methods: Male Sprague–Dawley rats received daily IP injections of LTG (15 mg/kg in DMSO) or its vehicle DMSO (0.5 ml/kg) or

saline (1 ml/kg) ($n = 6$, 5 and 7) during 4 weeks. CSD was elicited under chloral hydrate anaesthesia by applying 1 M KCl over the occipital cortex with a cotton ball. The electrocorticogram (DC-100 Hz) was recorded for 2 h ipsilaterally from occipital and frontal cortices (bregma R + 2, P-4 and A + 1) at a depth of 1 ± 0.2 mm. Fos expression was assessed by immunohistochemistry. Fos-immunoreactive nuclei were manually counted on the side of the stimulation in the frontal cortex on coronal sections (bregma A + 1 ± 0.2) at a depth of 0, 1–2 mm from the cortical surface. All labeled cells were counted regardless of staining intensity.

Results: LTG significantly inhibited CSD occurrence at the frontal recording site (1.6 ± 0.3 CSDs/h) in comparison with DMSO (4.5 ± 0.4 CSDs/h). Fos immunoreactivity was markedly increased in the stimulated hemisphere compared to the non-stimulated one, with maximum of expression at the depth of 0.3 mm. Rats treated with LTG had a two to three times smaller expression of Fos in the frontal cortex at depths of 0.9–1.6 mm (cortical layers 5 and 6). In the NaCl-treated group there was a significant correlation between the number of CSD in the 2nd hour and Fos expression at depths where the expression of Fos was maximal: 0.3–0.7 mm (cortical layers 2, 3 and 4) and 1.3–1.6 mm (layer 6)

Conclusion: CSD predominantly activates neurons in superficial cortical layers. Lamotrigine which prevents migraine with aura attacks in patients, inhibits occurrence and propagation of KCl-induced CSD in rat. This effect is supported by a significant decrease of Fos expression in the cortex. It is thus likely that the LTG-induced CSD inhibition is responsible for its selective therapeutic effect in migraine with aura.

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P295

Sumatriptan powder delivered by the OptiNose™ nasal device provide excellent sustained pain-free plus no adverse events scores in acute migraine

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A new composite endpoint has been developed to allow comparison of different migraine headache treatments. The endpoint combines Sustained Pain-Free (SPF) defined as freedom from pain within 2 hours, with no use of rescue medication or headache recurrence within a period of minimum 24 h and the absence of adverse events (AEs) over the same period. The new composite endpoint SPF plus no AEs (SNAE) is defined by SNAE = SPF (1-AE) (Dodick 2007). Delivery of 10 and 20 mg sumatriptan powder using the novel OptiNose nasal device has shown excellent pain relief at 2 h and SPF rates. The results compare favourably with all marketed triptan formulations. Rapid absorption (Tmax = 20 min) as well as possible direct nose-to-brain transport may explain the excellent clinical results despite minimal systemic exposure (AAN 2008, Poster 07 039).

Objectives: To calculate the SNAE for the sumatriptan succinate powder delivered with the OptiNose nasal device and compare the results with marketed triptan formulations and new migraine therapies.

Methods: We used previously reported results from an in-clinic three-armed placebo controlled phase II study with 10 and 20 mg sumatriptan powder in 110 migraine patients (1:1:1) delivered with the novel OptiNose nasal delivery device to calculate SNAE rates and compared them to published data (AHS 2008, Poster LBS70).

Results: The absolute SPF rates at 48 h were 47.4 and 48.6% and absolute AE rates were 17.9 and 23.1% for the 10 and 20 mg doses, respectively. The most common side effect was a bitter taste accounting for the majority of AE's (10.3, 12.8% respectively). The SNAE rates for 10 and 20 mg OptiNose nasal sumatriptan powder were 38.9 and 37.4%, compared with a median of 13% (range 6–22%) for marketed oral triptans, 18.3% for the new sumatriptan/naproxen combination (85/500 mg) and 25.6% (Phase II) and 12.7% (Phase III) for a new oral CGRP-antagonist (300 mg telcagepant).

Conclusion: Due to the high SPF rates and low AE rates for the OptiNose nasal sumatriptan powder, the SNAE becomes higher than all marketed triptan formulations, a new sumatriptan/naproxen combination and a new oral CGRP-antagonist (telcagepant). The SNAE results must be interpreted with caution, but if confirmed in future studies, the fast onset of action coupled with superior SNAE results suggest that nasal delivery of sumatriptan powder with the OptiNose device offers the attributes considered most relevant to patient satisfaction and safety.

Per G Djupesland is CSO and shareholder in OptiNose AS sponsoring the study.

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CADASIL and International Classification of Headache Disorders: do we need a new category?

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Objectives: Headache in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) was coded according to the classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain (ICHD), among the Headaches associated with other vascular disorder (6.9) and according to the International Classification Of Headache Disorders, second edition (ICHD-2), is now coded among the Headaches attributed to cranial or cervical vascular disorder (6.7.1). Our aim is to verify the external consistency and appropriateness of the ICHD-2 criteria in the different papers published.

Methods: A bibliographical search and review was conducted on Medline/Pubmed for papers published between 1993 and 2008 including patients diagnosed as affected by CADASIL.

Results: We identified 82 papers; 48 papers were excluded since they included patients already reported in other studies by the same authors. Included papers reported 356 CADASIL patients diagnosed as suffering with any migraine and 31 with headache. Among the 356 migraineurs, 111 (31.2%) suffered from migraine with aura, 7 (2%) from migraine without aura, 7 (2%) from migraine with prolonged aura, 5 (1.4%) from hemiplegic migraine, 2 (0.6%) from basilar migraine, 156 (43.8%) from unspecified migraine, and 68 (19%) from more than one type of migraine. We also analyzed whether migraine was the first symptom of CADASIL; after excluding papers without this information, there were 81 patients suitable for the analysis. Among them, migraine was the first symptom in 66 (81.5%) while 9 (11.1%) had a previous stroke or TIA and 6 (7.4%) other symptoms. In the 31 patients who had headache, this was classified as unspecified in 18 (58.1%), as chronic in 6 (19.3%), as resembling migraine with aura in 4 (12.9%), as resembling migraine without aura in 2 (6.5%), and as tension type in 1 (3.2%) patient.

Conclusion: In the considered papers, no headaches in patients with CADASIL were coded according to the ICHD or ICHD-2. The most common form of headache in those patients was migraine; besides considering that migraine is usually the first symptom of the disease, in our opinion it is inappropriate its classification as merely attributed to a vascular disorder. Consequently, we suggest to classify the headache in patients with CADASIL as Migraine attributed to

CADASIL to be included in a new more wide category of Migraine attributed to genetic disorder.

P297

Evaluation of cerebrovascular reserve in migraine patients

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Objectives: Cerebral vasomotor reactivity (VMR) is known as the vasodilatation capacity of cerebral arterioles to perfusion changes. We aimed to evaluate VMR in the anterior circulation, the posterior circulation and the ophthalmic artery in interictal period in migraine patients.

Methods: Breath holding index (BHI) calculated from bilateral middle cerebral artery (MCA), posterior cerebral artery (PCA) using temporal window insonation and ophthalmic artery (OA) using orbital window in 13 migraine patients and 10 age and gender matched healthy individuals.

Results: Breath holding index (BHI) was found 1.32 ± 0.53 in migraine patients and 1.60 ± 0.58 in control group for MCA, 1.23 ± 0.42 in migraine patients and 1.53 ± 0.47 ($p < 0.05$) in control group for PCA, 1.01 ± 0.53 in migraine patients and 1.19 ± 0.72 ($p > 0.05$) in control group for OA. There was no statistically significant difference between BHI for MCA ($p < 0.05$) and PCA ($p < 0.05$) while comparing of anterior and posterior circulation in migraine and control groups.

Conclusion: Current literature data on VMR in interictal period in migraine patients is contradictory. Frequently the increase of VMR was shown in literature but there are some studies suggesting the decrease and no change of VMR as our study. Consequently VMR is impaired in migraine patients. There is no study evaluating VMR of OA in migraine patients. Our results show that there is no relationship between attenuated cerebral VMR and OA in migraine.

P298

Is paediatric headache correctly diagnosed in time? A cross-sectional outpatient survey

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Objective: The aim of our study is to evaluate in a pediatric outpatient survey the latency occurring between the onset and the correct diagnosis of headache (according to IHS criteria).

Methods: We studied 91 patients (average age 11.6 years; 65% female) consecutively enrolled at a first visit in a 9 months observational period. Patients and parents were submitted to a semistructured interview to evaluate headache characteristics and the diagnostic procedures.

Results: The average latency between the onset of Headache and the diagnosis according to IHS criteria is 24 months (median = 12 months). A positive familiar history of headache is associated with a more delayed diagnosis ($p = 0.08$, Mann–Whitney; 24 vs. 12 months). Males are usually diagnosed earlier than females (median:12 vs. 18 months; trend $p = 0.07$). A correlation between age and delay in diagnosis is present ($p = 0.009$, $R = 0.27$, Pearson). Furthermore, children with a diagnosis of MWA (19%) are diagnosed earlier (median 8 months) than those presenting with other headaches (median MWA 12, MWoA 18, TH 10 months; ns difference with Kruskal–Wallis test). The first specialist's evaluation was neurological in 45% cases, ophtalmological in 31.8%, ENT in 12% and others in 11.2%. The main reason for presenting to neurologist is the increase in frequency of attacks (49%) or a correct diagnosis (31%). The 18% of our population was misdiagnosed (epilepsy 43%, sinusitis 38%, other 19%) leading to a later diagnosis (median = 21 months). No differences in misdiagnosis percentage are noticed into the subgroups (TH 15%, MWA 15 %, MWoA 17%, $p = 0.99$ Chi-Square). Patients with the presence of childhood periodic syndromes (16.5%) have been examined even later than the others (delay:27 months, median = 18). Almost half of patients (49%) were not suggested to undergo further investigations. No difference is underlined even if an instrumental examination is performed. Therapy was prescribed preferentially by the neurologist (63%) to the 56% of patients. Furthermore, children suffering from headache visited in the last two years are subjected to an earlier diagnosis (Spearman $R = -0.74$, $p < 0.0001$) probably due to the increased awareness of the specialist about the disease.

Conclusions: We underline how the knowledge of the correct criteria for Headache diagnosis is still not completely exhaustive, both between paediatricians and the different specialists, being paediatric headaches easily misdiagnosed and delayed in their clinical definition.

P299

Isolated trigeminal nerve neurosarcodosis masquerading as trigeminal schwannoma

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Objective: To describe a case of isolated trigeminal neuropathy secondary to neurosarcoidosis. The neurological manifestations of sarcoidosis are uncommon, occurring in 5% of patients with the condition. Isolated cranial nerve injury is rare and typically involves the seventh cranial nerve. Sarcoid of the trigeminal nerve is exceedingly rare.

Design/methods: We describe the clinical, radiological and neuropathological features of a patient with isolated trigeminal sensory neuropathy secondary to neurosarcoidosis.

Results: A 40 year old lady presented with subacute onset of numbness of the left side of her face associated with sharp pain in the same distribution. Examination showed impairment of light touch, pinprick and temperature in the first and second divisions of the trigeminal nerve. Corneal reflex was intact. Past medical history was notable for pulmonary sarcoidosis diagnosed 20 years previously based on presence of erythema nodosum and hilar lymphadenopathy. She was not on any treatment.

Extensive laboratory investigations, CT thorax and cerebrospinal fluid analysis were all within normal. Magnetic resonance (MR) brain imaging revealed a high signal abnormality on T2 W images and post contrast enhancement on T1 W images in relation to Meckel's cave on the left side extending along the course of the left trigeminal nerve. The appearances were highly suggestive of trigeminal schwannoma.

A tapering course of steroids resulted in an incomplete and transient response. Biopsy of the trigeminal nerve lesion confirmed neurosarcoidosis. The patient was recommenced on steroids and azathioprine was added as steroid sparing agent. This resulted in clinical and radiological response which is stable to date.

Conclusion: Our search of the literature revealed that this is the fifth report of isolated involvement of the trigeminal nerve by sarcoidosis and though rare, it should be considered in the differential diagnosis of lone trigeminal nerve neuropathy.

P300

Mesencephalic glioma presenting with migraine with aura

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We report the case of a 25 year old male with no relevant previous medical history, who referred to the Emergency Unit complaining of left unilateral throbbing headache, associated with nausea and photo and phonophobia. Pain was preceded by flickering spots in his left visual field as well as paraesthesias in his left hand. Such symptoms appeared simultaneously and lasted 12 h, spontaneously disappearing a few minutes before the onset of headache.

Patient was diagnosed as suffering from a migraine with aura attack and was treated with Indomethacine 50 mg iv, with relief from pain. The day after he was referred to a neurologist for evaluation.

Neurological exam was normal, except for an apparent limitation of the gaze towards left. A CT scan was then performed and showed a midbrain hypodense lesion. Further analysis included Goldmann visual field analysis which showed left superior quadrantanopia and a brain MRI which showed a mesencephalic glioma involving right periacqueductal grey (PAG).

An association between brainstem lesions, such as those seen in MS, and an increased likelihood of migraine has already been reported. Moreover, rostral brainstem, particularly the contralateral midbrain periaqueductal grey matter is considered to be one of the possible generators of migraine attacks, potentially by dysfunctional control of the trigeminovascular nociceptive system. Therefore, taking into account the correspondence between the side of lesion and the side of migraine, we hypothesized a role of the PAG in actually triggering such migraine with aura attack.

We report this case in order to highlight the role of PAG in the genesis of migraine, as well as to underline once again the crucial importance of performing neurological examination and spotting out aura atypical features in the differential diagnosis of migraine.

P301

Acute reversible myopia induced by low-dose topiramate: a case report

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Background: Topiramate is a neuro-modulatory molecule used for migraine prevention. Its effects on ocular pressure are well known, generally linked to preexistent glaucoma and in most cases in a dose dependent way.

Methods: We observed the appearance of acute myopia after 3 days of low-dose topiramate migraine prophylaxis in a young woman.

Case presentation: a 25 year-old Caucasian woman developed acute bilateral severe visual loss over 12 h. In the previous 3 days she had been treated with topiramate (25 mg/day) for migraine prevention. Visual acuity loss was enough severe to prevent face recognition; she was however still able to count fingers with both eyes. Intraocular pressure in left and right eyes was 30 and 31 mmHg respectively. Conjunctival chemosis and corneal edema were present. Topiramate was immediately stopped. After discontinuation, a near-complete resolution of the visual impairment was observed. Intraocular pressure dropped to 15 mmHg bilaterally. After three days visual acuity was normalized and conjunctival and corneal aspect were normalized.

Discussion: Topiramate is generally well tolerated, the main side effects reported being mild-moderate paresthesias and cognitive disturbances. The occurrence of elevated intraocular pressure and, less frequently, of acute angle closure glaucoma with myopic visual loss is well known, but generally this adverse event appears less quickly, most cases having occurred within 2 weeks since the start of the therapy. No known reports exist about the occurrence of glaucoma at the low dose of 25 mg daily and after only three days of treatment. Patients treated with topiramate and prescribing physicians need to be alerted about this uncommon side effect.

P302

Headache with neurological deficits and lymphocytic pleocytosis syndrome, an underestimated diagnosis?

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Objectives: We discuss the clinical and paraclinical features of 4 patients, admitted in a primary care hospital, with the diagnosis of headache with neurological deficits and lymphocytic pleocytosis (HaNDL) syndrome.

Methods: Retrospective study, over a two years period, of clinical and paraclinical data, including neurological status, complete blood analysis, brain magnetic resonance imaging (MRI), electroencephalogram (EEG), and cerebrospinal fluid (CSF) examination.

Results: The study included 2 males (cases 1 and 2) and 2 females (cases 3 and 4) patients, age ranging from 20 to 34 years old. A prior history of migraine was reported in cases 3 and 4. All patients developed daily migrainous headaches and transient neurological deficits over a period of 2 to 6 weeks. The neurological deficits lasted less than 12 h in the 3 first patients and 3 days in the case 4. They included confusion and aphasia (cases 1 to 3), alternating hemiparesis (case 2), and right hemiparesis with hemihypoesthesia (cases 3 and 4). All patients had diffuse slowing of the EEG, normal brain MRI, a mild CSF pleocytosis, varying from 56 to 182 lymphocytes per microlitre, and negative CSF polymerase chain reaction (PCR) for Herpes simplex viruses. Transcranial Doppler and brain HMPAO-single photon emission computed tomography were consistent with a cerebral vasoconstriction in case 3. Autoimmune and exhaustive anti-infectious serologies were negative in all patients, except for positive Cytomegalovirus Immunoglobulins-M in case 2 and transient low titers (1/80) of anti-Mycoplasma Pneumoniae antibodies in case 4.

Conclusion: HaNDL is known as a rare clinical disorder with a benign course. The disease has usually a total clinical recovery within a period of 8 to 12 weeks. This diagnosis should only be evoked after exclusion of other pathological conditions such as stroke, migraine with aura, viral encephalitis, and cerebral vasculitis. The relationship between HaNDL and some viral or bacterial infections remains controversial. The hypothesis of an autoimmune leptomeningeal vasculitis, similar to the immunoglobulin therapy-related aseptic meningitis, has been proposed. The observation of 4 HaNDL patients, over a 2 years period, in a primary care hospital led us to suspect that this diagnosis could be underestimated.

P303

Altered resting state networks in patients with cluster headache

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Objective: The assessment of low-frequency (< 0.1 Hz) fluctuations in functional magnetic resonance imaging (fMRI) data at rest has demonstrated the presence of high temporal coherence between spatially distinct, functionally-related brain regions, which characterizes the resting state networks (RSNs) of the human brain. Abnormalities within selected RSNs have been characterized in several psychiatric diseases and Alzheimer's disease, and more recently, in chronic pain conditions. In this study we wished to investigate abnormalities of brain RSNs in patients with episodic cluster headache (CH), outside the bout phase, in comparison with healthy individuals.

Methods: RS fMRI scans were acquired from 13 CH patients and 15 matched healthy controls. Independent component analysis (ICA) was used to decompose RS fMRI data into spatially independent maps and time courses using the GIFT software. This analysis produced 40 spatially independent maps. SPM2 was used to assess within- and between-groups activations (one-sample t test and ANOVA). Then, for each RS spatially independent map, the average percentage signal change of RS fluctuations of each significant SPM cluster was compared between controls and patients.

Results: We detected 11 RSNs with potential functional relevance. Significant between-groups difference were found for the sensorimotor network (decreased fluctuations in the primary sensorimotor cortex and supplementary motor area, bilaterally, in CH patients), and the primary visual network (decreased fluctuations in V1 in CH patients) (p values ranging from 0.03 to 0.007). No difference was found in the default mode network. RSNs abnormalities were significantly correlated with disease duration.

Conclusions: RSNs analysis reveals abnormalities of the visual and motor networks in CH patients outside the acute attack. These findings suggest a diffuse dysfunction of functional connectivity which extends beyond the antinoceptive system.

P304

Prophylactic treatment of chronic tension-type headache with trigger points. Comparison of gabapentin and local injection of Depomedrol

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Objectives: Chronic tension- type headache (CTTH) is one of the most common disorders affecting quality of life. Trigger points(TrPs) play an important role as a causative factor. Gabapentin and Local injection of trigger points with corticosteroids are noted to be effective in prophylactic treatment of (CTTH).

Materials and methods: We selected CTTH patients who had active trigger point in the head and divided them in two groups of Depomedrol and Gabapentin. Depomedrol was injected 10 mg per each TrPt up to total dose of 40 mg in each patient. Gabapentin was initiated with 200 mg/day and gradually increased to 300–600 mg daily.

Results: Headache Intensity × Duration index showed marked decrease in both groups. It was significantly lower in Depomedrol receiving patients at the end of first (368.13 ± 195.75 vs. 467.73 ± 203.09, $p < 0.05$) and second months (165.44 ± 62.75 vs. 238.68 ± 81.39 $p < 0.05$). similar superiority was detectable for intensity, duration and frequency of headaches.

Conclusion: We found trigger point injection more potent in comparison to daily Gabapentin. This superiority was statistically significant after 4 weeks and continued up to 8th week. It should be noted that trigger point injection was more effective to decrease all aspects of headache including intensity, duration and frequency.

P305

Health-related quality of life measures and psychiatric co-morbidity in patients with migraine

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Objectives: The identification of factors associated to health-related quality of life (HRQoL) measures in patients with migraine has major implications in terms of prognosis and treatment. This study aimed at investigating associations between HRQoL and comorbid mood and anxiety disorders.

Methods: Consecutive adult outpatients with a diagnosis of migraine with or without aura were assessed using the Mini International Neuropsychiatric Interview (M.I.N.I.) Plus version 5.0.0 and the Migraine-Specific Quality-of-Life Questionnaire (MSQ).

Results: Data of 112 patients (82 females), 69 without aura, mean age 41.2 ± 13.3 years were analyzed. According to the MINI, 50% patients had a lifetime or current DSM-IV diagnosis of mood or anxiety disorder. There was no between-groups difference in MSQ total and subscale scores in relation to the presence/absence of psychiatric comorbidity, independently whether that was current or lifetime. In the group of subjects with psychiatric disorders, age at onset of migraine correlated with MSQ-total (rho $= -0.407$ $p = 0.002$), and subscale scores (role function-restrictive, rho $= -0.397$, $p = 0.002$; emotional function, rho $= -0.487$, $p < 0.001$).

Conclusions: Our findings suggest that current and/or lifetime psychiatric comorbidities are not associated with HRQoL measures in patients with migraine. However, patients with migraine and psychiatric comorbidities may represent a specific subgroup deserving particular attention for targeted interventions.

P306

L-kynurenine combined with probenecid prevents the NTG-induced CGRP expression changes in the rat caudal trigeminal nucleus

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Objectives: One of the human models of migraine is the systemic administration of the nitric oxid donor nitroglycerin (NTG). It triggers a delayed attack without aura in many migraineurs but not in healthy volunteers. In the rat NTG (10 mg/kg bw) activates the second order nociceptive trigeminal neurons in caudal trigeminal nucleus (TNC). It decreases there the expression of the calcitonin gene-related peptide (CGRP), a key molecule in migraine and pain conditions, probably due to the activation of the trigeminal primary nociceptive afferents. Kynurenic acid (KYNA), a derivate of tryptophan metabolism, may have a modulatory effect in many neuropathological conditions via its N-methyl-D-aspartate (NMDA) antagonism. L-kynurenine (L-KYN)

as a precursor of KYNA can cross the blood brain barrier and increase the level of kynurenate in the central nervous system.
Since peripheral and central NMDA receptors play a crucial role in trigeminal pain processing the aim of our study was to examine the possible modulatory effect of KYNA on the NTG-induced CGRP decrease in the rat TNCi.

Methods: Immunohistochemistry was used for detection of CGRP-immunoreactivity. The digital photos were analysed using Image-Pro® Plus 6.2 software (MediaCybernetics).

Results: We demonstrated that the pretreatment of L-KYN (300 mg/kg bw, i.p.) with PROB (200 mg/kg bw, i.p.) attenuated the NTG-induced CGRP expression decrease in the TNC.

Conclusion: Our results suggest that trigeminal activation can be modulated by NMDA receptors and thus kynurenines and its derivatives may alter the trigeminal nociception and can be considered as new therapeutic agents in migraine and head pain conditions.

P307

Recurrent dyspeptic symptoms and migraine: whom to blame?

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Objectives: Assessment of gastric and gallbladder motility behavior in patients with dyspeptic symptoms and migraine in inter attack periods.

Patients and methods: We studied 15 patients(11 women,4 men), age between 21–48 years, with diagnosed migraine without aura(International Headache Society criteria) and associated dyspepsia, and 10 controls. None of them undergone prior gastric surgery or recent treatment modifying gastric and gallbladder motility; they had no gastric lesions, negative antibody anti helicobacter pylori, no infection with HBV or HCV, being classified as functional dyspepsia (Rome II criteria) Gastric and gallbladder motility were assessed by ultrasound approach. Gastric emptying was evaluated according to the method of Bolondi,gallbladder motility was assessed using ellipsoid method(Dodds). Ultrasound examination was made after 12 h fasting,before and after eating a mixed solid–liquid meal in patients and controls. Measurements were made from time 0 every 15 min until 90 min. We draw gastric and gallbladder motility curves in controls and patients. We calculated maximal antral distension (percentage of antral area distension after finishing meal), half time of gastric emptying T1/2, initial and residual gallbladder volume, gallbladder ejection fraction. and compared to those of controls.

Results: Gastric and gallbladder motility response displayed various patterns in our cohort of patients. Most of patients had both decreased gastric and gallbladder motility:8 female patients(53,33%) had a parallel response of the gastric and gallbladder with delayed motility; 2 patients (1 man, 1 woman) had delayed gastric emptying but normal ejection fraction of gallbladder; 3 male patients:20%, had a normal curve of gastric motility but delayed gallbladder emptying, and 2 female patients:13.33%, with associated recurrent vomiting syndrome had features of rapid gastric and gallbladder emptying.

Conclusions: A high percentage of patients with migraine without aura carrying on dyspeptic complains between migraine attacks, showed gastric and gallbladder motility disorders. There was not an unique pattern of gastric and gallbladder response to the test meal:66.66% of patients had parallel response of gastric and gallbladder motility with either delayed emptying or in a couple of cases rapid emptying.The rest of patients had various types of response, displaying separately disorders of gastric or gallbladder motility.

P308

Assessment of menstural head ache in students in a university of medical sciences, Tabriz

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Background and subjects: Menstrual headache was described by Von Der Linder (1666) . Menstrual headache has recently been divided by the international headache society into 2 subcategories.

- Menstrually (attacks occurs during premenstrual and other times of the month)
- Pure menstrual (don't occurs at the other times).

Materials and method: In this study 300 female students by aged 18-26 years old . Fifty percent of them were medicine students, 50% dentistry, 50% pharmacology, 50% Nutrition, 50% obstetric and 50% nursing students at TABRIZ University from April 2005 to April 2006 were studied.
This was a cross sectional descriptive analytic study.

Results: All of the interviewers completed the questionnaire. The prevalence of pure menstrual headache was 27.3% .A positive family history of headache found 62.9%. Twenty percent of native and 34.2% of in native students had experienced of menstrual headache. The prevalence of migraine was 30.5% and tension type headache was 69.5% . In 47.6% of students had attacks occurring 2 days before onset of menstruation and 41.6% had 3 days after the menstrual period.

Conclusion: The result of this study shows the menstrual headache is highly prevalent among medical students at this university specially in medicine students.

Neurorehabilitation

P309

Evidence of language comprehension in patients with low levels of consciousness

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Objective: An accurate and reliable assessment of the arousal and awareness of consciousness in patients with severe brain damage is of greatest importance for their management. Although most of these patients recover from coma within the first days after the injury, some permanently lose all brainstem function (brain death), whereas others progress to "wakeful unawareness" (vegetative state, VS). Those who recover typically progress through different stages before fully or partly recovering consciousness (minimally conscious state - MCS). The objective of this study is to detect residual cognitive function in patients in VS and MCS using the functional magnetic resonance imaging (fMRI).

Design/methods: We apply a hierarchical fMRI auditory processing paradigm to determine the extent of retained language processing in a group of 20 aetiologically heterogeneous patients who met the diagnostic criteria for either the VS ($n = 10$), the MCS ($n = 10$). We employed multiple validated behavioural scales such as the Glasgow Coma Scale and the Clinical Unawareness Assessment Scale to classify the patients. Three different levels of speech processing were assessed: (a) Low-level auditory responses were measured using a contrast between a set of auditory stimuli and a silence baseline; (b) mid-level speech perception processing abilities

were assessed by comparing intelligible speech to unintelligible noise stimuli and (c) high-level semantic aspects of speech processing were assessed by comparing sentences that were made difficult to understand by the presence of words that were semantically ambiguous compared to matched low-ambiguity sentences. The stimuli were administered by a MRI-compatible headphones. Significantly activated voxels within each area were calculated, using the FSL package.

Results: MCS showed preserved speech processing at all three levels. However, contrary to the diagnostic criteria defining the VS, four patients demonstrated some evidence of preserved speech processing. The remaining six patients with a diagnosis of VS showed no significant activation in response to sound compared with silence.

Discussion/Conclusions: We are working to implement these data to include a most numerous population and to follow these patients during their long hospitalization. These results provide further evidence that a subset of patients fulfilling the behavioural criteria for the vegetative state retain islands of preserved cognitive function.

P310

Botulinum toxin improves lower limb spasticity in multiple sclerosis

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Objective: spasticity is a disabling complication of nearly all patients with multiple sclerosis (MS). It is recognised that no single treatment or combination of treatments for spasticity is completely satisfactory. Oral medications are often gravated with undesired effects. In an open label study we assess the efficacy of botulinum toxin type A (BT-A) injection and additional physiotherapy in subjects affected by progressive multiple sclerosis (MS) with lower limb spasticity.

Methods: 12 patients able to walk with assistance (EDSS score < 7), who had chronic disabling spasticity of the lower limb, with no or poor effect of oral treatment, were recruited consecutively. Each patient received one set of intramuscular injections of BT-A (Botox, range 200–400 U) according to each patient's individual pattern of spasticity (hip adduction, knee flexion/extension, equino-varus foot) followed by additional physiotherapy. Each patient was assessed at baseline, 6 and 12 weeks after BT-A injections for muscle tone (Modified Ashworth Scale, MAS), spasms frequency (Spasm Frequency Scale, SFS), leg pain (Visual Analogical Scale, VAS Pain), gait velocity (GV, m/s), mobility-related disability (Rivermead Motor Assessment-RMA), self-analysis of gait function (VAS Gait Function).

Results: we observed a significant ($p < 0.05$) reduction of scores of MAS, SFS and VAS Pain and a partial improvement of GV and VAS Gait Function after 6 weeks. The results did not change at 12 week follow-up. RMA did not change significantly indeed, likely because motor disability in MS has different causes other than spasticity and because one-time injection of BT-A can modify only focal patterns of spasticity

Conclusions: injections of BT-A, followed by additional physiotherapy, are effective on several MS lower limb spasticity variables, mainly on spasms and pain. BT-A injections can otherwise improve gait function in patients able to walk with assistance.

P312

Vestibular rehabilitation in patients with brainstem stroke in acute phase. Preliminary report

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Objective: The purpose of this study is to investigate the effect of early vestibular rehabilitation (VR) in patients with brainstem stroke.

Background: Despite there is not enough data about VR in patients with central vestibular disorder, the published data suggest that those patients improve balance after VR. In addition, there is not any study comparing the effect of rehabilitation in a selected group of patients in acute period.

Method: Fifteen patients with brainstem stroke included after their discharge from the stroke unit into the study. Average age of the patients was 62.87 ± 10.72 (46–80) years. Patients were randomized into two groups VR and control group. There were eight patients in the control and seven patients in the rehabilitation group. Control group was instructed to do the exercises given routinely to stroke patients before discharge. Rehabilitation group was also randomized to two groups-home exercise and static posturography group provided by physiotherapist. There were three patients in the posturography group and four patients in home exercise group. Static and dynamic balance abilities were assessed before and six weeks after the rehabilitation and in the sixth month. We did not analyse the data of the rehabilitation group separately in this preliminary report.

Results:

1. There was not any difference between the disability scores of control and the rehabilitation group.
2. Control and the rehabilitation group were significantly improved in balance parameters after six weeks of rehabilitation but there was not any difference between control and the rehabilitation group.
3. When control group and the rehabilitation group were compared in the sixth month in balance parameters after rehabilitation there was not any difference.

Conclusion: In a small group of patients our results show that in acute phase VR is not necessary as it is expected.

P313

Blood flow velocity in medial cerebral artery during visual-motor tasks using a mirror: a transcranial Doppler study

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Objectives: Mirror illusion consist in the fact that, standing in front of a mirror put in a sagittal plane, with our head on one side and one arm stretched forward, we can see one side of our body reflected as if it were the other side, by mirror visual feedback.

The aim of this study was to monitor blood flow changes in medial cerebral artery (MCA) by means of Transcranial Doppler (TCD) in individuals during motor tasks as well as tasks using mirror visual feedback.

Subjects and methods: Eight young healthy volunteers (four male and four female), participated in this study. TCD recording of MCA was done during each task consisting of various motor and visuo-motor activities using mirror illusion. Both MCA mean blow flow velocity

(MBFV) were measured while individuals seated in a comfortable chair.The obtained MCA MBFV are presented as baseline values.

Results: During the illusion of motoric hand activation, when the subject is making right hand flexions and watching it's reflexion in the mirror,while the left hand is immobile, increase of mean blood flow velocity of contralateral MCA was observed (task 3 + 4.5% than in baseline values,$p = 0.017$).
Furthermore, when the subject made left hand flexions while watching the reflection of the immobile right hand in the mirror, there was increase of MBFV in right MCA (+5.6% than in baseline values $p = 0.044$), more pronounced than during the illusion of motoric hand activation (task3) and less than during direct vision of hand flexion (task 2 +6.3%than in baseline values $p = 0.005$).

Conclusion: Our data showed that visual illusion of action, as well as direct action observation can increase mean blood flow value in MCA, which brings forward the possible usage of mirror illusion as a tool for motoric neurorehabilitation.

P314

Dysphagia and gastro-oesophageal complications in developmental and juvenile population affected by brain injury

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Dysphagia is one of the most common clinical problems following cerebral injury. Moreover, other gastro-esophageal complications add to dysphagia, such as gastro-esophageal reflux, that negatively influence the clinical management and the weaning from enteral nutrition.

Objectives: This study aims to evaluate the clinical entity of dysphagia and gastro-esophageal complications in a group of patients affected by cerebral injury in developmental and juvenile age.

Methods: We selected a group of patients hospitalized in our Rehabilitation Institute between 2002 and 2007.
The following data were collected: patients' age at insult, aetiology, the Glasgow coma scale score (GCS), the Glasgow outcome scale (GOS), the modality of nutrition, clinical and instrumental evaluations of dysphagia.

Results: We evaluated 426 patients. Their mean age at insult was 13 years (Standard Deviation (SD) 10.8); mean GCS at admission was 5.7 (SD 2.9); mean GOS at admission was 3,0 (SD 0.8), while at discharge was 3.5 (SD 0.9). 34% of total patients had dysphagia at admission. There were significant differences between dysphagic versus non dysphagic patients in favour of the former, regarding mean age, aetiologies, mean GCS score, days of coma, and the presence, at follow up, of a vegetative state.
Regarding gastro-esophageal problems, non dysphagic patients at admission did not develop these kind of complications. Among dysphagic inpatients, 20 had gastro-esophageal reflux, 15 of which were put in therapy, 3 required percutaneous endoscopic jejunostomy (PEJ); 1 needed dygiunostomia; 1 needed PEJ followed by funduplicatio by microinvasive way. Mean age of patients with gastro-esophageal complications was significantly lower than of patients without complications. The possibility of weaning from enteral nutrition was significantly lower in the former than in the latter. There were no significant differences concerning aetiologies, mean GCS score, days of coma. Moreover, the younger age, the presence of seizures, and the vegetative state had a negative role on feeding disorders.

Conclusions: Globally, in our database, 56.3% of patients with enteral nutrition reached oral feeding during rehabilitation program. Only 5% had gastro-esophageal reflux at discharge, 1/4 of which required a endoscopic/surgical intervention.

P315

Neurophysiological changes and motor recovery after Botulinum toxin type A injection in children with cerebral palsy

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Objectives: Cerebral Palsy (CP) is due to immature brain lesion involving the motor descending pathways and it is characterized by movement and posture disorders.
Previous studies of somatosensory evoked potentials (SEPs) have observed that their transmission was abnormal in children with CP. The botulinum toxin injection produce a reduction of hypertone both through synaptic blockade and both for inhibition of stretch reflex loop. These changes may influence not only the spinal cord but also the central nervous system (CNS).
The purpose of our study was to determine the effect of spasticity on cortical SEPs through an evaluation of their amplitude variation in comparison with the amplitude variation of H wave, that is the index of excitability of stretch reflex loop, after botulinum toxin type A injection.

Methods: Eleven children with CP (7 with diplegia and 4 with emiplegia), aged between 5 and 12 years, were recruited at Children's Hospital "Bambino Gesù" of Rome.
All children underwent a clinical evaluation with videotaping, passive range of motion (PROM) of ankle joint, modified ashworth scale (MAS) of plantar flexor muscles, selective control scale (SC) of lower limb before and 1 month after the botulinum toxin type A injection. Neurophysiological measurement outcome were performed before and 1 month after the botulinum toxin injection through lower limb SEPs and Soleus H wave recording. Children were not treated with pharmacological or surgical treatment six month before and during the period of the study, but they continued rehabilitation therapy.

Results: The results showed a statistically significant improvement of MAS, PROM and SC after the injection. The response of cortical SEPs and Soleus H wave increased after the injection.

Conclusions: The observed improvement of cortical SEPs with associated reduction of spasticity induced by botulinum toxin type A injection suggests that spasticity itself can be considered as a factor affecting the cortical SEPs. This change is not directly related to the synaptic inhibition induced by botulinum toxin type A but it could be the expression of the modulation of afferent fibers that, after the treatment, are more sensitive to the rehabilitation training.
Therefore, the period of chemodenervation induced by botulinum toxin could be utilized to obtain a real no-drug-dependent change of motor pattern in children with spastic CP.

P316

Impact of fatigue on rehabilitation outcome in multiple sclerosis patient

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Background: Fatigue is considered to be one of the most common and disabling symptoms among individuals with multiple sclerosis (MS). It often determines a severe impact on motor and social activities of patients and it is believed that it could interfere in the rehabilitation outcome of MS patients.

Objectives: The aim of this study was to investigate if inpatient rehabilitation is able to improve fatigue in MS and if fatigue could be considered as a negative predictor in clinical and functional outcome of rehabilitation in MS patients.

Methods: We considered 64 subjects with MS who underwent to a programme of rehabilitation in our Neurorehabilitation Unit. We measured entity of fatigue symptom with the fatigue severity scale (FSS) administered at the beginning and at the end of rehab treatment. We defined fatigue MS (FMS) subjects with a FSS score equal or over 36 points and Non-Fatigue MS (NFMS) all with a FSS score below 35. As clinical outcome measure of rehabilitation we considered expanded disability status scale (EDSS) and FIM for the functional evaluation of these patients.

Results: In our cohort of patient rehabilitation determined a significant improvement on FSS score in 39 patients with a strong statistical significance ($p < 0.0001$).However, the most interesting data is that fatigue seems to have no impact at all in clinical and functional outcome of rehabilitation. In fact, despite both EDSS and FIM improved significantly in our 64 subjects, Mann-Whitney analysis highlighted that fatigue is not able to influence both outcome measure: $Z = -0.725$ for EDSS with $p = 0.468$ and $Z = -0.838$ with $p = 0.402$ for FIM.

Conclusions: This data support the evidence that fatigue does not impact on the efficacy of rehabilitation, in spite of its subjective clinical impact on daily life of MS patients. Moreover, our data underline that rehabilitation could significantly reduce fatigue reported by subjects with MS.

P317

Predictors of short-term outcome in brain-injured patients with disorders of consciousness

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Objectives: To investigate predictors of recovery from the vegetative state (VS) and minimally conscious state (MCS) after brain injury as measured by the widely used Disability Rating Scale (DRS) and to explore differences in rate of recovery and predictors of recovery during inpatient rehabilitation in patients with non traumatic (NTBI) and traumatic brain injury (TBI).

Design: Longitudinal observational cohort design and retrospective comparison study, in which an initial DRS score were collected at the time of study enrollment. Weekly DRS scores were recorded until discharge from the rehabilitation center for both NTBI and TBI patients.

Setting: Seven acute inpatient rehabilitation facilities in the United States and Europe with specialized programs for VS and MCS patients.

Participants: Patients with a non traumatic ($N = 48$) and a traumatic ($N = 118$) brain injury who were in the VS or MCS states.

Interventions: Not applicable.

Main outcome measures: DRS score at 13 weeks after injury; change in DRS score over 6 weeks post admission; and time until commands were first followed (for patients who did not show command following at admission).

Results: For both TBI and NTBI samples, DRS score at admission, rate of change in DRS score in the first 2 weeks after enrollment, and the time between injury and enrollment predicted the DRS score at week 13, although the time to enrollment appeared to be more strongly predictive in those with TBI. DRS score at admission and rate of change in DRS score in the first two weeks after enrollment (but not the time between injury and enrollment) also predicted the time to follow commands in both groups. Finally, change in DRS score over the 6 weeks post enrollment was more strongly predicted by the rate of change in the first two weeks after enrollment in the TBI group than the NTBI group, and the time between injury and enrollment was also a good predictor among those with TBI.

Conclusions: These results suggest that several readily available clinical variables can predict meaningful proportions of the variance in short term functional improvements among individuals in with disorders of consciousness. Different ways of measuring functional improvement are predicted by similar clinical variables, with some minor differences. The variables that are predictive of improvement are similar for those with TBI and NTBI, although the strength of prediction tends to be greater in the TBI group.

P318

Assessment of gait recovery in children after traumatic brain injury

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Objective: To quantify the functional limitation of pediatric patients at recovery of independent ambulation after Traumatic Brain Injury (TBI) and over five months by means of clinical-functional scales and quantitative measures of gait (GA) and to investigate the correlation between variables of motor performance, clinical assessment and trauma-related measures.

Methods: 14 hemiplegic children with severe TBI were evaluated at independent gait recovery (S0) and 5.5 months later (S1) by clinical assessment (Glasgow outcome scale (GOS), disability rating scale (DRS), functional independence measure for children (Wee-FIM) gross motor function measure (GMFM)) and 3D GA (spatio-temporal parameters, kinematics and kinetics).

Results: At S1 all clinical measures had improved. Regarding spatio-temporal parameters, velocity of progression and anterior step length improved. Significant progress is evident at the distal joint and the ankle joint (both kinematic and kinetic parameters), while a worsening appears at the proximal joint, particularly for hip intra-rotation which increased its intra-rotation. Significant correlations were found between motor performance, clinical assessment and trauma-related measures.

Conclusions: The precise characterization of gait pattern in quantitative terms (spatio-temporal parameters, kinematics and kinetics) can also help clinicians to define a rehabilitative program aimed at achieving a fast and effective gait recovery in children sustaining a TBI.

P319

Multiple sclerosis: kinematic evaluation of constraint-induced movement therapy effects

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Objective: Cortical plasticity contributes to functional recovery after brain injury also in Multiple Sclerosis (MS) by means of Constraint Induced Movement Therapy (CIMT). At present few studies have performed quantitative evaluation of results after treatment with CIMT in MS patient. Aim of this pilot study was to evaluate if MS patients with upper limb dysfunction could tolerate an intensive rehabilitation program, and to evaluate by means of kinematic measures and clinical scales, potential benefits introduced by CIMT approach.

Methods: 12 MS patients (mean age: 54 ± 11 years, expanded disability status scale, EDSS: 6 ± 3) with different symptoms in the upper limb were recruited. All patients received the same intensive upper limb rehabilitation program (10 exercises, 10 times per day, 12 days): 6 patients underwent to CIMT approach (group1), and 6 were free to move and use also the less involved limb (group2). Patients were clinically (nine hole peg test, NHPT) and quantitatively (kinematics of pointing movement) examined before and after the treatment. Specifically we investigated parameters about movement smoothness (IC: index of curvature, the ratio between fingernail 3D path length (LTR) and linear distance between initial position and reaching position (L0); NMU: number of movement units), and about speed (VP: velocity peak).

Results: In group1, VP of the most involved limb (not blocked) was the only parameter that showed statistically significant improvement (pre: 1.09 ± 0.07 m/s; post: 1.16 ± 0.06 m/s; $p < 0.05$). A trend was observed in NHPT time values of the most involved limb (NHPT pre: 31.8 ± 14.7 s; NHPT post: 28.0 ± 15.6 s; $p < 0.07$) while, no changes occurred in the less involved limb. In group2, IC of the most involved limb showed statistically significant improvement (IC pre: 1.19 ± 0.14; IC post: 1.16 ± 0.15; $p < 0.05$). As concerned the less involved limb, patients demonstrated statistically significant improvements in IC (IC pre: 1.19 ± 0.17; IC post: 1.14 ± 0.18; $p < 0.05$) and in NHPT time values (NHPT pre: 32.7 ± 14.3 s; NHPT post: 29.3 ± 12.8 s; $p < 0.05$).

Conclusion: All patients were able to follow the rehabilitative protocol. Our pilot study suggests that CIMT improves abilities of the most involved limb without affecting those of the blocked one. Conversely control subjects showed more improvements on the less involved limb than on the most involved one.

P320

Diagnostic of neurogenic bladder dysfunction in intermediate and late period of spine cord injury

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Objectives: The aim of the investigation is to determine the type of neurogenic bladder dysfunction after spine cord injury.

Methods: We have evaluated 138 consecutive patients, including 116 men and 22 women in the age from 16 to 57 years old, with neurogenic bladder dysfunction which suffered spinal cord injury. The neurological level and degree of injury were established and testing according to American Spinal Injury Association classifications as following: type A 34.8% patients, type B 28.3%, type C 21%, type D 13% and 2.9% pat. with type E.

In examination the neurogenic bladder dysfunction questionnaire, urofloumetry, original method of acupuncture diagnostic, ultra sound diagnostic were applied.

We have developed our original questionnaire to define the degree of bladder function compensation. We examined miction impulse, spontaneous voiding, clean intermittent, chronic Foley catheterization and others. During urofloumetry we performed graphical monitoring of voiding speed and assessment of contractile detrusor function. We studied maximal voiding speed (Qmax), average voiding speed (Qm), voiding duration (t) and other parameters. Methods of diagnostics and planning of acupuncture are based on measuring of skin electro-conductivity. Ultra sound diagnostics of bladder volume, residual urine and urine reflux were observed.

Results: Significant differences were noted in study of following urofloumetry dates: miction volume and speed voiding. 36% patients had detrusor hyperreflexia, their miction volume had not exceed 121 ± 48 ml and voiding speed 27 ± 10 ml/s. Detrusor areflexia was in 41% of patients with increased miction volume to 222 ± 91 ml, and maximal voiding speed 6 ± 2 ml/s. Other patients had detrusor-sfincteric dissinergia, no significant differences were noted between urodinamic characteristics and bladder dysfunction. According ultrasound diagnostic, the majority of patients with detrusor areflexia had bladder volume more than 380 ml and residual urine volume more than 150 ml. Acupuncture diagnostics shows, that reduction of parasympaathetical activity is accompanied by detrusor areflexia.

Conclusion: Urodynamic evaluation, including questionnaire, urofloumetry, acupuncture and ultrasound diagnostics is mandatory for the complex evaluation of patients with spinal injuries. These methods are supplementary and correct each other to provide definition of the type of neurogenic bladder dysfunction.

Peripheral neuropathy

P321

Myocardial sympathetic innervation in patients with painful small fibre polyneuropathy with impaired glucose tolerance

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Objective: To report the 123I-MIBG myocardial scintigraphy findings in IGT patients presenting a PSFPN.

Background: Painful polyneuropathy is a frequent condition in clinical practice. Impaired glucose tolerance (IGT) is related to some painful small fiber polyneuropathy (PSFPN) cases and can course with autonomic dysfunction. Metaiodobenzylguanidine (MIBG) tagged with 123I can be used to image adrenergic receptors in the heart and represents its population, segmental distribution and function. The major advantage of 123I-MIBG myocardial scintigraphy is its ability to directly and non invasively assess cardiac sympathetic innervations, which cannot be accomplished by the traditional autonomic tests.

Design/methods: Five patients, a 52, and 48 y.o. females, and 3 males, respectively with 45, 56, and 62 y.o. were referred to us with a PSFPN with no familiar history. Presenting symptoms were sensory in all, being pain in the distal lower limbs the most prominent. Duration of symptoms was 6, 10, 12, 8 and 16 months, respectively. All patients

were submitted to oral glucose tolerance test (OGTT). There was no autonomic dysfunction or cardiac involvement assessed by the standard bedside tests. Echocardiography was normal in all patients. Electrocardiography and laboratorial tests had been performed. 123I-MIBG Myocardial Scintigraphy was performed to analyze cardiac sympathetic nervous anatomic distribution and activity.

Results: There was an accentuated decrease in the accumulation of 123I-MIBG in the heart 20 min and 4 h after the isotope injection, characterized by a decrease in heart/mediastinum relation and elevated washout rate suggesting that severe autonomic impairment had occurred in all five patients.

Conclusions: Our records suggest that IGT can correlate with PSFPN and a subclinically autonomic dysfunction as showed by reduced MIBG cardiac uptake and sympathetic hyperactivity. A large series study is needed for a better understanding of this association.

P322

Autonomic dysfunction in patients with Guillain-Barré syndrome: a clinical study

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Objective: Autonomic dysfunction in Guillain-Barre syndrome (GBS) is well recognized but not well described

Methods: In cross-sectional multicenter study, fifty patients with GBS were studied for evaluation of autonomic dysfunction (AD) according to methods described by Ewing and Clarke.

Results: Mean age at presentation was 21.1 years (range 1–60 years). All patients were studied for symptoms and signs of AD. None of them received IVIG or plasmapheresis. Autonomic function test (AFT) were performed in 30 patients. 20 patients (40%) had symptoms of AD, 27 patients (54%) had signs and 14 patients (28%) had symptoms and signs of AD. Abnormality in AFT was detected in 15 patients (50%) and showed that parasympathetic derangement was the most frequent followed by sympathetic and combined derangement. Derangement in AFT battery had a highly significant correlation with the development of respiratory paralysis (p value < 0.001) and death (p value $= 0.008$).

Conclusion: All patients with GBS should be observed for evidence of autonomic dysfunction and nursing care has to be adjusted to take into account the autonomic status of the patient.

P323

The rapid clinical progression and recovery in the axonal subtype of Guillain-Barré syndromes: a case report and review of literature

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The axonal variant of Guillain-Barré syndrome, termed acute motor axonal neuropathy (AMAN), is characterized by primary axonal damage. Electrophysiological evidence of axonal degeneration is thought to be an indicator of poor prognosis or slow recovery, but a considerable number of patients with AMAN usually reach their nadir quicker and recover as fast as those with demyelinating Guillain-Barré syndrome.

We aimed to elucidate the indicators of rapid clinical recovery in this severe disease.

A previously healthy 20-year-old Moroccan woman was admitted to our hospital because of highly progressive and descending weakness course with relative preservation of muscle force in the extremities, dysautonomic involvement and severe respiratory failure. Because of the prompt risk of respiratory arrest, mechanical ventilation was required within 8 hours of her admission (period between neurologic onset and intubation = 48 h).

The neurologic examination showed an hyporeflexia in upper limbs and preserved tendon reflex in lower limbs, strength was decreased in proximal muscles and sensation was intact.

The neuro-radiologic imaging was normal. Lumbar puncture performed at initial complaint indicated values within normal range. Serological tests were also negative for HIV, and hepatitis B and C viruses. C-reactive protein rate was mildly elevated. Nerve conduction studies were compatible with primarily acute motor axonal neuropathy (AMAN). The Helicobacter pylori infection was documented by histology.

Treated with intravenous immunoglobulins (IVIg), in a regimen of 0×4 g/kg bodyweight daily for 5 consecutive days. The clinical course was favorable with extubation at the day 10 after her admission and a complete recovery of her four limbs paresis and respiratory function twenty days later. This benign clinical course and this rapid clinical recovery (before eradication of H pylori) were intriguing.

The very rapid clinical recovery seen in our patient suggests that, as speculated in previous studies, instead of axonal degeneration or demyelination, reversible effects such as impaired physiological nerve conduction occur on the axonal membrane. These findings further suggest that the pathophysiology in the axonal subtype of Guillain-Barré syndrome is potentially reversible, especially in the early stages (with preserved tendon reflexes), and effective treatment could result in very rapid improvements.

P324

Hyperhidrosis after injection of botulinum toxin

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Objectives: Botulinumtoxin (BoNT) is a neurotoxin which blocks the exocytosis of acetylcholine from cholinergic synapses. It is used to treat muscular spasms but also focal hyperhidrosis. It reduces sweating dose-dependently. However, in previous experiments of our group, subjects who achieved injections of Dysport® in doses, which were too small to suppress sweating after 3 weeks completely, local sweating was increased 6 months after the injections. The aim of our study was, to determine if small doses of Dysport® might induce hyperhidrosis.

Methods: 19 subjects received subcutaneous injections of Dysport® in each lower leg in doses of 1.25 to 25 MU (mouse units). 3, 8 and 24 weeks later anhidrotic and hyperhidrotic areas were measured by iodine starch staining. The amount of sweating was assessed by quantitative sensory axonreflex testing (QSART). Sweating was induced by iontophoresis of acetylcholine 10%.

Results: After 3 and 8 weeks Dysport® doses of 6.25–15 MU reduced the amount of sweating dose-dependently (after 3 weeks: $p < 0.05$, $r = -0.62$, after 8 weeks: $p < 0.05$, $r = -0.68$), whereas doses <5 MU did not reduce sweating. After 24 weeks sweating was increased compared to baseline values at 16 out of 31 (51.6%) injected sites; the mean increase was 36%. An anhidrotic skin area could be found using doses >10 MU. A hyperhidrotic skin area could be found in 4 out of 24 cases, the size of these areas did not depend on applied dose.

Conclusion: Even small doses of Dysport® (6.25 - 25 MU) reduced the amount of cholinergic sweating dose-dependently. After 3 weeks even 10 MU Dysport® induced an anhidrotic area, but this anhidrotic effect persisted only 8 weeks in the applied low

doses. Therefore anhidrotic skin areas were detected only sparsely after 24 weeks, however in some cases increased sweating compared to baseline level could be found then. The possible mechanism of that hyperhidrosis after injection of small doses botulinumtoxin might be increased sensitivity of cholinergic synapses after axonal sprouting, referred to as regeneration super sensitivity.

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P325

Treatment of pain and paraesthesias in immune-mediated neuropathies: a retrospective analysis on the efficacy and tolerability of drugs for neuropathic pain

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Objective: A number of symptomatic drugs are currently used for pain in patients with neuropathy. The efficacy of these treatments has been established in several clinical trials on specific neuropathies, but little is known on their use in neuropathies of other aetiologies including immune mediated neuropathies. To analyse the efficacy and tolerability of symptomatic therapy for paresthesias and pain in patients with immune mediated neuropathies (immune PN) and with neuropathy of other or unknown causes (other PN).

Patients and methods We reviewed the reports of 88 consecutive patients with neuropathy including 33 with immune PN and 55 with other PN, examined in our Centre from 2004 through 2007 and treated for pain, paresthesias or both, with therapies for neuropathic pain including antiepileptic (gabapentin, pregabalin and carbamazepine) and antidepressant drugs (amitripyline and duloxetine). The main outcome of the study was the proportion of patient suspending therapies due to lack of or unsatisfactory effect or drug intolerance. The results were analysed in relation to the aetiology of the neuropathy and to different symptoms (pain, paresthesias or both).

Result: Symptomatic therapy for neuropathic pain was effective in 52.3% (46/88) of patients including 48.4% (16/33) of those with immune PN and 54.5% (30/55) with other PN. Pregabalin was the most effective drug in both groups being suspended by 44% (18/41) of the patients (50% with immune and 40% with other PN), mainly for inefficacy. It was particularly effective in patients with paresthesias only (38% suspension) or paresthesias and pain (30%). Gabapentin was discontinued by 73% (44/60) of patients (75% with immune and 72% with other PN) mainly for an unsatisfactory response with a similar effect on pain and paresthesias. Amitriptyline was also discontinued by 73% (19/26) of patients (86% with immune and 68% with other PN) being only effective on paresthesias (56% suspension). Duloxetine was interrupted by 80% and carbamazepine by 86% of the patients being both only effective on paresthesias with a similar efficacy in the two groups.

Conclusions: With the limits of a non trial retrospective analyses, which may be however more adherent to common clinical practice, drugs currently used to treat neuropathic pain were effective in approximately 50% of patients with either immune or other PN, indicating that their restriction to specific forms of neuropathy may not be justified.

P326

Does haemochromatosis affect the neuromuscular system? A clinical perspective

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Objectives: Many patients with hereditary haemochromatosis (HH) have symptoms suggesting involvement of the neuromuscular system: e.g., exercise intolerance, sensory complaints, muscle pain and weakness. The aim of this prospective study was to determine the frequency of these signs and symptoms in HH and possible underlying causes.

Methods: Patients with definite HH from the department of internal medicine of a large general teaching hospital were systematically examined for symptoms and signs of a neuromuscular disorder (NMD) by means of a structured interview and a clinical neurological exam. The data acquired in each patient were studied by a panel of three independent neurologists that reached consensus about the presence of a possible NMD and need for additional investigations. Only patients having a possible NMD of unknown origin were further analysed using additional investigations (mainly electrophysiological, laboratory). The results of these tests were reviewed by the panel again and a final diagnosis was made.

Results: We included 33 men and 16 women with a mean disease duration of 7.2 years (range 0.7–26.2). Muscle pain was reported by 69%, muscle cramps by 63%, exercise intolerance by 59%, paraesthesias of the extremities by 59%, muscle weakness by 51% and numbness of the extremities by 42%. Clinical exam was normal in 27 patients. After the first round, the panel preliminary diagnosed a NMD of known origin in 1, a possible NMD of unknown origin in 35 and no NMD in 13 patients. Ultimately after additional investigations, no NMD was found in 28 patients, a NMD of known origin (i.e., polyneuropathy by diabetes, chemotherapy, Sjogren, CMT 2) in 6, a carpal tunnel syndrome in 6, polyneuropathy of undetermined cause in 9 (axonal sensory-motor polyneuropathy in 7, axonal motor neuropathy in 1, small fiber neuropathy in 1). A polyneuropathy was suspected by the panel in 10 patients but this was not confirmed by electrophysiological testing. No patients were diagnosed with a myopathy. No significant differences in patient characteristics or haemochromatosis related data were found between patients diagnosed with polyneuropathy and those without.

Conclusion: A polyneuropathy of undetermined origin was found in a relatively large number of cases (18%) but no definite patho physiological relationship with HH could be demonstrated. There were no cases with a clinical myopathy.

P327

Subclinical peripheral neuropathy in Behcet's disease

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Objective: Central nervous system involvement is well known in patients with Behçet's disease but studies evaluating peripheric nervous system is not usual. The aim of this study is to evaluate the occurance, frequency and frequency and characteristics of subclinical neuropathy in patients with Behçet's disease.

Material and method: 33 Behçet's disease patients (23 male, 10 women) with no evident neurological sign and symptom and 33 healthy volunteers were enrolled to the study. To exclude the other

causes of peripheral neuropathy, some laboratary investigations were made. Electrophysiological studies of peripheral nerves were performed to all patients and healthy volunteers. The results were assessed according to the American Diabetes Association Diabetic Neuropathy Protocol.

Results: Nerve conduction studies were abnormal in 11 of 33 patients (7 men, 4 women; 33.3%). 5 patients (15%) had sensorymotor polyneuropathy, 4 (12%) has sural sensory polyneuropathy, 1 (3%) had median and tibial motor neuropathy. Sural nerve were unobtainable in 7 (21%) patients. 2 patients (6%) had prolonged F latancy. Control group were normal electrophysiologically and the difference was statistically important ($p < 0.0001$). There was no correlation between peripheral neuropathy and gender ($p = 0.696$).

Conclusion: Despite the detailed neurological examination, subclinical peripheral neuropathy can be seen in patients with Behçet's disease. Electrophysiological studies are useful for the early detection of peripheral neuropathy in these patients.

P328

Peripheral nervous system involvement in patients with sickle cell disease

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Objectives: Peripheral nervous system involvement is rare in sickle cell disease (SCD). The aim of this study is to determine the peripheral nerve involvement electrophysiologically in SCD patients without clinically evident neurological signs, symptoms and to determine the relationship between the frequency of sickle cell crisis and peripheral neuropathy.

Methods: Fifty-one patients with SCD and fifty-one healthy controls were enrolled to the study. Conventional electrophysiological studies of peripheral nerves were performed to all subjects. The data about the frequency of sickle cell crisis were obtained.

Results: Peripheral nervous system involvement was detected in ten (19,6 %) patients. Five (9,8%) patients had sensorimotor axonal neuropathy, two (3.9%) sensory axonal neuropathy, one (2%) patient had ulnar sensory neuropathy and two (3.9%) had median sensory neuropathy. Sural nerve sensorial action potential was unobtainable in eight (15.7%) patients and prolonged F latencies were observed in three (5.9%). The frequency of neuropathy was higher in SCD patients when compared with the controls. The frequency of sickle cell crisis was not significantly correlated with peripheral neuropathy.

Conclusion: Subclinical peripheral nerve involvement may be seen in SCD patients. Electrophysiological examinations are recommended in routine examination to diagnose early neuropathy in SCD patients without neurologic symptoms.

P329

A case of N-hexane neuropathy accompanied with abnormal evoked potentials

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We experienced a case of N-hexane neuropathy accompanied with conduction delay in brainstem auditory evoked potential (BAEP) and visual evoked potential (VEP). The case was 27 year-old woman, who complained of glove and stocking type paresthesia started from 4 month ago and developing leg weakness. On admission the weakness of orbicularis oculi, distal dominant weakness of the lower limbs, areflexia and the glove and stocking type hypesthesia was noted. The nerve conduction study (NCS) showed slow conduction velocity of motor and sensory nerves which met the diagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP). The conduction delay was found not only in NCS but also BAEP and VEP, which was atypical in CIDP. We tried intravenous immunoglobulin infusion (IVIG) but it didn ft improve her condition. Meanwhile the pathology of sural muscle and nerve showed axonopathy with giant axons and the axon ballooning and secondary demyelination which implied *N*-hexane toxicity. Later on, further interview revealed the history of *N*-hexane exposure.

N-hexane neuropathy has been reported to have diffuse or focal conduction delay or conduction block, which mimics CIDP. This case showed diffuse conduction delay in peripheral nerves including auditory and optic nerves and it may be an early specific detection sign of N-hexane neuropathy.

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Multiple cranial nerve palsies as presenting symptom in primary Sjögren's syndrome

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Introduction: Primary Sjögren's syndrome (PSS) is a systemic autoimmune disease characterized by xeroophthalmia and xerostomia. In up to 20% of patients PSS is associated with peripheral neuropathy, most commonly of the distal sensory symmetrical type. Isolated cranial nerve involvement in PSS has rarely been described. We report a case with multiple cranial nerve palsies as presenting symptom in PSS.

Case report: A 29-year-old male with a 6-month history of progressive bilateral facial palsy was admitted with dysphagia, dyspnea and hoarseness. Past medical history included Hashimoto thyroiditis. Neurological examination revealed bilateral facial palsy, paresis of the soft palate on the left, bilateral vocal cord paresis, right-sided tongue paresis and dysphagia. There was no clinical or electrophysiological evidence of peripheral neuropathy. Schirmer's test was abnormal. Laboratory data included normal ESR and other routine parameters. Anti-SS-A, anti-SS-B and anti-TPO antibodies were detected, whereas ANCA, ANA, rheumatoid factor, anti-GQ1b and ACE were negative. Immunofixation of serum and urine showed no monoclonal proteins. The examination of CSF gave no pathological results. Blink reflex R1-components and the masseter reflex latencies were bilaterally delayed. Electronystagmography revealed a vestibular paresis on the left. MRI of the brain was normal, and no gadolinium enhancement was observed along the course of the cranial nerves. Whole body FDG-PET did not reveal tumor suspect lesions. Salivary gland scintigraphy showed a pathologically reduced uptake of the radionuclide in both parotid glands. Based on the presence of autoantibodies, reduced tear production and impaired salivary gland function a PSS was diagnosed. Under an initial treatment with intravenous immunoglobulin (400 mg/kg/day for 5 days) followed by oral prednisolone (1 mg/kg/day) a partial improvement of the patient's condition was observed.

Conclusion: PSS should be considered as a possible cause of isolated cranial nerve palsies in addition to other well recognized diagnoses such as diabetes mellitus, localized infections, granulomatous diseases, and compressions by tumors or aneurysms. The diagnosis of PSS is possible even in the absence of extraneurological involvement. Early PSS diagnosis is important in order to provide an appropriate follow-up, since these patients have 44 times higher risk

of developing malignant lymphoma, and 50% chance of developing monoclonal gammopathy.

P331

Prospective study of efficacy of exercise training in sensory ataxic neuropathic patients

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Objectives: Rehabilitation therapy (RT) is considered as part of the treatment of neuropathic patients. However, there is little scientific evidence to evaluate the effect of exercise on functional ability in this group of patients. Moreover, it is still unknown weather the patient's functional improvement may rely on regression of the motor deficit or balance control improvement. We are thus performing a prospective trial analyzing the efficacy of RT in patients with sensory ataxic peripheral nervous system diseases.

Methods: We are planning to enrol 20 consecutive pts. Inclusion criteria comprise: chronic sensory PNS diseases of any aetiology, INCAT score (leg disability) ≥ 2, absent or mild motor signs (leg distal muscles MRC > 4, pts able to stand on their heels and toes), Balance Berg Scale score 5-40, clinical and therapeutic stability of at least 3 months.

Pts are scheduled to undertake a specific 3-week intervention RT regiment comprising balance and resistance training (two rehabilitation sessions a day: total time 2 hours). Outcome measures comprise: INCAT score, SF-36 quality of life scale, Balance Berg scale, FIM scale, 6-minute walk test. Pts evaluation will be done at baseline, at the end of the 3-week exercise program, and at 3 and 6 months of follow-up. Functional evaluation is blind for the pts treatment. Baseline and follow-up neurologic evaluation will be done by two different neurologists. Evaluating neurologist will be blinded both for pts baseline characteristics and for functional test results of the RT training.

Results: our preliminary results (No patients: 13) show a significant improvement in FIM, Balance Berg Scale and 6-minute walk test scores at the end of the treatment period compared to baseline ($p > 0.005$) and sustained at 3 mounts (FIM and Balance Berg Scale: $p > 0.05$) and at 6 months of follow-up (FIM: $p > 0.05$). INCAT and SF-36 quality of life scale have not been evaluated to avoid examinator's unblinding.

Conclusions: Our preliminary results show efficacy of rehabilitation treatment confirmed at the end of the treatment period and sustained at 3 and 6 month follow-up evaluation. However, sample-size increase is needed to draw more reliable conclusions. This clinical trial is still in progress.

P332

Peripheral "man-in -the-barrel" syndrome: two cases of acute bilateral neuralgic amyotrophy

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Objectives: To report two cases of bilateral neuralgic amyotrophy of upper limbs to illustrate the heterogeneous clinical presentation of this syndrome.

Methods: Case 1: A 56 yo man presented with acute onset of bilateral upper arm pain followed by severe bilateral upper limb paresis mimicking the "man-in-the-barrel" syndrome. On admission severe muscle weakness of shoulder abduction and external rotation was observed. Bicipital tendon reflexes were absent and hypaesthesia over both upper arm regions was detected.

Case 2: A 30 yo man complained of cervical, right scapular region and upper arm intense pain following hyperextension of the neck. He showed a winged right scapula and atrophy of right biceps, left supraspinatus and infraspinatus muscles. Right bicipital and estiloradial tendon reflexes were absent and hypaesthesia over the right lateral forearm region was observed.

Results: Case 1: Neurography: the lateral antebrachial cutaneous nerve showed a reduction of the SNAP amplitude in the rigt side and no response in the left side. Electromyography revealed signs of acute denervation in both biceps, infraspinatus, deltoids and right flexor carpi radialis muscle.

MRI of the cervical spine ruled out root involvement.

Case 2: Neurography: No response was evoked from the right lateral antebrachial cutaneous nerve. Signs of chronic denervation were found in right biceps, brachialis, serratus and infraspinatus muscles and in left infraspinatus and supraspinatus muscles.

MRI of both brachial plexuses showed high intensity signal changes in right serratus and left infraspinatus and supraspinatus muscles suggesting chronic neurogenic damage.

Conclusion:

- Amyotrophic neuralgia can be bilateral and symmetrical: peripheral "man-in-the-barrel" syndrome or asymmetrical and patchy, as a form of "mononeuropathia multiplex".
- The electrophysiological studies are helpful in detecting subclinical involvement of the opposite limb.
- There are differences in weakness and electrophysiological grade of denervation between muscles innervated by different peripheral nerves. These differences suggest involvement of individual nerves or nerve branches rather than a plexus lesion.
- MRI imaging findings revealed a neurogenic high signal intensity abnormality due to increased extracellular water content.
- MRI imaging can help to exclude other disorders such as cervical spondylosis, rotator cuff tears, shoulder impingement syndrome or a ganglion.

P333

Comparison of chronic inflammatory demyelinating polyneuropathy with and without diabetes

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Background and objective: Chronic inflammatory demyelinating polyneuropathy (CIDP) is a clinically heterogeneous disorder with an immune basis. Several diseases have been associated with CIDP, including systemic lupus erythematosus, human immunodeficiency virus (HIV) infection, monoclonal gammopathy, and diabetes mellitus (DM). There is growing evidence that idiopathic CIDP (I-CIDP) and polyneuropathy in patients with DM that meets the electrophysiological criteria for CIDP (DM-CIDP) have many similarities. However, some reports announce that DM-CIDP is different from I-CIDP due to less favorable treatment response, more biopsy-proven axonal loss, etc. Thus, we performed this study to determine whether a subset of DM-CIDP are similar to I-CIDP for clinical and electrophysiologic aspects.

Methods: We compared the clinical (age, sex, symptom duration, pattern, course, motor scale, sensory scale, total clinical scale, and M-

Rankin score, etc.) and electrophysiological (routine nerve conduction studies including median, ulnar, peroneal, and posterior tibial nerves) features of 11 patients (M = 5, F = 6) with DM-CIDP to those of 11 patients (M = 4, F = 7) with I-CIDP. For each motor nerve studied, amplitude-dependent slowing of conduction was analyzed using parametric linear regression analysis. Compound motor action potential (CMAP) amplitude and conduction velocity were converted to a percentage of the upper or lower limit of normal and then represented as a square root (SQRT) transformation, plotted with SQRT amplitude as the independent variable and SQRT conduction velocity as the dependent variables.

Results: The patients with DM-CIDP displayed clinical features that were similar to those in patients with I-CIDP. Regression analysis of the lower extremity nerve data showed that slowing of velocity were amplitude-dependent in DM-CIDP only ($r = 0.739$, $p < 0.001$). In the upper extremity, amplitude-dependent slowing of velocity was seen in DM-CIDP ($r = 0.795$, $p < 0.001$) and not in I-CIDP.

Conclusions: Our study showed DM-CIDP had clinical features similar to those with I-CIDP, but analysis of nerve conduction studies including amplitude-dependent slowing of conduction revealed more severe axonal loss in DM-CIDP. These differences most likely reflect the additive effects of superimposed diabetic axonal injury in DM-CIDP.

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Functional MRI correlates of fatigue in patients with hereditary and acquired peripheral neuropathy

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Objective: Fatigue is a frequent complaint of PN patients. Even if a few studies have shown functional magnetic resonance imaging (fMRI) abnormalities of the motor system in PN patients, the fMRI correlates of fatigue in these patients have not been investigated, yet. Aim of this study wax to explore the effects of fatigue on motor network recruitment in patients with peripheral neuropathy (PN) in comparison to controls and to evaluate the influence of disease duration on the previous findings by comparing patients with hereditary (H) and acquired (A) PN.

Methods: FMRI (during hand-grip) before and after a fatiguing exercise was acquired from 11 APN patients, 10 HPN patients, and 12 matched controls. Analysis of activations and effective connectivity were performed using SPM2 and dynamic causal modelling (DCM).

Results: After the fatiguing task, compared to controls, APN patients had more significant activations of the precuneus, bilaterally and the left supplementary motor area (SMA), while HPN patients had more significant activations of the SMA and of several visual areas. Compared to APN patients, HPN patients had more significant activations of V1 and V5, while the opposite comparison showed more significant activations of the precuneus in APN patients. In PN patients, significant correlations were found between changes of activation of the SMA and fatigue severity ($r = -0.78$) and changes in activation of the precuneus and disease duration ($r = -0.86$). Both groups of patients had a decreased connection between the SMA and the right primary sensorimotor cortex (SMC) and an increased connection between the SMA and the left primary SMC compared to controls. APN patients also had an abnormal connection between the two primary SMCs.

Conclusions: Motor fatigue in PN is related to impaired interactions between functionally related cortical areas of the motor system. These findings suggest that fMRI might be a valuable tool to monitor the efficacy of treatment aimed at reducing PN-related fatigue.

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Chronic demyelinating polyneuropathy and relapsing-remitting central demyelination: spreading autoimmunity from peripheral to central myelin?

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Objective: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is acquired neuropathy with progressions and relapses. Similarly multiple sclerosis (MS) may evolve with relapsing remitting course.

Methods: Case 1 A female when aged 18 developed episodes of facial weakness, distal limb paresthesias, imbalance. On 1st admission (April 1994) brain MRI was normal. In May 2004, she experienced occasional dysarthria, tremor, acral paresthesias. On examination there were ataxia on finger-nose and heel-shin tests,brisk deep reflexes, positive Romberg sign, loss of perception, vibration, position sense. Brain MRI was normal whereas there where multiple spinal cord unenhanced lesions from C2 to Th6. Electrophysiology showed demyelination with multiple conduction blocks. CSF was normal. Antibody assay for gangliosides, myelin associated glycoprotein was negative. Patient received high doses of steroids i.v. Because of recurrent episodes of lower limbs numbness, courses of immuneglobulin were given for four years. Case 2 was diagnosed having CIDP when aged 34 and MS at 36 years. When aged 35 she developed acute renal failure due to nephritis. Her neurological complaints were acral paresthesias, extremity weakness, recurrent imbalance, blurred vision. On examination patient exhibited tremor, ataxia, impairment of light touch, pin-prick, position and vibration, areflexia. Repeated brain MRI showed numerous periventricular and brain stem lesions fulfilling Barkhof's criteria for spatial dissemination. No antiganglioside antibodies were detectable nor anti- MAG activity. At diagnosis, CSF shored oligoclonal bands

Results and discussion: Few reported patients exhibit central and peripheral evidence of demyelination. Demyelination and gliosis in MS among central nervous system spare usually peripheral nerves. CIDP with clinical CNS signs are rare. In our cases, clinical symptoms and electrophysiological signs of neuropathy predated the possible diagnosis of relapsing remitting MS. CSF of case 2 showed ologoclonal bands At diagnosis, there was no evidence of infections or metabolic disorders. There are similarities between immunopathogenesis of CIDP and MS which might be considered result of interaction between cellular and humoral responses directed against antigens triggering responses. In our view the attractive hypothesis of some antigen similarity between central and peripheral nerve myelin has to be considered.

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High-resolution sonography of the median nerve in healthy volounteers

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Objectives: Although electroneuro- and electromyography are still leading diagnostic methods for investigation of peripheral nerves function, they do not provide information regarding their morphology. This study was conducted to evaluate the suitability of ultrasonography in visualization of median nerve in healthy volunteers.

Methods: Twenty-five asymptomatic volunteers (16 women and 9 men) have participated in this study, age ranging from 20–68 years. Device used was Aloka Prosound A10 Premier with 13 MHz probe, using custom preset for musculo-skeletal sonography. Following

dimensions of median nerve at the level of pisiform bone were measured bilaterally: cross-sectional area (CSA), circumference, longer and shorter radius. Subsequently, using latter values, flattening ratio was calculated.
Examinees' height was measured and handedness ascertained. Additional epidemiological data taken was the average daily time that individuals spent working on a personal computer as a possible factor for compression of the nerve in subject's dominant hand.

Results: Median nerve was easily depicted in all of the participants as well as the surrounding soft-tissue structures. Average CSA of median nerve was 9.67 mm^2 (range 5–15 mm^2, with standard deviation of 2.4 mm). Mean flattening-ratio (FR) (longer radius/shorter radius) was 4.18, ranging from 2.16 to 5.92.
Median height was 173.8 cm and only one subject was left-handed while the others (96%) were right hand dominant. Average daily time spent working on a personal computer (total average of 2.96hrs) did not correlate with CSA or FR values for the dominant hand.
Additionally, in two subjects, an aberrant artery accompanying n. medianus was visualized.

Conclusion: High-resolution sonographic imaging allows assessment of various morphological properties of median nerve, including its various dimensions and echoic architecture. Furthermore, ultrasound imaging is a very convenient (available, quick, inexpensive and noninvasive) method for examination of peripheral nerve morphology and could thus be used to enhance diagnostic efficiency.

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Fatal multifocal motor neuropathy

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Introduction: Multifocal motor neuropathy (MMN) is chronic immune mediated demyelinating neuropathy characterized by progressive asymmetrical weakness usually in distal limb muscles. Electrophysiological hallmarks are partial conduction blocks (CB), abnormal temporal dispersion normal sensory conduction We describe two patients exhibiting an unusual progression.

Case 1: This 63 year old woman was referred after one year and half duration of weakness which began in upper limbs spreading to lower extremities. On first admission (July 2001) neurological examination showed normal cranial nerves, sensory testing, 3/5 MRC asymmetric weakness mainly proximal in upper extremities and distal in lower, hand atrophy, weakened reflexes. Laboratory tests, CSF, anti-GM1 antibody assay were unremarkable. Electrophysiological study suggested MMN. Patient underwent periodic infusion of immuneglobulin without improvement. In October 2002, her conditions rapidly worsened: she became quadriplegic, unable to swallow, to chew. Admitted to Intensive Care Unit because, tracheotomy was performed. Repeated CSF and searches for anti GM1 antibodies. was negative. Her final history prior to death was characterized by autonomic instability and by repeated, sudden losses of consciousness.

Case 2: This 67 year old woman was diagnosed having MMN in May 2001. At evaluation (September 2001) she exhibited 2/5 MRC distal and proximal weakness, atrophy hand muscles, absent reflexes throughout. Cranial nerves were normal, upper motor neuron signs absent. Anti-GM1 antibodies were found (IgM 1380 OD 450 nm, normal < 50). Periodic treatment with immuneglobulin and oral cyclophosphamide (1 mg/kg/daily) monthly gave transient results. In May 2006, her conditions rapidly worsened with involvement of lower limbs.

Discussion and conclusion:The illness of our patients has fatal course. In case 1, there were rapid progression to quadriplegia within two years and half and acute worsening in absence of precipitating events or of systemic illness. Involvement of cranial nerves and respiratory muscles in such case suggests acute demyelinating process as Guillain Barre' syndrome might have overlapped .Case 2 died because of respiratory arrest. Phrenic nerve palsy is reported as cause of respiratory failure in MMN with autoptic findings of demyelination. Thus fatal prognosis and respiratory failure may be clinical features of MMN.

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Sialylation of intravenous immunoglobulin (IVIg): detailed analysis of a lectin-affinity-purified IVIg fraction associated with anti-inflammatory activity

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Background: Inflammatory peripheral neuropathies such as Guillan-Barrè syndrome or chronic inflammatory demyelinating polyneuropathy can be treated with high doses of human intravenous immunoglobulin G (IVIg). Several models have been proposed for explaining the mode of action of this therapy. In one of those models, the terminal glycosylation of the conserved Fc N-glycans of IgG, in particular its α-2,6-sialylation, has been associated with its anti-inflammatory activity (Kaneko et al (2006). However, a detailed, site-specific N-glycan analysis of the anti-inflammatory IgG fraction obtained with lectin-affinity chromatography has not been done until now.

Methods: We used Sambucus nigra agglutinin (SNA) to enrich the α-2,6-sialylated forms of commercially available IVIg preparations and determined the Fc N glycans by liquid chromatography-electrospray ionization-mass spectrometry of the glycopeptides obtained by tryptic digestion. In addition, we obtained a total IVIg N-glycan profile by analysis of the PNGase F-released N-glycans of IVIg. Fc fragments were prepared with papain, purified on protein A and subjected to SNA chromatography.

Results: The thorough analysis of the fractions obtained by SNA chromatography revealed noteworthy details. The binding of IVIg to the lectin was essentially caused by its Fab glycosylation where considerable amounts of disialylated N-glycans are present. Interestingly, the IVIg fraction not bound by the lectin showed similar levels of mono-sialylated Fc glycans to those in the starting material. The SNA-binding Fc fragment of IVIg contained essentially only sialylated N-glycans and thus the Fc fragment must have contained two sialic acids to be bound by the lectin. Such rare IgG glycoforms, however, make up only 1% or less in human IgG.

Conclusions: Methodical, state-of-the-art analysis revealed that only a minor subpopulation of sialylated Fc N-glycans bound to SNA. As this fraction was linked with anti-inflammatory activity this biological effect likewise appears to depend on the presence of two sialic acids in the Fc region.

JS, MP, FA received honoraria from Baxter Innovations GmbH, the other authors are full time employees of Baxter Innovations GmbH.

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Multifocal motor neuropathy in a patient with genetically confirmed familial CMT1A

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Background: Immune mediated neuropathies such as CIDP and paraproteinemic neuropathy may occur in patients with inherited neuropathy while little is known on the association with multifocal motor neuropathy (MMN).

Case report: A 58 years-old man with familial history of genetically confirmed Charcot-Marie-Tooth type 1A (CMT1A) presented with a 1 year history of progressive weakness and wasting of the right hand. He had difficulty in writing, using keys and buttoning up. Before these symptoms appeared he only complained difficulty in running and inability to walk on heels. Clinical examination showed bilateral pes cavus and calf hypotrophy, marked weakness and wasting of the muscle innervated by the right and, to a lesser extent, left ulnar nerves. Deep tendon reflexes were absent. Sensory testing revealed mild tactile sensory loss in the feet. Genetic analysis confirmed the duplication at chromosome 17p11.2-12. Electrodiagnostic studies revealed markedly reduced motor conduction velocities in upper limb nerves (range 15–20 m/s), no evoked response in lower limb nerves, absent sensory action potentials in all examined nerves. Conduction blocks (BC) without temporal dispersion were detected in the right (89% amplitude reduction) and left (56%) median nerve between Erb's point and axilla and in the right (84%) and left (78%) ulnar nerves in the forearm. CSF proteins were marginally increased (51 mg/dL). Anti-GM1, -GM2, -GD1a IgM antibodies were normal. The patient was treated with monthly courses of IVIg 0.5 g/kg for four and later two consecutive days with a progressive consistent improvement in muscle strength and function in the arms and, marginally, in the legs. Nerve conduction studies two weeks after the first IVIg course revealed a consistent increase in proximal and distal CMAP amplitude in both ulnar nerves and reduced CB in the left ulnar nerve.

Discussion: The purely motor subacute impairment restricted to the territory of ulnar nerves, the presence of CBs, and the clinical and electrophysiological improvement after IVIg supported the diagnosis of MMN superimposed to CMT1A. Even if it is unclear whether this association is coincidental or reflects an autoimmune reaction against genetically affected nerves, this observation confirms that an unexpectedly rapid progression or asymmetric distribution of weakness in a patient with inherited neuropathy should raise the suspicion of a superimposed, potentially treatable immune neuropathy.

Multiple sclerosis

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Epstein-Barr virus antibodies in serum and cerebrospinal fluid from multiple sclerosis, amyotrophic lateral sclerosis and chronic inflammatory demyelinating polyradiculoneuropathy

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Background : Although the aetiology of multiple sclerosis (MS) is still unknown, several studies suggest a correlation between viral infection and risk for MS. In particular Epstein-Barr virus (EBV) has been considered involved in the pathogenesis of MS. However literature lacks studies that compare the serum and cerebrospinal fluid (CSF) EBV- positivity between MS and other neurological diseases.

Aim of study: to evaluate the prevalence and the titres of anti-Viral Capsid Antigen (VCA) IgG and IgM, anti-Epstein-Barr virus nuclear antigen (EBNA) IgG in serum and in CSF of patients with MS, Amyotrophic Lateral Sclerosis (ALS) and Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP).

Patients and methods: In our study we included patients affected by clinically defined MS, ALS and CIDP admitted to our neurological ward from 1998 to 2007. Anti-VCA IgG and IgM and anti-EBNA IgG have been analysed by ELISA. Patients were considered EBV-positive when serum antibody titre to VCA was > 20 UA/ml and to EBNA > 20UI/ml. Both serum and CSF titres were determined simultaneously.

Results: We studied 267 MS, 88 ALS and 50 CIDP patients. Serum anti-VCA IgG were positive in 265/267 (99%) MS patients, in 82/88 (93%) ALS patients and in 47/50 (94%) CIDP patients. Serum anti-VCA IgM were positive in 18/267 (7%) MS patients, in 0/88 (0%) ALS patients and in 1/50 (2%) CIDP patients. Serum anti-EBNA IgG were positive in 261/267 (98%) MS patients, in 82/88 (93%) ALS patients and in 46/50 (92%) CIDP patients. We found higher serum titres of anti-EBNA IgG, anti-VCA IgG and anti-VCA IgM in serum from MS than from ALS ($p < 0.0001$, $p = 0.001$ and $p = 0.0013$ respectively) and CIDP ($p = 0.0002$, $p = 0.0284$ and $p = 0.0056$) patients. No significant difference between ALS and CIDP patients was observed. A mild elevation of IgG antibody titres against EBNA (= 1 UI/ml) and VCA (= 1 UA/ml) in CSF was observed in 20/262 (13%) and in 4/262 (1.5%) MS patients respectively. Only 1/66 (1.5%) ALS patients showed IgG antibodies a IgG antibody against VCA in CSF.

Conclusion: Our data demonstrate that serum titres of anti-VCA IgG an IgM and anti-EBNA IgG are significantly higher in MS than in ALS and CIDP patients. In addition, mild elevation of anti-EBNA antibodies in CSF was only observed in some MS patients indicating an immune response against latent EBV proteins in Central Nervous System.

These results suggest that EBV may play a role in the pathogenic process of MS.

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Use of herbal remedies among patients with multiple sclerosis: a nation-wide survey in Italy

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Objective: Little information exist regarding the use of herbal medicine among multiple sclerosis (MS) patients, although several lines of evidences suggest that medicinal plants and herbal remedies are quite popular in these subjects. Our aim is to assess prevalence, spectrum and clinical/epidemiological factors related to herbal use by MS patients in Italy.

Methods: In June 2008 a nation-wide multicentric survey was started, involving 14 Italian reference centres for MS. During the survey, MS outpatients consecutively attending a neurological clinic are given a semi-structured questionnaire investigating the use and attitudes towards herbal medicine. The survey is still in progress and will end in April 2009. As of the end of January 2009, 1,817 questionnaires were collected. Hereafter results from an interim analysis performed in October 2008 on 394 questionnaires are presented.

Results: Age of participants was (mean $\pm$ SD) 40.5 ± 11.1 years, and females were 68.9%. A current/past utilization of Cannabis was

declared by 9.6% of respondents. Among respondents, the use of herbals for MS or other diseases occurred in 9.9 and 29.6% respectively. Commonly used plants were ginseng (32.6%), liquorice (12.8%), gingko biloba (10,5%) and hypericum (10.5%). Reasons for use of herbal medicine included: herbals deemed less toxic than conventional drugs (33%), suggested by someone (24.3%), purpose to follow a "healthy lifestyle" (20.4%); failure of conventional therapies was indicated only by 1.9% of the respondents. Herbals were usually purchased from herbalists (57.4%) or a chemists (34%), upon advice from a herbalist (35.2%) or acquaintances (23.8%), rather than from a general practitioner (GP, 16.2%) or the caring neurologist (3.8%). Physicians were informed about herbal treatments in less than half of the cases (48.8%).

Conclusion: Preliminary results indicate that use of herbal remedies is frequent among MS patients, however limited information are provided to GPs and/or caring neurologists. Social and cultural factors, rather than failure of conventional treatments, seem to affect herbal use. Herbalist is the main reference point for both advice and purchase of herbal remedies. Upon completion, the present study will provide the first comprehensive description of herbal use among MS patients in Italy, and will allow interventions aimed at the proper use of herbal medicine, thus preventing adverse reactions as well as unwanted interactions with conventional drugs.

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Natalizumab treatment after autologous haematopoietic stem cell transplantation in patients with aggressive multiple sclerosis

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Objectives: To evaluate safety and efficacy on Natalizumab treatment after low dose conditioning haematopoietic stem cell transplantation (HSCT).

Methods: Observational case report.

Results: We report on four young multiple sclerosis (MS) patients (three females) who presented several clinical relapses and progressive increase of lesional load, with enhancing lesions at brain MRI, despite immunomodulant and immunosuppressive therapies. Between January 06 and January 07 they underwent HSCT. The mean disease duration was 8.4 years (4–10) and mean basal EDSS was 5.2 (2.5–6). Pre-HSCT brain MRI showed an increased lesional load with multiple enhancing lesions. After stem cells mobilization with Cyclophosfamide (Cy) patients were conditioned with Thiothepa followed by Cy. No in vivo or ex vivo manipulation of the graft was performed. The patients were followed with clinical evaluations every three months and with brain MRI every 6 months. No major adverse events occurred after transplantation, but they presented a clinical and neuroradiological reactivation of the disease. The first patient, after six months, presented new and enhancing lesions at the brain MRI and after 1 year developed a clinical relapse with persistent MRI activity. The second patient, after a clinical improvement during the first year, developed several clinical relapses with new and enhancing lesions at the brain MRI. The other two patients presented a clinical relapse with MRI activity respectively at one year and two years from HSCT. Due to the relevant and persistent inflammatory activity, the patients began monthly i.v. Natalizumab administration. This treatment was started after a mean period of 18 (13–27) months from HSCT and till now they have undergone 14 (8–20) cycles obtaining a complete clinical stability. Frequent MRI evaluations showed no increase in the lesional load or new enhancing lesions. No significant adverse events have occurred and no infections have been observed.

Conclusion: Natalizumab administration even after an extreme immunosuppression, is well tolerated without relevant side effects and is able to induce a clinical and neuroradiological stability in aggressive MS patients not responding to conventional escalating therapy. Further follow-up is necessary to establish the real risk-benefit ratio and to gain more experience on the long term effects in the use of Natalizumab after immunosuppressive treatments.

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Subclinical demyelinating lesions: clinical and magnetic resonance imaging follow-up of 13 patients

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Objectives: The wide use of magnetic resonance imaging (MRI) in clinical practice has led to the discovery of incidental white matter lesions suggestive of multiple sclerosis (MS) in asymptomatic patients. The aim of this study is to describe the clinical and radiological characteristics of patients with silent demyelinating lesions.

Methods: We selected all the patients that had been referred to our MS unit because of asymptomatic demyelinating lesions suggestive of MS. A retrospective observational study was performed with clinical and radiological data collected from patients that had been followed up in our unit.

Results: A total of 13 patients were identified (11 female and 2 male; mean age 37,2 years, range 21–56). Only one patient had a familial history of MS. Two patients suffered from migraine and five patients had a personal history of psychiatric disorders. The first brain MRI study was performed for the following reasons: headache / migraine ($n = 5$), psychiatric disorders ($n = 2$), craniocerebral trauma ($n = 1$), epilepsy ($n = 1$), loss of consciousness ($n = 1$), disorientation ($n = 1$), tremor ($n = 1$), uveitis ($n = 1$). Nine patients (69.2%) met Barkhof criteria for dissemination in space on the first brain MRI. Mean time for the second brain MRI was 24.4 months and new T2 lesions were found in 27.3% of cases. Clinical evaluation and paraclinical tests (blood tests, cerebrospinal fluid examination and visual evoked potential) were performed in order to exclude other diseases. Mean clinical follow-up time was 36 months (median 24.5). Two patients (14.3%) converted to clinically definite MS during follow-up and both met Barkhof criteria for dissemination in space on the first brain MRI scan. Mean time between baseline MRI and clinical onset was 6 years (range 1–11).

Conclusion: Patients with white matter lesions suggestive of multiple sclerosis may experience clinical events during follow-up, although the risk is low.

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Incidence of acute leukaemia in multiple sclerosis patients treated with mitoxantrone: a multi-centre retrospective Italian study

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Objectives: Mitoxantrone (MTX) is an immunosuppressive drug worldwide approved for the treatment of patients with aggressive Multiple Sclerosis (MS). The use of MTX requires careful monitoring for potential severe adverse events. Previous studies reported an incidence of acute leukaemia (AL) from 0.07% to 0.25% in MS patients treated with MTX (dose < 140 mg/m^2). We retrospectively collected data from a large cohort of Italian MS patients treated with at least one cycle of MTX, in order to detect the incidence of AL.

Material and methods: Up to now we have gathered a total of 2854 patients with relapsing-remitting (41%), primary progressive (8%) and secondary progressive (51%) MS, treated with MTX, since 1999, and observed for at least one year. Patients were identified by 36 Italian MS Centres. The following data were retrospectively collected: the total number of patients treated with MTX in each centre, the total cumulative dose (mg/m^2), the duration of follow-up from the beginning of therapy to the last contact with the patient. Clinical features and cytogenetic analysis were recorded for every AL patient.

Results: So far we have observed 21 cases of AL, of whom 8 died. The cumulative incidence of AL was 7.4 per 1,000; the incidence rate was 0.16 per 1,000 person-month. Patients who presented AL received a greater number of MTX administrations (8.6 cycles vs. 7.2 $p < 0.05$) and a greater cumulative dose (82.4 vs. 62.87 mg/m^2 $p < 0.009$) than patients who did not have AL. AL developed after an average period of 37 months from the beginning of MTX therapy and after a mean of 18 months from the end of treatment. Using as expositive factor the cumulative dose >82.4 mg/m^2 we observed an Incidence Rate Ratio of 2.74 (CI95% 1.06–7.35, $p = 0.01$).

Conclusions: The Incidence of AL in Italian MS patients treated with MTX is significantly higher than previously reported. The potential risks of AL, as well as the dose-related cardiotoxicity, should be carefully considered against the potential benefits of MTX treatment on every single MS patient. Moreover, all MS patients treated with MTX must undergo a prolonged and careful haematological follow up.

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The CARE-MS^{SM} II Trial (comparison of alemtuzumab and rebif$^{®}$ Efficacy in multiple sclerosis): updated design of a phase 3, open-label, rater-blinded study of alemtuzumab in patients with multiple sclerosis who have relapsed on therapy

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Objective: Present current design for CARE-MS II.

Background: Alemtuzumab, a monoclonal antibody targeting CD52 antigen on lymphocytes, demonstrated superior efficacy and manageable safety profile in CAMMS223, a randomized, open-label, rater-blinded, phase 2 study of treatment-naïve patients with relapsing-remitting multiple sclerosis (RRMS). Three-year results from CAMMS223 showed that alemtuzumab reduced the rate of sustained accumulation of disability by 71% and the annualized relapse rate by 74% compared with interferon β-1a (IFNB-1a; both $p < 0.001$). Moreover, mean expanded disability status scale (EDSS) scores improved by 0.39 point (approximately 22%) with alemtuzumab and worsened by 0.38 (approximately 13%) with IFNB-1a ($p < 0.001$). Principal adverse events associated with alemtuzumab included infusion associated reactions, mild to moderate infection, and autoimmunity. Two phase 3 studies are currently ongoing: CARE-MS I trial to confirm alemtuzumab's efficacy in treatment-naïve MS, and CARE-MS II trial, presented here, to extend these findings to patients with active RRMS who have relapsed during prior treatment with a disease modifying therapy (DMT).

Design/methods: CARE-MS II, a phase 3, multinational, comparator-controlled study is enrolling patients aged 18–55 with a diagnosis of RRMS, $\geq$2 relapses in the past 24 months, an EDSS score Γëñ 5.0, and symptom onset within the past 10 years. Patients must also have had $\geq$1 relapse on an interferon βor glatiramer acetate, after receiving the therapy for $\geq$6 months. Eligible patients are randomized 2:1 to 12 mg intravenous alemtuzumab (2 brief annual cycles) or 44 μg subcutaneous IFNB-1a 3 times/week for 2 years. The EDSS, multiple sclerosis functional composite, relapse, and MRI evaluations are performed by blinded raters. Suspected relapses are adjudicated by a blinded panel of MS experts. Patients also participate in the CARE-MS Safety Monitoring Program to optimize patient care.

Results: Enrollment will continue until approximately 573 patients are randomized to 12 mg alemtuzumab or IFNB-1a.

Conclusions: The rater-blinded CARE-MS II trial is designed to establish efficacy and safety of alemtuzumab in patients with RRMS who relapsed during prior treatment with a DMT. Based on the superior efficacy and manageable safety profile of alemtuzumab in CAMMS223, after 2 years on study, alemtuzumab and IFNB-1a patients may be eligible to receive alemtuzumab re/treatment as part of an extension study.

Supported by: Genzyme Corporation.

P346

Continuous versus non-continuous subcutaneous interferon β-1a treatment in relapsing-remitting multiple sclerosis: long-term data from the PRISMS study

B. Uitdehaag, L. Kappos, E. Verdun, J. Gardner, on behalf of the PRISMS Study Group

Objective: The 8-year PRISMS (Prevention of Relapses and disability by Interferon β-1a Subcutaneously in Multiple Sclerosis) long-term follow-up (LTFU) study supported the efficacy of interferon (IFN) β-1a in relapsing-remitting multiple sclerosis (RRMS) and demonstrated the importance of early, high-dose, high-frequency treatment. This analysis evaluated the effect of treatment interruption on long-term clinical outcomes in those patients who received IFN β-1a, 44 mcg subcutaneously (sc) three times weekly (tiw), in the PRISMS study.

Methods: A post-hoc exploratory analysis was performed using data from patients who were randomized to receive IFN β-1a, 44 mcg sc tiw, at the start of the PRISMS study and who were available for LTFU ($n = 136$); 48 of 184 patients randomized to this treatment [26.1%] were lost to follow up. Clinical outcomes in patients who received treatment without interruption from baseline to LTFU (continuous; $n = 45$; taking no other disease-modifying drugs [DMDs]) were

compared with those in patients who had medication interruptions (non-continuous; $n = 91$; irrespective of other DMDs being taken).

Results: Mean (SD) cumulative dose exposure was 49.4 (2.6) mg/patient in the continuous group and 34.0 (13.5) mg/patient in the non-continuous group. In the non-continuous group, 11% of patients received one or more other MS therapy at some time during the 8-year follow up. Mean (SD) annualized relapse rate was consistently lower in the continuous than in the non-continuous group from baseline to LTFU (0.51 [0.54] vs 0.61 [0.56]) and throughout the study (years 0–2, 0.80 [0.87] vs. 0.90 [0.97]; years 2–4, 0.54 [0.73] vs. 0.59 [0.74]; years 4–LTFU, 0.31 [0.50] vs. 0.46 [0.55]). The proportion of patients with 3-month confirmed expanded disability status scale progression was 46.7 and 64.8% in the continuous and non-continuous groups, respectively. Conversion to secondary progressive MS occurred in 11.1% of continuous patients and in 25.3% of non-continuous patients.

Conclusion: The findings from this exploratory analysis of the PRISMS LTFU data show that the best long-term efficacy outcomes were observed in patients receiving continuous treatment with IFN β-1a, 44 mcg sc tiw, compared with those with treatment interruptions. Although the potential impact of other factors must be considered, these data suggest that better outcomes may be expected in patients who adhere to treatment and who avoid treatment interruptions over the long term.

Supported by Merck Serono S.A., Geneva.

P347

Long-term treatment with subcutaneous interferon β-1a in relapsing-remitting multiple sclerosis: exploratory analysis of cumulative time and dose impact on clinical and magnetic resonance imaging outcomes

B. Uitdehaag, L. Kappos, E. Verdun, J. Gardner, on behalf of the PRISMS Study Group

Objective: The prevention of relapses and disability by interferon β-1a subcutaneously in multiple sclerosis (PRISMS) long-term follow-up (LTFU) study supported the beneficial effects of subcutaneous (sc) interferon (IFN) β-1a, 44 mcg three times weekly (tiw), in relapsing-remitting multiple sclerosis (RRMS) on clinical and magnetic resonance imaging (MRI) measures. We examined long-term (up to 8 years) clinical and MRI outcomes based on cumulative time of exposure to IFN β-1a sc tiw in RRMS in the PRISMS LTFU cohort. Similar analyses were performed for cumulative dose exposure.

Methods: This was a post-hoc exploratory analysis of data from the PRISMS LTFU study. From baseline to the LTFU visit, 178 of 560 randomized patients (31.8%) were lost to follow up. Patient data from the three original study arms (IFN β-1a 22 mcg [$n = 123$], 44 mcg [$n = 136$], and placebo [$n = 123$]) were pooled and ranked from lowest to highest (a) cumulative time on treatment and (b) cumulative dose exposure. Clinical and MRI outcomes were assessed in the minimal (lowest quartile, MIN) and maximal (highest quartile, MAX) groups.

Results: In the MIN and MAX time groups, mean (standard deviation; SD) cumulative time exposure was 156.8 (87.7) and 390.3 (5.9) weeks and mean (SD) cumulative dose exposure was 13.65 (9.37) and 38.28 (10.97) mg/patient. From baseline to LTFU, the MAX time group had a lower mean (SD) annualized percentage change in T2 burden of disease (44.3% [119.5] vs. 86.2% [183.1]), a greater proportion of relapse-free patients (16.8% vs. 7.3%), and a lower mean (SD) annualized relapse rate (0.51 [0.49] vs. 0.76 [0.55]), compared with the MIN time group. The analysis of outcomes by cumulative dose exposure to IFN β-1a sc tiw also showed that patients in the highest cumulative dose exposure quartile experienced better clinical and MRI outcomes than patients in lower dose exposure quartiles (baseline to LTFU).

Conclusion: Results from these exploratory analyses of data from the PRISMS LTFU study show that, in patients with RRMS, the greatest beneficial effects on clinical and MRI outcomes were observed with the highest cumulative time and dose exposures to sc IFN β-1a, for up to 8 years. Although the direction of causality cannot be established clearly and other contributing factors may also play a role, these findings support the importance of maintaining therapy over the long term with high-dose, high-frequency sc IFN β-1a.

Supported by Merck Serono S.A., Geneva.

P348

Beneficial effects of a new formulation of subcutaneous interferon β-1a on magnetic resonance imaging outcomes in patients with relapsing-remitting multiple sclerosis: results at 16 weeks from a double-blind, placebo-controlled study

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Objective: A new formulation of subcutaneous (sc) interferon (IFN) β-1a, produced without foetal bovine serum and without human albumin as an excipient, has been developed with the aim of improving injection tolerability and reducing immunogenicity. The efficacy of this new formulation of sc IFN β-1a was evaluated in patients with relapsing-remitting multiple sclerosis (RRMS) using frequent magnetic resonance imaging (MRI).

Methods: In this Phase IIIb, double-blind, placebo-controlled study, patients with RRMS (McDonald criteria; expanded disability status scale score $\leq$5.5; disease duration $>$ 12 months) were randomized (2:1) to IFN β-1a, 44 mcg sc three times weekly (tiw; $n = 120$), or placebo ($n = 60$) for 16 weeks. The primary endpoint was the number of combined unique active (CUA) brain lesions at week 16. A single-arm phase (IFN β-1a, 44 mcg sc tiw, for a further 24 weeks) is ongoing and MRI data at 20, 24, 28, 32, 36 and 40 weeks are being collected. Post-hoc analyses were conducted on MRI data at weeks 4, 8, 12 and 16.

Results: Baseline demographics and disease characteristics were similar between treatment groups. At week 16, the mean (median) number of CUA lesions (primary endpoint) was significantly lower in the IFN β-1a group (0.9 [0]) than in the placebo group (3.0 [1]; non-parametric analysis of variance: $p < 0.001$). The estimated ratio (95% confidence interval [CI]) of means (IFN β-1a/placebo) for the cumulative number of new gadolinium (Gd)-enhancing T1 lesions during 16 weeks was 0.23 [0.15–0.36], signifying 77% fewer new Gd-enhancing lesions with IFN β-1a versus placebo. At week 16, the change in T2 burden of disease was significantly lower with IFN β-1a than placebo ($p < 0.001$). Post-hoc analyses of the current study showed a significant 68% reduction in new Gd-enhancing lesions ($p < 0.001$) and a 40% reduction in CUA lesions ($p = 0.019$) with sc IFN β-1a versus placebo as early as week 4; these effects were sustained at all subsequent monthly time points.

Conclusion: This is the first pivotal study to demonstrate the beneficial effects of the new formulation of IFN β-1a sc tiw on MRI outcomes in patients with RRMS. The beneficial effects shown on MRI at 16 weeks were similar to those shown with the previous formulation of IFN β-1a sc tiw in the PRISMS study. Post-hoc analyses showed that the significant treatment effects occur very early after treatment initiation.

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P349

Correlation between temporal lobe involvement demonstrated by MRI and changes of cognitive performance in different clinical forms of multiple sclerosis

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Objectives: To assess temporal lobe (TL) involvement in multiple sclerosis (MS) by MRI and to find correlation between the number of lesions and neuropsychological performance, especially visuospatial and verbal memory in different clinical forms of the disease.

Methods: Patients (pts): 49 pts fulfilling Barkhof-criteria (men/women: 14/35, mean age: 36 SD = 9.3 years, mean time since the first symptom: 59 months, SD = 49.8). Radiology: 3T MRI (Philips Achieva), MS protocol. Neuropsychology: Zung Depression Scale, Mini Mental State, Fatigue-scale, Rey-complex, Rey Auditory-Verbal Learning Test (RAVL), digit span test. Statistics: Spearman-correlation, with significance level of $p < 0.05$.

Results: We investigated the number of T1 and T2 lesions in the different subregions of the TL, and we found that the total number of plaques correlates with the severity of clinical symptoms (Expanded Disability Status Scale, EDSS), and disease duration. On the contrary, the degree of depression and fatigue was independent of these radiological and clinical factors. We carried out neuropsychological tests focusing on memory functions, regarded to be mediated by TL. The poor performance in visuospatial memory tests (Rey-komplex) correlated significantly with medial TL (i.e. parahippocampal gyrus and subiculum) involvement. In addition, the impairment of verbal memory (RAVL) correlated with the total number of lesions in both TLs. Based on the frequency and severity of relapses, EDSS and clinical history we isolated 2 subgroups, one with 29 pts of relapsing-remitting course /RR/, and the other ($n = 7$) with a benign disease course /b-RR/. No significant difference was found between the two groups concerning the MRI lesions, and the results of the psychological tests.

Conclusion: A significant correlation was found between the total number of TL lesions and visuospatial and verbal memory performance. Furthermore, there was no significant difference in radiological and neuropsychological involvement between patients with clinically benign disease course and patients with the relapsing-remitting form. This raises the question whether a truly benign course of the disease exists.

P350

Natalizumab improves physical disability in patients with relapsing multiple sclerosis

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Objective: Sustained progression in disability, measured by an increase in expanded disability status scale (EDSS) score, is a standard measure of neurologic disability in clinical studies of patients with relapsing multiple sclerosis (MS). In the AFFIRM study, natalizumab (TYSABRI[R]) reduced the risk of sustained disability progression by 42–54% over 2 years ($p < 0.001$). In addition, recent analyses from this study have shown that 83.6% of natalizumab-treated patients were free of disability progression over 2 years. In light of these results, it was of interest to explore the effects of natalizumab on the cumulative probability of sustained improvement in disability as measured by the EDSS.

Methods: This was a post hoc analysis of data from AFFIRM patients who had an EDSS score of 2.0 or higher at baseline (natalizumab, $n = 417$; placebo, $n = 203$). Improvement in disability was defined as a 1.0-, 1.5-, or 2.0-point decrease in EDSS score that was sustained for 12 weeks. Treatment effects and baseline factors associated with sustained improvement in disability at 2 years were estimated from a Cox proportional hazards model.

Results: The cumulative probability of a 1.0-point EDSS improvement sustained for 12 weeks over 2 years was increased by 69% with natalizumab relative to placebo (hazard ratio [HR] = 1.69; 95% confidence interval [CI], 1.16–2.45; $p = 0.006$). Sensitivity analyses showed that the effect of natalizumab remained significant when the definition of sustained improvement was extended to 24 and 48 weeks. Baseline disease variables that were associated significantly with improvement included higher EDSS score, shorter disease duration, and greater brain parenchymal fraction; the treatment effect remained significant after adjusting for these variables (HR = 1.69, 95% CI = 1.16–2.47; $p = 0.006$). Natalizumab significantly increased the cumulative probability of a 1.5-point EDSS improvement (HR = 1.91; 95% CI, 1.06–3.45; $p = 0.030$) and a 2.0-point EDSS improvement (HR = 2.80; 95% CI, 1.17–6.66; $p = 0.020$) over 2 years relative to placebo. The effects of natalizumab versus placebo also were significant for 1.5-point ($p = 0.001$) and 2.0-point ($p = 0.040$) EDSS improvements sustained for 24 weeks.

Conclusions: Natalizumab significantly increased the cumulative probability of sustained improvement in physical disability.

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Natalizumab improves quality-of-life outcomes in patients with highly active multiple sclerosis

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Objective: In the pivotal AFFIRM and SENTINEL phase 3 studies of patients with relapsing multiple sclerosis (MS), natalizumab (TYSABRI[R]) significantly improved quality of life (QoL) measured using the Medical Outcomes Study Short Form-36 (SF-36) and a visual analog scale (VAS) of well-being. The objective of the present analyses was to assess whether natalizumab improves QoL outcomes in the subgroup of patients with highly active disease at baseline (defined as 2 or more relapses in the preceding year and 1 or more gadolinium-enhancing lesion at study entry).

Methods: Patients received natalizumab or placebo in AFFIRM and natalizumab plus interferon (IFN) β-1a or placebo plus IFN β-1a in SENTINEL. The SF-36 and VAS were administered at baseline and at study weeks 24, 52, and 104. Data from both studies were combined at baseline for comparisons between the subgroups of patients with highly active and non-highly active MS and correlations with expanded disability status scale (EDSS). Mean change from baseline to week 104 on the SF-36 physical component summary (PCS), SF-36 mental component summary (MCS), and VAS were compared between treatments within each study.

Results: Significant negative correlations between PCS scores and EDSS scores at baseline were observed in patients with highly active

MS ($r = -0.391$, $p < 0.0001$) and those with non-highly active MS ($r = -0.490$, $p < 0.0001$). Mean MCS score at baseline was significantly lower (indicating worse QoL) in patients with highly active MS than in those with non-highly active MS (45.8 vs. 47.2; $p = 0.023$). In patients with highly active MS in the AFFIRM study, natalizumab significantly improved changes in PCS (1.6 vs. −2.2; $p = 0.019$), MCS (3.4 vs. −1.3; $p = 0.030$), and VAS (3.7 vs. −7.6; $p = 0.013$) scores from baseline to 2 years compared with placebo. Natalizumab also improved changes in PCS (0.7 vs. −0.9; $p = 0.032$), MCS (2.1 vs. −2.4; $p = 0.123$), and VAS (1.0 vs. −3.5; $p = 0.044$) scores from baseline compared with placebo patients with highly active MS in the SENTINEL study.

Conclusions: Natalizumab improves QoL in patients with highly active relapsing MS.

Studies supported by Biogen Idec, Inc. and Elan Pharmaceuticals, Inc.

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A phase 4 study of acetaminophen and prednisone in the management of flu-like symptoms in patients with relapsing multiple sclerosis receiving intramuscular interferon β-1a

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Objectives: The phase 4 AIMS study investigated the efficacy of acetaminophen and prednisone in the management of flu-like symptoms (FLS) associated with intramuscular (IM) interferon (IFN) β-1a in patients with relapsing forms of multiple sclerosis (MS). Secondary endpoints included global impact of treatment and treatment compliance.

Methods: Three hundred and four patients either naïve to IM IFN β-1a or receiving IM IFN β-1a for less than 30 days and experiencing FLS were randomized to receive either acetaminophen 650 mg 1 h before and 4, 8, and 12 h after IM IFN β-1a injection, or prednisone 10 mg p.o. 1 hour before and 4 and 8 h after IM IFN β-1a injection. Patients were assessed for 12 weeks after randomization.

Results: At least 4 evaluable visits were completed by 254 patients. In the overall study population, 80.7% of patients were female and 86.2% were white. The mean age of the 254 patients was 41.8 years, and they had a mean disease duration of 2.8 years. There were no differences in endpoints between the 2 arms of the study. Overall, patients were highly compliant with IM IFN β-1a (98%), acetaminophen, and prednisone. The most common FLS reported by patients receiving IM IFN β1a plus acetaminophen was muscle ache, followed by asthenia, chills, and fever. FLS was most frequent and of the longest duration during week 1; thereafter, FLS significantly subsided in frequency and duration through the remainder of the 12-week period. Patients rated FLS as mild for the duration of the study, irrespective of symptom frequency and duration. The evaluable data from the end of study belief assessment ($n = 239$) completed by each patient showed that 77% of patients felt that IM IFN β-1a decreased the chance of their MS worsening, 74% believed that IM IFN β-1a provided a sense of control over their MS, and 85% indicated that IM IFN β-1a did not interfere with their normal activities.

Conclusion: This study demonstrates that FLS is mild, transient, and manageable in patients with relapsing MS receiving IM IFN β-1a plus either acetaminophen or prednisone.

Study supported by Biogen Idec, Inc.

P353

Five-year study of adherence to disease-modifying therapies in patients with relapsing multiple sclerosis: 2-year interim results

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Objectives: Disease-modifying therapies (DMTs) for multiple sclerosis (MS) must be taken over the long term. Treatment efficacy may be substantially affected by non-adherence. In Spain and Portugal, a 5-year follow-up study is in progress to evaluate long-term adherence in a subset of patients from the global adherence project (GAP; $N = 2{,}648$), a multicentre, observational study in patients with relapsing-remitting MS who were treated with the same DMT for at least 6 months. Here we report data from the first 2 years of the study in Spain.

Methods: A questionnaire assessing adherence to DMTs, including intramuscular (IM) interferon β-1a (IFN β-1a), subcutaneous (SC) IFN β-1a, IFN β-1b, and glatiramer acetate (GA) is distributed annually for 5 years to patients with MS who were enrolled in GAP, and their treating neurologists. Adherence was defined as not missing a DMT injection or changing a dose in the 4 weeks prior to completing the survey. Patients signed informed consent for follow-up, and ethics committees approved follow-up in 15 out of 18 centers in Spain.

Results: A subset of the 416 patients originally enrolled in GAP in Iberia is included in this follow-up study. At baseline, patients had a mean age of 37.5 years and 69.9% were female. They had been on their current DMT for a median of 29.0 months, and the overall adherence rate was 83.9%. Patients taking IM IFN β-1a were significantly more adherent (94.6%) compared with patients taking SC IFN β-1a 22 mcg (81.0%; $p = 0.0072$), SC IFN β-1a 44 mcg (74.4%; $p = 0.0002$), IFN β-1b (85.9%; $p = 0.0421$), and GA (81.3%; $p = 0.0069$). At year 1 ($n = 141$), the overall adherence rate was 86.6%, and patients on IM IFN β-1a were significantly more adherent than patients on IFN β-1a 22 mcg (93.9 vs. 66.7%; $p = 0.0251$). There were no significant differences in adherence among patients on the other DMTs. 131 patients (32 on IM IFN β-1a, 10 on SC IFN β-1a 22 mcg, 36 on SC IFN β-1a 44 mcg, 27 on IFN β-1b, and 25 on GA) had completed questionnaires at all periods. Overall adherence for these patients at year 2 was 82.4% (87.5, 80, 77.8, 85.2, and 80% respectively). There were no significant differences in adherence rates among the DMTs at year 2.

Conclusions: Adherence remained high among all DMTs over the first 2 years of the study. It was highest with IM IFN β-1a at first assessment (after nearly 3 years on therapy) compared with other DMTs.

Study supported by Biogen Idec, Inc.

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Neutralizing antibodies to interferon β: an observational multiple sclerosis clinic-based study

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Objective: to evaluate the frequency of neutralizing antibodies (NABs) to Interferon-b (IFN) in a population of MS patients treated with different types of IFNs and to detect their impact on patient management.

Methods: This is a retrospective, observational study. Patients attending San Raffaele MS Centre have been tested for NABs

presence since April 2005. NABs evaluation was performed at CRESM, S.Luigi Hospital-Orbassano.

Results: NABs detection was performed in 826 patients treated with different types of IFNs. In particular we investigated 96 (12%) patients treated with Avonex, 114 (14%) with Bferon, 328 (39%) patients with Rebif 22 and 288 (35%) with Rebif 44. First NABs determination disclosed a positive titre of antibodies (ten-fold reduction units -TRU- $>$ 1:20) in 165 cases (20%). Particularly NABs were detected in 6.2, 30.7, 17 and 23.6% of patients treated with Avonex, Bferon, Rebif 22 and Rebif 44 respectively. Nabs evaluation was repeated in 22% of patients ($n = 185$). The re-test showed that 11 (10%) out of 116 patients previously negative, presented Nabs positivity, while 22 (22%) out of 96 patients with a previous positivity became negative. Among the 160 patients with NABs positivity at one or more blood tests, 77 (48%) had a titre lower than 1:100 and 83 patients (52%) between 1:100 and 1:5120. We subdivided Nabs-positive patients into two groups: patients with a titre $<$100 and patients with a titre $>$100. Within the first group therapy was changed in 15 patients (19.5%), while in the second one therapeutic changes occurred in 73 subjects (88%). Clinical disease activity was evaluated all over the year before and after Nab testing, with the first group showing a mean pre-test annualized relapse rate of 0.53 and the second group of 0.77. The annualized relapse rate after NABs evaluation was 0.24 for the first group and 0,3 for the second group. Brain MRI data was analyzed too, detecting an MRI activity in the year before the test in 36% and 51% of the two groups, and in 16 and 24%, respectively, in the following year.

Conclusions: Our results confirm that NABs status can influence the clinical response to IFNs and this finding should be considered in the care of IFN-treated patients. The early characterization of patients developing high NABs titre is an easy and crucial procedure to optimize MS patients management. A future challenge should consider performing test to identify genetic variants predictive of NABs development.

P355

Multifactorial analysis of upper limb in patients affected by multiple sclerosis

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Objective: Aim of this study was: (1) to test whether kinematic analysis was able to quantitatively characterize functional limitation of upper limb movements in MS patients; (2) to evaluate potential correlation between clinical scores and computed kinematic parameters; (3) to propose a quantitative evaluation tool able to provide neurologists and rehabilitation specialists with a simple yet sensitive means to follow the progression of MS and to evaluate the effects of treatments.

Methods: Twelve patients with definite multiple sclerosis, seven women and five men (age: 53.5 $\pm$ 10.8 years, disease duration: 18.6 $\pm$ 9.8 years, phase: 10 secondary progressive, 2 relapsing remitting), and twelve age-matched healthy subjects (3 males, 9 females, age: 51.2 $\pm$ 6.1 years) participated in the study. Patients were clinically examined with following scales: medical research council (MRC), nine-hole-peg test (NHPT), Ashworth scale for spasticity, and cerebellar signs (0–5 scale). We performed quantitative kinematic analysis of pointing movement using the optoelectronic technology of a gait analysis laboratory. Following punctual parameters were computed: Normalized Jerk Score (NJS) and number of movement unit (NMU) characterized movement smoothness, while movement speed was characterized by peak velocity (PV).

Results: MS patients presented a segmented movement: both NJS and NMU were significantly higher than controls ($p < 0.0001$). The peak velocity was lower in MS patients ($p < 0.0001$) and it could be related to the underlying pattern of flexors and extensors muscle torques, being peak velocity well correlated with MRC ($R = 0.76$). Muscle weakness was also the main drive of observed jerkier movement (NJS $R = -0.51$, NMU $R = -0.67$).

Conclusion: The proposed experimental setup and related parameters can be the candidate for the clinical tool to evaluate MS current state and treatment results. Not only it can be accomplished in a gait analysis laboratory, but also it represents a quantitative evaluation able to characterize different aspects affecting functional movement of upper limb in MS patients.

P356

Cost of the diagnosis of multiple sclerosis

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Objective: Multiple sclerosis (MS) is a demyelinating disease with a variety of symptoms and a complex diagnosis. It causes an important socioeconomic cost. Although many studies have demonstrated the significant cost of the disease, the impact of the diagnosis has not been studied yet. The aim of this work is to study the socioeconomic impact of diagnosis of MS.

Methods: This is a prospective observational study performed in 2 MS units from 2 hospitals of Barcelona. We selected the 30 patients that had been diagnosed of MS between december 2006 and april 2008. A questionnaire was administered to patients between 2 and 4 months after the diagnosis. The collected data included information about demographic, social, employment and clinical aspects, and the consumption of sanitary and nonsanitary resources during the MS diagnosis process. We employed a cost-of-illness method. The human capital approach was used to estimate indirect costs, and EQ-5D scale was used to estimate the impact of diagnosis on quality of life (intangible costs).

Results: The mean age of patients was 33.1 years (SD 8.9), predominantly female sex (80%). All patients had recurrent–remitting MS with mild disability (EDSS 0–3.5). The mean time from onset to diagnosis was 714.5 (SD 754.1) days. The 87% of the patients reported to be employed.

The diagnosis of MS required a mean of 9.6 (SD 6.2) medical visits, 3.3 (SD 5.1) days of hospitalization, and 30.2 (SD 37.6) days off work. They reported that they had lost 14.6 (SD 16.5) days of their free time.

The diagnosis of MS resulted 8450.1 euros per patient. This included 2519.4 euros of direct costs (medical visits: 459.9 euros, complementary tests: 685.6 euros, hospitalization days: 1026.7 euros, outpatient hospitalization: 27.5 euros, displacements: 148.2 euros and informal care: 171.5 euros), 2489.5 euros of indirect costs (days off work) and 3441.2 euros of intangible costs.

Conclusions: This is the first study in our country that analyses the socioeconomic impact of diagnosis of MS.

Total cost of MS diagnosis resulted 8450.1 euros per patient. Most contributors to the cost of diagnosis were hospitalization, days off work and intangible costs.

The impact of diagnosis on quality of life of patients is relevant.

P357

Characteristics associated with health-related quality of life in multiple sclerosis patients after three natalizumab infusions

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Objective: To assess baseline characteristics associated with health-related quality of life (HRQoL) in multiple sclerosis (MS) patients after three natalizumab infusions.

Methods: In the United States (US), prescribers and patients are required to be enrolled in the TOUCH Prescribing Program allowing for close monitoring of safety during treatment with natalizumab. MS patients newly enrolled in TOUCH were recruited to participate in a 1-year longitudinal study of their experiences with natalizumab with 4 planned assessments: prior to treatment initiation and after the 3rd, 6th and 12th infusions. HRQoL was assessed with the SF-12v2 in which higher physical and mental component summary (PCS and MCS) scores indicate improvement in HRQoL. Multivariate linear regression models were used to identify characteristics associated with HRQoL after three natalizumab infusions. The factors included in the analyses were age, disease duration, number of prior MS treatments and baseline (BL) disease severity measures (disease step (DS), functional status (FS), modified fatigue impact score (MFIS) and cognitive functioning score (CFS)).

Results: At the time of this analysis 504 patients had completed BL and 3rd assessments. Mean age was 46.1 (SD 10.9) years, 78% of patients were female, and mean disease duration was 10.0 (SD 8.3) years. PCS and MCS scores improved significantly from baseline (BL PCS: 34.0 vs. 36.0; $p < 0.001$ and BL MCS: 43.2 vs. 47.2; $p < 0.001$). Multivariate analysis indicated that after three natalizumab infusions greater improvements in PCS scores were associated with the following baseline characteristics: younger age ($p = 0.005$), lower BL DS scores ($p < 0.001$), lower BL FS scores ($p < 0.001$) and lower BL MFIS scores ($p < 0.001$). Similarly, greater improvement in MCS scores were associated with lower BL DS scores ($p = 0.009$), lower BL FS scores (0.030) and higher CFS scores ($p < 0.001$).

Conclusions: Characteristics associated with greater improvement in PCS scores after 3 infusions were younger age and lower fatigue, better ambulation and functional status at baseline; characteristics associated with improvement in MCS scores were higher cognitive functioning, better ambulation and functional status at baseline. These results are suggestive of the beneficial effects of earlier natalizumab intervention and warrant further investigation.

This study was supported by Biogen Idec.

P358

Neuropsychological features in adolescents with multiple sclerosis

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Objectives: Analysis of neuropsychological changes in cohort of multiple sclerosis (MS) affected adolescents with minimal neurological deficit on early stages of the disease.

Methods: 30 adolescents at 13–17 ages, with definite relapsing-remitting MS were observed in the period of remission. All patients had mild neurological deficit with maximum EDSS score 3,5 and low duration of the disease (less than 3 years). Test battery included short variant of MMPI questionnaire, Spielberg's anxiety scale, Beck's scale of depression, ten words test, Schulte's tables test and Culture Free Intellect Test (IQ).

Results: According to the MMPI questionnaire, in all scales (hypochondrias, depression, hysteria, paranoia, psichasthenia, schizophrenia and hypomania) mean data occurred within the normal range (40–70 points). But for all that, 4 patients have demonstrated significant increase of hypochondrias (13.8%), 2 patients have shown increase of depression and psichasthenia (6.9%). According to the Spielberg's anxiety scale, mean level of reactive and personal anxiety was mild (35.12 ± 8.10 and 39.18 ± 7.48 points). Even so, high level of reactive anxiety (more than 45 points) have been found in 3 patients (14.3%), and high level of personal anxiety have been found in 7 patients (24%). Mean level of depression, tested by the Beck's scale, was 5.7 ± 0.3 points; nevertheless, 2 patients have demonstrated mild depression (10 points) and 2 patients—significant depression (20–29 points). Mean IQ index was also normal (95.18 ± 11.68), but 4 patients have shown the increase of IQ more than 11 points and 8 patients have shown mild IQ decrease (80–89 points). Ten words test have demonstrated short-term memory disturbance in 10 patients, and long-term memory disturbance in 8 patients. Finally, 22 patients have demonstrated decrease of mental functioning speed according to the Schulte's tables test (more than 41 s).

Conclusion: In MS affected adolescents with mild neurological deficit and low duration of the disease memory and mental functioning speed disturbances prevail. Overall an intellectual level in this group of patients is normal, but nearby 20% demonstrate symptoms of hypochondrias, depression and anxiety.

P359

Haematological profiles in patients treated with cladribine tablets for relapsing-remitting multiple sclerosis (RRMS): results from the CLARITY study, a 96 week, phase III, double-blind, placebo-controlled trial

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Objectives: Cladribine tablets are in development for the treatment of multiple sclerosis. Cladribine is a pro-drug, and activation in specific cell types provides targeted and sustained immunomodulation, permitting the investigation of an oral short-course annual treatment. Here we explore this further through investigation of the haematological profiles over time in the CLARITY (CLAdRIbine tablets Treating multiple sclerosis orallY) study.

Methods: RRMS patients (McDonald criteria; EDSS: 0–5.5) were randomised (1:1:1) to one of two cladribine regimens (cumulative dose 5.25 or 3.5 mg/kg) or matching placebo. Cladribine tablets were given as short courses (once daily for 4–5 days) in Weeks 1, 5, 9 and 13 (5.25 mg/kg arm) or Weeks 1 and 5 (3.5 mg/kg arm), and again in Weeks 48 and 52 (both arms). Blood was sampled at intervals from day 1 to Week 96 for complete blood cell counts and differential analysis, with additional analysis of lymphocyte surface markers (including CD3, CD19, CD4, CD8, CD4/CD8 ratio CD16 and CD56) in a subset of patients.

Results: The ITT population comprised 456, 433 and 437 patients randomised to 5.25, 3.5 mg/kg or placebo groups; 80, 81 and 79 provided samples for lymphocyte surface marker analyses, respectively. Cladribine 5.25 or 3.5 mg/kg resulted in a rapid decrease in leukocyte counts from baseline median 6.6 and 6.6 /nL after the first treatment course, reaching minimum levels at Week 16 (median 4.4 and 5.3 /nL) and Week 55 (median 4.2 and 4.35 /nL, respectively), separated by a period of recovery until redosing at Week 48, versus placebo median values of 6.6–6.9 /nL at each time point. This was

accompanied by a marked and immediate decrease in B cells (CD19) at Week 4 reaching their nadir at Week 13–16, and to a lesser extent natural killer cells (CD16/CD56) at these time points, with a period of more substantial recovery towards baseline until Week 48. CD3, CD4 and CD8 cell counts showed a linear decrease to Week 16 (5.25 mg/kg group) or 13 (3.5 mg/kg group) relative to baseline or placebo, remaining at relatively constant levels thereafter, even following re-dosing at Weeks 48 and 52.

Conclusions: Cladribine treatment resulted in rapid and sustained effects on cellular subtypes implicated in MS pathogenesis. The results help to clarify the mechanism of targeted and sustained efficacy achieved with cladribine tablet therapy, and confirm the relevance of the annual short-course dosing regimen with cladribine tablets.

Study supported by: Merck Serono S.A., Geneva, Switzerland.

P360
Safety of cladribine tablets in the treatment of relapsing-remitting multiple sclerosis (RRMS): results from the CLARITY study, a 96-week, phase III, double-blind, placebo-controlled trial

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Objectives: Cladribine tablets are in development for the treatment of multiple sclerosis. Cladribine is a pro-drug, and activation in specific cell types provides targeted and sustained immunomodulation, permitting the investigation of an oral, short-course annual treatment. Here we assess the safety of cladribine tablets compared with placebo over 96 weeks in patients with RRMS participating in the CLARITY (CLAdRIbine tablets Treating multiple sclerosis orallY) study.

Methods: Patients with RRMS (McDonald criteria; Expanded Disability Status Scale score 0 to 5.5) were randomised to cladribine tablets (cumulative dose of 5.25 or 3.5 mg/kg) or matching placebo (1:1:1). Cladribine tablets were given in short courses (once daily for 4–5 days) for 4 (5.25 mg/kg arm) or 2 (3.5 mg/kg arm) consecutive months in the first 48 weeks, then 2 short courses at weeks 48 and 52 (both arms). Safety and tolerability were assessed over the 96-week study.

Results: Of 456, 433 and 437 patients randomised to 5.25 or 3.5 mg/kg cladribine or placebo, 454, 430 and 435 received study drug and were evaluable for safety analysis, with 86.2, 91.2 and 86.3 of patients successfully completing full-course treatment, respectively. Overall adverse event (AE) frequencies were comparable between groups. Lymphopenia occurred more frequently with cladribine 5.25 or 3.5 mg/kg than placebo, as anticipated from its mechanism of action (31.5, 21.6 and 1.8% patients, respectively). Other AEs reported by $\geq$10% patients were headache, nasopharyngitis, upper respiratory tract infection and nausea. Other AEs reported more frequently with cladribine than placebo included Herpes zoster (all dermatomal) and uterine leiomyomas. In the 5.25, 3.5 mg/kg and placebo groups, 7.9, 3.5 and 2.1% patients discontinued treatment due to AEs, and 9.0, 8.4 and 6.4% experienced serious AEs, respectively. Four isolated cases of single malignancies occurred during study in cladribine 5.25 mg/kg ($n = 1$) and 3.5 mg/kg ($n = 3$) groups (ovarian, cervical and pancreatic carcinomas and malignant melanoma); one case of choriocarcinoma was noted post-study.

Conclusions: The favourable safety and tolerability profile observed in the CLARITY study, together with strong efficacy (reported elsewhere) suggest that annual short-course treatment with cladribine tablets may provide an important new option in MS therapy. This will be further supported by long-term safety and efficacy data from a 96-week CLARITY extension study.

Study supported by: Merck Serono S.A., Geneva, Switzerland.

Muscle disorders

P361
Six-year follow-up study for glucose intolerance in myotonic dystrophy

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Objectives: Insulin resistance is one of the characteristic features of glucose intolerance (GI) in myotonic dystrophy (MD), although the incidence of Diabetes Mellitus (DM) is not so high. It remains obscurely the natural course of glucose tolerance in MD. The aim of this study was to investigate chronological change of GI or insulin resistance in MD for the purpose of clinical management to MD.

Methods: Patients with MD type 1 (MD1) who had been examined by 75 g oral glucose tolerance test (OGTT) and diagnosed as normal or impaired glucose tolerance (IGT) were investigated again similarly six years later or three years later, besides patients who had been diagnosed as DM or had been dead during the period. Judgment of OGTT was decided according to the new recommendation of World Health Organization (WHO, 2003). Plasma glucose and insulin at fasting, 30, 60, 90 and 120 minutes during OGTT were measured. homeostasis model assessment IR index (HOMA-I) and total sum of plasma insulin during OGTT (sigma IRI) were also calculated.

Results: Thirty-five patients with MD1 were participated in three-years-follow up-study (fifteen female and twenty male, median value of age; 47 years). At the beginning of the chronological observation, twelve patients diagnosed as normal and twenty-three as IGT by OGTT. Three years later, only nine patients were normal, however, eleven belonged to IGT and eight were diagnosed as DM. Nine patients were dead (3 fetal respiratory infection, 2 heart failure, 2 sudden death, 1 gastric cancer, and 1 respiratory failure). Patients developed DM followed by IGT showed high HOMA-I or sigma IRI at the beginning. Nineteen patients with MD1 were also observed for six years (six female and thirteen male, median age; 51 years). At the beginning, five patients diagnosed as normal and fourteen as IGT. Six years later, only three patients were normal, two belonged to IGT, and six were diagnosed as DM. Eight patients were dead due to similar causes. Patients developed DM or died showed high HOMA-I or sigma IRI at the beginning.

Conclusion: Our data suggested patients with MD type I were classified under three groups according to types of GI. The first group consisted of patients whose glucose tolerance could be kept for long time. Second, aggravated GI developed DM in course of time. Third, death by complications preceded diabetic episodes. We should pay attention to the second and third groups and detect the features of them for management to MD.

P362
Tolerability and safety of mexiletine in patients with myotonic dystrophy type 1 over time

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Objectives: Although mexiletine is accepted as an antimyotonic agent in the non-dystrophic myotonias, there is still no general consensus

regarding safety in the dystrophic myotonias. In this study our primary aim was to assess tolerability and safety in patients with myotonic dystrophy type 1 (DM 1) over time. In addition our secondary aims were to determine of the effects of the drug on myotonia and muscle strength in these same patients.

Methods: 36 patients with moderately-severe adult DM1 were treated with mexiletine 200 mg tid and compared to age-, disease-duration and MRC- matched 34 untreated patients with moderately-severe DM1. Manual muscle strength (MRC), myotonia self-assessment scales (0–5 scale) and cardiac parameters (PR interval; QRS duration,QRSD; heart rate, HR;ejection fraction, EF) were determined before and after long-term mexiletine treatment (DM1: mean treatment duration 7.5 years ± 3.7; DM2: 5.2 ± 3.5 years). All patients filled in a form of reporting on tolerability and side-effects of treatment. In a subgroup of patients fulfilling criteria for electrophysiological study.

Results: Preliminary data suggest that initial and final PR, QRSD, HR, EF were similar in the treated and untreated DM1 groups. Side-effects were minimal. Myotonia improved significantly in the treated DM1 compared to the untreated patients ($p > 0.0001$).MRC decreased significantly in both treated and untreated DM1 patients ($p < 0.001$).

Conclusion: Although preliminary, our data suggest that mexiletine is safe and well-tolerated in DM1 patients. There are indications that myotonia but not muscle strength may improve with prolonged treatment. To further confirm or refute our data, we are extending the study to a larger group of patients. In addition, the effects of intravenous mexiletine on the main electrophysiological functional parameters and on the arrhytmia inducibility will also be determined.

P363

A new functional scale for myotonic dystrophy type 1

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Objectives: Myotonic dystrophy type 1 (DM1) is a multiystem disorder; in the literature there are no scales exploring all the aspects of the disease, but only tests for muscular strength and myotonia. We developed and validated a new functional scale for DM1 patients based on neuromuscular impairment and disability.

Methods: Thirty-three patients (mean age = 35.3 ± 16 years) with a genetic diagnosis of DM1 were tested in basal conditions and 18 patients after treatment with mexiletine. Clinical features (muscular strength at dynamometer and density at computed tomography, intelligent quotient (IQ), systemic comorbidities) and results from previously validated functional and disability scale, were compared to our new scale. This scale includes 35 ordinal items in 5 areas: neuropsychology, motricity, myotonia, daily life activities, systemic comorbidities. Total score ranges from 0 (normal) to 124 (worst condition). We added a Visual Analogue Scale (VAS) to quantify subjective myotonia and functional measurements of 4 relaxtion time (RT).

The scale was blindly administered by 2 authors. A descriptive and statistical analysis was performed to evaluate inter- and intra-observer reliability (K statistics and Spearman correlations, respectively), internal consistency (Cronbach's α), external validity (Spearman correlations among each area and other clinical measurements and scales) and sensitivity to clinical changes (Mann–Whitney test).

Results: According to the number of repeat expansions, 10 patients belonged to the class E1 (mild phenotype), 15 subjects to E2 (adult classical form) and 8 patients to E3 (congenital disease).

Total mean score of our scale was 35.3 ± 16, significantly increasing from E1 to E3 patients.

Inter-observer agreement was excellent, with K results ranging from 0.83 to 0.91; intra-observer reliability was good, with significant Spearman's correlations. Internal consistency was almost perfect for all areas (Cronbach's α over 0.80), except for myotonia area. Total score and single areas were significantly correlated to objective measurements of correspondent functions (muscular strenght and density, IQ), considered as gold standard. Finally, the scale was sensitive to clinical changes with significant improvement of myotonia area, VAS and RT after therapy.

Conclusion: The scale developed for DM1 patients is a new validated functional measurement that could be useful in clinical practice and research for tracking disease severity and progression.

P364

Novel CLCN1 gene mutations associated with Myotonia congenita in Italian patients

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Objects: Myotonia congenita is an autosomal dominantly or recessively inherited muscle disorder characterized by impaired muscle relaxation and variable degrees of permanent muscle weakness, associated with abnormalities in the muscle currents linked to the chloride channel gene (CLCN1) encoding the skeletal muscle chloride channel. It is well established that chloride channels play a role in the regulation of the muscle membrane and thus participate in the maintenance of the resting potential. On clinical grounds, the dominant and recessive forms may be indistinguishable. Here we describe 12 novel mutations in 19 unrelated Italian patients fitting clinical and laboratory criteria for dominant ($n = 1$) and recessive myotonia congenita ($n = 18$).

Methods: Clinical features including age and symptom at onset; distribution, severity, and triggers for myotonia; other additional clinical findings as well as response to treatment are described. DNA samples were PCR-amplified and sequenced. The mutations suspected to alter the splicing efficiency due to their positions in the coding sequence were examined by ESEfinder prediction system.

Results: Permanent muscle weakness affecting lower limbs was present in one third of patients while transient episodes were present in 25% of patients and were triggered in all cases by exercise. Warm-up was present in most cases and triggers for myotonia were in general rest and low outside temperature. Twelve new mutations were detected: c.1606G > C (*p*.Val536Leu), c.2533G > A (p.Gly845Ser), c.2434C > T (p.Gln812X), c.568_569GG > TC (p.Gly190Ser), c.1012C > T (p.Arg338X), c.2403 + 1G > A, c.2840T > A (p.Val947Glu), c.1598C > T (p.Thr533Ile), c.1110delC, c.590T > A (p.Ile197Arg), c.2276insA Fs800X, c.490T > C (p.Trp164Arg) plus others described elsewhere. Mutations suspected to alter the architecture and function of the channel were subjected to predictive analysis and evolutive comparison.

Conclusions: These data expand the spectrum of CLCN1 mutations and may further contribute to the understanding of genotype-phenotype correlations and to the development of more targeted treatment strategies.

P365

Study of atrophy factors in 7 patients with myotonic dystrophy type 2

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Objective: To investigate the extent of type 1 and type 2 fiber atrophy in myotonic dystrophy type 2 (DM2) we calculated atrophy factors of both fiber types in vastus lateralis or biceps brachial muscles from 7 patients.

Background: Myotonic dystrophy type 2 is a multisystem autosomal dominant disorder characterized by myotonia, proximal myopathy, muscle pain, cardiac conduction defects, endocrine disorders and cataracts. Muscle biopsies from affected patients usually show myopathic changes, including increased fiber size variation and internalized nuclei.

Methods: We have studied atrophy factors in 7 DM2 patients, 5 females and 2 males. To investigate the fiber size and to calculate the atrophy factors we have used fast and slow type myosin heavy chain immuno-histochemistry. In 4 patients atrophy factors were calculated with both acid and alkaline ATPase reactions and slow and fast myosin stains in serial sections. The size of muscle fibers was assessed by measuring the "smallest fiber diameter".

Results: In 5 patients there was a preferential type 2 fiber atrophy, using myosin immuno-stain (the mean atrophy factor was 628.9, normal values < 200). Type 1 fiber atrophy was present in 4 cases (the mean atrophy factor was 297.1, normal values < 150). ATPases reactions revealed in 3 patients a pattern similar to what observed with myosin stains and in 1 patient the results were different with the two methods.

Conclusions: our study confirms the preferential type 2 fiber atrophy in DM2, even if type 1 fiber atrophy was also sometime observed.

P366

Restrictive respiratory syndrome in DM2 patients

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Objectives: Respiratory involvement in myotonic dystrophy type 1 (DM1) is frequent. Respiratory insufficiency is, together with cardiac failure, the main cause of death in these patients. Reports on respiratory involvement in DM2 are limited. The aims of our study were to determine the frequency and severity of respiratory involvement and sleep apnoea in patients with DM2 compared to DM1.

Methods: 20 patients with genetically determined DM2 (mean age 64.3 ± 8) and 40 patients with moderately severe age-matched DM1 (mean age 38.5 ± 11) were subjected to muscle strength assessment and: (1) subjective assessment of excessive daytime sleepiness (Epworth Sleepiness Scale-ESS); (2) spirometry and nocturnal polygraphy (PSG).

Results: (1) 4 of 20 (20%) patients with DM2 and 12 of 40 (30%) patients with DM1 complained of daytime sleepiness; (2) 5 of 20 (25%) patients with DM2 and 14 patients with DM1 (35%) showed a restrictive respiratory impairment on respiratory function tests. Indication to nocturnal assisted ventilation (Bi-level) either due to nocturnal desaturation or sleep apnoeas was identified in 30% patients with DM1 subjected to PSG compared to 10% of patients with DM2 subjected to PSG.

Conclusions: Although preliminary, our results indicate that respiratory involvement in DM2 is present and needs to be considered in patients with DM2 just like in DM1, because of the potentially treatable nature of the associated symptoms. Whether severity of respiratory involvement correlates with muscle impairment (MMRC) and disease duration needs to be further explored on a larger number of patients.

P367

A novel SCN4A Asn440Lys mutation in a Korean family with paramytonia congenita

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Objectives: Paramyotonia congenita (PMC) is an autosomal dominant disorder with high penetrance, characterized by paradoxical myotonia, cold-sensitive myotonia, and intermittent weakness. Although corresponding mutations have been identified in various domains and transmembrane segments of SCN4A, the mutation on the sixth transmembrane segment of the first domain (S6/DI) is extremely rare for PMC.

Methods: We have recently identified a Korean family with 12 patients with PMC through 4 generations and conducted genetic and electrophysiologic analyses to elucidate phenotype-genotype correlations for the family.

Results: The needle electromyography showed abundant myotonic discharges in all tested muscles at rest and the exercise tests disclosed post-exercise myotonic potentials for 100% of affected members who consented to the test. The genetic analysis revealed a novel SCN4A Asn440Lys mutation which is located on S6/DI of the SCN4A where Asn is conserved in most known voltage-gated sodium channel ¥á subunit sequences dating back to jellyfish. The mutation was not found in 200 healthy controls.

Conclusion: We herein report a novel SCN4A Asn440Lys mutation that cosegregates with a typical phenotype of PMC.

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P368

Retrospective study of a population of patients affected by myofibrillar myopathies at muscle biopsy

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Objectives: The term myofibrillar myopathies (MFMs) was proposed in 1996 as a noncommittal designation for a group of chronic neuromuscular diseases associated with common morphologic features. These consist of a distinct pathologic pattern of myofibrillar disorganization that begins at the Z-disk and is followed by accumulation of myofibrillar degradation products and ectopic expression of diverse proteins that include desmin, aB-crystallin, dystrophin, myotilin, sarcoglycans, neural cell adhesion molecule (NCAM), plectin, gelsolin, ubiquitin, filamin C, Xin, and congophilic amyloid material. Several disease genes have recently been recognized in myofibrillar myopathies. We revised muscle biopsies from 110 subjects with muscle symptoms who had come to our observation in the last 10 years, but who had remained without a specific diagnosis. They answered the following criteria: clinical evidence of myopathy, hyperCKemia, EMG myopathic

pattern, and dystrophin, dysferlin, sarcoglycan, calpain, merosin, emerin and caveolin-3 normal protein expression at muscle biopsy. This revision allowed us to select 61 possible cases of myofibrillar myopathy. Indeed, 42 muscle specimens presented small vacuoles containing amorphous, granular or hyaline material at histologic examination, and 19 showed no light microscopy alterations, but streaming of the Z-line and focal dissolution of myofibrils at EM examination.

Methods: Immunohistochemistry for myotilin, desmin, aBC and gelsolin was performed.

Results: We identified 11 patients with strong immunoreactivity for aB-crystallin and desmin in muscle fiber cytoplasm. In the same areas a strong reactivity for Dystrophin was observed.

Conclusions: In the past decade, several disease genes in MFMs have been identified, but in more than half of the patients the molecular defects still remain unknown. A careful revision of selected muscle biopsies coming from our Tissue Bank, associated with specific immunological tests, allowed us to identify patients affected with myofibrillar myopathy. Mutation analysis of genes involved in myofibrillar myopathies will be performed on genomic DNA extracted from peripheral blood.

P369

Myopathy by chronic clevudine therapy: a case report

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Objectives: Clevudine [1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl) thymine, L-FMAU] is a nucleoside analog of the unnatural β-L configuration that has potent activity against HBV. The clinical trials have demonstrated no specific adverse events and have been explained the reason for the lack of cytotoxicity was the inability of human cellular DNA polymerase alpfa, β, γ and delta to utilize the 5-triphosphate of clevudine as a substrate. We report a case of long term clevudine treatment—associated myopathy.

Case: A 40-year-old man with chronic hepatitis B complained of progressive weakness of proximal muscles and edema of both legs for last 5 months. He had been receiving long-term clevudine (nucleoside analogue reverse transcriptase inhibitor, NRTI) therapy for hepatitis. Abnormality of extraocular movement, ptosis, facial muscle weakness, dysarthria, dysphagia, tongue atrophy, fasciculation, or myotonia were not observed. Opthalmoscopic examination showed no evidence of optic nerve atrophy or retinal pigmentation. The muscle strength test revealed proximal muscle weakness (MRC grade IV) of both upper and lower extremities. On laboratory test, serum creatine kinase level(960 IU/L) was increased (normal; 0-185 IU/L). His electromyography showed generalized myopathic process. The muscle biopsy showed numerous ragged-red fibers, degenerating myofibers with variable sized cytoplasmic bodies, prominence of type 1 fibers with type 2 fiber atrophy, and endomyseal mononuclear cell infiltration. Electron microscopic examination revealed necrotic myofibers including extremely dysmorphic mitochondria with extensive loss, blunting, focal clumping of cristae and concentric cristae. Since the muscle biopsy findings were consistent with NRTI induced myopathy, clevudine medication was discontinued. On the follow up examination after one month, he was able to go up and down stairs without any help and hop on one leg. The motor strength of proximal muscles was remarkably improved (MRC grade V).

Conclusion: Although clevudine has been known as a less cytotoxic agent among various NRTIs, a careful clinical attention should be paid to the patients under long-term clevudine therapy for occurrence of myopathy.

P370

Congenital myopathy with ptosis, ophthalmoplegia and muscle dystrophic changes: a possible sporadic case of myosin heavy chain type IIa myopathy

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Objectives: We report the case 28 years old man whose clinical history began at age 7 years with slight upper and lower limb girdle weakness, ptosis and ophtalmoplegia. Winged scapulae, pectus escavatum and bilateral pes cavus were evident at neurological examination. CK were, and still are, slightly elevated (400–500 U/L). He underwent left quadriceps muscle biopsy at age 15 years and a diagnosis of oculopharingeal dystrophy (OPMD) was made due to the presence of cores and rimmed vacuoles. In the last years the clinical picture got progressively worse showing marked proximal weakness and walking difficulties, bilateral facial paresis, complete ophtalmoplegia and severe bilateral ptosis without pharyngeal involvement. A clinical diagnosis of mitochondrial disorder was made. Family history is referred negative. A second muscle biopsy (left biceps) was performed and examined in our Department.

Methods: Conventional histology, histochemistry, immunohistochemistry, ultrastructural studies, and Southern blot analysis of mitochondrial DNA (mtDNA) were performed.

Results: We observed rimmed vacuoles, dystrophic changes (necroses and moderate increase of connective tissue) and a few COX-negative fibers, some of which are ragged red. Ultrastructural examination shows whorled myelin figures with areas of complete myofibrillar disintegration in the cytoplasm of some muscle fibers. These contain electrondense, autophagic material. Some fibers show slight increase of intermyofibrillar glycogen and rare, small accumulations of normal mitochondria. Southern blot analysis of mtDNA is negative.

Conclusions: Ptosis and ophtalmoparesis are features of both mitochondrial disorders and OPMD, the latter being also characterized, along with inclusion body myositis (IBM), by the evidence of rimmed vacuoles at muscle biopsy. In our case, lack of pharyngeal involvement and early clinical onset do not favor an OPMD diagnosis whereas a mitochondrial disorder is unlikely due to both muscle biopsy findings and lack of mtDNA deletions. Ocular symptoms and age of onset do not orient towards a diagnosis of IBM. The early onset of a progressive proximal myopathy with ocular involvement associated with the evidence of dystrophic changes, rimmed vacuoles, and myofibrillar alterations at muscle biopsy suggest a diagnosis of myosin myopathy due to mutations in myosin heavy chain type IIa gene (MYH2). Genetic analysis is underway. The clinical spectrum of myosin myopathies is discussed.

P371

Muscle cramps, insulin resistance, acanthosis nigricans and acral hypertrophy syndrome: a potentially treatable condition

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Objectives: A distinct syndrome characterized by muscle cramps, insulin resistance, acanthosis nigricans and acral hypertrophy (Flier's syndrome) has been described as a sporadic or an autosomal recessive condition. The patients described so far have no definite weakness or

specific abnormalities on neurological examination. The muscle cramps occur in proximal muscles and in the calves and worsen after exercise. CK levels in this syndrome are frequently increased, while EMG findings are usually normal. Muscle biopsy can show mild non specific abnormalities. Diphenylhydantoin has been suggested to improve muscle cramps and pain and to a minor degree, to improve glucose intolerance, in a limited number of patients. We describe 3 related and 1 unrelated patient with muscle cramps associated with insulin resistance, acanthosis nigricans, obesity.

Methods: The patients were subjected to: (1) physical examination (search for acanthosis nigricans, waist to hip ratio, body mass index-BMI); (2) muscle strength testings; (3) blood tests (CK; plasma hormone levels; fasting insulin, oral glucose tolerance test, homeostasis model assessment-HOMA to quantify the insulin resistance index); (4) EMG; (5) abdomen CT scan; (6) muscle biopsy. Patients were then subjected to: (1) diet and increased physical activity; (2) oral phenytoin 50 mg tid.

Results: The diagnostic work-up and differential diagnosis of painful myopathies and high CK is presented in 4 patients, including screening for insulin resistance, led to rule out muscular dystrophies and metabolic myopathies. The findings of mild proximal weakness, high CK, acanthosis nigricans and insulin resistance fulfilled the diagnosis of Flier's Syndrome. In the most affected patient, phenytoin controlled muscle cramps completely 4 months after starting treatment. Insulin resistance was also reduced significantly (HOMA before treatment: 5.2; HOMA after treatment: 1.68).

Conclusions: Unexplained muscle cramps or painful myopathy, in the presence of acanthosis nigricans should alert the clinician towards a possible associated insulin resistant condition. This underlying metabolic disorder should be thoroughly looked for, because despite the degree of severity of the insulin resistance, this may be clinically silent as it was in our patients. The diagnosis of the syndrome of muscle cramps, insulin resistance and acanthosis nigricans has important clinical implications given the treatable nature of this condition.

P372

De novo small duplication in Lamin A/C gene associated with congenital muscular dystrophy phenotype

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Background and objectives: Laminopathies are autosomal dominant inherited disorders involving skeletal and cardiac muscles, caused by mutations in lamin A/C .Usually, the childhood forms, associated with in-frame or missense mutations, are characterized by cardiac involvement and contractures.

We describe a new mutation in lamin A/C (LMNA) gene associated with a congenital muscular dystrophy (CMD) phenotype expanding the spectrum of these disorders. Furthermore, we stress the importance of muscle biopsy and clinical follow-up for a proper diagnosis.

Methods: We describe a 6-year-old boy presenting delayed motor milestones since 1 year of age. He showed severe infantile muscular involvement with myopathic face, severe calf hypotrophy, proximal and distal hyposthenia and hypotonia. Blood analysis revealed high CK level (up to 5×). Cardiac and respiratory assessments were normal as well as brain imaging. No cognitive impairment was present. Sequential muscle biopsies were obtained at age of 1 and 4 year and processed with standard techniques comprehensive of morphological, immunohistochemical and ultrastructural analysis. Acid maltase activity was investigated in muscle and fibroblasts. Finally, direct sequencing of Fukutin related protein, selenoprotein and LMNA gene was performed. Genetic analysis was extended to parents.

Results: The muscle biopsy performed at 1 year of age showed a normal pattern, without major ultrastructural alterations. The second biopsy showed a dystrophic pattern, with an increase of connective tissue and normal expression of alfa-dystroglycan. No mutations were found in FKRP and SEPN genes. Analysis of LMNA gene showed a new small insertion of 9 nucleotides within exon 7 (c.1326_1334dup). Parents showed no mutations and were asymptomatic.

Conclusions: Childhood forms of laminopathies are generally characterized by an Emery-Dreifuss-like phenotype. Our patients is peculiar for the clinical features of CMD phenotype, presenting at birth with severe muscular involvement without retraction or cognitive impairment. Moreover the mutation located in exon 7 leads to the production of an in-frame transcript, leading to a loss of function due to altered assembling of protein dimers. Up to date, only 5 duplications are described in LMNA gene associated to cardiomyopathy, which is not present in our patient.

P373

Molecular epidemiology and clinical features of a large Italian cohort of 291 dystrophinopathic patients

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Objective: New proposed pharmaco-genomic approaches for Duchenne (DMD) and Becker (BMD) muscular dystrophies, such as exon skipping and stop-codon readthrough, strongly rely on mutation detection along the dystrophin gene, definition of deletion/duplication boundaries and often mRNA and protein studies. Furthermore genetic and biochemical data are usually predictors of clinical evolution.

To estimate the relative frequency of different mutations and to define the accuracy of genotyping and muscle analysis in determining phenotype, we studied the genetic features of a large Italian cohort of dystrophinopathic patients.

Methods: We selected 291 patients (202 DMD and 89 BMD) belonging to 255 families, showing clinical/biochemical data suggestive for dystrophinopathy. A complete neurological, cardiac, and respiratory assessment was done at first evaluation and follow-up.Genetic analysis was performed with Multiplex PCR and Multiplex Ligation-Dependent Probe Amplification (MLPA), followed by direct sequencing of all 79 DYS exons and promoter region. Deletions and duplications breakpoints were mapped.

Results: Total mutation finding rate was 97%. Combination of multiplex PCR and MLPA identified deletions in 66% and duplications in 13% DMD cases; direct sequencing found 18 nonsense,5 splice-site, 1 missense mutations and 9 micro-rearrangements. In BMD distribution was as follows: 88% deletions, 6.4% duplications, 1 missense, 1 nonsense and 2 splice-site mutations. In 5 DMD and 3 BMD no mutations were found.

Deletions and duplications clustered in the first 60 exons, while point mutations were spread along the entire gene, without differences between DMD and BMD.

Breakpoints mapping extended limits of deletions in 17/68 DMD and 9/28 BMD patients, changing the reading frame respectively in 6 and 5 cases.

A correlation between clinical, genetic and biochemical data was found, except in few patients. Exception to the reading-frame rule was observed in 2 in-frame DMD and 2 out-frame BMD.In 6 DMD cases WB analysis showed partial deficiency, underling the role of protein functionality and not only residual amount in phenotype prediction.

Conclusion: Combined genetic analysis found mutation in 97% of patients. Some exception to the reading frame rule were found. Biochemical analysis seems to be the better predictor of clinical evolution with few exceptions. The extreme degree of genetic heterogeneity implies that pharmacogenomic approaches should be adapted to this genotypic diversity.

P374

Co-existence of GNE gene mutation in a case of genetically assessed oculopharyngeal muscular dystrophy

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Introduction: The autosomal dominant (AD) form of oculopharyngeal muscular dystrophy (OPMD) is caused by the GCG expansion of the poly(A)-binding protein 2 (PABP2) gene on Cr14 q 11.2-q13. Rimmed vacuoles as specific pathological feature are shared by hereditary inclusion body myopathy (HIBM) and OPMD. We describe a woman with adult-onset progressive eyelid ptosis, dysphagia and proximal limb weakness with rimmed vacuoles, in whom molecular analysis confirmed the PAB2 gene mutation and documented the association with a mutation of the gene encoding for UDP-N-acetylglucosamine 2 epimerase/N-acetylmannosamine kinase (GNE).

Material end methods: The proband is a 77-year-old woman who presented with eyelid ptosis and dysphagia worsening from age 50; at age 60 PEG was performed for severe dysphagia and proximal lower limb weakness became evident. Family history revealed that her mother and two maternal aunts presented ptosis and dysphagia in their late life; a sister had died from ab ingestis pneumonia; her living 72-year-old brother has eyelid ptosis; her 40-year-old single daughter is asymptomatic. Serological investigations, EMG,muscle biopsy and molecular analysis for HIBM and OPMD were performed.

Results: EMG showed mixed myopathic and neurogenic features; light microscopy routine stains showed variability in muscle fibre size with internal nuclei and scattered small angulated fibres; there were no inflammatory cells or ragged red fibres; the prominent feature in few fibres (about 1% of fibres) was the presence of rimmed vacuoles on hematoxylin-eosin and Gomori trichrome. Molecular analysis confirmed the GCG expansion in the PABP2 gene and a heterozygous 3 nucleotide deletion (2575-77 delATA) in the non-encoding region 3' of the GNE gene.

Discussion: The familiar, clinical, histological and genetic features are consistent with a diagnosis of the AD form of OPDM. To date, the GNE gene mutation has been identified only in HIBM and the possible pathogenic role of the GNE gene mutation in OPMD is unclear.

Conclusion: To our knowledge, this is the first report of co-existence of the PAB2 gene and GNE mutation in OPMD. The extension of molecular analysis to other family members and the immunoreactivity identification of the inclusions may clarify the significance of this observation.

Poster session 3

Cerebrovascular disorders: semiology

P375

Calculation disorders in patients with hemispheric stroke

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Objectives: Calculation disorders have been assessed in patients with focal hemispheric lesions, mostly parietal and of the left hemisphere, more rarely frontal or temporal. Little is know about disorders resulting from more extended stroke in the territory of the middle (MCA) and anterior (ACA) cerebral arteries. Our objective was to evaluate them in a systematic way.

Methods: Thirty-five patients were recruited in the few months following a stroke of the territory of the left ACM (16), right ACM (13), or ACA (6). We excluded those with severe aphasia or neglect. We presented (1) a test of calculation (TLC2) of fourteen subtests: lexical decision, matching, transcoding, counting, understanding the magnitude, completion of operations, grammaticality judgement, calculation, problem solving, numeral knowledge and ecological use of number (2) tests of language, spatial attention, executive functions and working memory.

Results: In comparison ($p < 0.05$) with healthy control subjects (35), lexical decision, matching, counting, completion of operations and grammaticality judgement were preserved. LMCA patients showed a deficit in transcoding (dictation of numbers written in letters, dictation of numbers written in Arabic numbers, transcribing Arabic numerals/verbal written, transcribing verbal written numerals / Arabic), understanding the magnitude (estimating a result), calculation (mental calculation, written operations to solve), problem solving, number knowledge (estimates of daily living) and ecological use of numbers. The ACMD were deficient in estimating a result, written operations to solve and ecological use of numbers. The ACA showed a deficit in written operations to solve and problem solving. Correlations were found between: (1) executive function tests or digit span and estimating a result, grammaticality judgement and problem solving, (2) BDAE subtests and transcoding, understanding the magnitude and mental calculation.

Conclusion: Transcoding operations are essentially under the control of lateral structures of the left hemisphere. Calculation is associated with the left hemisphere, but also with the right hemisphere and frontal structures. Problem solving also involves each main hemispheric structure. This study shows the multi-modular organisation of calculation and problem solving.

P376

Evaluating the effect of amantadine on the minimally conscious state using actimetry monitoring: a feasibility study

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Objectives: Patients in a minimally conscious state (MCS) show restricted self or environment awareness but are unable to communicate

consistently and reliably. The effect of pharmacological agents on recovery of MCS remains unsatisfactory. Amantadine, a dopaminergic agonist, has shown in retrospective studies to improve recovery in posttraumatic MCS [1]. Recently, a PET study showed that amantadine might also ameliorate brain metabolism and outcome in post-anoxic MCS [2]. We here performed prolonged motor activity monitoring (actimetry) to objectively assess the putative effect of amantadine in MCS.

Methods: Six chronic MCS patients (age range: 23–44 years; interval since brain insult range: 1 year 10 months–26 years 2 months; 3 traumatic, 3 non-traumatic) were studied using an ABA design: experimental periods of baseline (A), drug administration (B) and washout (A') each lasted six weeks. The behavioral assessment consisted of the Coma Recovery Scale Revised (CRS-R) [3]. Motor activity was recorded using actimetry wrist watches (Actiwatch-L, Cambridge Technology Ltd). Mean values of motor activity were computed for the last week of each experimental period. Experimental periods were compared using ANOVA.

Results: Amantadine-related increase in motor activity was shown in three patients ($p < 0.05$). CRS-R total scores during amantadine administration increased in two posttraumatic patients, decreased in one anoxic patient, and did not change in the other three patients.

Conclusion: Our results illustrate the interest of actimetry monitoring to objectively measure the therapeutic efficacy of amantadine on motor improvement in MCS patients.

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P377

Facial hemispasm caused by megadolichobasilar artery treated with botulotoxin, case report

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The megadolichobasilar artery, the widened, elongated and tortuous course of the basilar artery, is a rare vascular anomaly that can cause variety of clinical symptoms but is usually asymptomatic. Incidence is declared from 0.06 till 5.8%. It can be found isolated or as a part of more complex malformation of the cerebral arteries. The pathogenesis is not wellknown. It is supposed an important part of arterial hypertension and arteriosclerotic alterations in the vessel wall. But megadolichobasilar is observed by children too, it supports the hypothesis that there exists another cause, structural anomalies in the vessel wall that are probably congenital and linked to an unknown alteration in collagen metabolism. Clinically anomalies are discovered mainly as a result of the compression of neighboring anatomic structures, or ischemic vascular accidents. Ischemic brainstem syndromes and cranial nerve disturbances especially of the trigeminal and facial nerves are the most common. Also cerebellar dysfunction and cerebrospinal fluid circulation disturbances are observed. Seldom a subarachnoid or intracerebral hemorrhage is proven. We present a 55-year old man, nonsmoker, treated for arterial hypertension and hypercholesterolemia. In January 2003 subsultuses and spasmes of right part of mimical muscles. During the time the symptoms were more frequent. In December 2003 the patient was hospitalised for vertigo at neurological department in peripheral hospital. CT showed postischemic periventricular lesions and cerebral atrophy. During hospitalization he was treated with vasodilatation therapy, vertigo disappeared, other symptoms survived. Treatment with carbamazepin 400 mg/day was started without objective clinical effect. In January 2005 patient was admitted to our department. The neurological examination revealed facial hemispasm on the right side, no other neurological symptoms were observed. Blood tests were normal, except hypercholesterolemia. Motor evoked potentials of facial nerves with lower amplitude and longer latence on the right side. Brain magnetic resonance imaging(MRI): cranial T2 weighted MRI showed multiple periventricular and juxtacortical hyperintense lesions and megadolichobasilar. The examination was completed by magnetic resonance angiography that confirmed the dolichobasilar abnormality. We started the therapy with botulotoxin with very good clinical effect.

P378

Loss of ability to sneeze in lateral medullary infarct

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Introduction: The relationship between medullary lesion and inability to sneeze is based on animal studies and case reports for the present. We report a patient with lateral medullary infarct that couldn't sneeze despite the feeling the urge to sneeze.

Case presentation: A 39-year-old man was admitted to our hospital with vomiting, ataxia, and vertigo. He had left-beating nystagmus, and fell to the left when he attempted to stand. Pinprick and temperature sensation were absent on the right side of the trunk and limbs. An MRI scan revealed infarction of the left lateral medulla. At his control follow-up, he expressed that he couldn't sneeze. In fact he felt the urge to sneeze in response to a typical tickling irritation in the nose, he would inhale deeply, but the subsequent explosive exhalation would fail to occur. He was not given any medical treatment since this symptom did not affect his daily life.

Conclusion: Sneezing is a complex protective respiratory reflex, stimulated by an initial sensory or nasal phase, mediated by trigeminal afferents. These afferents feed back to a putative "sneeze center," where input appears to be integrated until threshold is reached, at which stage violent exhalation though the mouth and nose, accompanied by involuntary eye closure, occurs; the irritant is expelled from the airway. Our patient felt the sense of sneeze but was unable to complete the expiratory phase of a spontaneous sneeze. This suggests that sensory or nasal phase was intact whereas efferent phase was abnormal. In our patient medullary lesion on MRI was localized in the area that was shown as the 'sneeze center' in cats. Although loss of ability to sneeze is a very rare condition, it should be considered as a symptom in patients with lateral medullary infarct.

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Case report of primary angiitis of the central nervous system presenting with cranial pachymeningitis

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Background: Cranial pachymeningitis is a rare syndrome associated with inflammatory thickening of the intracranial dura mater and the underlying leptomeninges. Its etiology includes infections, autoimmune and vasculitic disease. Neurological involvement can be variable, frequently presenting in form of headache. We report a case of pachymeningitis as a rare manifestation of primary angiitis of the central nervous system (PACNS).

Case report: A 69-year-old female presented with progressive right occipital headache and transient paresthesia of the left arm and leg, without any history of migraine or other neurological disorders. The initial neurologic examination, elektroencephalography (EEG) and cranial computed tomography did not reveal any pathological findings. Within the next days the patient developed massive headache, blurred vision, and deficits of orientation and memory. Serial EEG control revealed general and bilateral temporal slowing of EEG activity. The cerebrospinal fluid was xanthochrome, with 66 lymphocytes/microliter and markedly elevated protein content of 583 mg/dl by normal glucose. Magnetic resonance imaging (MRI) showed a gyral swelling and hyperemia of both posterior cerebral hemispheres, a small subcortical intracerebral hemorrhage in the right precentral region and meningeal enhancement and thickening, involving particularly the dura mater. Repeated serologic tests and autoimmune screening were all within normal limits, with an exception of positive antinuclear antibodies (ANA) in a titer of 1:320. Cerebral panangiography was without any pathological findings. Histopathologically, a leptomeningeal biopsy revealed extensive granulomatous, partly necrotising vasculitis of the pachy- and leptomeninx, predominantly involving the small vessels, establishing the diagnosis of PACNS. The patient was treated with intravenous methylprednisolone (1 g/day) for 5 days and repeated pulses of intravenous cyclophosphamide (750 mg/m^2), with almost complete recovery.

Conclusions: Pachymeningitis, as demonstrated in the MRI, is a rare manifestation of inflammatory cerebrovascular involvement and should be considered in patients with severe and persistent headache and possible focal neurological or neuropsychological symptoms of unknown etiology. In rare cases where it can be secondary to PACNS, a leptomeningeal biopsy accompanied with cerebral angiography is recommended for the accurate diagnosis and treatment.

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Multiple cerebellar microhaemorrhages – Rare presentation in hypertensive encephalopathy

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43-year old lady presented with severe headache, neck stiffness, vomiting, lethargy and confusion. She noticed petechial rash on right forearm. There was history of hypertension in pregnancy and previous alcohol dependency. Blood pressure on admission was 261/160 mmHg. Neurological examination revealed mild gait ataxia and bilaterally delayed diadochokinesis. There was impaired concentration with minimental score 19/30, having difficulties to recall objects and copying drawing. Fundoscopy showed bilateral papilloedema. CT brain demonstrated non-communicating hydrocephalus with right frontal cerebritis. Blood film showed mild anaemia (10.6 g/dL), moderate thrombocytopenia of 90 × 109/L, raised reticulocytes and presence of schistocytes. There was hyperbilirubinaemia of 105 umol/l, raised LDH at 527 u/L, but preserved liver function. Urine dipstick was positive for protein and blood. Renal function was impaired with creatinine 195 umol/L, urea 8.5 umol/L and GFR of 25 ml/min. She was started on intravenous antibiotic and antiviral therapy for possible meningoencephalitis. Raised blood pressure was slowly reduced using oral calcium channel blocker. MRI brain showed multiple focal T2 high signal abnormalities in the periventricular white matter, deep subcortical white matter of frontal, temporal and occipital regions, thalami, cerebellum and bilateral cerebellar peduncles. The gradient echo sequence showed evidence of haemosiderin deposition in the left cerebellar folia as well as petechial microhaemorrhages in the body of the cerebellum. To control high blood pressure four additional antihypertensive drugs were added during the admission. Confusion improved, headache resolved and renal function normalised in two weeks. Repeated MRI in 2 months showed improvement in the white matter oedema, but the haemosiderin deposition in the cerebellar brain parenchyma persisted.

Hypertensive encephalopathy is acute, progressive neurological syndrome associated with predominantly white matter oedema, showing selective transient MRI hyperintensities in the parieto-occipital white matter, basal ganglia, brainstem and cerebellum. Cerebellar microhaemorrhages are rarely described, though micro-angiopathic haemolysis is well-documented entity in renal failure with malignant hypertension.

P381

A case of brachial diplegia and anterior spinal infarcts from vertebral thrombosis

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Background: Infarcts in the territories of the anterior spinal arteries are rare events usually presenting with unilateral neck pain or occipital headache. We present the case of a woman whose brachial diplegia was associated with MRI hyperintensity of the anterior cervical spinal cord and right vertebral artery thrombosis.

Case report: A 48-year-old woman without risk factors for cerebrovascular disease was admitted to our hospital for acute headache, hematemesis with anaemia.

Few minutes later she developed respiratory failure and cardiac arrest. She recovered in a short time after basic life support procedures, but she was admitted to intensive care unit in coma state.

Brain CT scan was negative, while MRI T2-weighted and DTI images showed vermian and right cerebellar hemisphere hyperintensity along with medial bulbar-pontine hyperintensity. MRI angiograms showed partial right vertebral artery thrombosis. After few days she regained full consciousness: neurological examination revealed brachial diplegia. Cervical MRI examination showed bilateral hyperintense lesion of spinal anterior horn from the lower part of C3 to the upper C5 levels.

Blood exams for syphilis, virus antibodies, extended coagulation screening, autoantibodies associated with vasculitis were negative.

Esophagogastroduodenoscopy with biopsy showed low grade gastric cancer, responsible for the early hematemesis. Patient underwent a sub-total gastrectomy.

Conclusions: We describe a case of a woman with brachial diplegia due to vertebral artery and anterior spinal artery thrombosis that we relate, despite negative haemocoagulative tests, to a pro-thrombotic status secondary to the gastric cancer.

P382

Silent strokes and palmomental reflex in patients with first ischaemic stroke: a prospective study

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Background: Palmomental reflex is part of classical neurological examination, but it has lost practical real usefulness because its low specificity for a particular lesional localization. On the other hand, silent strokes are frequently discovered by radiological methods (CT or MRI) in 10–38% of patients with first stroke.

Methods: We combined two independent studies realized simultaneously in the same population of patients with vascular risk factors and first stroke: a study of prevalence of palmomental reflex versus a control-matched for age and sex population of healthy subjects, and a prospective study of prevalence of silent infarcts determined by CT in the same populations with vascular disease. The aim of the combined data was to observe the correlation of the clinical presence of palmomental reflex and of silent strokes within a population of 564 patients with vascular risk factors and first stroke.

Results: 53% of patients with first ischemic stroke had silent ischemic strokes on CT (read by two independent raters, inter-rater variability 7%). There was a significant correlation between silent strokes and high blood pressure and smoking. Palmomental reflex was searched by two blinded examining physicians and was found in 51.4% of first stroke patients and 9.2% of healthy controls ($p < 0.05$). Silent infarcts were found in 71% of stroke patients with palmomental reflex, and 36% of those without. There was a significant correlation between palmomental reflex and the presence of more than 2 silent ischemic lesions on CT scan. There was not a unique pattern of distribution of slient infarcts in those with palmomental reflex, but all patients with subcortical ischemic lesions had the reflex.

Conclusions: We suggest that palmomental reflex presence is significantly correlated with the presence of silent multiple ischemic lesions in first stroke patients with vascular risk factors. Further study is needed in population with vascular risk and using MRI, but if this correlation will be confirmed, palmomental reflex may be used in the screening of patients with no stroke history but with vascular risk factors in order to delimit a group with high probability of silent strokes, for which cerebral imaging is indicated.

P383

Isolated nodular infarction as cause of central paroxysmal positional vertigo

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Objectives: Central positional vertigo is rarely been observed in lesions of the dorsolateral pontomedullary brainstem and the vermis.

Methods and results: We report on two patients with isolated sudden onset of vertigo which was provoked by sitting up or turning to the right side. The vertigo attacks lasted about 30 s and were perceived as rotatory and linear body movement. No spontaneous, gaze-evoked, or positional nystagmus under Frenzel goggles was observed. Head impulse test was normal. Both patients showed a slight gait imbalance but no limb ataxia and no brainstem signs. Brainstem auditory evoked potentials (BAEP), horizontal saccades, smooth pursuit, optokinetic nystagmus, and caloric responses were normal. MRI studies with diffusion weighted images revealed an isolated nodular infarction due to the occlusion of a distal vertebral artery. In one patient the initial computed tomographic perfusion study revealed a perfusion deficit in the area of the medial branch of the posterior inferior cerebellar artery (PICA). In both patients vertigo and gait imbalance resolved within several days.

Conclusion: This is the first report on paroxysmal positional vertigo due to nodular infarction of the cerebellum. Previously only patients with non-positional vertigo due to nodular infarction have been described (Schwartz et al. 2007; Jeong et al. 2007; Moon et al. 2008). Most patients showed spontaneous nystagmus, mimicking peripheral vestibulopathy, other patients showed gaze-evoked nystagmus, periodic alternating nystagmus, perverted head shaking nystagmus or paroxysmal positional nystagmus.

P384

Initial presentation and course of aphasia due to watershed cerebral infarct

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Objective: Watershed infarcts (WI) account for 5–10% of strokes. Literature on related aphasia is poor. In particular, initial presentation and course of aphasia has not been studied in details. The aim of this study was to refine the early clinical pattern of aphasia due to WI and its short term evolution.

Methods: We prospectively studied consecutive patients referred to our stroke unit within a one year period to identify right-handed patients with a confirmed diagnosis of left-sided hemispheric WI and aphasia. These patients had standardized language examination in the first 48 h after stroke and at discharge from the stroke unit. They had intensive language rehabilitation between the two evaluations.

Results: Among 430 patients seen in the stroke unit, four were enrolled in the study. Watershed infarcts involved the junction between: anterior cerebral artery (ACA)/middle cerebral artery (MCA) in patients A and D, ACA/MCA and MCA/posterior cerebral artery (PCA) in patient B, MCA/PCA in patient C. All four patients had transcortical mixed aphasia on first examination with altered naming and comprehension but preserved verbal reproduction,. Aphasia improved quickly in all patients. At discharge (day 7–27), patients C and D had fully recovered, patient B evolved towards transcortical sensory aphasia and patient A towards transcortical motor aphasia.

Conclusion: This small series of patient provides further evidence that aphasia associated with hemispheric WI is of transcortical type. The strength of this study is the early language evaluation in our patients: within the first 48H as opposed to day 4, at the best, in previous studies. This approach allows us to identify a new initial pattern of aphasia amongst our patients and suggests the possible evolution from transcortical mixed aphasia to transcortical sensory or motor aphasia depending on the stroke location. In addition we found that outcome of aphasia in this setting is usually good.

P385

Léger de main: the thalamus and the automatic limb

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Introduction: Alien hand syndrome (AHS) is a rare condition associated with involuntary limb movement. AHS has been reported in the setting of anterior cerebral artery occlusion, commonly referred to as the "frontal" or "callosal" subtype. More recently, a posterior or "sensory" subtype has been described. Further characterization of possible subtypes of this syndrome may facilitate diagnosis and minimize morbidity.

Case: A 56 year-old, right-handed, male farmer with a history of headache and hypercholesterolemia presented with a one day history of numbness and involuntary movement of the left arm. The patient was in his usual state of health when he noted the sudden onset of difficulty manipulating objects with his left hand. He further described his arm as "floating uncontrollably." This was followed fifteen minutes later by numbness and tingling of the left hand that progressed cephalad along the left upper extremity. He also noted transient numbness of the left leg and left side of the face. A 911-emergency call was placed and respondents administered 325 mg

aspirin. On arrival to the emergency department, he was noted to have mild proximal left upper extremity weakness with residual numbness to pinprick. The remainder of the neurologic examination was unremarkable. An electrocardiogram, head CT, cardiac enzymes, and carotid artery ultrasound were all normal.
On hospital day two, the patient reported two more episodes of tingling and uncontrolled, "floating" movements of the left arm. An EEG failed to demonstrate epileptogenic activity during the awake or sleep recordings. An MRI revealed a faint zone of abnormal T2 signal with abnormal diffusion involving the right thalamus, most suggestive of a subacute right thalamic lacunar infarct.

Discussion: Prior studies have attempted to show correlation between the site of lesion and the clinical manifestation of AHS. The most commonly described AHS involves the corpus callosum or medial frontal cortex, and manifests clinically as intermanual conflict or impulsive reaching and grasping, respectively. Recently, a "sensory" subtype of AHS has been described with lesions involving the basal ganglia, right thalamus, right occipital, or inferior parietal lobe. To our knowledge, this is the first presentation of AHS presenting predominantly with positive sensory phenomena. Further characterization of possible AHS subtypes may facilitate localization, expedite therapy, and ultimately minimize morbidity.

Sleep disorders

P386

Hypnotic drugs intake in cerebral stroke patients

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Objectives: The cerebrovascular ischemic accident is one of the most common reasons for emergency hospitalisations. Previous research pointed at occurrence of serious sleep disorders among cerebral stroke survivors.
The aim of our project was to establish the frequency and characteristics of hypnotics intake in cerebral stroke patients.

Methods: We evaluated the intensity of hypnotic drugs usage in post-stroke group by using medical charts and also inquiry form, concerning demographic features of the subjects. The study was performed by trained interviewers. They collected data of patients who were hospitalised because of ischemic cerebral stroke in the Hospital in Gdynia in years 2000–2005.

Results: The studied group consisted of 244 cerebral stroke survivors (51.6% men and 48.4% women). The mean age was 66.0 years. Previous study revealed that over half of the subjects complained of night-rest disturbances and it had a significant influence on their quality of life (results of SIS and NHP—correlation coefficient = 0.568). What is more 7.79% of the studied population used hypnotic drugs and 5.74% of the subjects refrained from taking any medicines 2 weeks before admission to hospital. Additionally, each patient in this subgroup took at least one medicine more. In 57.14% of cases benzodiazepines were used to reduce symptoms of various sleep disorders and in 21.43% of cases zolpidem was taken. Finally in 92.1% of cases sleeping pills were taken by insomniacs.

Conclusion: Cerebral stroke patients are at risk of developing various sleep disorders, which greatly influence the patients' quality of life. No correlation was found between mal usage of hypnotics and sleep pattern disturbances. Therefore, hypnotics therapy should be considered in every case.

P387

Cerebral haemodynamics in acute stroke patients with sleep disordered breathing: a near infra-red spectroscopy study

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Objective: Sleep disordered breathing (SDB) is a risk factor for cerebrovascular morbidity and mortality. Its impact during the acute phase of stroke is poorly known. We compared bilateral cerebral hemodynamic relative changes occurring during SDB in acute stroke patients, using near infra-red spectroscopy (NIRS).

Methods: Six patients (3 males and 3 females, mean age 58 ± 15 years) with acute middle cerebral artery (MCA) stroke (NIHSS score 10 ± 7, range 2–18), normal or increased daytime MCA blood flow velocity on the affected hemisphere (Transcranial Doppler, TCD), and SDB (AHI 39 ± 36/h, range 5–94) were assessed by means of nocturnal polysomnography coupled with bilateral cerebral NIRS recording.

Results: NIRS recording showed asymmetric patterns of haemoglobins' evolution on the two hemispheres during SDB, with major cerebral oxygen saturation reductions on the normal hemisphere (-0.80 ± 0.54 and $0.01 \pm 0.42\%$ per second respectively in the normal and affected side, $p = 0.001$). Moreover, events of obstructive type impacted more than central ones on the cerebral oxygen saturation of the normal hemisphere (-1.17 ± 0.52 and $-0.44 \pm 0.22\%$ per second respectively for obstructive and central apnea, $p = 0.003$).

Conclusion: Our data disclosed higher cerebral oxygen saturation reductions on the normal hemisphere than on the affected one during SDB in acute stroke patients, with a more profound effect during obstructive (versus central) apneas. Our finding could be ascribed to asymmetric oxygen metabolic consumption, given the otherwise normal (or increased) blood supply on the affected side (daytime TCD). Further studies are needed to clarify pathophysiological relevance of present observation.

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Cognition and high-definition EEG in sleep after paramedian thalamic stroke

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Introduction: Functional recovery after stroke depends on the adaptive plasticity of the human brain. Sleep contributes essentially to brain plasticity and learning. The exact link between sleep, EEG and cognition in stroke recovery remains unclear. The aim of the study is to investigate the relationship between sleep and stroke recovery by: 1) comparing EEG power in the slow wave (SWA) and spindle frequency ranges (SFR) in the acute phase after stroke and 3 months later, 2) correlating these EEG parameters to clinical and behavioral changes during the recovery process.

Patients and methods: Seven patients, two with bilateral paramedian thalamic stroke (PMTS) and five with unilateral PMTS and five matched controls underwent detailed neuropsychological examination, actigraphy, 24 h-polysomnography (PSG) and high-density EEG (hd-EEG) during sleep. The patients were studied in the acute phase after stroke and 3 months later.

Results: Patients performed worse in verbal fluency test, had longer total sleep time in PSG and higher percentage of day rest in actigraphy (acute and chronic). The patients with bilateral PMTS had more profound hypersomnia and impairment in behavioral tests. In hd-EEG both SWA and sleep SFR were recorded in typical locations without gross

asymmetry. In comparison to healthy controls patients had significantly lower power in SWA in frontal and occipital regions after 3 months; power in SFR was lower although not statistically significant.
After 3 months hypersomnia and behavioral tests improved, especially in the patients with bilateral PMTS. A significant decrease in the SWA power was found while power in SFR did not change.

Conclusion: Behavioral and EEG changes were more profound after bilateral than after unilateral PMTS. Power in SWA after PMTS decreased after 3 months and was significantly lower than in controls while power in SFR was low initially and did not change. Improvement of cognition in bilateral PMTS was not accompanied by increase in SFR or SWA power.

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Circadian rhythm of temperature and melatonin in restless legs syndrome

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Introduction: In restless legs syndrome (RLS) a circadian distribution of symptoms with an increase in the evening/night is an essential diagnostic feature. Previous studies suggested a circadian component in the pathophysiology of RLS. The objective of this study was to test the hypothesis of a circadian dysfunction in RLS patients based on temperature curves and melatonin secretion.

Methods: A baseline polysomnography was followed by a modified constant routine (20 h bedrest under 10 lux with sleep 11 p.m.–7 a.m.) in 10 drug-free, idiopathic RLS-patients (5 females, age 49.2 ± 4.7 years, BMI 25.4 ± 1.2) and 8 healthy age and gender-matched controls. Salivary melatonin was assessed every 30 min during waking. CBT, proximal and distal skin temperature was recorded continuously. The midrange crossing time of the evening decline of CBT was visually estimated and used as circadian phase marker along with the dim-light melatonin onset (DMLO).

Results: Melatonin levels and DMLO did not differ between patients (21:09 ± 0:41 h) and controls (21:15 ± 0:28 h). In heart rate, controls had a prominent decline at lights off, whereas in patients heart rate was steadily declining from the early evening. CBT showed the typical time course with a peak in the late afternoon/early morning hours, whereas RLS patients had an earlier decline. The difference between the CBT maximum and minimum was significantly larger in controls (0.86 vs. 0.66°C; $p < 0.1$).

Conclusion: This study does not support the hypothesis of a primary circadian dysfunction in RLS. The slight differences found between groups indicate a need for larger studies, in particular under normal life conditions which could reveal significant differences.

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Prostaglandin D synthase: the first biomarker distinguishing excessive daytime sleepiness from fatigue?

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Background/Objective: Endogeneous sleep-promoting substances such as prostaglandins are suggested to be involved in homeostatic sleep-wake regulation. Lipocalin-type prostaglandin D synthase (L-PGDS) catalyzes the production of somnogenic prostaglandin D, and appears to be decreased in the cerebrospinal fluid (CSF) of patients with excessive daytime sleepiness (EDS). It is, however, not known whether CSF L-PGDS levels are decreased also in patients with fatigue. We aimed at measuring CSF L-PGDS levels in relation to the presence of EDS and fatigue.

Methods: In this prospective study, we included consecutive patients with neurological disorders, and with a clinical indication to perform a lumbar puncture. Patients with primary sleep-wake disorders (e.g. narcolepsy) were excluded from this analysis. We performed all lumbar punctures between 10 a.m. and 1 p.m. Thereafter, CSF was immediately frozen at −80°C and sent to Japan for L-PGDS determination by ELISA. We analyzed data from 15 patients (9 women), mean age was 43 years (range 22–61). For the assessment of EDS and fatigue, we administered validated questionnaires (Epworth sleepiness scale; ESS, and fatigue severity scale; FSS).

Results: Six of 15 subjects suffered from EDS (ESS > 10), 8 subjects from fatigue (FSS > 4.0). EDS patients had lower L-PGDS levels (16.3 ± 3.4 μg/mL) than non-EDS patients (22.6 ± 7.5 μg/mL, $p = 0.048$). On the other hand, levels were similar between patients with (20.2 ± 9.0 μg/mL) and without fatigue (19.9 ± 3.3 μg/mL, $p = 0.94$). An association between CSF L-PGDS and gender or age was not found.

Conclusion: The first preliminary results of this ongoing bicenter study indicate L-PGDS may be the first biomarker differentiating EDS from fatigue.

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Sleep disorders in patients with generalised anxiety disorder: prevalence and change under pregabalin therapy

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Objectives: Generalised anxiety disorder (GAD) is characterised by feelings of threat, restlessness, irritability, and tension, accompanied by symptoms such as palpitations, dry mouth, and sweating. Sleep disorders are frequent and contribute to the substantial loss of quality of life. On the basis of the characteristics of a large prospective cohort of ambulatory GAD patients we aimed to describe the prevalence of sleep disorders; and their response to treatment with pregabalin, an α2-delta-ligand.

Methods: A total of 331 physicians (mainly psychiatrists) throughout Germany included 578 consecutive adult patients with GAD in a 4-week observational, non-interventional trial. Quality and quantity of sleep and somnolence were assessed at baseline and final visit using the medical outcomes study (MOS) Sleep Index. Further, patients rated quality of sleep in diaries using a 100 mm visual analogue scale (VAS). GAD was rated using the hospital anxiety and depression scale (HADS-A) and a daily anxiety VAS, and treatment response by patient global impression of change (PGIC).

Results: Sleep disturbance was the most often reported concomitant condition (n = 261 or 45.1% of total population). A significant improvement was observed in the quality and/or quantity of sleep. The 9-item MOS Sleep Index was reduced from a baseline mean of 58.8 units by a mean of 22.7 units (95% CI 24.4; 21.1), the 6-item MOS from 71.8 by 27.0 units (29.1; 25.0). Changes on subscales were as follows: for sleep disturbances (baseline 63.9 units; change to final visit −26.0 units), snoring (32.8; change −8.0), awakening short of breath (36.6; change −14.5), quantity of sleep (5.8; improvement +1.0), sleep adequacy (30.2; improvement +24.5); remarkably, also somnolence (43.4; change −15.5) improved despite the well known sedating side effects of pregabalin. HADS-A, VAS-anxiety-scores and

PGIC showed similar or slightly better improvements in GAD patients with vs. without concomitant sleep disorder.

Conclusions: This study confirms the substantial burden of disease by sleep disorders in patients with GAD. Pregabalin treatment was associated with significant improvement of sleep in the MOS Indices and daily sleep VAS ratings. GAD patients with concomitant sleep disorder show comparable or even higher treatment response even for non-sleep parameters.

This study was performed by Pfizer Pharma GmbH, Germany; Matthias Brasser is an employee of Pfizer Pharma GmbH.

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Sleep pathology in SCA2 patients reveal early degeneration in pons, thalamus, and striatum

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Objective: To characterize the sleep pathology in presymptomatic relatives of SCA2 by polysomnographic recording.

Methods: We analyzed 32 SCA2 patients with disease durations of 1 to 20 years and 36 presymptomatic relatives, all with medium size SCA2 expansions (CAG 32 to 44), clinical scores, sleep interviews, and video-polysomnography recordings.

Results: Almost all presymptomatic reported good subjective sleep quality free of REM behaviour disorders (RBD). Nevertheless, REM sleep was abnormal in 60% of the presymptomatic relatives. The most striking and consistent pathology of REM sleep was its significant reduction, decrease of REM density and significant reduction of sleep efficiency in all SCA2 carriers.

Conclusions: The anatomical substrate is linked with degeneration at pons, nigrostriatal and thalamus. The highly and puntuacted ataxin-2 expression in these structure even in presymptomatic stages support the notion. Thus, REM pathology is a sensitive SCA2 endophenotype, reflecting early brainstem degeneration and preceding ataxia manifestation.

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A characterisation of the menopausal transition: the role of sleep and psychological well-being

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Major purpose: According to the 2008 demographic data from the US census bureau, women between the ages of 40–59 represent approximately 22% of the world's population. During this stage of life women enter menopause, often experiencing physical and cognitive symptoms such as mood disorders, hot flashes, night sweats, and changes is sleep patterns. Prior research indicates sleep disturbances (SD) may increase the risk of being formally diagnosed with a psychological disorder (PD). These issues are further complicated and controversial because pharmacological treatment of PDs may disrupt sleep. To examine these concerns, we evaluated the sleep architecture and psychological characteristics of women before, during, and after the menopausal transition.

Procedure: We assembled an interdisciplinary team from a broad spectrum of specialty areas and constructed questionnaires to assess sleep habits, sleep observations, past medical and psychological history, prior treatment approaches for SDs, and medications. We used the questionnaires in conjunction with nocturnal polysomnography (NP) studies, multiple sleep latency tests (MSLT), the Epworth Sleepiness Scale (ESS), and medical chart reviews of people for evaluation of SDs.

Results: Our study includes 256 female participants (age range: 1.17–83.25; : 49.66), of which 26 are in menopause, 136 in post-menopause, and 94 are non-menopausal. A sample of findings include significant differences in the ESS total score, total number of prescriptions, percent of time spent in stages one, three, and four of sleep, and the total time asleep when comparing these three groups. Additionally, we found significant differences in reports regarding anxiety, irritability, and headaches.

Discussion: Despite their prevalence, SDs remain inadequately reported, diagnosed and understood. Further knowledge about the relationship shared by sleep disorders, psychological well-being, and the use of psychotherapeutics is needed to contribute to enhancing overall health and quality of life of women in and after menopause.

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Agrypnia excitata: microneurographic study of sympathetic activity

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Objectives: Agrypnia Excitata (AE) is a generalized neurological disorder characterized by severe insomnia, loss of slow waves sleep, enacted dreams associated to motor and autonomic overactivity. It is a common feature of different clinical conditions such as Delirium Tremens (DT), Morvan's syndrome (MS) and Fatal Familial Insomnia (FFI) where a dysfunction of the thalamo-limbic system has been suggested. The aim of the present study is to investigate the pattern of sympathetic activation in acquired and genetic AE.

Methods: We describe three patients (two with Morvan's Syndrome and one with Fatal Familial Insomnia).
The two Morvan's syndrome patients (62 and 71 years old men) complained progressive cognitive impairment, weariness, nocturnal insomnia, diurnal drowsiness and gait disorder. A mediastinal neoplasm was detected in one patients whereas the other patient underwent partial thyroidectomy for medullary thyroid carcinoma. Both patients presented high level of serum antibodies to voltage-gated potassium channels.
The Familial fatal insomnia patient, genetically confirmed, was a 45 years old man, with a familiar history of sleep disorders, nocturnal insomnia, hyperidrosis, lower limbs weakness, progressive diplopia, memory impairment, impotence and gait ataxia in the last 9 months. All patients underwent microneurography to assess muscle sympathetic nerve activity (MSNA) and heart rate (HR). Multiunit postganglionic MSNA was recorded with a tungsten microelectrode with a tip diameter of a few microns, inserted into a peroneal nerve, posterior to the fibular head. A recording of MSNA was considered acceptable when it revealed spontaneous, pulse-synchronous bursts of neural activity. Microneurography activity was compared with the findings in twenty healthy subjects.

Results: Microneurography showed a resting mean level of resting MSNA and HR significantly increased compared to controls (MSNA: 96 ± 5 and 56 ± 18 bursts/100 HB respectively, $p < 0.01$; HR:

81 ± 10 and 64 ± 10 beat/min, $p < 0.05$). Patients presented a similar pattern of MSNA with a normal cardiac rhythmicity and a very high burst incidence expressed in each cardiac beat approximately.

Conclusion: Our data pointed out that acquired and genetic AE presented a common resting sympathetic overactivity suggesting a similar autonomic dysfunction.

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A randomised, double-blind, placebo-controlled study with armodafinil in patients with residual excessive sleepiness associated with CPAP-treated obstructive sleep apnæa and co-morbid depressive disorders: patient characteristics and treatment effect

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Objectives: Even with continuous positive airway pressure (CPAP) treatment, many patients with obstructive sleep apnea (OSA) experience residual excessive sleepiness (ES). Patients with OSA frequently have a comorbid depressive disorder. The clinical implication of a comorbid depressive disorder on the treatment of residual ES in this population is unknown. Armodafinil, the R- and longer-lasting isomer of modafinil, is a non-amphetamine, wakefulness-promoting medication. This report characterizes the population of a study of armodafinil in patients with ES associated with CPAP-treated OSA who have a comorbid depressive disorder.

Methods: Patients in this multi-center, randomized, double-blind, placebo-controlled, parallel-group study had residual ES despite CPAP-treated OSA and a comorbid depressive disorder (DSM-IV-TR criteria for major depressive disorder or dysthymic disorder) requiring antidepressant monotherapy. Inclusion criteria included a Clinical Global Impression of Severity (CGI-S) score of moderately ill or worse for ES, an Epworth Sleepiness Scale (ESS) score of $\geq$10, and a 17-Item Hamilton Rating Scale for Depression (HAM-D-17) score of $<$17. A blinded, per-protocol baseline summary was conducted when 50% of the planned sample had completed the study. Efficacy data will be available for presentation.

Results: Of 134 patients, 50% were male, 92% were diagnosed with major depressive disorder and 8% with dysthymia. On the CGI-S for ES, 53 and 34% of patients were moderately or markedly ill, respectively. At baseline, the mean maintenance of wakefulness Test sleep latency was 20.5 (8.4) min and the ESS score was 14.7 (3.2). The mean HAM-D-17 was 6.7 (4.3), indicating remitted depressive disorder, and the mean worst score from the Brief Fatigue Inventory of 6.7 (2.0) suggested moderate fatigue. The patients showed functional impairment by a score of 14.4 (2.9) on the Functional Outcomes of Sleep Questionnaire. The effects of armodafinil on wakefulness as measured by mean sleep latency and the proportion of patients with at least minimal improvement in ES will be reported, along with secondary and tolerability outcomes.

Conclusions: Patients with residual ES associated with treated OSA who have a comorbid depressive disorder report fatigue and functional impairment. This will be the first study of the efficacy and tolerability of armodafinil in patients with residual ES associated with treated OSA who have a comorbid depressive disorder.

Sponsored by Cephalon, Inc.

Extrapyramidal disorders: Parkinson's disease

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Impact of dopamine transporter 123I-ioflupane SPECT for the diagnosis and clinical uncertain parkinsonian syndromes management

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Objectives: This study evaluated use of imaging with 123I-Ioflupane-SPECT for the diagnosis in a group of patients affected by clinically uncertain parkinsonian syndromes (CUPS).

Patients and methods: The study was conducted on 122 patients examined from Feb/2005-Nov/2008. All patients were assessed through SPECT 30 days after the Visit 1 where the neurologist assessed the suspected presynaptic damage. The following 30 days Visit 2 all patients were assessed by a different neurologist for either starting or reviewing therapy. Visit 3 was conducted after 180 days by the same former Visit 2 neurologist for a clinical follow-up and UPDRS assessment.

Results: At former baseline 122 patients, 12 were excluded as drop-outs during the follow-up. Visit 1: 48 patients classified as suspected presynaptic PS (parkinsonism associated with nigro-striatal degeneration such as PD, MSA and PSP)[PPS], 33 non presynaptic PS (parkinsonism without nigro-striatal degeneration including suspected essential tremor) [NPPS] and 29 patients with uncertain diagnosis [UD]. Visit 2: conducted within 30 days from visit 1 all patients underwent SPECT imaging which changed former diagnosis in 46 patients (42%), particularly in 29 patients with uncertain diagnosis: 17(59%) classified as PPS, 7(24%) as NPPS, 5(17%) classified as uncertain diagnosis (UD). In a 33-patient-group with NPPS: 28(85%) reported a normal imaging pattern, whereas 5 were classified as PPS. In a 48 patient an initial diagnosis of PPS 43(85%) showed a SPECT imaging pattern with a nigro-striatal damage, 3(13%) reclassified as NPPS and 2 patients as UD. Thusly through both imaging pattern and clinical follow-up out of 33 patients firstly classified as NPPS, 23 were reclassified as essential tremor (ET), 3 pyschogenic tremor (PGT), and 3 with mood disorders (MD). Out of 65 patients with PPS, 57 classified as Parkinson Disease(PD), 8 showed different extrapyramidal disorders (1 Lewy-body disease, 3 Atypical Parkinsonism as MSA, 3 Vascular Parkinsonism, and 1 mixed ET-PD). Sensibility reported for 93%, specifity 85% with a positive predictive score of 89% and negative of 90%.

Conclusion: The study reports, using both imaging pattern and clinical follow-ups confirmed the high specifity and sensibility of the 123 I-Ioflupane SPECT to identify the CUPS with a change from the initial diagnosis of 37% in this sample.

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Microstructural integrity of white matter in patients with Parkinson's disease: diffusion tensor imaging and MR-tractography study

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Objectives: We study relation between white matter (WM) integrity, macrostructural changes, such as atrophy of WM, microstructural abnormalities in WM, and cognition dysfunction in patients with PD using Diffusion Tensor Imaging (DTI) and MR-Tractography methods.

We propose the quantitative indicators for the characteristics of the microstructural integrity of the WM in nondemented patients with PD and in patients with PD and cognitive dysfunction.

Methods: Two groups of patients are studied by high resolution anatomical MRI, including DTI ($b = 1{,}000$ s/mm^2, 25 directions), with 1.5T SIGNA EXCITE (GE). The first group includes 26 nondemented patients with PD (PDG). The second group (PDCG) includes 15 patients with PD and cognitive dysfunction. Brain tissue was segmented automatically using the k-nearest neighbor classifier. The fractional anisotropy (FA) values and mean apparent diffusivity coefficients (ADC) were measured in cortical WM and in subcortical structures that involved in cognitive dysfunction process.

Results: We assessed the association of DTI parameters with cognition using linear regression, adjusting for relevant confounders and additionally for volumes of normal appearing WM and WM with appearances of atrophy. From analysis of DTI data for two groups of patients there was a significant reduction of the FA values of temporal WM (PDG vs PDCG, 392.4 $\pm$ 70.3 vs. 520.5 $\pm$ 64.7) and parietal WM (268.3 $\pm$ 30.3 vs. 360.1 $\pm$ 31.2). Results of stepwise regression analysis showed the FA values of temporal and parietal WM were associated the scores of short-term memory and orientation. The higher ADC values and lower FA values in WM in subjects of PDG, and PDCG are related to worse performance on tasks assessing memory, executive function, information processing speed, global cognition and motor speed.

Conclusions: White matter integrity in temporal and parietal WM is compromised in patient with PD and cognitive dysfunction. The microstructural alterations in temporal and parietal WM may account for the more pronounced impairment of short-term memory observed in patient with PD and cognitive dysfunction relative to nondemented patients with PD.

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Determination of therapeutic efficacy in PIRIBEDIL-treated patients with Parkinson's disease: 1H MRS study

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Objectives: We propose the quantitative indicators for the characteristics of the therapeutic efficacy in patients with Parkinson's disease (PD) and cognitive dysfunction after two month course monotherapy treatment by PIRIBEDIL (150 mg/day)—nonergolinic dopamine agonist's receptors.

Methods: Three groups of patients are studied by 1H MRS with 1.5TSIGNA EXCITE(GE). The first group (TPG) includes 26 PIRIBEDIL-treated subjects with PD and cognitive dysfunction. The second group (PG) includes 15 untreated subjects with PD and cognitive dysfunction. The third group (VG) consists of 20 healthy volunteers. For all subjects, spectra are recorded with STEAM method:TR/TE = 1,500/144 ms. For subjects of TPG and PG the spectra are obtain in the putamen, in the central part of hippocampus, in the gray matter of brain (occipital lobe, OL), and in the substantia nigra (SN).

Results: We found a significant reduction in NAA/Cho ratios from the putamen contralateral to the most affected side in the PG, but not in the PIRIBIDIL-treated TPG groups compared with VG. There were no significant differences in NAA/Cr or Cho/Cr ratios. In untreated patients, PG reduced putaminal NAA/Cho ratios may reflect loss of nigrostriatal dopamine terminals or alternatively indicate a functional abnormality of striatal putaminal neurons, such as membrane dysfunction due to striatal deafferentation. It is obtained, that in patients with PD the content of Cho in the SN is substantially above, and NAA are below in comparison with the healthy elderly people (VG). For all patients with PD before the beginning of treatment the decrease of NAA/Cr ratio in the central part of hippocampus is characteristic, but there is no dependence between the decrease of NAA/Cr ratio, with the degree of movement disorders and with the duration of disease. In OL of the both cerebral hemispheres of the value of ratios of NAA/Cho and Cho/Cr for the patients with PD and subjects of the VG the nonsignificantly differences, and in the region of basal ganglia—it is substantial. It is shown, that the increase of the NAA and Cr concentration and decrease of Cho content can be used for the comparative estimation of the efficiency of PIRIBIDIL.

Conclusions: Quantitative characteristics of various brain structures integrity, provided by MRS data, may serve to derive markers of therapeutic efficacy of PIRIBEDIL which aim at slowing or even stopping the progression of cognitive dysfunction in patients with PD.

P399

Neuroleptic malignant syndrome after dopaminergic drug dose adjustment in two patients with Parkinson's disease

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Objectives: Neuroleptic malignant syndrome (NMS) is a rare and potentially fatal clinical condition. The syndrome usually occurs with anti-psychotic drug treatment or withdrawal of dopaminergic agents. Suspicion and early recognition of NMS are the most important steps in its management. It's a treatable condition by restarting dopaminergic drugs, excluding triggering agents, dantrolone therapy and supportive care of hyperthermia and fluid replacement.

Case reports: We present two patients who had NMS after dose adjustment of dopaminergic therapy.

A 76-year-old female patient's anti-parkinsonian therapy was readjusted as visual hallucinations occurred three days ago. 2 days after lowering the drug dose, she manifested with speech difficulty, limited cooperation and orientation, fever and high serum creatine kinase levels. Then she was treated with dantrolene and dopaminergic drugs with a dramatical clinical and laboratory response.

A 74-year-old male patient's dopaminergic agents were withdrawed suddenly owing to uncontrolled movements and hallucinations. Two days later he was admitted to a hospital with fever, confusion and haloperidol was administered for agitation. He was transferred to our hospital for investigation of fewer of unknown etiology. Serum creatine kinase levels were elevated and clinical and laboratory findings supported NMS. His body temperature decreased after 6 h of dantrolone therapy. Although NMS was treated successfully the patient died due to sepsis in the neuro-intensive care unit.

Conclusion: Clinicians must be alert about the early signs of NMS in patients with Parkinson' disease especially if their drug doses have been decreased or withheld or they have been treated with anti-psychotic drugs.

P400

Pain threshold and tolerance in parkinsonian patients with and without pain

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Objective: To assess pain threshold and tolerance in patients with Parkinson disease (PD) with or without pain.

Background: Patients with PD can experience pain of various categories such as dystonic and non dystonic pain. A recent case–control study recruiting a large number of subjects, reported a significant association between PD and non-dystonic pain with features of muscular or neuropathic pain starting at or after the onset of parkinsonian symptoms (Defazio G, Arch of Neurol 2008). Moreover, we reported abnormal pain-evoked responses to laser stimulation in hemiparkinson pain-free patients suggesting alterations of nociceptive inputs processing (Tinazzi Pain 2008).

Patients and methods: 70 patients affected by PD were selected. These included 45 patients without pain, and 25 patients with muscular or neuropathic pain to one body part present at the time of the study, developing at/after the onset of parkinsonian motor symptoms. Patients with headache or other facial pain, medical conditions associated with or predisposing to painful symptoms, cognitive impairment and depression were excluded from the study.
In all patients, pain threshold and tolerance were assessed after overnight withdrawal of dopaminergic medications, using electrical stimulation delivered to the little finger and big toe. Both right and left hand and foot were tested separately in each patient. Results were compared with those obtained in 45 aged-matched controls.

Results: Pain threshold and pain tolerance were significantly lower in PD patients for both right and left hand and foot than in normal subjects. In PD patients with pain, pain threshold and tolerance obtained on the painful limb (regardless of muscular or neuropathic pain) were lower compared to those obtained on the non painful limb and in pain-free PD patients.

Conclusion: These results extend previous data indicating that the processing of nociceptive inputs is altered in PD patients and this abnormality appears to be greater in presence of muscular or neuropathic pain.

P401

t-DCS-preconditioned low-frequency rTMS of the hand area of M1 to improve bradykinesia in Parkinson's disease

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Introduction: State of the art treatment for idiopathic Parkinson-syndrom (IPS) is dopaminergic medication or deep brain stimulation. Both strategies allow a distinct amelioration of symptoms, but have side effects or are invasive. Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) are safe, non-invasive methods to modulate cortical excitability. We investigated the effect of tDCS-preconditioned 1 Hz rTMS over the hand area of the primary motor cortex to improve bradykinesia of the upper limb in IPS.

Methods: 11 IPS patients (6 male, 5 female, mean age 65.7 years, mean UPDRS 23) received tDCS preconditioning with either anodal, cathodal or sham stimulation over the hand area of the primary motor cortex for 10 min (±1 mA). The order of anodal, cathodal or sham tDCS was counterbalanced across patients. Immediately after tDCS patients received 1 Hz rTMS (90% of the resting motor threshold; 15 minutes, 900 pulses) over the hand area of the primary motor cortex. The motor tasks were recorded with an ultrasound based motion analysis system (Zebris) before (baseline condition), directly after rTMS and 30 min after rTMS. Patients performed four different tasks: index finger tapping, hand tapping, horizontal pointing movements and reach-to-grasp movements with both upper limbs.

Results: Low frequency rTMS preconditioned by cathodal tDCS improved index finger and hand tapping movements with the hand contralateral to the side of stimulation, whereas motor performance of the hand ipsilateral to the side of stimulation remained unchanged.

Conclusions: Our preliminary results show a beneficial effect of cathodal tDCS-preconditioned 1 Hz rTMS over the hand area of M1 on motor function of the contralateral hand in IPS. The combined application of tDCS and rTMS may provide a useful adjunct therapy for IPS patients in the later stages of their disease suffering from severe side effects of dopaminergic medication and are not suited for surgical treatment.

P402

Co-morbid vascular diseases in patients with Parkinson's disease and parkinsonian syndrome: preliminary results

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Background and purpose: The cause of Parkinson disease is still unknown. Changes in cerebral blood flow are considered as one of important pathogenetic factors. On the other side cerebral angiopathy plays role in etiology of Parkinsonian syndrome. Non-invasive neurosonology methods are known to be convenient tool in the assessment of vascular changes.
The aim of this study was to assess the character and frequency of comorbid vascular diseases in patients with Parkinson disease and Parkinsonian syndrome. The second aim was the comparison of changes in cerebral blond flow between these groups.

Material and methods: Eighty eight patients (36 women and 52 men, mean age 68,3 ± 8,1 years) were included into the study. Parkinson disease was diagnosed in 66 patients and Parkinsonian syndrome in 22 of them. All patients were underwent internal and neurological examination, transcranial doppler evaluation (mean blond flow velocity and pulsatility index in middle cerebral artery), computed tomography and magnetic resonance imaging of head, neuropsychological examination .

Results: Arterial hypertension was observed in 14 patients (21,2%) with Parkinson disease and in 12 patients with Parkinsonian syndrome (54.5%) while coronary heart disease in 10 patients (15.2%) with Parkinson disease and in 11 patients (50%) with Parkinsonian syndrome.
Diabetes mellitus was diagnosed in 6 patients (9,1%) with Parkinson disease and in 4 patients (18.2%) with Parkinsonian syndrome.
Mean blood flow velocity and pulsatility index in patients with Parkinson disease were in normal range, while in patients with extrapyramidal syndrome mean blood flow velocity in middle cerebral artery was significantly lower and pulsatility index was significantly higher in patients with Parkinsonian syndrome.

Conclusions: (1) Vascular diseases and cerebral angiopathy are more frequent in patients suffered from Parkinsonian syndrome then

from Parkinson disease. (2) Transcranial doppler examination is useful in differential diagnosis in patients with extrapyramidal damage.

P403

Palilalia in Parkinson's disease

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Introduction: Palilalia is a speech disorder characterized by compulsive repetition of word, phase, or part of sentence. Palilalia is a rare symptoms in neurodegenerative disorders like Parkinson's disease (PD), progressive supranuclear palsy (PSP), Alzheimer's disease.

Objective: This study was performed to investigate the frequency of palilalia symptom and the levodopa effect on palilalia in patients with PD.

Methods: We searched the palilalia symptoms in PD patients from March 3, 2008 to September 31, 2008. For PD patients with palilalia symptom, we examined speech analysis at each time of medication "on" and "off" state and the presence of dyskinesia in any body part concomitant with palilalia.

Speech analysis consisted of motor speech protocols including phonation, diadochokinetic task, autonomic speech task, repetition, propositional speech, picture description, and reading standard passage "Autumn".

Results: Total 12 patients out of 385 PD patients showed palilalia symptom and five patients performed speech analysis in each state of medication "on" and "off". The mean duration of palilalia appearance from parkinsonian symptom onset was 7.4 years, and frequent accompanying symptom was freezing of gait. Three out of 8 patients (37.5%) showed newly developed palilalia during medication "on" state with peak-dose dyskinesia. On speech analysis, all of three patients showed increment of speech rate and variation of pitch and loudness in "on" state compared with "off" state. Two patients showed consistent palilalia during both medications "off" and "on" state.

Conclusion: In our study, palilalia symptom is rare manifestation in PD patients. Three patients showed newly developed palilalia with levodopa increment and it may be another manifestation of oromotor hyperkinesia as a result of peak-dose effect of levodopa.

P404

Specific influence of depression on the early stages of cognitive impairment and dementia in Parkinson's disease

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Mild cognitive impairment (MCI) and dementia are often associated with Parkinson's disease (PD), even in its early stages. However, the risk factors of MCI development and eventually dementia in PD are not fully established.

Objectives: To determine the influence of depression on the early stages of cognitive impairment and dementia in PD.

Methods: We investigated 35 PD patients with mild dementia (PDD), 74 PD patients with MCI (PD-MCI) and 66 normal controls. All subjects underwent a comprehensive neuropsychological assessment, as well as the 15-item Geriatric Depression Scale for assessment of depression.

Results: Relative to controls, depressive subgroup of PD-MCI demonstrated significant deficits on more cognitive tests, including digit span forward ($p < 0.04$) and backward ($p < 0.001$), TMTA ($p < 0.03$) and Stroop test ($p < 0.001$). Compared to non-depressive PD-MCI, depressive subgroup of PDD also showed significantly lower scores on much more cognitive measures, including digit span forward ($p < 0.004$) and backward ($p < 0.000$), TMTA ($p < 0.001$), immediate ($p < 0.001$) and delayed ($p < 0.001$) total recall, as well as recognition ($p < 0.001$) of the Free and Cued Selective Reminding Test, semantic fluency ($p < 0.001$), phonemic fluency ($p < 0.02$) and Boston Naming Test ($p < 0.001$).

Conclusion: This cross-sectional study has demonstrated that depression influences the cognitive functions even in the stage of PD-MCI. Moreover, we found that depression in PD-MCI patients was related to attention/executive deficits, while in mild PDD group it also contributed to cognitive impairments in language and episodic memory. Therefore, the careful assessment and treatment of depression even in the early stages of cognitive impairment and dementia in PD should be a part of the diagnostic and therapeutic strategies of these patients.

P405

Copper levels and ceruloplasmin oxidase activity in Parkinson's disease

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Background: Parkinson's disease (PD) has a multifactorial aetiology, which includes host-related and environmental factors. Copper is a ubiquitary trace element which acts as a cofactor for several enzymes and plays an important role in central nervous system development. Copper is also involved in free radical-mediated mitochondrial and neuronal damage. Derangements of copper metabolism are possible risk factors concurring for neurodegenerative disorders including PD. Objective: to compare copper levels and ceruloplasmin oxidase activity in sera from PD patients and healthy age-matched controls.

Methods: Free copper levels and ceruloplasmin oxidase activity were measured in sera from 20 patients affected by PD since at least 12 months and 67 age-matched healthy control subjects (HC).

Results: copper levels were comparable between PD patients and controls (respectively 1.29 ± 0.29 vs 1.22 ± 0.26 mg/L; $p =$ NS by T test). Ceruloplasmin oxidase activity was significantly decreased in PD patients compared to controls (respectively 8.08 ± 2.3 vs. 9.93 ± 3.35 mg/dl; $p = 0.024$ by T test).

Conclusions: The parallel evaluation of total copper level and ceruloplasmin oxidase activity show if copper is correctly linked in a functional way to its fundamental carrier. The finding in our group of PD patients of low ceruloplasmin oxidase and normal copper level can express a condition of copper deficiency with decreased ceruloplasmin active form. An unbalanced copper status may therefore contribute to the modification of synaptic transmission and development of neurodegeneration.

P406

Human parkinsonism after acute and repeated CIS-permethrin exposure

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Objective: To report 2 cases of clinical human parkinsonism after direct cis-permethrin insecticide exposure.

Background: Epidemiological studies usually report an increased risk of developing Parkinsonian disorder after chronic exposure to pesticides. In other words, these studies evidence that patients are significantly more likely to have been exposed to or have managed direct pesticides application than unaffected individuals of the samples they evaluate. Few researchers report and conclude with a decisive and direct association between human clinical parkinsonism and organochloride or organophosphate compound pesticide use and lesser report the relationship with just a single product instead of a mixed product. On the other side, in vitro and in vivo animal researches have shown that permethrin modifies dopamine uptake at striatal level, increased uptake of dopamine associated with low permethrine level and decreased uptake of dopamine associated with higher level of permethrine exposure.

Method: Clinical evaluation of two urban policemen (32 y.o and 37 y.o.) who suffered subacutely appearing tremor—rigid—akinetic syndrome after heavy cis-permethrin insecticide exposure because of a seven days fumigation work, on alternate days, that had taken place at a rural house belonging to their police station. This was the only prior risk condition.

Results: After the second fumigation day one policeman developed headache, nausea and low fever, that improved during the resting day, until the new exposure.

At the end of the rencommended task policemen came back to their police station but they felt so bad and medical assistance was required. Two months later during neurological evaluation one policeman was found with evidence of rest tremor in both hands, expressionless face and postural instability, and the other one showed rest tremor hands and generalized slowing to perform motor activities. Routine biochemical studies and Brain MRI were normal.

Conclusion: The clinical course and the quasi on-time heavy exposure to cis-permetrhin insecticide as a single product represent an in vivo human observation of the relationship between pyrethroids and parkinsonism, a heretofore situation only described in animal research in which high doses of permethrin affect and provoke a decrease of dopamine uptake in striatal synaptosomes.

P407

Balance in virtual reality in Parkinson's disease: a preliminary study

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Objective: The aim of this study was to evaluate the effects on balance of the immersion in virtual reality (VR) environment, in patients with Parkinson's disease (PD).

Methods: Five PD patients and 15 controls were studied by means of an optoelectronic system (VICON, UK) including force platforms, graphic workstation and head-mounted display (HMD). The latter, driven by subjects' head position, showed a virtual laboratory closely resembling the real laboratory by a human model's (avatar) point of view. The study was randomly performed under the following conditions: with eyes open (EO), eyes closed (EC), with transparent HMD but not immersed in VR (EOHMD), immersed in VR (VR), and immersed in perturbed VR (15° roll of the virtual laboratory—VR15). The patients were instructed to stand upright with their feet together on the force platform while their body sway was recorded for 60 s. Quantitative parameters related to postural activity (CoP velocity) and related to postural stability (CoP displacements along the anterior-posterior direction—AP and mediolateral direction—ML) were computed. Statistical analysis was conducted using non parametric tests ($p < 0.05$).

Results: While in controls there are not significant variations, in PD patients there are statistical differences: Comparing EO and EOHDM, HMD introduced only higher CoP velocity along AP ($p < 0.04$). When VR and VR15 were compared with EOHMD, differences were reported about higher CoP velocity along ML ($p < 0.04$).

Comparing with OC the VR conditions, the immersion induces a reduced velocity of CoP in PD ($p < 0.015$).

Conclusion: In contrast with findings in controls, where there are not significant variations, in PD patients, the immersion of VR reproduces a situation of stress of postural control, but induces a compensatory motor response, much more than it happens with eyes closed conditions.

Even if the same visual system can be defective (by the impairment of dopaminergical retinal neurons), the use of visual cues can ameliorate postural performances.

VR might be used as experimental methodological for evaluation of impairment of visual-proprioceptive control in PD.

P408

Suicide and suicidal ideation in Parkinson's disease

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Introduction: Little is known about the prevalence and correlates of suicidal behavior in Parkinson's disease (PD).

Material and methods: In the first part of the study, we followed a cohort of 102 consecutive PD patients for 8 years and found that the suicide-specific mortality was 5.3 (95% CI 2.1-12.7) times higher than expected. In the second part, we tested 128 PD patients for death and suicidal ideation and administered an extensive neurological, neuropsychological and psychiatric battery.

Results: Current death and/or suicidal ideation was registered in 22.7%. On univariate logistic regression analysis, psychiatric symptoms (depression, but also anxiety and hopelessness), but not the PD-related variables, were associated with such ideation. On multivariate logistic regression analysis this association held for major depression (odds ratio = 4.6; 95% CI 2.2-9.4; $p < 0.001$), psychosis (odds ratio = 19.2; 95% CI 1.4–27.3; $p = 0.026$), and increasing score of the Beck Hopelessness Scale (odds ratio = 1.2; 95% CI 1.0–1.4; $p = 0.008$).

Conclusion: the suicide risk in PD is maybe not as high as it may be expected, but is certainly not trivial. According to our data almost a quarter of PD patients had death and/or suicidal ideation, that may significantly influence their quality of life.

P409

Motor cortex plasticity in drug-naive young-onest Parkinson's disease: preliminary data

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Objectives: Abnormal synaptic plasticity in the corticostriatal inhibitory system has been found in Parkinson's disease (PD) and linked with development of levodopa-induced dyskinesias (LID). Patients with young-onset PD (YOPD) are at particular risk for development of LID even after a short course of levodopa treatment.

Methods: Transcranial magnetic stimulation (TMS) elicited motor evoked potentials (MEP) in abductor pollicis brevis muscle, MEP

input-output (IO) recruitment curve, silent period (SP), short latency intracortical inhibition (SICI), and intracortical facilitation (ICF) were studied before (Tb), immediately after (T0), and 30 minutes after (T30) the paired associative stimulation (PAS) protocol, an experimental intervention involving repeated delivery of TMS pulses preceded 25 ms by median nerve stimulation, capable of producing long-term potentiation (LPT) like changes in sensorimotor system. The more affected side was studied. Here we present the preliminary results from 5 drug-naive YOPD patients (3 female), mean age 51.5 years (range 44–56), mean UPDRS score 22.2 (range 11–32) and Hoehn and Yahr stage 1–2.5 (mean 1.5).

Results: PAS induced only modest increase in MEP size and only minor variations in SP. These results were generally similar to those reported for levodopa-exposed PD patients of later onset off medication. There has been no published report so far regarding effects of PAS on IO curve, SICI, and ICF in PD. Pre-PAS results for MEP IO curve were similar to previously reported for PD patients off medication, with manifest lack of MEP increase at higher TMS intensities. The MEP IO curve following PAS became much steeper, particularly for 150% rest motor threshold intensity; in normal subjects PAS has no effect on IO curve. The mean SICI before PAS was −47% which was similar to the values reported for healthy subjects and different from reported weak inhibition in levodopa-exposed PD patients of later onset off medication. There was no change in SICI and ICF at T30 compared to baseline, which was similar to the results published for healthy subjects.

Conclusions: Results suggest reduced plasticity of motor cortex inhibitory mechanisms in drug-naïve YOPD patients similar to finding in other PD patients off medication. Essentially normal pre-PAS SICI results, in contrast with reduced SICI in levodopa exposed PD patients, suggest potential deleterious effect of levodopa treatment on intracorical inhibitory mechanisms.

P410

Neuropsychological guidelines for Parkinson's disease patients undergoing bilateral DBS treatment: considerations from a two-year neuropsychological follow-up

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Background: Bilateral chronic deep brain stimulation (DBS) has emerged as an appropriate therapy for patients with advanced Parkinson's disease refractory to medical therapy, but this procedure, aimed at targets within the globus pallidus and subthalamic nucleus circuitry, can further influence the cognitive functioning. Motor performance improvement is inadequate to explain the effective results of this neurosurgery procedure. Clinical evidence underlines the importance of the identification of appropriate neuropsychological guidelines in carefully select and monitoring the patient in post-operatory systematic evaluations.

Objective: To discuss about neuropsychological guidelines to DBS treatment from monitoring the cognitive pattern of 23 DBS-PD patients at a 2 years follow up;

Method: 23 patients with PD (mean age = 63.6; mean education = 9.6) underwent an extensive cognitive evaluation before the neurosurgical intervention, after 6 months, one and two years from implantation (with stimulation). The battery of test was composed to examine general cognitive functioning, verbal memory, executive function, verbal abilities, and degree of depression.

Results: Examining the overall group results with ANOVA Paired-samples with post-hoc T Student analysis we found only a significant reduction of: (1) phonemic verbal fluency (ANOVA (p) = 0.003; baseline versus 2 years ev. ($p = 0.000$); (2) semantic verbal fluency (ANOVA (p) = 0.002; baseline vs. 2 years ev.: $p = 0.008$). Evaluating the individual results in the interval base-line-2 years follow up: 8 of 10 pts that had a normal cognitive pre-DBS profile remain stable as 1 of 2 patients with selective memory deficit; 8 patients had executive dysfunction with (4pt) memory dysfunction at base-line and they worsened over time. Finally 3 patients with polyfunctioning deficit showed a global worsening over time.

Discussion: Examining the overall group results DBS treatment seems to be a cognitive safe procedure, since we found only reduced phonemic and semantic verbal fluency during a two years follow up period. Evaluating the individual cognitive performance over time only subjects with a cognitively-intact profile at the pre-op neuropsychological evaluation seem to remain preserved. Cognitive functioning must be considered one of the most important key that interfere with a complete return to autonomy of the patients, to ensure a favorable outcome of DBS procedure.

P411

A variation in a brain nicotinic receptor subunit gene preferentially linked to attentional performance in Parkinson's disease patients

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Objective: To investigate whether a nicotinic receptor genetic marker correlates with cognitive performance in a sample of PD patients.

Methods: A consecutive series of PD patients taking part to an ongoing gene-disease association study also received detailed neuropsychological evaluation. 42 PD patients judged not to suffer frank dementia according to conventional DSM-IV criteria and not to have psychosis or severe depression were scored on measures of attention, psychomotor speed, executive functions (set shifting ability and inhibitory control), visuospatial perception and visual constructive ability. They were also genotyped for a single nucleotide polymorphism at position 11615 of the gene coding for the a4 subunit, the primary subunit of the most commonly occurring nicotinic acetylcholine receptors in the brain. Analyses of covariance were employed to test for significant effect of genotype on neuropsychological measures independent of age, level of education, L-dopa dosage and severity of motor impairment. Log-transformation was previously employed on distributions of scores that showed positive or negative deviations from normality.

Results: Among all measures, CC homozygotes had significantly better performance than T carriers on measures of attention and psychomotor speed ($F = 5.96$, $p = 0.020$ for trail making test part A and $F = 6.46$, $p = 0.016$ for Symbol Digit Modalities Test). These results however were not significant when controlling for possible multiple comparison effects. Moreover, none of the CC homozygotes had impaired performance in the above two measures compared to the normative data of their reference population, whereas in the rest of cases various proportions of impairment were observed.

Conclusions: It is indicated that genetic variation within a nicotinic receptor subunit gene may produce a measurable effect on overt cognitive performance of yet not-demented PD patients, specifically the part loading on attentional capacities. This may be relevant with existing evidence that brain nicotinic acetylcholine receptors are reduced even in non-demented PD patients, the degree of their

reduction nevertheless correlating with the degree of cognitive decline.

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P412

Neurophysiological correlates of muscular pain in Parkinson's disease

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Objective: Patients with Parkinson's Disease (PD) often complain of painful sensations that may involve body parts affected and unaffected by dystonia. Pain in non-dystonic body parts may have features of muscular or neuropathic pain.

The recording of CO2 laser evoked potentials (LEPs) is an useful tool to explore the functional status of some cerebral structures involved in nociceptive input processing.

In pain-free PD patients with hemiparkinson, we have recently reported that the amplitude of the N2/P2 complex, originating from the cingulate cortex and insula, was significantly lower (regardless of the clinically affected body side) than in controls, and that acute L-dopa administration yielded no significant change in N2/P2 amplitude as compared to the off state (Tinazzi et al. 2008).

The aim of the present study was to assess in the off state LEPs in PD patients with muscular pain to one arm and to compare the results with those obtained in pain-free PD patients and in controls.

Methods: We recorded LEPs to arm stimulation (skin over deltoid muscle) in 12 pain-free and 11 PD patients complaining of muscular pain to one arm with hemiparkinson during the off state. Results were compared with those obtained in 11 normal subjects matched for age and sex.

Results: N2/P2 peak-to-peak amplitude was significantly lower in both group of PD patients than in controls, regardless of the clinically affected body side. Comparisons between the two groups of PD patients showed that the N2/P2 amplitude obtained following stimulation of the painful arm was significantly reduced compared to the one obtained on the non painful arm and those obtained in pain-free PD patients.

In PD patients with muscular pain, the N2/P2 amplitude did not change after acute L-dopa administration.

Conclusion: The present results suggest an abnormal nociceptive input processing which appears to be independent of clinical expression of parkinsonian motor signs. These alterations appears greater in presence of muscular pain and are not modified by dopaminergic stimulation.

P413

The effects of bilateral subthalamic nucleus deep-brain stimulation on cognition according to the electrodes position

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The effects of subthalamic nucleus deep brain stimulation (STN DBS) on cognition and mood have not been well established. Moreover, the location of the electrodes has not been investigated. The authors estimated the cognitive and mood effects of bilateral STN DBS according to the electrode position in patients with Parkinson's disease (PD) at 6 months and 1 year postoperatively.

Fifty-three patients were recruited from the Movement Disorder Center at Seoul National University Hospital. Neuropsychologic tests were performed three times, before, 6 months after, and 1 year after surgery. Mean patient age was 58 and mean education duration eight years. Twenty-four of the 53 patients were men.

We localized the electrodes by fusion image of preoperative MRI with 3-D stereotactic CT scans taken 6 months after bilateral STN stimulation. The participants were divided to three groups : Group I, both electrodes in the STN ($N = 35$); Group II, only one electrode in the STN ($N = 14$); Group III, neither electrode in the STN ($N = 4$). Repeated measured ANOVAs were performed to observe the within-factor effect of 3 times measured at the baseline before surgery and 6 and 12 months after surgery and the between-factor effect of 3 groups (group I, II, and III).

Of these tests, the verbal memory test, the Stroop test, and the fluency test showed statistically significant changes. The verbal memory test using the Rey-Kim memory battery showed a decline in delayed recall and recognition at 6 months and one year postoperatively, whereas nonverbal memory showed no meaningful change. In terms of frontal lobe function tests, Stroop test and fluency test findings were found to be aggravated at 6 months and this continued at 1 year postoperatively. However, there were no significant differences in neuropsychological tests between the three groups classified by the electrode positions in STN. Of the baseline characteristics, age at onset, number of years in full-time education, and L-dopa equivalent dosage were found to be correlated with a postoperative decline in neuropsychological test results.

In conclusion, bilateral STN DBS in Parkinson's disease did not lead to a significant global deterioration in cognitive function regardless of the electrode positions. However, our findings suggest that it has minor detrimental long-term impacts on memory and frontal lobe function.

Infection

P414

Balint's syndrome due to progressive multifocal leukoencephalopathy in an acquired immunodeficiency syndrome patient

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We report a 37 year-old man with progressive multifocal leukoencephalopathy (PML) presenting with Balint's Syndrome (BS). At presentation, he complained of progressive visual disturbances, speech difficulties and unsteady walking which began six months before admission. His neurological exam revealed dysarthria, optic ataxia, simultanagnosia, oculomotor apraxia, left hemiparesis, and mild truncal ataxia. His brain MRI revealed bilateral T2 hyperintense lesions in the parietal and occipital lobes. His cerebrospinal fluid (CSF) exam was unremarkable except positive JC virus (JCV) PCR. His laboratory workup revealed lymphopenia and HIV seropositivity and thus was put on HAART therapy. His detailed neuropsychological evaluation confirmed the presence of BS.

BS is a disorder of visual perception, which is generally caused by bilateral occipitoparietal dysfunction. BS patients display simultanagnosia (visual attention deficit; inability to see entire visual field any given time), optic ataxia (visuomotor disorder of reaching targets with intact upper limbs) and oculomotor apraxia (difficulty redirecting gaze from one fixed object to another). Our patient's neuropsychological examination showed all of these BS features. PML is a disease that results from infection of oligodendrocytes by a papovavirus called JCV and consequent demyelination. Almost 80% of

immunocompetent population has dormant JCV infection and in some cases the virus is reactivated causing PML. While, various visual symptoms emerge in about 1/3 of PML patients due to the predilection for the occipitoparietal region, BS has very rarely been reported as the first manifestation.

P415

Acquired human immunodeficiency virus infection presenting with subacute motor impairment. Different MRI findings in AIDS-related encephalopathy

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Objectives: to depict neuroimaging features in 2 cases of progressive encephalopathy, which led to initial diagnosis of HIV.

Case 1: A 19 years old woman developed subacute left sensory-motor syndrome, paraparesis, fever, without cognitive impairment. She had not prior opportunistic infection. Her metabolic testing was unremarkable. Decrease of CD4/CD8 T cells with HIV infection on serum and cerebrospinal fluid (CSF) was observed. Lumbar puncture (LP) showed 11 cells, increased proteins and IgG, no blood-brain barrier (BEE) disruption. MRI of encefalo showed multiple, hyperintense, subcortical demyelinating lesions in the supratentorial white matter, basal ganglia, thalamus. Acute Disseminated Encephalomyelitis was suspected but there was no improvement after Methylprednisolone treatment. After 1 month MRI hyperintense signal extended across corpus callosum and brainstem, with increased diffusion. Progressive multifocal leucoencephalopaty (PML) related to HIV disease was diagnosed, even if JC virus was not detected in CSF. After 2 months VII cranial nerve palsy, dysartria, bradikynesia, trunk dystonia appeared. MRI spectroscopy showed N-Acetil-Aspartate reduction and choline increase. Combination antiretroviral therapy was started. Mirtazapina was introduced to block serotoninergic receptor supposed to be implicated in PML. Patient died after 3 months.

Case 2: A 61 years old man developed flu-like syndrome, paraparesis, psyco-motor slowing, disorientation in space and time. His metabolic testing was unremarkable; decrease of CD4/CD8 T cells was observed. LP showed increased proteins and BEE disruption. MRI of encephalo showed hyperintense, dysomogeneous, ring enhancing lesions in white matter and basal ganglia, suggesting infection. Toxoplasma encephalitis was diagnosed (PCR detected HIV and Toxoplasma in CSF). Patient had worsening of consciousness dying 2 months later.

Discussion: MRI lesions correlated with immunodeficiency and clinical deterioration, confirmed respectively PML and Toxoplasmosis encephalitis, excluding autoimmune, paraneoplastic, vascular or metabolic diseases. Bradikynesia reflects basal ganglia involvement; cranial nerves and cognitive impairment reflect brainstem and subcortical white matter damage. Progressive encephalopathy may be hallmark for possible AIDS.

Conclusion: neurologic involvement in AIDS predicts a poorer outcome. Neuroimaging and laboratory test are important in early course of AIDS, thus in early treatment.

P416

Should HSV-PCR be performed if cell count is normal?

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Objectives: The Herpes-simplex-virus encephalitis (HSVE) caused mainly by Herpes simplex virus Type 1 (HSV-1) is a severe disease of the central nervous system with a mortality of 70% if untreated. With Aciclovir the mortality rate decreases to 19%. Neurological sequelae are still common including the inability to work. Apart from the clinical aspects diagnosis is confirmed by analysis of the cerebrospinal fluid (CSF): pleocytosis, specific immunoglobulin production and polymerase chain reaction (PCR). However, the later often is time consuming and treatment has been started before conclusive results are available

Methods and results: We present 5 patients with typical clinical signs and brain imaging of HSVE. Interestingly all had normal cell count in the primary lumbar CSF analysis. The PCR was in all cases positive for herpes simplex encephalitis. All patients had a past medical history of cancer including bronchial carcinoma with metastases ($n = 2$), aggressive B-cell lymphoma ($n = 2$), and adenoid cystic carcinoma of the maxillary sinus ($n = 1$). Furthermore, all patients had a cerebral radiation therapy not longer than 4 months before the onset of the HSVE. All patients died despite of therapy with Aciclovir.

Conclusions: In intensive care patient with newly diagnosed neurological symptoms or a prolonged awakening phase and with a history of cancer and radiation therapy it is important to perform an HSV-PCR of the CSF even if the cell count was found to be normal and early start of antiviral therapy.

P417

Encephalomyeloradiculopathy associated with Varicella Zoster virus

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Introduction: Varicella Zoster virus (VZV) is a neurotrophic virus whose primary infection causes varicella, after which it establishes latency and can subsequently reactivate to cause herpes zoster. Neurological complications are rare, occurring in less than 1%, and generally are benign.

Objective: Description of an encephalomyeloradiculopathy associated with VZV primary infection.

Results: A 21-year-old woman of African origin manifested a primary infection by VZV; two days after the rash, she complained of progressive ascending paresthesias until the inter-mamillary line, rapidly followed by acute onset of paraparesia and urinary retention. She was transferred to Portugal 2 weeks after the disease onset. Clinical examination disclosed a cicatricial rash, flaccid paraplegia with a level of algic and vibratory sensibility at D4, absence of lower limbs reflexes and absent cutaneous-plantar reflexes. Virological studies (HIV 1 and 2, HTLV 1 and 2, HSV 1 and 2, coxsackie, echovirus, CMV and EBV), Lyme disease and syphilitic serology (both in serum and LCR), were negative. VZV serology showed IgG and IgM positivity. PCR analysis for mycobacterium tuberculosis, enterovirus, CMV, HSV, EBV and VZV was negative. LCR analysis disclosed a mild linfocytic pleocytosis and hyperproteinorraquia. MRI documented T2 hyperintense lesions in corona radiata, semi oval centers, deep white matter, corpus calosum, right middle cerebellar peduncle and left anterior area of the medulla oblongata. Cord MRI disclosed an extensive myelitis from C5 to the conus with contrast enhancement at the conus and cauda equine. Electromyography documented a bilateral severe radiculopathy L3-L4-L5-S1-S2 with total denervation of the corresponding muscles, and recent lost of motor units. After a 21-day course of acyclovir, high-dose intravenous methylprednisolone, and a 6-week period of oral prednisolone, the patient showed no improvement.

Conclusions: We describe an encephalomyeloradiculopathy associated with VZV primary infection which is a rare neurological

complication. Etiopathogenic mechanisms involved are unknown. Acyclovir is a therapeutic option assuming the active virus replication in the CNS. Despite the absent recommendations, we did corticotherapy as the mechanism involved could be similar to the one in ADEM. The bad outcome in our patient can be related with the delayed treatment onset.

P418

Parvovirus B-19 and Epstein-Barr virus encephalitis: case report

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Introduction: Atypical encephalitis are a group of diseases with high rate of mortality and morbidity because of difficulties in diagnosis and treatment. Encephalitis caused by Ebstein-Barr Virus (EBV) and Parvovirus B-19 have been commonly presented separately in the literature, whereas only one case which has association with EBV and Parvovirus B-19 together was reported. We report a case of atypical encephalitis because of very rare observation and difficulty in isolation the agents, although negative result occurs in cerebrospinal fluid (CSF) examination.

Case presentation: A 29-year-old male had administered our clinic with progressive weakness on his left side of the body. Left homonym hemianopsy, left hemihypoestesia, increased deep tendon reflexes, left hemiparalysis were present on admission. Cerebral magnetic resonance imaging (MRI) revealed lesions on the right parietal cortex, right motor cortex, right parietooccipital vertex spreading to the occipital lobe, which has caused minimal diffusion restriction, hypointensity on T1, hyperintensity on PD, T2 and FLAIR images. In EEG, irregular background activity with left hemispheral temporal, frontotemporal slow wave paroxysms of theta-delta frequency have been observed. Although CSF study was negative, as a result of clinical, radiologic and electroencephalographic findings, encephalitis has been diagnosed and aciklovir treatment has been started. 8 days later biopsy has been performed from the parietal cortex. EBV and Parvovirus B-19 have been isolated from biopsy via PCR method. Gansiclovir therapy for EBV and plasmapheresis for Parvovirus B-19 have been started. But, the patient's clinic had progressed and he died 24 days after admission, the 6th day of the treatment. As a result of autopsy findings of generalised encephalitis are detected at the parenchyma of the brain and the brainstem.

Conclusion: Isolation of these two agents together in a case of encephalitis were reported only in an old immune compromised patient. In the literature, detection of materials of viral agents by PCR or serological methods have been reported to be quite important for diagnose. Cranial MRI showing no contrast has been interpreted in favour of encephalitis. In some rare cases, especially in progressive ones we have to start therapy without wasting time for biopsy to detect the infectious agent, in spite of normal values of CSF examination.

P419

VZV-related myelitis in immunocompetent patients: report of two cases

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Introduction: Complications of varicelle zoster virus (VZV) infection in the central nervous system are multiple. VZV-related myelitis is uncommon. We report two immunocompetent cases with acute transverse myelitis.

Cases: The first is a 55-year old man with intercostal herpes zoster who presented a subacute medullar syndrome. The second is a 19-year-old boy who developed myelitis after breakthrough varicella infection, despite immunization with the VZV vaccine.
MRI was normal in the first case and had demonstrated a cervicomedullar hyperintensity on the T2-weighted images in the second case. Cerebrospinal fluid (CSF) analysis showed 1.4 g/L protein in the first case and normal proteinorrachy in the second case, 50 leukocytes/mm^3 (100% lymphocytes), Negative VZV PCR, elevated rate of anti-VZV IgG without oligoclonal bands in the two cases. Both of them were HIV negative. The course was partially favorable after a 3-day regimen of corticosteroid and 3 weeks of acyclovir.

Discussion: VZV myelitis is uncommon, it affects essentially immunodepressed patients. The pathology of VZV acute transverse myelitis is unknown. Postinfectious, inflammatory and vascular mechanisms may be responsible. Most often, the clinical outcome is good.

Conclusion: We highlight the importance of considering the possibility of VZV related myelitis, even in immunocompetent patients. Combination of corticoids and aciclovir must be instituted, as soon as possible, to improve functional outcome.

P420

A case of neurocysticercosis with a single brain lesion – Diagnostic aspects

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Introduction: Neurocysticercosis (NCC) is the most common CNS parasitosis worldwide. It is caused by infection with larvae of the tapeworm Taenia solium. While NCC is the most frequent cause of adult-onset seizures in Latin America, South East Asia and Africa, it is rare in Europe and mainly occurs in immigrants from endemic regions.

Case report: A 69-year-old German male patient presented with a first generalized epileptic seizure. His travel history revealed no trips to foreign countries.
On examination the patient was afebrile, fully conscious and orientated without neck stiffness or focal neurological deficits. MRI demonstrated a solitary cystic lesion with gadolinium enhancement in the left temporal lobe surrounded by a perifocal edema. EEG showed left temporal intermittent slowing with delta rhythm. Hematologic and blood chemical tests as well as a lumbar puncture and repeated stool sample analyses gave no pathological results. Despite extensive microbiological examinations no infectious agents could be detected. The left temporal lesion was operatively removed with sonography-assisted microsurgical techniques via temporal osteoclastic craniotomy. Histological examination revealed a scolex of a pork tapeworm with four suckers and one row of hooks, surrounded by chronic granulomatous inflammatory infiltrates, leading to the diagnosis of NCC. An enzyme-linked immunoelectrotransfer blot assay did not detect specific antibodies against Taenia solium in serum or CSF. Chest and abdominal CT scan and radiography of the legs disclosed no extraneural involvement.
The patient received a treatment with albendazole in combination with corticosteroids and remained seizure-free under a therapy with lamotrigin.

Conclusion: The clinical picture of NCC is variable with seizures, focal neurological signs, and intracranial hypertension. Serological techniques can vary depending on the activity of the cyst and the number of lesions. Thus, negative results on serological testing do not rule out NCC and sometimes, as in our case, invasive procedures are required to confirm the diagnosis. Specific anthelminthic therapy is recommended for patients with non-calcified, viable cystic lesions. Although the diagnosis of NCC is rare in Europe, increasing intercontinental travel and immigration demand greater awareness of this parasitic infection in the western hemisphere, which should be considered in the differential diagnosis of adult-onset seizures with cystic brain lesions.

P421

Eosinophilic meningitis due to Angiostrongylus cantonensis in Germany

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Introduction: The most common cause of eosinophilic meningitis in South East Asia and the Pacific basin is Angiostrongylus cantonensis. Adults of this nematode parasite reside in the pulmonary arteries of rats. Humans become infected with third-stage larvae by consuming raw snails, contaminated vegetables or carrier hosts such as shrimps and crabs. After being hematogeneously transported to the CNS, third-stage larvae cause an inflammatory reaction.

Case report: A 32-year-old Asian male presented with a 10-day history of ongoing moderate treatment-resistant headache. He had visited Thailand four months ago and recalled eating raw fish, clams, vegetables and salad during this trip. On examination the patient was afebrile, fully conscious and orientated. The patient suffered from general mild lassitude, but neither neck stiffness nor focal neurological deficits were noted.

His blood leukocyte count was 8,500 cells/μl with a blood eosinophilia of 15.7%. Chest radiograph findings were normal, as were CT of the brain and MRI of the brain and spinal cord. Electroencephalography showed normal α rhythm. A lumbar puncture revealed 699 WBCs/μl (predominantly eosinophilic granulocytes) with an elevated CSF protein level of 71 mg/dl. As the patient's headache persisted, a second lumbar puncture was performed demonstrating an eosinophilic pleocytosis with an increase to 1109 WBCs/μl. CSF culture for bacteria yielded no growth. Gram stain and Ziehl-Neelsen stain of CSF were negative. Despite extensive bacteriological and virological examinations no infectious agents could be detected. Serum and CSF samples were sent to the Swiss Tropical Institute in Basel. Western Blot analysis using soluble antigen from young adult worms revealed antibodies against Angiostrongylus spp. in serum but not in CSF.

The patient received an antiparasitic treatment with albendazole in combination with corticosteroids. Under this treatment regime the patient's condition improved and he became completely asymptomatic after 2 months.

Conclusion: The diagnosis of angiostrongyliasis is extremely rare in Europe. Nevertheless, increasing intercontinental travel and immigration from South East Asian countries demand greater awareness of this parasitic infection in the western hemisphere, which should be suspected in cases of eosinophilic meningitis with appropriate exposure history. The diagnosis is confirmed by detection of specific antibodies against Angiostrongylus cantonensis by Western blot.

P422

Myeloradiculopathy associated to a Schistosoma mansoni infection

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Background: Schistosomiasis is an infectious disease caused by Schistosoma. In Minas Gerais, Brazil, the endemic specie is Schistosoma mansoni (Sm), and Portugal is not an endemic country. Schistosoma reaches, in rare cases, the central nervous system (Neuroschistosomiasis (NS)). The diagnosis of NS is presumptive based on clinical findings (conus medullaris/cauda equine syndrome), epidemiology, CSF and MRI findings, positive parasitological and serological tests and response to antibilharzial treatment.

Case report: A 18-year-old Brazilian woman, born in Minas Gerais, arrived to Portugal two years before manifesting the neurological symptoms.

She reported urinary retention, numbness and diminished muscle strength in the legs one week previous to admission. On examination, there was a distal flaccid paraparesis unabling walking, normal knee and weaker ankle jerks, an absent cutaneo-plantar reflex, and a saddle area and distal hiposthesia. Thoracic and lumbar spine MRI showed an expanded conus medullaris, with patchy pathological gadolinium enhancement. Brain and cervical MRI were normal. Needle electromyography showed acute axonal damage of peripheral nerve and radicular bilateral L5-S1-2 lesion in lower limbs. CSF examination: lymphocytosis (174.4 cel/mm^3) with eosinophils (4%), a T cell predominance, high protein level (2.96 g/L), positive Pandy reaction (+++), and positive oligoclonal bands. Surgical biopsy showed a lymphocyte infiltrate without neoplasic cells. No schistosoma eggs were found in urine or stool. Immunodiagnostic techniques showed: positive CHR (Cercariae Hullen Reaction) in CSF and serum, and positive immunoelectrodiffusion for circulating antigens detection. ELISA reaction in serum was 0.252 and in CSF 0.096. One month after praziquantel and corticosteroid therapy, there was clinical and imagiological improvement, and she walked independently 7 months later.

Discussion: NS is a rare and severe disease which can lead to permanent neurological damage if left untreated, but complete recovery is possible if diagnosed early and treated promptly.

P423

Posterior cervical ligament abscess presented with progressive ascendant weakness

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Introduction: Neurobrucellosis is a common disease in our country and it might present with central and/or peripheral nervous system involvement. We present a patient with brucellosis that manifests with progressive ascendant weakness resembling acute polyneuropathy.

Case report:A 52 year-old man who had suffered neck pain for 15 days admitted with motor and sensorial loss below his shoulders after 2 days following weakness in the lower limbs, imbalance, and anuresis. Neurological examination revealed tetraplegia, anaesthesia below T4 level, urinary retention, and bilateral Babinski sign. Bilateral median nerve somatosensory evoked potentials (SSEPs) were normal whereas bilateral tibial nerve SSEPs were absent. Motor evoked potentials (MEPs) of the bilateral abductor pollicis brevis (APB) and anterior tibial (AT) muscles elicited by stimulation over

the motor cortex were absent whereas the latencies and amplitudes of MEPs of bilateral APB and AT muscles elicited by stimulation over the cervical and lumbar spine respectively were normal. Cervical magnetic resonance imaging (MRI) showed the abscess which causes the thickening of C2–C4 posterior cervical ligament. He was operated urgently by neurosurgery department. There was no change in his neurological examination in the postoperative 7th day. High titres of Brucella antibodies were detected in serum, cerebrospinal fluid and abscess material. Ceftriaxone at 4 gr/day combined with rifampicin at 600 mg/day treatment was initiated. He died after a 37-day hospitalization.

Conclusion: Brucellosis is an infection caused by a non-encapsulated, aerobic, and gram-negative cocobacillus. Spinal lesions was found 2–9.7% in wide series. Cervical lesions are rare but their prognosis is worse. Usually surgery is not necessary in spinal brucellosis, but the patients with cervical brucellosis need surgery because of the spinal cord pressure and serious neurological deficits. There is an urgent surgery indication for the purpose of decompression for acute progressive clinical cases like our case. The final diagnosis in brucellosis is usually made by demonstrating a high or rising serum antibody titer to Brucella. We present this case because of its clinical manifestation resembles acute polyneuropathy.

P424

Transient biclonal gammopathy associated with Tsutsugamushi meningitis

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Background: Biclonal gammopathy has two different monoclonal proteins and the clinical findings are similar to those of monoclonal gammopathy. It is associated with a variety of malignant conditions and immune disorders, and it is also found in infectious diseases related to limited numbers of pathogens. An association between biclonal gammopathy and Tsutsugamushi meningitis have not been previously reported.

Case report: A 55-year-old man was admitted with fever and decreased mentality. A cerebrospinal fluid (CSF) test and an indirect immunofluorescent antibody test for Orientia Tsutsugamushi revealed Tustusgamushi meningitis. Results of a CSF and serum immunofixation electrophoresis (IFE) showed biclonal gammopathy (IgA-kappa, IgA-lamda). After antibiotics treatment, his symptoms began to improve, and the biclonal band completely disappeared after 4 months.

Conclusions: We suggest that Tsutsugamushi meningitis is associated with transient biclonal gammopathy. To the best of our knowledge, this is the first report of biclonal gammopathy with Tsutsugamushi meningitis.

P425

Unilateral hypoglossal nerve palsy: as a presentation of tuberculosis

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Objectives: Here we present a rare case of Tuberculosis (TB)osteomyelitis of basiocciput adjacent to the right hypoglossal canal resulting right 12th. nerve paresis.

Case presentation: (Video presentation of patient's sign is available also). A 41-year-old woman,computer engineer, who was healthy until 40 days before admission, presented with neck and suboccipital pain and stiffness. There was not any history of important disease including TB in her and her family. A day before admission she noted speech difficulty and tongue deviation to right on protrusion (unilateral right hypoglossal nerve palsy). On admission she had normal vital signs and was not ill or toxic. She had normal general examination except tenderness at right occipital condyle posterior to right mastoid process. Right ear otoscopy was normal. neurologic examinations were normal but right 12th nerve paresis.

All laboratory tests including: complete blood count, biochemistry, liver function tests, vasculitis survey, Wright test, and Coombs wright, syphilis serology were normal. Chest X-ray and cervical spinal X-ray were normal.

Only laboratory abnormalities were: purified protein derivative (PPD) test = 8 mm and erythrocye seimentation rate (ESR) = 73

Axial CT scan at the level of foramen magnum,bone window,revealed lytic,destructive lesion in right condyl of occiput with sequestrated bone fragments adjacent to the right hypoglossal canal.Brain MRI was normal.

Cerebrospinal fluid analysis was normal. Routine smear and culture and smear and culture for TB and fungi in cerebrospinal fluid (CSF) were negative. Polymerase Chain reaction (PCR) for TB in CSF was also negative. Abdominal and pelvic sonography were normal.

Diagnosis: Neurosurgical consultation was done for open biopsy and tissue diagnosis. Sample was sent for tissue culture and pathologic examination. In microscopic examination the sample had granuloma formation and caseation necrosis suggestive for TB and acid fast bacilli were cultured later.

Treatment: After receiving tissue diagnosis, 4 drugs antimycobacterial regimen was begun. Gradually occipital pain and stiffness subsided and right hypoglossal nerve palsy resolved. Until now (after a 30 months follow up) the patient is asymptomatic with totally normal systemic and neurological examination.

P426

Neurolisteriosis in the adult: revision of a series of seven cases

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Listeria monocytogenes is an intracellular bacteria ubiquitous in the nature. Listeriosis is considered a foodborne infection, with pathogeny related to the virulence and the immunological condition of the host. We describe seven cases of neurolisteriosis (NL), and evaluate risk factors and the most relevant clinical findings.

We examined the clinical records of 7 patients diagnosed of NL from 2004 to 2008. Demographic facts and data about underlying diseases, immunosuppression, toxic habits and previous treatments were collected. A positive CSF and/or blood culture was required to the diagnosis. Clinical, diagnostic and therapeutic characteristics are described.

The range of age was 22–73 years (mean: 45′7). One or more risk factors were found in 5 cases: Crohn disease, rheumatoid arthritis, steroids therapy, alcoholism and age older than 50 years. Four cases developed gastrointestinal symptoms 3–9 days before admission and 2 had respiratory symptoms 7–15 days before. Most started with meningeal syndrome, but one severely immunosuppressed patient presented with meningoencephalitis. Focal neurologic deficits occurred in 4 cases, 3 of which had predisposing factors. CFS revealed pleocytosis in all (predominant polymorphs in 50% and lymphocytes in 50%), hypoglycorrachia in 5, hyperproteinorrachia in all. Gram stain was positive in 1. CSF culture was negative in 2 patients, both with severe

immunosuppression and with sequels (seizures and cranial nerve paresis) at outcome. Six patients recovered with ampicillin alone and 2 combined with an aminoglycoside.

The incidence of NL, a potentially fatal infection, has increased in the last years, and amazingly in healthy adults. Digestive tract is considered the infection gate, as suggest initial gastrointestinal symptoms described here. In the cases with initial respiratory symptoms, it is possible that a viral coinfection might lead to a transient immunodeficiency, as it has been proposed to explain NL in healthy cases. Clinical features and CSF findings don't allow differentiate NL from other bacterial acute meningitis and the Gram stain usually is negative, so, diagnosis remains difficult requiring high suspicion to start early therapy. As previously described, NL is more frequent in immunodeficient states, who have more probability of neurological affection, sequels, worse prognosis and negative cultures. Guidelines about avoiding potentially contaminated food are emerging, especially in patients at risk.

P427

Outbreak of enterovirus meningitis, Georgia, 2006

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Objectives: Sentinel enterovirus surveillance identified a large-scale outbreak of aseptic meningitis in Georgia in 2006. The present study was conducted in order to identify the etiologic agent and describe clinical and epidemiologic characteristics of the outbreak.

Methods: Cerebrospinal fluid (CSF) specimens from aseptic meningitis patients were tested for enteroviruses by RT-PCR for 5′-URT which detects all enteroviruses. Enterovirus serotypes were determined by identification of genomic sequences of VP1 region which correlates with enterovirus serotype, using RT-PCR with primers targeting a section of VP1 followed by sequencing of amplicon. Clinical and demographic information on patients was obtained form hospital records.

Results: Of the 81 suspected cases, 60 were clinically confirmed as aseptic meningitis (i.e. had compatible symptoms and CSF pleocytosis). Cases occurred during May-October (83% in June–August); males accounted for 61%. The age ranged from 1 day to 75 years (median, 6 years); children aged <12 accounted for 88%. Cases were reported throughout the country. Median hospital stay was 11 (range, 1–60) days. Six (10%) cases required ICU treatment. There were no deaths. Of 47 cases with CSF specimens available for testing, 34 (72%) were enterovirus-positive. Identification of enterovirus serotype by partial VP1 sequencing identified echovirus 9 in 28 (82%) of enterovirus-positive cases. These cases were from 12 districts of both eastern and western Georgia. Other contributing serotypes were echovirus 18 [three (9%) cases], coxsackievirus B5 [two (6%)], and echovirus 33 [one (3%)], detected exclusively in cases from eastern Georgia. Phylogenetic analysis of VP1 sequences revealed that the echovirus 9 strain from this outbreak was distinct from previously characterized echovirus 9 strains.

Conclusion: A large-scale outbreak of aseptic meningitis in Georgia was primarily associated with a distinct strain of echovirus 9. The actual extent of the outbreak was likely much higher because cases were reported only by selected hospitals participating in sentinel surveillance. The identification of a new distinct strain of echovirus 9 could reflect the introduction of a new genetic lineage or result from incomplete surveillance.

P428

Movement disorders in encephalitis

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Objective: This study evaluates the pattern of movement disorders in encephalitis patients and their correlation with MRI changes.

Methods: 74 out of 209 patients with encephalitis having movement disorders were included and they were subjected to clinical evaluation and recoding of type, pattern and severity of movement disorders. The location of cranial MRI abnormality was recorded. The specific diagnosis of viral encephalitis was done by CSF IgM ELISA and PCR. The patients were followed clinically at 3 and 6 months and outcome was defined at 6 months into complete, partial and poor on the basis activities of daily living.

Results: Their median age was 19 (1–67) years and 16 female. Movement disorders were present in 67.6% in JE, 11% in dengue, 9% in mumps and measles and 34% in nonspecific encephalitis. None of the HSE patients had movement disorder. Three broad types of movement disorders were found; parkinsonian features in 36, dystonia 6 and parkinsonian features with dystonia in 32 patients. The severity of different component of parkinsonian features and dystonia ranged from 2 to 4 in a 0–5 grade scale. At 3 and 6 months PD features improved more frequently compared to dystonia although the mean severity score in the remaining patients also improved significantly ($p = 0.001$). Different type of movement disorders was not related to location MRI change except PD with dystonia had more frequent thalamic and substantia nigra lesion compared to putamen, globus pallidus and caudate. Patients with parkinsonian features with dystonia had worse outcome at 6 months compared to parkinsonian features alone (0.003).

Conclusion: Both hypo and hyperkinetic movement disorders occur following encephalitis especially following JE which may be due to involvement of thalamus, basal ganglia and substantia nigra in JE. Parkinsonian features improve more frequently compared to patients with additional dystonia.

P429

Psychiatric manifestations of neurosyphilis in Kyrgyzstan

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Objectives: Analyse present-day psychiatric manifestations of syphilitic meningoencephalitis in Kyrgyzstan and their response to antibiotic therapy.

Methods: We performed retrospective analysis of 14 neurosyphilis cases (13 men and 1 woman). The diagnosis was confirmed by positive CSF serology (RPR, EIA, TPHA, TPI tests) as well as elevated CSF protein level and/or pleocytosis. Mental disorders in all the patients predominated over neurological signs. The latter were mild and included pupillary changes, cranial neuropathy, ataxia, and sensory impairment. Penicillin preparations or ceftriaxon were administered parenterally, but the doses and duration of treatment varied in different cases.

Results:

1. Denial of illness was revealed in 14 cases (100%), cognitive impairment—in 13 cases (93%), affective disorders—in 13 cases

(93%), regressive behaviour—in 8 cases (57%), paranoid-hallucinatory syndrome—in 5 cases (36%), seizures—in 4 cases (29%), delirium—in 3 cases (21%), neurotic and somatoform syndromes—in 3 cases (21%), catatonic syndrome—in 1 case (7%).
2. The above symptoms subsided after treatment in 4 patients only (29%), which can be explained either by the inadequate dosage of the antibiotic failing to achieve treponemicidal level in CSF or by the resistance of syphilis-related mental disorders to treatment.

Conclusions: Neurosyphilis can present with a variety of psychiatric syndromes mimicking other mental disorders. National guidelines should be elaborated and introduced into clinical practice to provide early detection of the disease and increase the success rate of antibiotic treatment.

Neuro-genetics

P430

Adverse reactions to comt inhibitors in Parkinson's disease patients: possible association with the ugt1a9 gene haplotype

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Objectives: Entacapone and tolcapone are catechol-O-methyltransferase (COMT) inhibitors used for the treatment of patients with Parkinson's disease (PD). Tolcapone was previously withdrawn from the market due to serious hepatotoxicity, and subsequently reintroduced with recommendation to perform regular liver function text. Entacapone seems better tolerated, however some cases of mild hepatotoxicity have been reported. Some of us recently provided circumstantial evidence that the tolerability profile of COMT inhibitors could be related to individual genetic variations in drug metabolism (Martignoni et al. 2005), which occurs mainly through UDP-glucuronosyltransferase (UGT) 1A9. The expression and activity of UGT1A9 is affected by several single nucleotide polymorphisms (SNPs), thus their combination effect should be taken into account.

Aims: To assess the association between occurence of adverse reactions (AR) to COMT inhibitors and the UGT1A9 haplotype resulting from the combination of SNPs UGT1A9*1 (wt); UGT1A *1b; UGT1A *3; and UGT1A *5.

Methods: PD patients treated with COMT inhibitors were enrolled in the study and screened for the occurrence of AR, which were defined as any events leading to discontinuation of therapy with COMT inhibitors. Genotyping was performed by direct sequencing and haplotypes were defined as: extensive metabolizers (EM); intermediate metabolizers (IM) and poor metabolizers (PM) according to specific combination of SNPs. Correlation between AR and allelic frequency of SNPs was performed by Chi-square test with confidence interval of 95%. The study was approved by the ethics committee of the "Ospedale di Circolo-Fondazione Macchi", Varese, Italy.

Results: 38 PD patients were enrolled so far in the study (age: 72.9 ± 8.5; gender: 20F/18 M). Of these patients, 9 (23.7%) presented with AR. In patient without AR haplotypes were: EM = 8 (27.6%); IM = 19 (65.5%); PM = 2 (6.9%). In patient with AR haplotypes were: EM = 1 (11.2%); IM = 4 (44.4%); PM = 4 (44.4%), ($P < 0.05$). AR occurrence was not associated with individual SNPs, however patients with AR had statistically significant increased frequency of the PM haplotype.

Conclusion: PD patients with UGT1A9 PM haplotype seem at higher risk of AR leading to discontinuation of COMT inhibitors. Assessment of the cost-effectiveness of genetic screening as a tool to guide COMT inhibitor treatment is warranted.

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P431

Association study of dopamine D2 receptor and COMT gene polymorphisms with magnitude of motor response to levodopa in patients with Parkinson's disease

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Background: Pharmacodynamic variables, correlated to disease progression, influence the magnitude of motor response to levodopa in Parkinson's disease (PD). It is unknown whether genetic factors may also contribute in determining an individual susceptibility to levodopa-induced motor response.

Objective: The aim of the study was to investigate the relationship between some genes polymorphisms, correlated with dopaminergic receptors activity or in metabolism of levodopa, and the magnitude of motor response to levodopa in patients with (PD).

Methods: In 189 patients (age, 62.1 ± 9.3 years, mean ± SD) with sporadic PD, who underwent an acute levodopa test, we investigated three polymorphisms (CA-STR, TaqIA e TaqIB), located in the dopaminergic receptor D2 gene (DRD2), and one polymorphism (A/G) of the gene coding for Cathecol-O-Methyltransferase (COMT). The acute oral levodopa test consisted of the administration of 250 mg of levodopa plus 25 mg of carbidopa at unmedicated baseline status, after prolonged washout from previously administered levodopa therapy. Clinical status was assessed by means of the Unified PD Rating Scale, section of Motor Examination (UPDRS-ME) and Movement Time (MT) recordings, through "Movement Time Analyzer", assessed at baseline and at 30, 60, 120 and 240 min after levodopa administration. Blood samples were collected at the same times and plasma levodopa levels were later assayed with high-performance liquid chromatography. The magnitude of motor response to levodopa was defined as the percentage of MT improvement between baseline status and peak values. Patients with a magnitude of response lower than 30% were considered to have a small response (SR) and patients with a magnitude greater than 30% to have a large response (LR).

Results: We found that 106 patients (56%) had a SR and 83 patients (43%) had a LR to levodopa. DRD2 allelic and genotypic frequencies analysis of the CA-STR polymorphism showed that 13,14- genotype (absence of either 13 or 14 allele) was associated with a LR to levodopa ($p = 0.003$, OR = 3.36, 95% CI = 1.53–7.35). The other investigated polymorphisms had similar frequencies in both groups.

Conclusions: Individual susceptibility to motor response to levodopa could be influenced by genetic factors correlated to DRD2 gene polymorphism status.

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P432

Risk of levodopa-induced dyskinesias in Parkinson's disease associated with dopamine D2 receptor gene polymorphisms

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Background: Peak-dose dyskinesias are the most common side effects of levodopa therapy for Parkinson's disease (PD). The identified predictors may only partially account for the risk of developing peak-dose dyskinesias because a substantial proportion of patients never develop peak-dose dyskinesias. Genetic factors could play a role in determining the occurrence of peak-dose dyskinesias.

Objective: The aim of this study was to investigate whether polymorphisms in the gene for dopamine receptor D2 are associated with the risk of developing peak-dose dyskinesias in PD.

Methods: A case-control study of 196 subjects with sporadic PD and 204 population control subjects was performed. We studied three polymorphisms involving the dopamine receptor D2 gene (Taq1-A, Taq1-B, and STR-CA polymorphisms).

Results: The polymorphisms of the dopamine receptor D2 gene Taq1-A and Taq1-B were not associated with the risk of developing PD or peak-dose dyskinesias. The 15 allele of the STR-CA polymorphism of the dopamine receptor D2 gene was more frequent in parkinsonian subjects than in control subjects. More important, the frequency of both the 13 allele and the 14 allele of the STR-CA dopamine receptor D2 gene polymorphism was higher in nondyskinetic than in the dyskinetic PD subjects.

Conclusions: Certain alleles of the short tandem repeat polymorphism of the dopamine receptor D2 gene reduce the risk of developing peak-dose dyskinesias and could contribute to varying susceptibility to develop peak-dose dyskinesias during levodopa therapy.

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P433

12-Month European Phase III clinical study of SNT-MC17/idebenone in the treatment of Friedreich's ataxia: baseline neurology data and interim safety results

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Objectives: A 12-month Phase III clinical study is under way in Europe to determine the efficacy and safety of different doses of idebenone in patients with Friedreich's ataxia (FRDA). FRDA is an autosomal recessive congenital disorder and the most common inherited ataxia. Idebenone is a potent antioxidant and an electron carrier that promotes mitochondrial adenosine triphosphate (ATP) production.

Methods: In this ongoing double-blind, placebo-controlled, multicentre European study, FRDA patients aged 8 years and older are randomly assigned to placebo or to one of three body weight-adjusted doses of idebenone (i.e., 180, 450, or 1350 mg/day for patients weighing 45 kg or less, and 360, 900, or 2,250 mg/day for patients weighing more than 45 kg). Efficacy end points include absolute change in International Cooperative Ataxia Rating Scale (ICARS) score from baseline to week 52 (primary end point), as well as changes in Friedreich's Ataxia Rating Scale (FARS), Left Ventricular Mass Index (LVMI), and other measures of cardiac and neurological function. Safety evaluations include adverse events reporting, electrocardiograms, laboratory tests, and standard clinical assessments.

Results: A total of 232 patients were randomised. Mean age was 30 years. Of those, 123 (53%) had completed the study at the time of abstract submission. In addition to demographic characteristics and baseline data for neurological function scores (ICARS, FARS), activities of daily living and blinded interim safety and tolerability results will be presented. As of January 2009, 28 serious adverse events (SAEs), 10 discontinuations (4.3%), and no deaths had been reported. Twenty of the SAEs (71%) were considered by the investigator to be unrelated to study treatment.

Conclusion: Interim safety analyses suggest that idebenone is well tolerated in patients with FRDA.

This study was funded by Santhera Pharmaceuticals.

P434

Erythropoietin in patients with Friedreich's ataxia: preliminary results of a double-blind clinical trial after six months of treatment

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Objectives: Friedreich ataxia (FRDA) is a rare autosomal recessive disorder caused by a mutation in the FXN gene, encodin a protein named frataxin. As a result of the mutation, frataxin is quantitatively reduced but qualitatively normal. Recent evidences demonstrated the efficacy of recombinant human erythropoietin (rhuEPO) in increasing frataxin levels in lymphocytes of FRDA patients (Boesch et al. 2008). We are conducting a clinical study aimed at assessing the efficacy and the toxicity of rhuEPO in FRDA patients.

Methods: We have started a monocentric, randomized, double-blind, placebo-controlled, dose-finding study. Sixteen adult patients affected by FRDA have been randomly assigned to receive rhuEPO ($n = 11$) or placebo ($n = 5$). During the first 6 months, three consecutive cycles of treatment have been performed: (a) 20,000 IU of rhuEPO i.v. every 3 weeks, for 9 weeks; 40,000 IU every 3 weeks, for 9 weeks; and 40,000 IU of rhuEPO every 2 week, for 6 weeks. Frataxin and EPO levels have been determined in patients' peripheral blood lymphocytes before each drug dispensation. Scale for the assessment and rating of ataxia (SARA) was performed at enrollment and after the six-month scaling-up period.

Results: The enrolled patients were 9 women and 7 men. Mean age of 28.1 ± 5.5 years, and mean age of clinical onset was 12.7 ± 4 years. At baseline, the mean SARA score was 21.2 ± 6.8 (range 11–31), and the patients had a mean level of frataxin protein in peripheral lymphocytes of 25.7% $\pm$10.7 of normal controls. During the first six months of treatment no serious adverse event occurred. The monitoring of hematological parameters for safety evaluation showed increased levels of hemoglobin (>16 g/dL) in three patients assigned to the rhuEPO group, while the hematocrit remained < 50% in all cases. After each cycle of treatment, the levels of frataxin protein in lymphocytes remained unchanged both in the group of the patients assigned to rhuEPO and in the patients assigned to placebo.

Conclusions: Our preliminary results indicate that the doses and the drug schedules adopted during the six-month-scaling-up period of the study were safe, but not effective in increasing the levels of frataxin protein in FRDA patients. A different dose and route of administration is now being testing for the remaining six months of treatment.

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P435

The Cuban pathological CAG mutation causing SCA2 was introduced by Hispanics and probably originated between 1408 and 1733 in the Cuban population

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Objective: (1) To determine genetic similarity around of CAG repeat in Cuban SCA2 pedigrees. 2) To gain insights in the mutational history of SCA2 in Cuba by using chronologic and molecular approaches.

Methods: We performed CAG repeat size determination by gene sequencing and haplotype analysis by using microsatellites markers (STR) in families with SCA2 from the homogeneous Cuban population. Availability of sequence and haplotype data in this sample enable us to determine the probably Age when SCA2 mutation arose in Cuba.

Results: STR haplotypes from SCA2 families are very homogeneous, with sparse famillies and individuals showing rare haplotypes. Our calculations based on DMLE + 2.3, using 6 STR spanning a region of 3 cM with growth rate 0.45-fold per generation, estimated that this mutation originated around 392 years ago, showing a clear picture of a recent mutation origin at about 15.68 generations ago (95% Confidence Interval, 10.23 to 24.56 generations). This 392 year range places the arrivement of SCA2 mutation at 1615CE in the period (1408CE-1733CE) with the foundation important villes by Hispanics at western region of Cuba and out of the slavery introduction.

Conclusion: The importance of estimating age of mutation revolves around the conditions and life style by which SCA2 was fixed and reached the tremendous prevalence in our region.

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P436

Are the somatic mosaicisms of the CAG repeat expansions in similar Machado-Joseph disease/SCA3 and SCA2 patients?

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Objective: (1) To compare the somatic mosaicism in MJD and SCA2 Cuban patients and (2) To determine phenotypical association between somatic mosaicism in SCA2 and MJD.

Methods: GeneSCAN analysis used to determine somatic mosaicism in genomic DNA. 100 and 13 SCA2 and MJD respectively were recruited. Somatic mosaicism measured as Mosaicism Index (MI) and Peak Number (PN) were compared in SCAs patients. Also, genotype phenotype correlations were performed.

Results: Somatic instability was more pronounced in SCA3 than in SCA2 patients. CAG size of ataxin 3 was not associated with somatic mosaicism measured as: Mosaicism Index (MI) or peak numbers (PN). Also, disease duration (DD) was none correlated neither MI nor PN. Contrary to SCA2 in which we found a strong correlation ($R2 = 0.78$, $p = 0.00$) with MI and PN with CAG and with the other phenotypic and genotypic markers.

Conclusions: Differences in somatic mosaicism in similar substrates (CAG stretch) reflect different acting mechanisms generating instabilities. These molecular events are relocated perhaps out of CAG. Further studies in CNS structures are necessary to decipher the contribution of somatic mosaicism to the selectivity of cell death and the resulting neuropathological features in MJD and SCA2. CNS ataxin's mRNA expression profiling is a demanding task to decipher the role somatic mosaicism in the toxic load of compromised structures in these two neurodegenerative disorders.

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P437

Toward an integrative regulome of ataxin 2 and modifiers

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Objective: (1) Gaining insights about the regulation of proteins causing or modifying ataxia phenotype (2) To identify regulational nodes of ATXN2 modifiers.

Methods: Support Vector Machine predictions and Osprey resource were used to predict interaction and CpG density on SCAs proteins. Extensive predictions on SCAs subnetwork (Lin et al. 2007) were performed in all gene promoters.

Results: ATXN2 core promoter shown a high concentration of CpG (100 CpG). Support Vector Machine based tools predicted that 34% of CpG are methylatable (CpGm) with overrepresentation toward downstream 2nd ATG, perhaps reflecting a strong epigenetic control of putative more toxic ataxin-2 variants. CpG in dyads around the 1st in frame ATG, but none methylated, are potential targets for a more dynamic epigenetic control of the most common ataxin-2 isoform. ATXN2 promoter shows high (80%) similarity with RBMPS a critical "hubs" from SCAs Subnetwork, connecting ATXN2 with current SCA2 modifiers ATXN3 and ATN1 through ATXN1, reflecting a global role of epigenetic control by Methylation of critical genes causing, modifying or related with SCAs. We present regulation map based in the principal homology core promoter motifs of ataxia network genes.

Conclusion: The present data will enable us to develop assays to decipher functional the links between modifiers and proteins causing ataxia phenotype.

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P438

Oxidative stress increased activities of mutant protein kinase C γ, a protein causative for spinocerebellar ataxia type 14, leading to neuronal cell death

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Objectives: Spinocerebellar ataxia type 14 (SCA14) is an autosomal dominant cerebellar ataxia, caused by mutations in the gene encoding protein kinase C γ (PKCg). PKCg is predominantly expressed in cerebellar Purkinje cells, which are primarily degenerated and lost in

this disease. Oxidative stress is involved in many neurodegenerative diseases, but its involvement in SCA14 remains elusive. This study is aimed to clarify the roles of oxidative stress in the SCA14 pathomechanism.

Methods: Wild-type (WT), SCA14-associated mutant (S119F, C150F, and F643L), and kinase-dead (KD)-mutant (KD-S119F and KD-C150F) PKCg cDNAs were cloned separately into a C-terminal GFP plasmid vector. These plasmids were transfected into human neuroblastoma SH-SY5Y cells, which were then incubated in the presence or absence of L-buthionine-(S,R)-sulfoximine (BSO), a glutathione-depleting agent that accumulates endogenous reactive oxygen species. PKCg proteins expressed in SH-SY5Y cells were purified by immunoprecipitation, and subjected to kinase assay. Viability of cells expressing various PKCg under BSO-associated oxidative stress was assessed by MTS assay.

Results: SCA14-associated mutants had significantly higher kinase activities (S119F > C150F > F643L) than WT. Activities of both WT and mutants increased further by oxidative stress. By contrast, kinase activities were lost in KD-S119F and KD-C150F. Oxidative stress-induced cell death was observed in cells expressing S119F, C150F, and F643L, in this order, but not in those expressing WT or KD mutants. Thus, kinase activities were positively associated with ratios of cell death under oxidative stress. The observed cell death was significantly reduced by a specific kinase inhibitor, calphostin C.

Conclusion: Oxidative stress increased kinase activities of SCA14-associated mutant PKCg and thus neuronal cell death, suggesting its importance in the pathomechanism of this disease. The result also suggests that treatment with kinase inhibitors is a therapeutic option.

P439

Autosomal recessive spastic ataxias – Clinical review of 19 Portuguese families

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Background: Autosomal recessive ataxias and spastic paraplegias are clinically and genetically heterogeneous. There is a phenotypic continuum between the two groups which creates some difficulties in classification. Autosomal recessive spastic ataxias share clinical manifestations from both groups. The autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is the only recessive spastic ataxia with consistent phenotypic and molecular characterization.

Objectives: To describe Portuguese families with autosomal recessive spastic ataxia.

Patients and methods: Through a population-based survey of hereditary ataxias and spastic paraplegias in Portugal, covering 10 million individuals, we identified 19 families with autosomal recessive spastic ataxia. No molecular studies were performed, namely ARSACS gene screening.

Results: Clinical data was available for 28 patients with autosomal recessive spastic ataxia (17 women, 11 men). Two families with 4 patients, 3 with 2 patients and 14 with 1 patient (5 families with consanguinity). These families represented 8.1% of the Portuguese families with autosomal recessive ataxias and 18.8% of the families with recessive spastic paraplegia. The mean age of onset for motor manifestations was 10.4 years (2–33). The main clinical pattern could be defined as a "mermaid-like" model: ataxic and hypotonic upper limbs with spastic and paretic lower limbs. All patients had cerebellar dysarthria. Cranial MRI showed isolated cerebellar atrophy.

Conclusions: These families with autosomal recessive spastic ataxia have a characteristic clinical presentation. The recognition of this model can be easily made in clinical practice. This may foster future molecular understanding of this group. Otherwise it will continue underdiagnosed as non-specific ataxias or spastic paraplegias.

P440

Clinical features of SPG11 sporadic cases

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Objectives: Autosomal recessive hereditary spastic paraplegia (AR-HSP) with thin corpus callosum is a distinct and usually severe form of complex hereditary spastic paraplegia classified as SPG11. Recently, mutations in SPG11gene (KIAA1840) localized to chromosome 15q13-q15 were shown to cause the majority of SPG11 cases. Our objective was to study the clinical features and to identify potential sporadic SPG11 patients.

Methods: We analysed a group of 3 sporadic patients with signs and clinical history suggestive of the SPG11 complicated HSP form. They were aged 29, 28 and 22 years respectively, with normal early motor and mental development. Onset of symptoms was at the age of 9, 6 and 13 years respectively; in two cases symptoms at onset was abnormal gait while in the other was slow decline in school performances. The last neurological examination was showing in all of them slowly progressive spastic paraparesis with cognitive impairment (IQ levels 45, 62, 50), mild cerebellar signs while neuropathy was found in one case and distal muscle wasting at lower limbs in two cases. In all patients MRI revealed mild diffuse non progressive T2 signal alterations of cerebral white matter and thinning of the body and genu of the corpus callosum, without cortical and cerebellar atrophy (despite the cerebellar signs).

Results: Mutations in SPG11 were found in all three sporadic cases. One case was found to carry a known homozygous mutation while the other two patients were both compound heterozygous for one novel and one know mutation.

Conclusions: SPG11 mutations may be also involved in apparently sporadic SP cases without parental consanguinity. Therefore the SPG11 mutation screening is justified as one of the first diagnostic choices not only in familial recessive cHSP patients but also in sporadic cases presenting with variable combination of neurological signs and symptoms typical of SPG11-HSP form. Moreover the sequence of motor and mental symptoms is variable: the cognitive decline may appear many years before the motor signs.

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Clinical and genetic study in ataxia-oculomotor apraxia type 2

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Objectives: Ataxia with oculomotor apraxia type 2 (AOA2) is a recently discovered autosomal recessive cerebellar ataxia (ARCA) caused by mutations in the SETX gene.
The function of senataxin, the SETX gene product, is almost unknown; a DNA-RNA helicase domain is found at the carboxi

terminus of the protein, which has been postulated to participate in various aspects of DNA transcription, DNA repair, and processing of noncoding RNAs.
In the present study we described three affected patients with an homogeneous phenotype related to two novel mutations of SETX gene.

Methods: We analyzed a family of four siblings with two affected sisters and a sporadic case, all born to consanguineous parents.
The patients underwent clinical examination, routine laboratory tests, nerve conduction studies and brain MRI.
We examined two sisters, respectively at the age of 60 and 61 years old, showing dysmetria and movement decomposition; dysartria, horizontal gaze nystagmus, positional tremor of the head and the upper left limb, and saccadic ocular pursuit; severe distal muscular atrophy of the of the upper limbs with a pseudomyotonic phenomenon, severe impairment of vibration and position sense.
The clinical onset was around the age of 20 for both, with unsteadiness during walking, motor incoordination and frequent falls.
Cerebellar ataxia was progressive and by the age of 40 years they were wheelchair bound.
The sporadic case has a phenotype similar to the one previously described in the two sisters with an earlier onset and more severe clinical course. An additional oculomotor apraxia was present.
An increase serum α-fetoprotein level, a severe axonal motor and sensory neuropathy, a cerebellar atrophy without brainstem involvement and a borderline intelligence quotient were detected in all three patients.

Results: In the familial cases a novel mutation was found: a deletion of three bases in the 5' of the SETX gene, leading to a single aminoacid deletion in the putative protein-protein, interaction domain of senataxin.
In the sporadic case a novel nucleotidic substitution in exon 10 was detected.

Conclusions: The clinical phenotype of oculomotor apraxia type 2 is fairly homogeneous, showing only subtle interfamilial variability. Oculomotor apraxia is an inconstant finding. The identification of new mutations expands the array of SETX variants.

P442

Early-onset SCA17 with 43 repeats: phenotype-genotype mismatch?

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SCA17 is an autosomal dominant cerebellar ataxia caused by a trinucleotide repeat expansion within the TATA-binding protein gene (TBP). The clinical phenotype includes ataxia, dementia and other psychiatric symptoms, epilepsy, chorea and extrapiramidal features, among others; at the MRI brain scan these patients display both cerebellar and cortical atrophy. The age of onset is extremely variable and, according to some reports, not completely correlated with the size of the trinucleotide repeat expansion.

Here we describe the case of a 38-years old male, referred to our attention for an acute confusional state. At the examination the patients was anxious, disoriented, cognitively impaired, and presented severe dysarthria and marked trunk and limb ataxia. Ataxia clinical onset was reported since age 23, associated to slowly progressive dysarthria; few years later, a brain MR documented cerebral and cerebellar atrophy, not further investigated. At age 28 he was referred for epilepsy and treated accordingly. Family history was negative for movement disorders.

We decided to test the SCA genetic panel, and the analysis of the TBP gene yielded 43 repeats on one allele and 37 on the second. Genetic analysis of TBP triplets on parents and siblings was consequently proposed: both mother and sister of the proband resulted carrying 43 repeats on one allele of the TBP gene, in the complete absence of symptoms.

Conclusions: Usually the normal trinucleotide repeat size of the TBP gene encompass up to 42 repeats; between 43 e 44 is usually reported the grey zone; and the allele is pathologic with 45 repeats or more; moreover, available data suggest an incomplete penetrance between 43 and 48 repeats. In this case we can not rule out the possibility that the SCA phenotype could be the result of more than one interacting factor, possibly acting in a synergistic way in determining a "worse" clinical picture with respect to the one predictable based on of the genotype-phenotype relationship. Partially sustaining this hypothesis there is the evidence that both the mother and the sister of the patient are asymptomatic carriers of the 43-repeat allele. Nevertheless, the case we report clearly presented with a full-blown ataxic phenotype and an early age of onset, suggesting that intermediate alleles might play an important role, at least contributory, in the determination of SCA17.

P443

Novel spastin mutation (IVS14 + 5G > A) in a Greek family with hereditary spastic paraplegia

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Mutations of the spastin (SPAST) gene are commonly found in patients with hereditary spastic paraplegia (HSP) inherited in an autosomal dominant manner, with more than 150 mutations having been identified to date. Here we study a HSP kindred in which the IVS14 + 5G > A mutation in intron 14 of the SPAST gene was identified. The proband, a 68-year old woman, presented with a progressive gait disorder due to leg weakness and spasticity of 10 years duration, numbness of the lower extremities and urinary incontinence. On examination she showed paraparesis, spasticity of the lower extremities, hyperreflexia, extensor plantar responses and decrease in vibratory sensation in the lower legs. Electrophysiological testing showed disruption of the pyramidal tracts to the lower extremities bilaterally (increased Central Motor Conduction Time in Transcranial Magnetic Stimulation). This patient, as well as her affected sister and four affected cousins, who had a similar clinical picture, were genotyped. All six were found to be heterozygous for a novel spastin intronic mutation (IVS14 + 5G > A). This mutation was not found in a phenotypically normal sibling and in unrelated healthy controls from Crete, Greece. Segregation of the IVS14 + 5G > A mutation with the disease in this family supports its pathogenicity. Furthermore, as predicted by splice site prediction software, analysis of mRNA isolated from peripheral lymphocytes revealed that the IVS14 + 5G > A mutation affected normal splicing of spastin exon 14, causing a heterozygous frameshift with the truncated protein encompassing 514 aa instead of the 616 residues of the wild type protein. The present report of this SPAST mutation in Greek patients expands further the genetic and ethnic variability of HSP.

P444

Phenotypic characterisation of five patients with Gerstmann-Sträussler-Scheinker syndrome associated with Pro102Leu mutation: deep tendon areflexia with normal electrophysiological findings may guide early diagnosis

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Objectives: Gerstmann–Sträussler–Scheinker (GSS) is an autosomal dominant disease caused by mutations in the gene coding for the prion protein (PrP). The disease is characterised by cerebellar signs and progressive dementia. Pathologic findings include neurodegeneration of the cerebello-spinal and cortico-spinal tracts with multifocal PrP-positive plaques in the cerebellum and cerebral cortex. Aim of the study was to determine the clinical and electrophysiological features of GSS associated with Pro102Leu mutation.

Methods: We report clinical, genetic and electrophysiological data of 5 Italian patients (2 females and 3 males), from 3 unrelated and previously unreported families, with the Pro102Leu mutation.

Results: The patients were two male cousins from Family 1, two sisters from Family 2, and a young man with no family history, from Family 3. The age at onset ranged from 30 to 52 yrs; the mean age at examination was 46.2 yrs. Presenting symptoms were gait difficulties with lower limb weakness, unsteadiness, slurred speech and mood depression. At neurological examination all patients presented saccadic pursuit, nystagmus, dysarthria, limb ataxia, bilateral Babinski sign, and absent deep tendon reflexes in lower limbs. Four patients had saccade alteration, 3 cases presented ophthalmoparesis and pseudobulbar signs. Brain MRI was normal in 3 cases, while in 2 patients it showed mild cerebellar atrophy. Nerve conduction studies were normal in all cases; electromyography showed chronic denervation signs only in one case. H-reflex was absent in the 2 evaluated patients. Electroretinogram (ERG) and visual evoked potentials (VEP) were altered in all 4 tested patients. Somatosensory evoked potentials (SEP) were normal or showed minimal abnormalities. Brainstem auditory and motor evoked potentials were normal.

Conclusions: The neurological phenotype of our GSS-Pro102-Leu patients was consistent with that previously described in cases harbouring the same genetic mutation. In particular, we confirmed that, in the early stages of the disease, all patients present the peculiar association of lower limb areflexia (with absent H-reflexes) and normal findings at SEP and nerve conduction evaluations, supporting the localisation of the pathologic process to the posterior horns of the lumbar spinal cord. In addition, our study suggests that ERG and VEP alterations are common in GSS-Pro102Leu patients and may contribute in guiding clinical and molecular diagnosis.

P445

Dementia, hearing loss, and myoclonic jerks as manifestations of the rare 3291T > C mutation in the mitochondrial DNA MT-TL1 gene

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Objective: To report a case of dementia, hearing loss, and myoclonic jerks associated with the 3291T > C mutation in the mitochondrial DNA (mtDNA) MT-TL1 gene encoding a tRNA for leucine. Mutations in MT-TL1 are most frequently associated with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome, typified by seizures, non-ischemic, stroke-like episodes, lactic acidosis, and frequent childhood onset. Among the individuals with MELAS, the 3243A > G transition in the MT-TL1 gene is the most common mutation, while the 3291T > C transition has been reported only in a single Japanese patient who suffered from a devastating MELAS syndrome, and in an Italian child with an apparently isolated myopathy.

Case Rreport: A 23-year-old female presented with progressive hearing loss since puberty and recent onset of cognitive impairment. Family history was unremarkable. Neuropsychological, neurological and ophthalmological examinations revealed: cognitive decline (i.e., defects of verbal expression, visual perception, ideomotor and orofacial praxia, and long-term memory), nasal voice, severe hearing loss, small-amplitude jerks of fingers and toes, brisk tendon reflexes, pale optic discs. She had slight increase in serum CK, lactate and pyruvate. Brain MRI disclosed diffuse supratentorial and infratentorial atrophy; BAEPs and ERG were abnormal; EMG showed diffuse chronic denervation; 1H-MRS, EEG, nerve conduction velocity studies, MEPs, VEPs, and SEPs were normal; EKG revealed Wolff–Parkinson–White syndrome. Muscle biopsy showed ragged-red fibres and two COX-negative fibres; biochemical assays on muscle homogenate showed reduction of activity of the respiratory chain complex I. Analysis of the mtDNA showed a heteroplasmic 3291T > C transition in the MT-TL1 gene. Patient's muscle contained more than 95% mutant mtDNA, while mutant mtDNA was approximately 40% in lymphocytes.

Conclusions: At difference with previously reported cases harbouring the 3291T > C mutation, our patient presented dementia, hearing loss and myoclonic jerks, further confirming that no obvious genotype-phenotype correlation exists also for this rare mtDNA mutation. Moreover, the presence of brain atrophy without T2-weighted MRI abnormalities suggests that in the MT-TL1-related mitochondrial disorders dementia may be caused by a progressive neurodegenerative process, other than by injury accumulation due to stroke-like episodes.

P446

Phenotypic heterogeneity of GBE1 mutations: congenital glycogen storage disease type IV and adult polyglucosan body disease

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Objectives: Reduced glycogen branching enzyme (GBE) activity is found in both adult polyglucosan body disease (APBD) and glycogen storage disease type IV (GSD IV). Here we describe the diversity of clinical presentations of two novel pathological genotypes in the same glycogen branching enzyme (GBE1) gene.

Methods: GBE1 gene was sequenced. Brancher and glycogen synthase enzyme activities were measured on muscle, liver, heart and fibroblast samples.

Results: The first proband was an Italian male infant affected with congenital GSD IV. The mother had noticed decreased foetal movements. At birth, he had arthrogryposis, dysmorphisms and no spontaneous movements, requiring mechanical ventilation. He died at one month of age. GBE activity was ubiquitously absent. A homozygous G454T change determined a nonsense GBE1 E152X mutation. The second proband was 43-year-old male who had

presented since age 27 recurrent episodes of transient paraparesis and dysarthria, and more recently developed progressive dysarthria, lower limb weakness and spasticity, cerebellar and sensory ataxia, lower limb sensory abnormalities, anhydrosis, sphincter disturbances, cognitive dysfunction. He was firstly diagnosed with Fabry disease (FD), due to reduced á-galactosidase A activity and a missense A143T mutation in the GLA gene. However, this mutation has been reported in patients with atypical late onset FD, with no brain involvement, and he worsened despite enzymatic replacement therapy. Skin biopsy was within the norm. Electrophysiology showed a motor neuronopathy. Brain MRI revealed a severe leucoencefalopathy, cerebellar, bulbar and cervical spinal cord atrophy. Muscle biopsy showed granular amylopectin-like deposits. Gene analysis revealed two novel heterozygous GBE1 mutations (D413H and G534 V).

Conclusions: The reported cases illustrate the opposite ends of the clinical presentations associated with GBE1 mutations: a homozygous stop codon resulted in a congenital presentation, while two missense compound heterozygous mutations resulted in APBD. All these mutations are new, indicating a still incomplete genetic characterization of these disorders. The adult patient presented two rare, unrelated genetic disorders, and his neurological impairment was most likely due to APBD

P447

Metachromatic leukodystrophy: from natural history study to the design of a protocol of ex vivo gene therapy

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In the last six years we have studied the natural history of Metachromatic Leukodystrophy (MLD) on 27 patients, in the perspective of the clinical translation of a gene therapy approach based on autologous hematopoietic stem cells and lentiviral vectors.

Clinical and instrumental observation confirm that patients with early onset disease (late infantile and early juvenile) have a homogeneous and rapid clinical progression, while patients with later onset (late juvenile and adult) are more heterogeneous in their presentation, although characterized by a relative stability of the disease. Moreover, this study allowed us to validate clinical (Gross Motor Function Measure, GMFM) and instrumental (brain Magnetic Resonance, MR; ElectroNeuroGraphic recordings, ENG) tests to monitor disease progression.

For the design of the clinical trial we took into account both the information gained from our natural history study and some ethical considerations. According to the information obtained from our clinical study, early onset patients might represent better candidates, being more homogenous and thus more informative, and having a better risk-benefit ratio, given their severe disease. On the contrary, in late onset patients, it would be difficult discriminating between the potential clinical benefit and the natural benign course of the disease. Regarding ethical considerations on MLD, we focused on the principles of autonomy, beneficence, and non-maleficence. They point out that, in the case of MLD where the proxy has to provide the consent and where the procedure is irreversible and associated with potential severe risks, the clinical trial must aim at a significant clinical benefit.

Therefore, we will consider as eligible patients, pre-symptomatic late infantile patients and pre- or early-symptomatic early juvenile patients. According to the ethical considerations, we will include, among primary end-points, an end-point of clinical efficacy. We will consider the stability or reduced progression of patients' motor abilities by comparing the GMFM scores in treated patients with values obtained from control untreated subjects. As secondary end-points for clinical efficacy we will consider the stability or reduced progression of the disease evaluated through the use of the validated instrumental read outs ENG and brain MR. We will therefore evaluate the scores obtained in the treated patients, compare to those obtained from our cohort of untreated patients.

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P448

Frequency of HLA-DRB1 alleles and disease-modifying effects in a large West Australian multiple sclerosis cohort

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Objective: Genetic susceptibility to multiple sclerosis (MS) is predominantly determined by polymorphism at the HLA-DRB1 gene locus. The HLA-DRB1 *1501 allele is found in over half of MS cases in Caucasians. Western Australia (WA) is a geographically isolated State with a reasonably uniform and stable Caucasian population, providing a unique opportunity for genotype-phenotype studies.

Methods: The Perth demyelinating disease database (PDDD) recruited over 1000 patients representing approximately two-thirds of the MS population in WA. HLA-DRB1 genotyping was performed using a high-resolution DNA sequencing technique on a cohort of 495 well-characterized patients with demyelinating disease from the PDDD and genotype-phenotype correlations were examined. Among the study participants, 465 had clinically definite or probable MS (MS), comprising 41 cases of primary progressive MS (PPMS) and 425 cases of relapsing remitting/ secondary progressive MS (RR/SPMS). A cohort of 189 Caucasian individuals from a rural WA Community comprised the control group.

Results: A total of 34 DRB1 allele variants were detected in the study cohort. A significantly increased frequency of DRB1*1501 was observed in the RR/SPMS (54.1%, $p < 10^{-6}$ OR = 4.8) and PPMS (58.5%, $p < 10^{-6}$) groups compared with the control group (19.5%). Frequencies of four other DRB1 alleles (DRB1*0101, *0701, *0901 and *1101) were significantly decreased in the MS group. No association was found between the presence of DRB1*1501 and gender, age of onset, disease duration or frequency, of brain or spinal MRI or visual evoked potential abnormalities. Frequency of DRB1*1501 homozygosity was not increased in the MS cohort. However, a gene-dose effect was found for level of disability (median EDSS: DRB1*1501 homozygote 4.0, heterozygote 3.0, and DRB1*1501 negative group 2.5, $p = 0.009$). A correlation was also observed between DRB1*0301 gene-dose and spinal cord MRI abnormalities (100% in homozygotes, 94.1% in heterozygotes and 85.6% in DRB1*0301 negative cases, $p = 0.026$).

Conclusion: This is the largest Caucasian MS cohort studied to date in the Southern Hemisphere. Our results demonstrate the important role of HLA-DRB1 alleles in determining risk of MS and clinical outcomes in this population.

P449

Familial partial lipodystrophy associated with heterozygous LMNA mutation Arg482Gln in a Polish family

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Background: Familial partial lipodystrophy (FPLD) is a rare human disorder, which belongs to so-called laminopathies—a group of disorders associated with mutation in lamin A/C gene (LMNA). FPLD is characterized by partial loss of subcutaneous adipose tissue from the limbs, trunk and buttocks with its concomitant accumulation on face, neck and intra-abdominal region and is associated with insulin-resistant diabetes mellitus, hypertriglyceridemia and hormonal imbalance. Women are more severely affected.

Case report: We present the first Polish family, in which FLPD was confirmed genetically. A 34-years old woman was admitted to the hospital because of myalgia and cushingoid appearance. On physical examination we found round face with double chin and neck bump, prominent loss of subcutaneous fat on arms and legs. Muscle strength and tendon jerks were normal. EMG and ENG were normal. Diagnostic tests revealed increased liver enzymes, impaired glucose tolerance, high level of insulin and peptide C and slight dyslipidemia. Serum CK, thyroid hormones and cortisol were normal. On ultrasonography hepatic steatosis was found. Cardiological evaluation (ECG, echocardiography) did not reveal abnormalities. We also examined two children of our proband. The 9-years old daughter presented phenotype similarity to her mother as for general appearance and posture, but without fat loss. Basing on clinical examination the initial diagnosis of FLPD was established. Taking into account the existence of the LMNA "hot spot" for FPLD in exon 8, we started genetic screening in our patient exactly from this exon. We confirmed the presence of heterozygous nucleotide substitution (c.1445G > A) in highly conserved codon 482, resulting in arginin to glutamine change in the patient and her daughter, but not in her son. The patient had introduced successful treatment with metformin to improve insulin resistance and diabetes.

Conclusion: Genetically confirmed diagnosis of FPLD allowed introducing a therapy of polymetabolic syndrome preventing further cardiovascular complication of diabetes and hyperlipidemia.

P450

Association of apolipoprotein-E alleles in myasthenia gravis patients

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Background: Myasthenia Gravis (MG), an autoimmune disorder of neuromuscular junction, has variable presentation with respect to age of onset, gender, distribution of muscle weakness, immunological status and histopathology of thymus gland. Studies from different parts of the world have provided evidences that, apart from autoimmunity, the role of multiple genes like HLA, MHC, TLC and pro inflammatory and anti-inflammatory cytokines etc. also play a significant role in the development of the disease. Apolipoprotein E (Apo-E) is an important fat-linked protein, responsible for metabolism of cholesterol and other fats into small molecules. Apo-E mobilization of cholesterol in central nervous system (CNS) is important for synapse plasticity and repair of damaged neurons. It is postulated that Apo-E modulates the synthesis of T-lymphocytes, important in development of autoimmune disorders.

Objectives: To find the association of Apolipoprotein-E (Apo-E) alleles with the disease severity and AChR-antibody status in MG patients.

Methods: The study subject consisted of 115 MG patients, 25 multiple sclerosis patients (disease control) and 120 healthy subjects matched for age, sex and ethnicity. Apo-E gene was amplified by polymerase chain reaction (PCR) using forward and reverse primers, following a step down protocol. The PCR products were digested using appropriate restriction enzyme and resolved on 15% polyacrylamide gel electrophoresis (PAGE) to determine the Apo-E genotyping.

Results: Association of Apo-E genotype was analyzed using case-control approach. Comparison between seropositive (AChR-Ab positive) and seronegative (AChR-Ab negative) MG patients and controls did not show any significant association with Apo-E allelic variants. However, a significant association of Apo-E4 allele with the AChR-antibody positive MG patients (i.e. seropositive) was observed ($p = 0.007$). Also among AChR-antibody positive cases, a marginal significance of association was seen ($p = 0.059$) between female gender and Apo-E4 allele. We did not find any association between disease severity and Apo-E genotypes as reported by others.

Conclusion: Our results show that the association of specific apolipoprotein E i.e. Apo-E4 allele with seropositive status of MG, might influence AChR- antibody positivity in MG patients.

P451

Treatment with riboflavin in patients with Friedreich's ataxia

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Objectives: Friedreich Ataxia (FRDA) is a recessive autosomic neurodegenerative disease without a specific treatment. The enzymes of the mitochondrial respiratory chain that interact with the frataxin depend on the FAD coenzyme, which comes from riboflavin. The supplements of riboflavin in patients with FDRA could improve the mitochondrial function and the symptoms of the disease.

Methods: Open therapeutic study of 1-year treatment with riboflavin, 10 mg/kg/24 hours, in patients with FRDA genetically confirmed and ICARS score lower than 75 points. Periodic revisions of the functional situation (ICARS scale). Cardiac MRI at the outset and at the end of the study was done. Statistic: nonparametric test and linear regression.

Results: 22 patients (11 M/11 W) with an average age of 31.68 years old were selected, symptomatic average evolution of 17.4 years and ICARS score average of 36.8 points.
Seventeen finished the year of treatment. A functional improvement ICARS score was seen significantly ($p = 0.041$), mainly in the kinetic function ($p = 0.011$). Cardiac MRI showed an increase of the ejection fraction of ejection ($p = 0{,}031$).

Conclusions: Riboflavin produces a functional improvement of the neurological symptoms in Friedreich Ataxia and an increase in the cardiac fraction of ejection. More studies are needed to confirm the results reached.

Multiple sclerosis

P452

Optical coherence tomography in clinically isolated syndromes

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Objective: Optical coherence tomography (OCT) is a non-invasive, accurate and simple high resolution technique to quantify the thickness of retinal nerve fiber layer (RNFL). Measurement obtained with OCT may represent a surrogate biomarker for multiple sclerosis (MS).
The aim of the study was to examine retinal nerve fiber layer measured by OCT in patients with clinically isolated syndromes (CIS) and to investigate whether RNFL thickness is useful for determining the prognosis of patients with CIS.

Methods: Patients with CIS underwent a complete neurological examination. High field brain MRI(3T), cervical MRI and lumbal puncture were performed within three months of the first attack. They also underwent an ophthalmological evaluation including visual acuity and optical coherence tomography (OCT) within the first week after diagnosis.

Results: Twenty-four patients with CIS were recruited, including 8 patients with optic neuritis (ON),6 with spinal cord syndrome, 5 with brainstem symptoms and 5 with sensory and other syndromes.Oligoclonal IgG bands were present in 57% of patients. Seven patients fulfilled at least three out of four Barkhof criteria in MRI. 54.2% of all patients and 56.3% of the patients without ON showed the presence of at least one quadrant of an optic nerve with a decreased RNFL thickness.
The presence of at least one quadrant of an optic nerve with a RNFL thickness at a $p < 5\%$ cut-off value had a sensitivity of 71% and a specificity of 59% for predicting positive MRI (dissemination in space). Specificity increased to 82% if the cut-off value is set at $p < 1\%$.

Conclusion: Patiens with CIS but without ON showed affected RNFL thickness. OCT is an easier, faster and more cost-efficient exploration than MRI. OCT may be useful for predicting conversion in multiple sclerosis and useful as a surrogate biomarker . Follow-up is needed to confirm these preliminary results.

P453

Inappropriate use of disease-modifying therapy in severely disabled patients with progressive multiple sclerosis

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Background: Disease modifying therapy (DMT) is not effective in slowing progression in disabled patients (EDSS > 6.5) with secondary progressive MS without superimposed relapses and is ineffective in PPMS. Many patients who initially had RRMS 10–12 years ago and who now have SPMS continue to use IMT. They often experience adverse side effects; the enormous costs of inappropriate IMT further burden health service budgets. Regular neurology assessment is recommended to monitor progression and treatment responses, and to guide discontinuation of IMT if no longer effective. However, this is unavailable to many patients, particularly in rural areas.

Aim: To observe in an epidemiological study of MS the use of IMT in patients with progressive MS and EDSS > 6.5.

Methods: During an epidemiological study of MS in three regions in Ireland (South Dublin city, an urban area and Wexford and Donegal Counties, rural areas), we recorded the IMT details of patients with SPMS or PPMS and EDSS > 6.5.

Results: A total of 336 patients were seen from November 2007 to March 2008: 88 from south Dublin city, 99 from Wexford County and 149 from Donegal County. Forty-four patients of the 336 patients had an EDSS > 6.5: twelve of these were still on DMT. Eight of these patients had secondary progressive MS (SPMS) and 4 had primary progressive MS (PPMS). Eleven of the 12 were from rural counties; nine were living in rural Donegal, two in Wexford and one in southeast Dublin city.

Conclusion: A significant proportion of disabled patients with SPMS or PPMS (27%) were receiving inappropriate therapy. Eleven of the twelve patients on inappropriate therapy were from rural counties, reflecting poorer access to neurology services in these areas. The cost of IMT in this group (approximately €12,000—€16,000 per person/annum) could be re-directed towards development of neurology and rehabilitation services, to optimise management of these patients, or towards funding second-line immunomodulatory therapies for patients with highly-active relapsing remitting MS, to prevent disease progression and accumulation of disability. When applying these findings to Ireland as a whole, between €900,000 and over €3,000,000 could potentially be saved yearly, by identifying patients using DMT without likely benefit.

P454

Change in patient-reported disability, functional status and disease-specific quality of life in multiple sclerosis patients receiving natalizumab in the USA

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Objective: To assess the overall change in patient-reported disability, functional status and disease-specific QoL in multiple sclerosis (MS) patients receiving natalizumab in the USA.

Methods: In the USA, natalizumab is available only through the TOUCH Prescribing Program, a restricted distribution program focused on safety and developed in conjunction with the USA Food and Drug Administration. One must be enrolled in TOUCH to either prescribe or receive natalizumab. A subset of MS patients newly enrolled in the TOUCH program are participating in a longitudinal study of their experiences with natalizumab and complete assessments prior to treatment initiation and after the 3rd, 6th and 12th infusions. At each assessment, patients report their disability using the disease steps (DS) scale, functional status (FS) and disease-specific QoL using the Multiple Sclerosis Impact Scale (MSIS-29). The DS scale is a patient-reported measure that has been validated against the expanded disability status scale (EDSS) with lower scores indicating greater ambulation. Functional status is assessed with a single question with lower scores indicating a greater ability to carry out the functions of daily living. There are two MSIS-29 summary subscale scores, physical and psychological, with lower scores on each indicating better QoL. This analysis reports changes in all three measures between baseline and after the 3rd natalizumab infusion. Paired t-tests were used to compare differences in scores.

Results: Results of this ongoing study are presented for 504 patients completing the baseline (BL) and 3rd infusion assessments. The mean age is 46.1 (SD = 10.7) and the majority of patients are

female (78%). The mean number of years since MS diagnosis is 10.0 (SD = 8.3). Patient-reported DS improved significantly from baseline (BL 2.9 versus 2.7; $p < 0.001$) as did FS (BL 2.6 versus 2.3; $p < 0.001$). For the MSIS-29 subscales, there were significant improvements from baseline for the physical (BL 48.6 versus 40.3; $p < 0.001$) and psychological (BL 43.6 versus 34.6; $p < 0.001$) scores.

Conclusions: Rather than just maintaining their baseline disease status and disease-specific QoL, patients entering into treatment with natalizumab reported significant, broad-based improvements in ambulation, functional status and MS-related QoL as early as after three natalizumab infusions.

This study was supported by Biogen Idec.

P455

Cognitive impairment predicts the clinical conversion to multiple sclerosis in patients with clinically isolated syndromes

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Objective: To assess the prognostic value of the presence of cognitive impairment (CI) for the clinical conversion to multiple sclerosis (MS) in a cohort of patients with clinically isolated syndromes (CIS).

Background: Significant CI has been found in 20-30 % of CIS cases; however, little is known about its possible predictive value for conversion to MS.

Methods: We included all the CIS patients consecutively referred to our Department since 2002 followed-up for at least one year. Cognitive functions were assessed through the Rao's Battery and failure of a test was defined using the Italian norms (scores > 2SDs below the mean of normal controls).

Results: Fifty patients (35 women; age 34.6 + 8.6 years; EDSS 1.2 + 0.7) were recruited. During the follow-up (3.4 + 2.5 years), 23 patients (46%) converted to MS. At baseline, 25 patients (50%) fulfilled MRI criteria for dissemination in space (DIS). Moreover, 16 patients (32%) failed at least one, 12 (24%) at least 2 and 7 (14%) at least 3 tests. Conversion to MS was observed in 38% of cognitively preserved patients, and in a significantly higher proportion of cognitively impaired subjects, depending on the degree of CI. In particular, 63% of patients failing > 1 test, 66% of patients failing > 2 tests and 85% of patients failing > 3 tests converted to MS by the end of the follow-up. In the Cox regression model, including the main demographic and clinical variables as well as oligoclonal banding in the CSF, the failure of at least 3 tests (HR 2.9;95% CI 1.1–7.7; $p = 0.028$) and the presence of MRI DIS at baseline (HR 3.2;95% CI 1.2–8.1; $p = 0.016$) resulted to be the only independent predictors for conversion to MS.

Conclusions: Different degrees of CI are detectable in CIS patients. The presence of significant CI predicts the clinical conversion to MS independently of other clinical, laboratory and MRI features.

P456

Cognitive and psychosocial features of childhood and juvenile multiple sclerosis: a reappraisal after 2 years

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Objective: To assess the evolution over time of cognitive impairment and its psychosocial impact in childhood/juvenile Multiple Sclerosis (MS) cases.

Background: In a previous multicentric study, we found a 31% prevalence rate of cognitive impairment, with profound impact on school and everyday activities. To date, little is known on the evolution of neuropsychological impairment in the childhood/juvenile age range.

Materials and methods: After a mean follow-up of 2.0 + 0.3 years, 26 out of the 63 cases from the original cohort (14 females; age 17.0 + 2.4 years; disease duration 5.2 + 3.8 years) have been reassessed using an extensive neuropsychological battery. Performance of cases was compared with that of 22 demographically matched healthy controls (HC). Cognitive impairment (CI) was defined as the failure of at least 3 tests (2 SDs below HC mean scores). Fatigue was assessed on the Fatigue Severity Scale, affective disorders on the Children Depression Inventory (CDI) and the Kiddie-SADS, Present and Lifetime Version diagnostic interview. Finally, an interview on school and daily living activities was obtained from the parents.

Results: After two years, the proportion of cognitively impaired cases raised to 42% (10 out of 26 cases). Cognitive functioning worsened in 70%, whereas it remained stable or improved in the remaining 30% of cases. Demographic and clinical variables were not significantly different between cognitively worsening and stable/improving patients. Cognitive domains showing prominent deterioration included verbal memory, attention and receptive language. On the basis of the diagnostic interview, 46% of the patients received a formal diagnosis of affective disorders. CDI and fatigue scores did not significantly change over the study period. Finally, 50% of the subjects exhibited problems in school achievements, hobbies and sport activities, and 30% experienced behavioural changes.

Conclusions: Worsening of cognitive performance over time should be expected in a great proportion of cases with childhood/juvenile MS, with increasing negative impact on a patient's life.

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P457

The onset of multiple sclerosis in Greece: a 5-year single-centre study of 1001 consecutive patients

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Objectives: The onset of multiple sclerosis (MS) in Greece has not been systematically studied in large consecutive patient-cohorts. We have investigated the initial symptomatology and course of MS in all patients seen over a period of 5 years at a single MS center in Athens, with a view to comparing it to better-studied Western populations.

Methods: The MS center at the Neurology Department, University of Athens is situated in central Athens and acts as a primary, secondary and tertiary referral center for MS patients from Athens, southern and central Greece. During a period of 5 years from 2004 to 2008, the initial symptomatology and course of MS in 1001 consecutive patients seen as inpatients or outpatients was recorded. A subgroup of 291 patients seen from disease onset was assessed independently.

Results: In the total patient cohort 90.6% of patients had bout-onset MS and 9.4% primary progressive MS. Initial symptomatology was optic neuritis in 22.5%, brainstem dysfunction in 18.5%, long tract sensory and/or motor dysfunction in 47.9%, cerebellar dysfunction in 2.6%, multifocal in 5.2% and other in 3.4%. In the cohort seen from onset 85.9% had bout-onset MS and 14.1% primary progressive MS. Initial symptomatology was optic neuritis in 23.4%, brainstem dysfunction in 17.2%, long tract sensory and/or motor

dysfunction in 47.4%, cerebellar dysfunction in 4.5%, multifocal in 4.5% and other in 3.1%.

Conclusion: The initial symptomatology and disease course of MS in Greek patients is remarkably similar to what is observed in other better-studied Western populations. The onset of MS in Greece appears to have a Western phenotype.

P458

Myelitis in patients with systemic sarcoidosis: neurosarcoidosis or demyelination? A report of 4 cases

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Sarcoidosis is an inflammatory multisystemic disorder. Involvement of the nervous system occurs in 5%-15% of patients with sarcoidosis and diagnosis may be difficult.
Neurological symptoms are more commonly associated with involvement of the hypothalamus and cranial nerves while spinal involvement is relatively uncommon.

Objectives: We screened 1001 consecutive patients, followed at the Unit of Demyelinating Diseases of the Neurology Department, University of Athens from 2004–2008. We reviewed clinical features, magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) findings as well as other tests such as high resolution computed tomography (HRCT), bronchoalveolar lavage (BAL), serum angiotensin-converting enzyme (SACE), trasbronchial biopsy, Gallium Scan.

Results: We found 4 patients with a history of systemic sarcoidosis who presented with neurological symptoms. Diagnosis of systemic sarcoidosis was based on transbronchial biopsy in two patients whereas the other two had positive HRCT and/or BAL and Gallium Scan. At presentation, three patients had inactive sarcoidosis. All four patients presented with myelitis. Myelitis was the first neurological manifestation in three of them, with one having relapsing steroid-responsive myelitis. The fourth patient had a history of involvement of the hypothalamus and inappropriate antidiuretic hormone secretion (SIADH). Occurrence of neurological manifestations ranged between 1 and 12 years after diagnosis of sarcoidosis.
All patients had abnormal brain MRIs with multiple clinically silent lesions. Spinal MRI showed that one patient had a gadolinium-enhancing lesion in the thoracic spinal cord while three patients had gadolinium- enhancing lesions in cervical spinal cord. CSF examination revealed presence of oligoclonal bands and increased IgG index in two patients and pleocytosis in one. The fourth patient had normal CSF findings. SACE was found increased in one patient.

Conclusions: Although spinal involvement is a rare manifestation of sarcoidosis, it should be considered in the differential diagnosis of myelitis, especially in patients with a history of systemic sarcoidosis. Neurological manifestations may arise in patients with inactive sarcoidosis. The clinical dilemma of sarcoidosis or demyelination in these patients cannot be easily settled.

P459

Psychological status of primary caregivers in families of patients with secondary progressive multiple sclerosis

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Background and purpose: Because of its chronic, progressive and disabling nature, secondary progressive multiple sclerosis (SPMS) can often be associated with altered psychological and physical function of patients as also of their family members. Primary caregivers providing daily assistance to a disabled patient are more likely to experience depression, anxiety and decreased quality of life (QOL). Therefore, the aim of the current study was to assess the psychological status and quality of life of primary caregivers of patients with SPMS.

Methods: Twenty primary caregivers (12 males and 8 females with mean age 50 $\pm$ 13.8 years) of an equal number of patients with SPMS completed the Greek validated version of the Hospital Anxiety and Depression Scale (HADS), a reliable measure of psychological distress and the EuroQOL (EQ-5D), a standardised instrument for measuring health outcome and quality of life.

Results: According to the grading of the HADS (scores between 8–10, 11–15 and 16–21 are in keeping with mild, moderate and severe anxiety and depression, respectively), our study sample experienced higher degree of anxiety than depression. The mean score in the 7-item HADS-anxiety subscale (range 0–21) was 10 $\pm$ 3.7 (range 3–15) and the mean score in the 7-item HADS-depression subscale (range 0–21) was 7.7 $\pm$ 3.3 (range 2–14). Fourteen caregivers were diagnosed as manifesting anxiety (4 mild and 10 moderate anxiety), whereas 9 also had depression (3 were diagnosed with mild and 6 with moderate depression). The manifestation of increased psychological distress was supported further by the responses in the anxiety/depression dimension of health of the EQ-5D. Twelve persons reported moderate degree and 3 extreme degree of anxiety/depression. The mean values in the EQ-VAS (rating of health status on a thermometer taking the values from 0 = worst imaginable health to 100 = best imaginable health) were 60 $\pm$ 15 (range 40–100). Five caregivers rated their health status with a score of 50 or lower.

Conclusion: Our study revealed that a significant proportion of primary caregivers of patients with SPMS experience significant emotional distress and report decreased QoL. Early recognition of caregivers' elevated degree of distress is important in designing appropriate psychopharmacological interventions.

P460

Comparison of interferon β-1a subcutaneous and interferon β-1b on medication adherence in patients with multiple sclerosis

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Objectives: To compare medication adherence in patients with multiple sclerosis (MS) receiving interferon β(IFNb)-1a subcutaneous (SC) or IFNb-1b.

Methods: In this retrospective analysis of a national managed care database, patients 18–65 years of age were included if they had a diagnosis of MS; had $\geq$1 outpatient disease-modifying drug (DMD) claim during the 1 July 2002, to 31 December 2005, selection period; and were continuously enrolled for 6 months before and 24 months after their initial drug claim (index date). Patients were excluded if they used >1 DMD after the index date, had a severe MS relapse in the 6-month pre-index period, received an office-based DMD injection in the 24-month post-index period, used natalizumab at any time during the study, or had unevaluable drug data for days supply or quantity dispensed. Medication possession ratios (MPRs) were calculated as the percentage of ambulatory days during the 24-month post-index period from the date of first use of the index DMD. The likelihood of adherence by treatment group was predicted by logistic regression, with age, sex, and region of the country as covariates.

Results: Study criteria were met by 530 MS patients (IFNb-1a SC, $n = 324$; IFNb-1b, $n = 206$). Patients had a mean age of 43.6 years, 77.2% were women, 49.0% were located in the Midwest, and 94.2% had commercial insurance. The average MPRs were 63.7% for IFNb-1a SC and 57.9% for IFNb-1b ($p = 0.020$). The percentage of patients who were adherent (MPR $\geq$85%) was 49.4 and 39.3% for IFNb-1a SC and IFNb-1b, respectively. Adherence was significantly more likely in IFNb-1a SC patients than IFNb-1b patients (odds ratio [OR], 1.603; $p = 0.0110$). Older age (in 10-year increments) was a predictor of adherence (OR, 1.301; $p = 0.0037$), whereas sex and region of the country were not.

Conclusion: Over a 2-year period, this retrospective analysis suggests that MS patients using IFNb-1a SC are more likely to be adherent to their DMD therapy, as measured by MPR, compared with those using IFNb-1b.

This study was supported by EMD Serono, Inc. and Pfizer Inc.

P461

Economic comparison of interferon β-1a and natalizumab in patients with multiple sclerosis

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Objectives: To compare the cost associated with multiple sclerosis (MS) care in patients receiving interferon β(IFNb)-1a subcutaneous (SC) and natalizumab

Methods: In this post hoc analysis, a national managed care database was used to identify patients (aged 18–65 years) with an MS diagnosis, $\geq$1 new medical or prescription claim for IFNb-1a SC or natalizumab during the 1 July 2006 to 31 Dec 2006 selection period, and continuous eligibility for 12 months before and 12 months after the initial disease-modifying drug (DMD) claim in the selection period. Both total and component costs (e.g, inpatient, outpatient, prescription) were considered and evaluated by analysis of covariance. A propensity score was calculated from preperiod variables (eg, relapses, comorbidities, steroid use) to control for differences between patient populations.

Results: A total of 421 patients (IFNb-1a SC, $n = 222$; natalizumab, $n = 199$) were included in the analysis. Most of the patients were women (IFNb-1a SC, 77.9%; natalizumab, 74.4%). Natalizumab patients tended to be older than IFNb-1a SC patients (mean [SD], 45.5 [9.7] vs. 42.2 [10.7] years, respectively), and a greater percentage of natalizumab patients, compared with IFNb-1a SC patients, were enrolled in health maintenance organizations (43.2 vs. 32.4%, respectively). The proportion of patients with no evidence of DMD use in the preperiod was 63.5% for IFNb-1a SC compared with 26.6% for natalizumab. Least squares (LS) means differences between IFNb-1a SC and natalizumab for total and prescription costs were dependent on the number of days of exposure. Following an average exposure of 290 days, the total LS mean costs were $26,433 for IFNb-1a SC and $35,980 for natalizumab ($p < 0.0001$). Significantly higher prescription costs were associated with natalizumab ($26,775) compared with IFNb-1a SC ($20,187; $p < 0.0001$). Outpatient costs were significantly greater for natalizumab patients ($8640) compared with IFNb-1a SC patients ($4,930; $p < 0.0001$).

Conclusion: Findings from this observational study suggest that patients initiated on natalizumab had greater total, prescription, and outpatient costs compared with patients initiated with IFNb-1a SC. The higher costs of natalizumab are due to its higher unit cost and a higher cost associated with healthcare administration.

This study was supported by EMD Serono, Inc., and Pfizer Inc.

P462

Prevalence of disease-modifying drug treatment gaps in patients with multiple sclerosis

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Objectives: To evaluate gaps in disease-modifying drug (DMD) therapy in patients with multiple sclerosis (MS)

Methods: In this retrospective analysis, a national managed care database was used to identify patients with a diagnosis of MS. Eligible patients (aged 18–65 years) had to have at least 1 claim for a self-injectable DMD (index claim) between 1 July 2000, and 31 December 2005; be continuously enrolled for 6 months before and 24 months after the index date; and have no nursing home claims. Patients receiving natalizumab were excluded from the treatment gap analysis because the majority of natalizumab claims did not contain the necessary days supply information. Treatment gaps were evaluated over a 24-month observation period, and a gap was defined as the number of days between the lapsing of the days supply of the prior prescription and the fulfillment of a new prescription. Gaps in treatment were categorized as $\geq$0 and <11 days, $\geq$11 and <31 days, $\geq$31, <61 days, $\geq$61, <90 days, and $\geq$90 days across all DMDs.

Results: Study criteria were met by 1914 patients. The study population had an average (SD) age of 44.5 (9.2) years, 78.4% were women, and the majority (55.4%) were from the Midwest. Of the patients included in the analysis, 31.5% had a treatment gap of $\geq$0 and <11 days, 34.9% had a treatment gap of $\geq$11 and <31 days, 14% had a treatment gap of $\geq$31 and <61 days, 6.1% had a treatment gap of $\geq$61 and <90 days, and 13.5% had a treatment gap of $\geq$90 days.

Conclusion: More than one third of the patients in this analysis had a treatment gap of at least 31 days over a 24-month period suggesting that maintaining continuous therapy with DMDs remains a challenge for MS patients.

This study was supported by EMD Serono, Inc. and Pfizer Inc.

P463

Time from multiple sclerosis diagnosis to the first use of a disease-modifying drug

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Objectives: To evaluate the time between the diagnosis of multiple sclerosis (MS) and the first prescription of a disease-modifying drug (DMD)

Methods: Patients who were first diagnosed with MS between 1 July 2000 to 31 Dec 2005 were selected from a national managed care database. The time of diagnosis was designated the index date for the study. Patients were included in the study if they were aged 18–65 years, had 6 months of continuous eligibility (i.e., same health benefits during the entire study period) before the index date and 24 months after MS diagnosis, and received $\geq$1 DMD (interferon β[IFNb]-1a intramuscular, IFNb-1a subcutaneous, IFNb-1b, glatiramer acetate, or natalizumab) during the 24-month observation period. The analysis excluded patients who had a prescription for natalizumab or whose first DMD prescription was given $\leq$6 -months before their first MS diagnosis or after the study end date (31 Dec 2007). The time between first diagnosis and first prescription of a DMD is presented. Subgroup analysis evaluated the percentage of patients with evidence of relapse before and after DMD initiation.

Results: Inclusion criteria were met by 2,427 MS patients. The average (SD) age was 42.2 (9.7) years, and 76.3% of the patients were women. The average (SD) time from MS diagnosis to first DMD use was 140.1 days (171.7) with a median of 61.0 days. Examination of the time to first treatment by 30-day increments showed that 27.9% received their first DMD in < 30 days, 48.9% in < 60 days, 59.6% in < 90 days, and 74.3% in < 180 days. A substantial number of patients (25.7%) did not receive their first DMD for $\geq$180 days following their first diagnosis. The risk of an MS relapse was approximately 50% lower after DMD treatment among the subset of patients ($n = 666$) who initiated DMD therapy 90–360 days after their MS diagnosis.

Conclusion: This observational study showed that many patients delayed therapy for 6 months after initial MS diagnosis. The decreased likelihood of relapse following initiation of DMD treatment suggests that newly diagnosed patients should be encouraged to begin therapy as soon as possible.

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P464

Autoimmune disorders in patients with multiple sclerosis: a one-year experience

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Introduction: Multiple sclerosis (MS) is an inflammatory disease of central nervous system that runs with myelin lesion, various degrees of axonal loss and progressive neurological dysfunction. The real causes of MS are largely unknown, but both genetic and environmental factors have been implicated on its manifestation, emphasizing the autoimmune nature of this clinical entity.

Objective: To study a group of MS patients, from our outpatient clinic, in order to identify concomitant autoimmune diseases or laboratorial markers (autoantibodies) of an underlying autoimmune process.

Methods: We revised the clinical files of 134 different patients from our Demyelinating Disorders consultation, from January to December 2008 and performed a selection of MS cases. Some epidemiological data were collected, like patient's sex and age and clinical profile of the disease. We recorded patients' usual medication and concomitant diseases, particularly autoimmune diseases and laboratorial abnormalities suggestive of an autoimmune disturbance (presence of any kind of autoantibody).

Results: Seventy percent ($n = 94$) of the totality of the revised cases corresponded to MS patients, 29 men (31%) with 37.7 ± 11.2 years old and 65 women (69%) with 39.3 ± 12.0 years old. Relapsing-remitting MS was the more frequent disease profile, with 78.5% of the cases, secondary progressive accounted for 17.2% and, finally, primary progressive only for 4.3% of the patients. The diagnosis was supported by MRI criteria in 97% of the patients and oligoclonal CSF bands were identified in 52% of them. Sixty-three patients (68%) were exclusively under treatment with immunomodulators. Diabetes mellitus type 1 was identified in 1 patient, autoimmune thyroiditis in 3 (all women), chronic rhinitis in 2, asthma in 1, psoriasis in 1, ulcerative colitis in 1 and vitiligo in 2 patients. In the other hand, 3 different patients had positive reactions for antinuclear antibodies (ANA), 1 for antimitochondrial antibodies (AMA and anti-M2) and 1 for anti-C reactive protein (CRP) antibody. No statistically relevant associations were observed in this data.

Conclusion: In our group of MS patients, 15 (16%) had clinical or serological evidence of an autoimmune process. However, more studies are needed to understand if MS patients have really a more positive likelihood of developing another autoimmune diseases and, more precisely, what kind of diseases.

P465

Elements of a patient support programme influencing quality of life in patients with MS: one-year results from an international, observational study

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Objective: Treatment support programmes are designed to help patients to become familiar with treatment management. This study evaluated the effect of different support elements on the quality of life (QoL) of patients with multiple sclerosis (MS).

Methods: The analysis used data from the longitudinal, observational, 24-month BPlus study conducted in 15 countries. This analysis covered a time frame of 12 months. At baseline, BPlus included 1077 patients with relapsing remitting MS (RRMS) or secondary progressive MS (SPMS) whose physician switched them from another drug to interferon β-1b (IFNB-1b; Bferon®) 1–3 months before inclusion. At inclusion and at each of the six-monthly visits, patients' choice of the support elements was documented. Support elements included the autoinjectors Bject® or Bject® Light, specialist nurses, or the MS-Gateway website. Random effects generalised least squares regression was used to analyse the effect of choosing a support element on the change in QoL within the 12-month time frame measured by the Functional Assessment in MS total score (FAMS-TS) controlled for age, sex and MS type (RRMS/SPMS).

Results: At baseline, the mean age of all patients was 35.9 years (standard deviation [SD] = 10.2); 71% were women, 74% had RRMS and 26% had SPMS. The mean FAMS-TS was 106.6 (SD = 31.9). According to regression analysis the use of the specialist nurse programme ($p = 0.04$) or the MS-Gateway website ($p = 0.01$) next to age and MS type, results in a more pronounced increase in patients' QoL within the 12-month time frame compared with the use of the remaining elements.

Conclusions: The 1-year interim results of the study suggest that the use of the specialist nurse programme or the MS-Gateway website is an effective support element in the treatment of patients with MS.

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Homocysteine, vitamin B12, folic acid and MTHFR C677T mutation in MS patients

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Objectives: There is increased interest in the role of homocysteine and Methylentetrahydrofolate reductase (MTHFR) gene mutations, B12 and folic acid levels in multiple sclerosis (MS) and other white matter lesions. Purpose of our study was to measure levels of homocysteine, B12, folic acid and percentage of MTHFR C677T gene mutation in our MS patients.

Methods: 33 patients investigated for possible MS were included in this study. 25 of them fulfilled the new McDonald criteria for definite MS and 8 for probable. Homocysteine, B12 and folic acid blood levels were checked in all patients. The MTHFR C667T mutation, common in Greek population (35%) was examined in: (a) all patients who showed elevated homocysteine levels, (b) all patients with possible MS and (c) 6 definite MS patients selected randomly.

Results: B12 levels were within normal range for all patients. 3/33 (9%) showed folic acid deficiency whereas 4/33 (12.1%) high levels of homocysteine, results similar to those found among the general population. Concerning investigation for MTHFR C667T, heterozygous mutation was found in: (a) 3/3 patients (1with possible, 2 with definite MS) with high blood homocysteine levels who were able to be checked, (b) 3/6 (50%) of the rest of possible MS patients, (c) 5/6 (87%) of the random sample of definite MS patients.

Conclusion: There is a highly increased percentage of MTHFR C667T gene mutation in our MS patients, (especially those with definite MS) compared to that met throughout the general population.

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MS Register in Germany: immunotherapy and drug discontinuation

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Objectives: The German MS Society, National Association (DMSG Bundesverband e.V.) initiated a national multiple sclerosis (MS) register in 2001. This register provides information about disease characteristics, health care provision and demographic situation of MS in Germany.

Methods: The minimal data set has been agreed in consensus with leading MS experts in Germany and was modified after a 2-year pilot phase. In the extension phase, new centres were recruited. As of January 2009, a total of 103 participating centers throughout Germany collected 16.881 data sets which passed stepwise quality checks.

Results: As described earlier, 71% of the patients were female, mean age was 44.1 ± 11.6 years, and mean age at diseases onset was 30.0 ± 10.1 years. In general, 79.4% ($n = 8881$) of the patients were on immunotherapy, 11.0% had received immunotherapy in the past, and 9.6% had never received any immunotherapy at all. Whether patients received immunotherapy depended on the course of the disease: 86.7% of patients with relapsing-remitting MS were on immunotherapy, while 73.7% of patients with secondary progressive MS and 58.9% with primary progressive MS were treated with this kind of therapy. The most frequently administered agents were β-interferons (51%).

Nearly half of all patients (44.7%) who currently have or ever had any immunotherapy had changed or stopped therapy mainly due to a perceived lack of efficacy. 57.8% of these patients did so within the first two years.

Conclusions: In agreement with other studies the updated results from the German MS register show that a high proportion of MS patients are treated with immunotherapy. However, a considerable proportion of patients (25.8%) changed or even stopped therapy during the first 2 years. A more detailed analysis will be presented at the meeting.

P468

Bladder dysfunction in patients with multiple sclerosis. Assessment by a self-report questionnaire and bladder ultrasound scan

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Objectives: The self-report questionnaire "International Prostate Symptom Score" (I-PSS) has been proposed recently to self-evaluate bladder dysfunctions in male as well as in female MS patients. We aimed to assess reliability and practical utility of the the I-PSS scale in a large MS population, in relation to clinical, quality of life (QoL) and bladder functional measures.

Methods: We gave the I-PSS to 175 outpatients (150 females) with relapsing-remitting SM, mean disease duration 12.5 years (range 1–35), mean EDSS disability 2.4 (0–6.5). The I-PSS comprises 7 questions addressing the severity of urinary straining, frequency, intermittence, urgency, weak stream, nicturia and bladder emptying and an additional question on QoL. The answers range from 0 (no symptoms) to 5 (always). The sum of the scores of the 7 questions gives the global score. Scores 0-7 mean no/mild symptoms, 8–19 moderate symptoms and 20–35 severe symptoms. Bladder capacity and post-micturition residual volume were evaluated with a suprapubic ultrasound scan (Bladderscan® BVI 3000, Diagnostic Ultrasound Corporation, Redmond, USA) by an expert nurse (CP) in 96 patients (71 females). According to these measures, patients were divided in 3 subgroups: no/low (<20 ml), moderate (20–100 ml) or severe (>100 ml) residual volume.

Results: Only 11.4% patients were asymptomatic at the I-PSS scale, in contrast to 60.5% at the Kurtzke's sphincter FS score. We found a good correlation between I-PSS and QoL scores related to bladder dysfunction ($r = 0.75$) or FS scores ($r = 0.5$). Bladder scan evaluations resulted in 35.4% patients with no or low, 38.5% with moderate and 26% with severe residual volume, and a modest linear correlation with I-PSS scores ($r = 0.33$). No differences emerged among patients of the three I-PSS groups as for disease duration and bladder capacity. Conversely, we found highly significant differences in the three I-PSS groups as far as disability, sphincter FS, QoL scores ($p < 0.0001$) and, to a lesser degree, residual volumes ($p < 0.05$) were considered. In the severely symptomatic group, a remarkable correlation with QoL scores was found ($r = 0.77$).

Conclusion: The I-PSS is an easily self-administered scale that demonstrated a high sensitivity for minimal bladder constraint dysfunctions. In addition to simple functional bladder measures obtained with a suprapubic scan, the I-PSS might represent a first step evaluation of bladder dysfunctions in early MS, even in asymptomatic patients.

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Efficacy of interferon β-1a 44 mcg subcutaneous in two relapsing multiple sclerosis patient cohorts by baseline expanded disability status scale score

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Objectives: To evaluate the efficacy of interferon β (IFNb)-1a 44 mcg subcutaneous (SC) 3 time weekly (TIW) in 2 cohorts of relapsing multiple sclerosis (MS) patients, one with baseline Kurtzke Expanded Disability Status Scale (EDSS) scores > 3.5 and the other with EDSS of ≤3.5.

Methods: An exploratory analysis of data obtained from the 2-year, double-blind, randomized phase of the Prevention of Relapses and Disability by IFNb-1a SC in MS (PRISMS) study was performed to evaluate the effectiveness of IFNb-1a 44 mcg SC TIW versus placebo in the cohort of patients with baseline EDSS scores >3.5–6.0 and in a cohort with EDSS scores ≤ 3.5. Comparative results for IFNb-1a SC versus placebo are provided for both cohorts.

Results: There were 59 (IFNb-1a 44 mcg SC, $n = 31$; placebo, $n = 28$) and 312 (IFNb-1a 44 mcg SC, $n = 153$; placebo, $n = 159$) patients who had baseline EDSS scores of >3.5 and ≤3.5, respectively. Over the 2-year study period, the mean number of relapses was similar in both the >3.5 and ≤3.5 cohorts. In the >3.5 cohort, the mean number of relapses at 2 years was 1.2 in the IFNb-1a SC group versus 3.1 in the placebo group ($p < 0.0001$) and in the ≤3.5 cohort, it was 1.8 in the IFNb-1a SC group versus 2.5 in the placebo group ($p = 0.0033$). In the IFNb-1a SC group, 32.3 and 32.0% of patients in the >3.5 and≤ 3.5 cohorts, respectively, were relapse-free. In both cohorts, the difference in the percentage of relapse-free patients was significantly greater with IFNb-1a SC versus placebo ($p < 0.02$). The median time to first relapse with IFNb-1a SC was 10.6 months in the >3.5 cohort and 9.3 months in the ≤3.5 cohort. Median time to first relapse was significantly prolonged for patients on IFNb-1a SC in both cohorts versus placebo ($p < 0.002$).

Conclusion: Based on a variety of clinical outcome measures, the results from this exploratory analysis of PRISMS data strongly suggests the effectiveness of IFNb-1a 44 mcg SC TIW in relapsing MS patients who were at both the low and higher end of the EDSS at baseline.

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P470

6-year clinical data of patients treated with natalizumab. Comparison with age, sex and disease-duration matched controls treated with other disease-modifying drugs

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Objective: Natalizumab is a monoclonal antibody that showed high efficacy in the original 2-year placebo controlled AFFIRM trial. Unfortunately, a potentially fatal viral infection raises safety concerns. Thus, long term efficacy and safety data are needed. The objectives of this small study were to address the 6-year clinical course of 13 patients from our center who participated in the original trial and to compare their clinical course with age, sex and disease duration matched groups treated by other disease modifying drugs (DMD).

Methods: We present the data of 13 patients (group1 = G1) with relapsing remitting multiple sclerosis who were enrolled in the trial during the spring of 2002. They received 56 natalizumab infusions on average until May of 2008 (there was an obligatory 15 month drug safety suspension during 2005). The second group (G2) represents 13 patients who participated in another clinical trial in our center and were treated with different DMDs. For clinical evaluation we used expanded disability status scale (EDSS) performed every 6 months, annual relapse rate (RR) and the parameter of EDSS 24 weeks sustained progression. We also looked at the laboratory results (blood tests and biochemistry over the 6 year interval).

Results: The baseline characteristics of G1 (mean age 28.9 years, sex ratio F/M 9/4, disease duration 5.4 years and baseline EDSS 1.7) were without significant differences compared to G2, except for a significantly higher RR rate one year before the study in the G2 group (1.19 vs. 1.81, $p = 0.006$).
In the G1 group, there was no significant difference in the EDSS over the 6 year study (using Wilcoxon paired test, $p = 0.67$), the relapse rate decreased to 0.26 and remained stable over the 6 year study.
Contrary to G1, there was a significant increase in the G2 EDSS over the 6 years ($p = 0.01$) and significantly higher annual RR (0.58, $p = 0.043$), this significance disappeared after adjustment for higher RR one year before the study.
2 out of 13 patients in G1 and 7 out of 13 in G2 reached sustained progression within 6 years. This difference did not show significance ($p = 0.13$) when we performed survival analysis defined as time to confirmed sustained progression by means of Kaplan–Meier.

Conclusions: Overall, the natalizumab treatment showed high efficacy regarding the disability and relapse rate and this effect seems to be stable over years. There were no safety problems in this particular group of patients.

General neurology

P471

Lose weight fast. Is gastric reduction surgery a safe solution to the obesity epidemic?

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Objectives: There is a recent interest in surgical treatment of obesity. However any surgical procedure involving the stomach carries a risk of vitamin malabsorption as an early or late complication. A deficiency of various vitamins may present with neurological symptoms. We present two cases with postgastrectomy neurological complications.

Methods/results: The first case is a 70 year old female patient who developed non alcoholic Wernicke encephalopathy 20 years after Billroth II gastrectomy. Two weeks prior to admission the patient developed unsteadiness, vertigo and diplopia. She was referred to the clinic by a neurologist with the possible diagnosis of brainstem stroke. On admission she was alert and oriented, had marked truncal ataxia, diplopia and hyporeflexia. MMSE score 28/30. An urgent MRI head scan showed enhancement of the mammillary bodies, a hallmark of Wernicke encephalopathy. Vitamin B1 levels test was unavailable on admission and it was performed 24 h after initiation of treatment with IV thiamine 150 mg/day. Then, vitamin B1 was found at the lower laboratory reference levels. The

next day, the patient complained no longer of diplopia, but unsteadiness persisted as well as hyporeflexia. She followed a course of IV thiamine 150 mg/day for a week and was discharged with IM injections of thiamine. On follow up one week after discharge, the patient showed marked improvement of ataxia.

The second case is a 30 year old female patient who underwent sleeve gastrectomy in order to lose weight. Three months after the operation and after losing 30 kgs, she showed numbness and weakness of the lower extremities. The neurophysiologic examination revealed a mixed peripheral neuropathy. CT of the brain and spine was unremarkable. In the absence of other possible causes, peripheral neuropathy was attributed to malabsorption syndrome. She was given IM B-complex vitamins with gradual resolution of symptoms.

Conclusions: There should be increased alertness for recognizing both early and late neurological complications of hypovitaminosis in postgastrectomy patients considering the fact that gastric reduction surgery is nowadays being presented as an "easy" way to lose weight.

P472

Safety monitoring of miglustat in patients with Niemann-Pick disease type C

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Background and objectives: Niemann-Pick disease type C (NP-C) is a rare and devastating genetic disorder arising from abnormal cellular lipid trafficking. Miglustat was approved for use in Gaucher disease type 1 (GD1) in March 2003. On 18 December 2008 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for the use of miglustat in patients suffering from NP-C. The miglustat post-marketing surveillance (PMS) programme was implemented at the time of miglustat marketing authorisation for GD1 in Europe. It collects clinical information on miglustat use in patients with GD1 and other lysosomal storage diseases. The programme is conducted in accordance with standard of care practice and miglustat product characteristics, and aims to enhance awareness of appropriate safety precautions and monitoring in miglustat use.

Methods: The miglustat PMS programme is formulated as a prospective non-interventional, password-protected web-based programme. Physicians are encouraged to enter data from patients receiving miglustat.

Results: From March 2003 to 19 October 2008, information was available on 98 NP-C patients (56.1% female) prescribed miglustat in 11 European countries (32 centres). Mean age (SD) was 13.4 (9.9) years; 44 patients (44.9%) were < 12 years old. As of 19 October 2008, overall exposure to miglustat represented a cumulative period of 232.0 patient-years; the median exposure (range) was 25.9 (0.4–78.2) months. The majority of patients (65.3%) received a daily miglustat dose of < 600 mg/day. Safety signals (adverse events that might be associated with the use of miglustat) were reported in 40 patients (40.8%), with most adverse events due to disease progression. Diarrhoea was observed in 17 patients (17.3%) and body weight decrease $>10\%$ occurred in 16 patients (16.3%). Four patients died because of disease progression. Thirteen patients discontinued; six due to disease progression, three due to the request of the patient or the relatives, three due to diarrhoea, and one due to inability to swallow the capsule (lack of compliance).

Conclusion: Miglustat is well tolerated in NP-C patients in clinical practice. NP-C patients in the miglustat PMS programme exhibit disease signs and symptoms that are characteristic for NP-C; thus analyses based on miglustat PMS findings should be applicable to the clinical NP-C population as a whole.

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P473

Relapsing Bickerstaff encephalitis presenting as hypothalamic polydipsia – Case report

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Objective: Bickerstaff Encephalitis is a rare, usually monophasic, post viral autoimmune illness. It is characterized by progressive ophthalmoplegia,ataxia and disturbance of consciousness and or hyperreflexia. Very few cases of recurrent Bickerstaff encephalitis are reported in literature. We report unusual presentation of relapse of Bickerstaff encephalitis(BE) with hypothalamic polydipsia.

Method: Case report of the unusual presentation of Bickerstaff Encephalitis with relapse in the form of hypothalamic polydipsia and demonstration of MRI abnormality

Result: We report a 26 years old lady who presented in May 2008 with vertigo, vomiting, diplopia,seizures and drowsiness and examination revealed complete opthalmoplegia, ataxia, bulbar weakness, drowsiness and hyperreflexia. Her MRI brain revealed T2 hyperintense lesions in posterior medulla, pons, both occipital and high parietal regions. Her complete blood count, vasculitic screen, ESR, GQ1b antibody, Herpes Simplex Virus 1 and 2, CSF examination was normal .Nerve conduction study, Somatosensory evoked potential were normal and EEG showed diffuse slowing . She had to be ventilated and was started on steroids and antiepileptic medication to which she responded and improved completely in 8 weeks. She again presented in Jan 2009 with fever, seizures and polydipsia, polyurea and hyponatremia. Her new MRI brain showed resolution of previous lesions and a appearence of new hyperintense lesion in left hypothalamus and thalamus.She responded to steroids and water deprivation.

Conclusions: We report a very rare case of Bickerstaff Encephalitis who relapsed with unusual presentation of polydipsia and the MRI demonstrated hypothalamic lesion.

P474

Episodic loss of consciousness occurring with unexpected and localisation-specific sensory triggers: report of a family

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Introduction: The reflex seizures triggered by various environmental stimuli are known for a long time, among them those caused by sensory triggers are rare and familial occurrence is not well established. Our aim was to report an index patient and her two family members with similar attacks of loss of consciousness occur only when they suddenly hit their elbows and knees unexpectedly or get a shock in the stomach area.

Report of the family: Eighteen-year-old female patient was admitted with fainting after sudden painful and unexpected hits

only on her elbow, knees or abdomen. Since her childhood, she had been experienced a total of 5 faints of this kind and had a few spontaneous faints during painful menstruation periods. Her attacks consist of short spells with loss of consciousness and falling loosely to the ground. She denied any medical history except migraine without aura. Her parents were second-degree relatives. Forty-eight-year-old father and 23-year-old sister had also very similar fainting attacks triggered by unexpected similar hits to the same localizations. Attacks did not occur in every occasion, important determinants are their severity, the specific localization and unexpected appearance. All three had normal physical, cardiologic and neurological examinations. The index patient had consistent generalized spike and wave discharges during intermittent photic stimulation in two EEGs. Her father has slow waves only during hyperventilation and her sister's EEG was normal. Biochemistry (except for iron deficiency anemia), thyroid hormones, vitamin B12, ECG and cranial MRI examinations were normal. Autonomic function tests (RR interval variability, the sympathetic skin responses), median and tibial SEP studies were normal, C reflexes were not identified.

Conclusion: These similar attacks occurring only in specific situations of our patients could be considered as reflex syncope or reflex epilepsy when EEG findings are taken into account. The familial occurrence suggests a genetic picture probably a unknown channelopathy due to its episodic nature.

P475

Bickerstaff brainstem encephalitis: a severe disease with a benign course

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Background: Bickerstaff Brainstem Encephalitis (BBE) is a rare entity with a benign course, despite its clinical severity. Aetiology is unknown, but it is probably associated with immune mechanisms. Sharing similarities with Miller Fisher and Guillain Barré syndromes, the three constitute different patterns of a same disease.

Case report: A 40-year-old woman, previously healthy, presented acute gastroenteritis. At the third day she developed dyplopia, dysarthria and imbalance. The next day she had recovered from the gastroenteritis, but her neurological deficits aggravated. At the emergency department she was awake but lentified, with limitation of right eye abduction, slight dysarthria, no motor deficits but brisk reflexes and a right Babinski sign, right hemi-hypoesthesia and ipsilateral clumsiness in finger-nose test. Routine blood tests and brain CT scan were normal. Spinal tap evidenced 8 lymphocytes, normal glucose and protein content. Brain MRI was unremarkable. At this time, the most likely diagnosis was brainstem encephalitis (viral/bacterian—Lysteria) and antibiotics were started.

By day 5 she was awake, with severe limitation of ocular movements (only capable of conjugate levoversion), facial diparesis, anarthric, aphagic, with spastic tetraparesis (MRC 1/5), generalized hiperreflexia, and bilateral Babinski sign. Repeated brain MRI (with DWI) and CSF study were normal. By now, BBE was the most likely diagnosis and IgIV therapy was initiated. Her status remained unchanged until day 10, when she started gradually recovering. Broad blood analysis revealed reactive ANA (1/320) and positive anti-ds-DNA. Anti Campylobacter jejuni antibodies were positive (IgM and IgG), with negative Anti GQ1b and onconeuronal antibodies. EMG (day 20) was normal. She was discharged home (day 28), with only minor dysarthria and ataxia.

Discussion: Diagnostic criteria of BBE include acute ataxia and ophthalmoplegia, associated with somnolence, hiperreflexia, Babinski sign and hemi-sensitive impairment. Infectious prodrome can be detected in 90% of patients. CSF is commonly normal. MRI is normal in 50% of patients and EMG in 30%. Positive anti GQ1b are found in 2/3 of patients and IgM anti-Campylobacter jejuni antibodies in 1/3. Our patient presented the typical severe clinical picture with benign evolution of BBE. The presence of reactive ANA in the acute phase may support the evidence that BBE is an autoimmune disorder.

P476

Nucleoplasty in the treatment of lumbar discogenic pain

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Introduction: Lower back pain is a common, chronic disabling condition usually related to disk herniation. Various treatments such as common analgesic, NSAIDs, physiotherapy and surgical procedures have been used in managing the pain. Nucleoplasty is a procedure, which uses radiofrequency energy to disintegrate and evacuate the disc material.

Objectives: To evaluate the efficacy and safety of percutaneous nucleoplasty in patients affected by painful and disabling lower back pain due to disk herniation.

Methods: We studied 10 patients with 1 year history of back pain, resistant to common analgesic treatment and physiotherapy. They also suffered a quite severe pain radiating down to the lower limb in a radicular territory. Five were females and 5 males with a mean age of 56.6 years. Neurological examination was normal except for one female patient who had loss of sensation in a L5-I1 distribution and also diminished Achilles reflex.

All patients underwent MRI scan in order to confirm the presence of the herniated disk responsible for the pain. Five of them had small or medium sized herniated discs (contained disc herniation <6 mm) whilst the rest 5 had large herniated discs (> 6 mm). Visual analogue scale (VAS) for pain was used to assess the intense and improvement of the pain with 0 corresponding to no pain and 10 being the worst pain experienced. VAS was recorded before and 3 months after the procedure. All patients had a VAS > 5/10 before the procedure.

Results: Nine out of ten patients experienced complete resolution of the pain with the improvement being obvious the first 24 h after the procedure. The female patient with numbness and loss of sensation in the distribution of the involved root, showed normal neurological examination 3 months later. A year later 8 patients were free of pain and stopped analgesic consumption and the ninth patient has an 80% reduction of pain 3 months post nucleoplasty. Finally in one patient nucleoplasty didn't help at all and he had to undergo open surgery. We assume that the patient's lack of improvement was related to the heavy degeneration of the nucleus pulposus and the presence of multiple vacuums in the disc.

Conclusion: Given the small number of patients we studied, we can assume that percutaneous nucleoplasty is a safe, well tolerated and minimal invasive procedure that can provide alternative to microdiscectomy even in cases with big herniated discs and abnormal neurological examination.

P477

Characterisation of NMO spectrum disorders in 40 Italian patients

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Objective: Recent evidence suggests that Neuromyelitis Optica (NMO) represents a spectrum of disorders rather than a single nosological entity. Our aim is to clinically characterize a cohort of patients affected by NMO, recurrent myelitis and optico-myelitis.

Methods: All patients presenting with optic neuritis and myelitis attending our Centre since 2006 were recruited. Their clinical, neuroradiological, neurophysiological and immunological features were assessed. Multiple sclerosis and infections were excluded.

Results: Forty patients were evaluated and divided into two groups, according to the revised diagnostic criteria for NMO by Wingerchuk et al.

The first group fulfilled these criteria and consisted of 19 patients (89% females) with a mean age at onset of 31.5 years (range 15–62 years). Brain MRI was negative in 17 cases, whereas a longitudinally extensive transverse myelitis (LETM) of 3 or more segments was evident in 16 patients (84%), with Gd-enhancement in all but one case. Abnormal CSF findings (elevate protein and cellular count) were found in 21% of the patients, oligoclonal bands (OB) were detected in 32%, and no abnormalities were found in 48%. The onset of the disease was acute in all cases and the first clinical presentation was myelitis for 11 patients. No response was observed to steroids in 63% and to immunosuppressive treatment in 74% of patients. NMO-IgG were detected in 15 patients (79%).

The second group included 21 patients (14 recurrent myielitis and 7 optico-myelitis) not fulfilling Wingerchuk's diagnostic criteria, with a mean age at onset of 36 years, 66% females. Brain MRI was negative in 86% while a LETM was present in 52%, with Gd-enhancement in 76%. CSF analysis showed no abnormalities in almost half of the cases (48%), while OB were detected in 14%. They all presented with an acute onset, predominantly a myelitis (81%) with a relapsing course. No response was observed to steroids in 67% and to immunosuppressive treatment in 57% of patients. NMO-IgG were found in 10 out of 21 patients (48%).

Conclusions: The group fulfilling the NO revised criteria was distinguished by a higher frequency of IgG-NMO detection, a higher rate of LETM and a worse response to therapy; some features however overlapped in the two groups (CSF, brain MRI). A prospective clinical, MRI, neurophysiological and immunological follow-up is going on to better characterize the spectrum of NMO.

P478

Metronidazole-induced encephalopathy in a patient with hepatic encephalopathy

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Objectives: Metronidazole is a 5-nitromidazole compound known as an antimicrobial agent widely used for the treatment of protozoal, anaerobial and Helicobacter pylori infections and hepatic encephalopathy. The most frequently reported neurological adverse event is peripheral neuropathy, but central nervous system (CNS) disorders are rare. Metronidazole-induced encephalopathy is tipically associated with brain imaging changes by magnetic resonance images (MRI). We report a case of CNS toxicity caused by metronidazole in a patient with hepatic encephalopathy, presenting with seizures, encephalopathy and progressive cerebellar dysfunction.

Methods: We present the case of a 55-year-old male patient with a history of alcoholic liver cirrhosis who was admitted to the hospital because of hepatic encephalopathy and pre-renal acute renal failure. Since admission he received metronidazole as coadjuvant treatment for hepatic encephalopathy. Six days later, when hepatic encephalopathy had resolved, he presented complex partial seizures, which were treated with levetiracetam adjusted for renal function. After three weeks, sleepiness, confusion, dysarthritic speech, and severe gait and limb ataxia progressively developed. Generalized seizures required treatment with phenytoin.

Results: MRI of the brain performed two weeks after treatment onset was normal. Ammonia levels were normal. Metronidazole was discontinued after 30 days of treatment and the patient′s condition progressively resolved in four weeks. Follow-up imaging performed one month after cessation of metronidazole therapy was normal.

Conclusion: CNS toxicity of metronidazole may cause severe encephalopathy and cerebellar dysfunction and pharmacological-resistant seizures. It must be kept in mind, particularly in cases of prolonged treatment and renal failure, since it may be completely reversible after drug withdrawal. Neuroimaging findings are not indispensable for making the correct diagnosis.

P479

Cortical laminar necrosis with early involvement of the corpus callosum

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Background: Cortical laminar necrosis (CLN) can be defined by image as high intensity cortical lesions on T1 weighted MRI images with a gyral distribution. It represents death of neurons located in the third and fifth cortex layer. Several pathologies like cardiorespiratory arrest, carbon monoxide (CO) poisoning, status epilepticus and hypoglycemia resulting in hypoxia have been pointed as causative factors. White mater changes are usually described from day 14 to day 20.

Clinical case: A 61-year-old woman with a history of depression and a clinical suspicion of systemic lupus erythematosus treated with corticosteroids and quetiapine, was admitted due to consciousness impairment. She had been found unresponsive sitting on her sofa where she had fallen asleep twelve hours before. On admission she had a Glasgow Coma Scale Score of 8 (eye opening and localizing response to pain, no verbal response). Blood analysis was unremarkable including toxics and CO levels. EEG disclosed bilateral fronto-temporal epileptic activity without criteria for status epilepticus. Brain CT showed several cortico-subcortical hypodense lesions with a temporo-parieto-temporal disposition. MRI with diffusion weighted imaging (DWI) performed seven days after the event showed bilateral hypersignals with a gyral distribution in the parieto-temporal-occipital cortex, globus pallidus, cerebellum and splenium of the corpus callosum. These lesions were dark on apparent diffusion coefficient maps.

During hospital stay, a pattern of nocturnal arterial hypotension was noticed, reaching values of 50 mmHg of systolic blood pressure. Cardiac evaluation was normal. After quetiapine suspension, hypotension improved.

MRI performed thirty days after admission showed T1 and T2 hyperintensities following a fronto-parieto-temporo-occipital cortical gyral pattern and basal ganglia involvement. DWI showed extensive hypersignal in the deep white matter with a bilateral fronto-parietal predominance. Clinically she had spontaneous eye opening, said some words, did not follow commands and had a cortical blindness. She could mobilize the four limbs spontaneously and walk with guidance.

Discussion: There are only few reports of early involvement of white matter in the setting of CLN. Corpus callosum is a structure relatively resistant to ischemic injury. We believe that the corpus callosum DWI changes seen seven days after the insult could be due to early Wallerian degeneration.

P480

Reversible cerebellar syndrome and neuroimaging abnormalities in a case of metronidazol toxicity

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Introduction: Metronidazol is a widely used antimicrobial, with usually few adverse effects- mainly nausea and vomiting- but rarely, severe neurological side effects such as dysarthria, ataxia, neuropathy, seizures and encephalopathy may develop. Only recently these have been correlated with MRI abnormalities that affects primarily deep cerebellar nuclei and tends to reverse, along with neurological deficits, upon Metronidazol suspension. We report a case of a reversible subacute cerebellar syndrome in a patient taking high dose of Metronidazol.

Case report: A 74- year-old female was admitted for progressive dysarthria and disabling ataxia over a period of 2 months, that ultimately unabled her to ambulate. She had a history of hypertension, diabetes mellitus, dyslipidemia, ischemic stroke with mild gait unsteadiness, and a chronic diabetic foot lesion for which she had been medicated with high dose of Metronidazol (Flagyl). On neurological examination, at admission, she had a dysarthric speech, appendicular ataxia and a wide-base stance with marked retropulsion. A brain MRI disclosed bilateral increased signal intensity in the dentate nuclei on T2/FLAIR, with no mass effect, no diffusion- weighted imaging (DWI) or ADC abnormalities, and no enhancement after gadolinium. After discontinuation of Metronidazol, there was a rapid remission of dysarthria and significant improvement of ataxia, being the patient able to ambulate fully independent at discharge. On last follow up she had no appendicular or gait ataxia and a residual postural instability.

Conclusion: Central nervous system toxicity by Metronidazol must be kept in mind in the setting of neurological symptoms, as it can be reversed by discontinuing the offending agent. The diagnosis is supported by reversible MRI abnormalities. It is important to recognise and document such cases in order to avoid iatrogenic harm.

P481

Cerebral white-matter lesions associated with vitamin B12 deficiency

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Objectives: To describe a clinical case of a patient with marked white matter abnormalities on brain MRI who present cognitive impairment and vitamin B12 deficiency and report the changes in both clinical and MRI in response to therapy. MRI abnormalities in brains of such patients could be expected but are rarely present.

Methods: We reviewed the clinical history, cognitive tests, brain and spinal MRI, evoked potentials and all laboratory work up that were needed in the differential diagnosis of one patient whose final diagnosis presented an unexpected vitamin B12 deficiency.

Results: A 55-year-old woman with a history of depression was referred to the Multiple Sclerosis consultation after an abnormal brain MRI. The scan had been obtained because she had a recent 4-year old history of chronic headaches. Careful clinical history revealed no other past or current focal neurologic symptoms. Her family noticed memory impairment interfering in daily activities. Neurological examination revealed no abnormalities. Neuropsychological testing was notable for a mild general cognitive impairment. T2-weighted brain MRI showed multiple periventricular and juxtacortical white matter lesions; there was no enhancement or infratentorial lesions. Spine MRI was normal, but somatosensory evoked potentials of lower limbs were abnormal. Laboratory data revealed a low serum vitamin B12 concentration and an increase of homocysteine levels. After ruling out the other potential causes of demyelinating diseases she was put on cyanocobalamin intramuscular therapy. After nine months of vitamin treatment there was clinical improvement and partial imaging recovery.

Conclusion: This rare case indicates that Vitamin B12 deficiency should continue to be considered in the differential diagnosis of neurology disorders associated with multiple areas of white matter hyperintensities on T2 weighted brain MRI. Early detection and treatment may be associated with potential for recovery.

P482

Kennedy's disease: an under-diagnosed and under-reported neuroendocrinopathy

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Kennedy's disease is an X-linked condition presenting with neurological and endocrine symptoms. Neurologically, it is a hereditary form of bulbospinal neuronopathy, characterised by slowly progressive muscle weakness and atrophy with onset in adult males. Endocrinally, it is an androgen insensitivity syndrome, manifesting as testicular atrophy, gynecomastia and reduced fertility, although add on features like diabetes mellitus are also reported. The incidence is reported to 1:40,000 men in USA. A study from Scandinavia suggested a prevalence of 1.3/8,500 making this as the most common form of motor neuron disease in the specific area studied. It is a polyglutamine gene disorder caused by increased number of CAG repeats at the Xq11-q12.

A 57 year old man was referred to neurology for late onset progressively worsening mobility, muscular weakness and recurrent falls. He gradually developed speech and swallowing difficulties and became wheel chair bound. He also had hypothyroidism and hypocalcemia. Examination showed proximal muscle and bulbar muscle atrophy and weakness with fasciculations. He had a number of neurological investigations including MRI brain and spine. His electromyography and nerve conduction studies initially showed features of motor and sensory neuropathic process with chronic denervation, but on repeating the tests after a year showed recruitment of giant motor units. The suspicion of Kennedy disease arose only after a vigilant systemic examination showing gynecomastia and testicular hypotrophy. His Genetic testing confirmed the diagnosis of mutation in androgen receptor gene.

The diagnosis of this uncommon and relatively new disease can be challenging, especially considering the fact that, it can mimic motor neuron disease and falls at the interface between neurology and

endocrine medicine. We present this case and review the literature in order to raise awareness about this entity.

P483

Long-term safety and patient preference for dose frequency in patients receiving ropinirole prolonged-release in early or advanced Parkinson's disease

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Objective: To summarize the interim safety and tolerability data from 2 ongoing, long-term studies of ropinirole prolonged release in patients with early or advanced Parkinson's disease (PD). Also, to establish patient preference for alternative dose regimens of PD treatments.

Methods: Patients were enrolled into 2 multicentre open-label, flexible-dose, extension studies: 101468/196 and 101468/248. Safety and tolerability of once-daily (OD) ropinirole prolonged release (2–24 mg/day) were assessed by the incidence of treatment-emergent adverse events (TEAEs), serious TEAEs (TESAEs) and TEAEs leading to withdrawal. Patients who had previously received ropinirole immediate release, three-times daily (TID), completed a balanced design questionnaire 4 weeks after enrolment to elicit preferences for OD or TID dosing.

Results: This analysis included patients followed for up to 4.6 years. 502 patients had received ropinirole prolonged release: 194 monotherapy, 357 adjunct therapy. Overall, 418/502 patients had been exposed for >1 year and 276/502 patients were still receiving ropinirole prolonged release at the data cut. Patient distribution across the modal dose groups ≤ 8, > 8–16 and > 16 mg/day was 22, 38 and 40%, respectively; mean (SD) dose was 15.9 (6.31)mg/day. TEAEs were reported by 404/502 patients, whether related to treatment or not. Peripheral oedema was the most commonly reported TEAE (64/502). TESAEs occurred in 96/502 patients, with chest pain reported most frequently (10/502). Withdrawal due to a TEAE was cited for 75/502 patients. The only TEAE leading to withdrawal in $\geq 2\%$ of patients was hallucination (12/502; monotherapy $n = 2$, adjunct therapy $n = 10$). At the data cut there had been four deaths; none was considered treatment related.
Of the 75 patients who completed the preference questionnaire, significantly more (85.3%) preferred OD to TID dosing (Week 4 $p < 0.0001$). Reasons spontaneously offered for preferring OD dosing included: less likely to forget (37%); more convenient (30%); simplicity (9%); fewer side-effects (5%) and more effective (5%). Subsequent, elicited responses indicated 96% of patients thought the OD regimen was more convenient and 89% thought it easier to remember.

Conclusions: Long-term therapy with ropinirole prolonged release is well tolerated by patients with early or advanced PD. The TEAEs reported are as expected for non-ergot dopamine agonists. Patients preferred OD dosing as it is more convenient and less likely to be forgotten.

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P484

Standardisation of magnetic bead-based proteome diagnostics in cerebrospinal fluid

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Introduction: While cerebrospinal fluid (CSF) proteome analysis offers a range of diagnostic and research possibilities for clinical neurology, preanalytical requirements have not been thoroughly addressed. We aimed to establish magnetic bead-based sample preparation combined with MALDI-TOF MS for the analysis of human CSF and to validate a standardized sampling, processing and storage procedure.

Methods: We evaluated magnetic beads with different surface functionalities (C8, WCX and IMAC Cu) in combination with different targets (anchor chip, polished steel target) for profiling of human CSF by MALDI-TOF MS (Bruker Daltonics). Furthermore, we investigated effects of storage time, temperature, freeze-thaw-cycles, blood contamination and high protein or immunoglobulin (Ig) content on proteomic analysis of CSF samples.

Results: A comparable number of signals could be detected using different combinations of beads and targets, ranging from 218 to 274 (S/N > 10), with an overlap frequency of 35%. Inter-assay- and intraassay variability ranged from 20 to 25%. High albumin or Ig content influenced the CSF preparation with some beads only. Storage of CSF at room temperature for up to 6 hours and at 4°C for up to 3 days showed no influence on mass spectra. Consecutive freeze-thaw-cycles affected the mass spectra. Contamination of CSF with blood had deleterious effects on mass spectra beginning at hemoglobin concentrations of 3.8×10^{-4} mmol/l.

Conclusion: Proteome analysis in CSF using bead-based MALDI-TOF-MS shows high quality of mass spectra and good reproducibility. To minimize preanalytical effects, CSF has to be frozen within 6 hours. Blood contamination of CSF has to be excluded for proteomic analysis.

Poster session 4

Cerebrovascular disorders: epidemiology and risk factors

P485

Homocysteine, vitamin B12 and folic acid levels in cerebrovascular accident: a case-control study

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Objectives: The effects of homocysteine and group B vitamins on cerebrovascular accident have been widely debated. We conducted a case-control study to compare the mean plasma levels folate, vitamin B12 and homocysteine between those with and without cerebrovascular accident.

Methods: We recruited 82 patients with ischemic stroke as cases and 60 subjects as controls (using simple non-random sampling). Homocysteine was measured by fluorimetric high-performance liquid chromatography. Serum folate and vitamin B12 levels were measured by an ion-capture method.

Results: Mean plasma level of vitamin B12 in cases and controls were 388.4 ± 390.3 and 369.8 ± 110.4 Pg/ml, respectively which did not show any significant difference. Mean plasma level of folic acid in cases was significantly lower than the controls (6.8 ± 4.5 vs. 12.2 ± 3.0 ng/ml, $p = 0.001$). It was also shown that mean plasma level of homocysteine in cases was significantly higher than the controls (12.1 ± 9.8 μM vs. 13.5 ± 3.2 μM/L, $p = 0.001$). Homocysteine and folic acid but not serum B12 had linear relation with age.

Conclusion: High levels of homocysteine and low levels of folate were significantly higher in ischemic stroke patients than controls.

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Does Ramadan fasting influence the incidence and short-term survival of stroke?

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Background: Fasting during Ramadan, the ninth month of the Islamic lunar calendar, is a duty for all healthy Muslim adults. During the fasting month, Muslims are required to refrain from taking any food, beverages, or oral drugs, as well as from sexual intercourse between dawn and sunset.

Methods : Data were obtained from the department of surveillance of Isfahan cardiovascular research center (ICRC)—a WHO collaborating center in Iran. The Stroke registry in ICRC is in agreement with MONICA (monitoring trends and determinants in cardiovascular disease) project that was conducted by WHO for monitoring of cardiovascular diseases. Stroke was defined as rapidly developed signs of focal (or global) disturbance of cerebral function lasting >24 h (unless interrupted by surgery or death), with no apparent nonvascular cause; this category included patients presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage or cerebral ischemic infarction. Data were collected by professional staff stroke registrar in surveillance department with cold pursuit approach, and then registered in special registry software which had been prepared in ICRC surveillance department. The database of stroke registry I surveillance department of ICRC was used for this study. We selected the patients who had been admitted during, one month before and one month after Ramadan from the aforementioned database.

Results: A total number of 3,340 patients with stroke were registered in surveillance department of ICRC between 2000 to 2006 during, a month before and a month after Ramadan. The stroke was confirmed by a neurologist. The sex ratio was 50.3% male and 49.7% female. The mean age was 68.4 ± 13.5. Among them, 1,116 cases had occurred before Ramadan, 1,114 case during Ramadan and 1,110 case were registered after Ramadan. There were no statistical differences between the three months for the sex ratio,mean age of patients, stroke type and stroke occurrence. The case fatality rate in before, during and after ramadan were 25.3, 24, and 26.1% respectively. Kaplan–Meier survival analysis determined that the mean survival of stroke patients were not different statistically between Ramadan and month before and after it.

Conclusion: According to our study it could be concluded that physiological and biochemical changes that occur during fasting in Ramadan are not a risk factor for stroke and do not affect the short-term survival of patients.

P487

Components of the metabolic syndrome and clinical course in patients with ischaemic stroke

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The metabolic syndrome (MetSyn), which is the constellation of visceral obesity, hypertension, lipids and carbohydrates abnormalities is a predisposing factor for cardiovascular disease.

Objective: The aim of the study was to analyze the prevalence of MetSyn components in patients with ischemic stroke and it's association with the outcome of therapy and clinical course.

Material and methods: The group of 101 (50:M/ 51:F) patients with ischemic stroke, consecutively admitted, in mean age 70.5 years (±11.6) was analyzed. The prevalence of MetSyn was defined according to NCEP/ATP III criteria as the presence of three from five disturbances (abdominal obesity (based on waist circumference), increased blood pressure, increased triglycerides, low HDL cholesterol and fasting hyperglycaemia or diabetes mellitus). Clinical state was assessed by clinimetrical analysis, based on functional (FIM, Rankin) and injury (NIH, Orgogozo) scales in 1st and 10th day of stroke.

Results: MetSyn was diagnosed in 64.4% of cases with significantly higher prevalence in women (75.5%) than in men (54%). Hypertension was the most frequent disturbance (100%). Abdominal obesity and low HDL cholesterol level were significantly more frequent in women than in men (visceral obesity: 80.4 vs. 56%; low HDL cholesterol: 64.7% vs. 38% respectively) but diabetes mellitus was frequently diagnosed in men (52%) than in women (35,3%). There were no significant correlations between MetSyn components (either number and type) and clinical scales score in both 1st and 10th day of stroke.

Conclusions: MetSyn can predispose to the cerebral ischemia cause over half of acute ischaemic stroke patients gain it's criteria. It is more important stroke risk factor for the female population (MetSyn is 1.5 times more frequent than in men). The components of MetSyn seem to have no prognostic value for the stroke outcome prediction.

P488

Cerebral vein thrombosis and hypothyroidism

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Introduction: Many systemic diseases can be associated with cerebral vein thrombosis (CVT). Some studies suggest the implication of dysthyroidism in the development of thromboembolic diseases; however, the association of hypothyroidism and CVT was recently reported in only two cases. In this study we report a patient with a CVT and hypothyroidism.

Observation: A 37-year-old woman with a past history of hypothyroidism was evaluated because of an intracranial hypertension syndrome of acute onset and focal motor seizures. The cerebral MRI and MR venography confirmed the diagnosis CVT. In the acute phase thyroid function evaluation showed an unbalanced hypothyroidism. Homocysteine level was normal. The only recorded risk factor for CVT was oral contraception.

Patient was treated with anticoagulation, anti-epileptic drugs and thyroid replacement therapy. The clinical outcome was favorable.

Comments and conclusion: Only two cases of concomitantly diagnosed hypothyroidism and VCT were recently reported. This association did not seem to be the result from chance, because of many studies has demonstrated that several haemostatic and fibrinolytic parameters were disturbed in hypothyroidism suggesting a possible role of this disease in CVT pathogenesis. We recommend that thyroid function must be included in the usual workup of CVT patients.

P489

Stroke recurrence in patients with patent foramen ovale

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The role of patent foramen ovale (PFO) in the genesis of ischaemic stroke is uncertain. Stroke recurrence was estimated to be 1–2% year while on medical therapy and <4% year after PFO closure. The best treatment to prevent recurrent stroke is still an issue of debate.

Objective: To describe all patients with stroke and PFO admitted to our centre and compare two age groups for associated risk factors, treatment and rate of event recurrence.

Methods: We retrospectively analysed the clinical records of all patients admitted to our stroke unit from February 2005 to December 2008. Patients were divided into group A < 55 years and group B ≥ 55 years. For each patients group we reviewed stroke type, risk factors, diagnostic work-up and treatment. Follow-up was made by phone on a 3 monthly basis.

Result: Overall 1,000 patients had ischemic stroke (IS) or transient ischemic attack (TIA). Transesophageal echocardiography was done in 286 patients: 81 group A (82%) and 205 group B (23%). PFO was found in 27% of group A mean age 41.7 years and in 19% of group B mean age 65.3 years. Stroke type was TIA in 31% of group A versus 18% of group B, and IS in 68% of group A versus 82% of group B. PFO was the only risk factor in 82% group A versus 33% group B patients; one associated risk factor was present in 9% group A versus 28% group B; 13% group B had two associated risk factors; 9% group A versus 26% group B had coexisting cause of stroke. Among patients with cryptogenic stroke, IS determined the first and only lesion in 44% group A versus 54% group B; silent lesions were present in 56% group A versus 46% group B. PFO closure was done in 77% group A versus 62% group B, all patients maintained antithrombotic therapy. During the follow-up period (mean 21 months) both groups had stroke recurrence rate of 0.

Conclusion: We reported a retrospective series of non selected patients with PFO and stroke comparing two age groups of patients with cryptogenic stroke up to 47 months.Both groups had a high rate of PFO closure. No one in either group had stroke recurrence regardless of associated risk factors, coexisting cause and treatment. The 20 years difference in the time to first stroke between the two groups suggests that the causative role of PFO remains presumptive. In addition older patients with PFO did not have a greater rate of silent lesions nor a greater lesion load. A better knowledge of the natural history and factors associated with higher risk of recurrence would contribute to establish the best treatment.

P490

Severe stroke in neurological intensive care unit

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Background: Prognosis of patients with stroke requiring specialized neurological intensive care management is considered to be poor, and mortality is very high. Our objective was to determine overall and stroke-type related mortality and presence of selected neurological and systemic symptoms.

Method: A retrospective review of 87 adult patients (female 42) hospitalized at Neurological Intensive Care Unit during one year period. Study included patients with all types of stroke, as well as those admitted because of complications of earlier stroke. Glasgow coma scale (GCS) and NIH stroke scale were used for evaluation of neurological status at admission, and all patients were divided in three groups—ischemic stroke (65 patients), hemorrhagic (12 patients) and subarachnoid hemorrhage (7 patients). Survivors were examined for functional outcome using modified Ranking scale at discharge. Presence of various physical and neurological complications, and need for respiratory support was recorded. All data were statistically analyzed.

Results: The median age was 59.2 ranging 28– 82 years. Average NIHSS at admission was 20.8, varying from 18.7 in IS patients, to 33 in patients with SAH. Neurological complications were found in 85% of patients, brain oedema standing as the most prominent feature, registered in 53 patients, followed by onset of coma, brain stem disturbances and seizures. Mortality rate was 37% for all patients included, rising to 86% in group of patients with SAH. This group had the worst functional outcome at discharge, followed by patients with ICH with average mRS of 5.
Need for respiratory support, including mechanical ventilation (MV) was in correlation with onset of neurological complications, and strongly associated with highest mortality rate (26 out of 30 ventilated patients), longer hospitalization time and higher risk of complications. Bronchopneumonia was most frequently registered physical complication in 29 patients, lung diseases (in three patients related to MV) and urinary infections were found in 18 cases, respectively.

Conclusion: Severe stroke patients have very poor prognosis and high mortality rate, high incidence of all types of complications, and low functional outcome in short-time follow up.

P491

Prevalence of metabolic syndrome in patients with different ischaemic stroke subtypes

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Objectives: The purpose was to assess the prevalence of Metabolic Syndrome in ischemic stroke patients, by focusing on ischemic stroke subtypes.

Methods: We recruited 65 ischemic stroke patients (atherothrombotic infarction, n = 15-24%; lacunar infarction, n = 25–39%; cardioembolic infarction, n = 25–39%) admitted to our Stroke Unit. 60% had arterial hypertension. All patients underwent complete cardiovascular and laboratory assessment. Diagnosis of metabolic syndrome was made according to ATP III criteria.

Results: 24 h ambulatory and daily oscillometric blood pressure (BP) monitoring confirmed high BP in 80% (20% undiagnosed) of ischemic stroke patients. The prevalence of impaired glucose tolerance was 38%, with no statistical difference among groups (40% atherothrombotic infarction, 40% lacunar infarction and 36% cardioembolic infarction). 21% of pts had Hypertriglyceridaemia (27% atherohtrombotic infarction, 20% lacunar infarction and 20% cardioembolic infarction; p = ns); 42% of pts had low HDL levels (47% atherothrombotic infarction, 40% lacunar infarction and 40% cardioembolic infarction; p = ns). 37% of patients had abdominal circumference exceeding normal levels (mean waist circumference 111 ± 4 cm men, 93 ± 3 cm women). Metabolic syndrome was diagnosed in 38% patients (40% atherothrombotic infarction, 40% lacunar infarction and 36% cardioembolic infarction). These patients, according to ATP III criteria, had significantly higher glycemia ($p < 0.01$), triglycerides ($p < 0.001$) and significantly lower HDL ($p < 0.001$). No statistical difference was found in other blood parameters including inflammatory markers (CRP, fibrinogen- p = NS).

Conclusions: a large percentage of our patients were found to have disorders of glucose metabolism, dyslipidemia, hypertension. Metabolic syndrome was present with a greater frequency as compared to

uncomplicated hypertensives, but no statistically significant differences were found between subtypes of stroke. A satisfactory primary prevention for cerebral infarction seems to require greater attention also to metabolic problems.

P492

Cerebral vein and dural sinus thrombosis: analysis of 68 cases in a Spanish university hospital

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Objectives: To retrospectively review the cases of cerebral vein and sinus thrombosis (CVST) ever admitted and followed at our Hospital.

Methods: Retrospective analysis of the clinical records of our University Hospital electronic data base (Excalibur, including all the clinical reports from 1977 to January 2009). Research was performed with the key words "cerebral or sinus thrombosis". Neurology and Haematology Departments own databases were also searched for identical terms.

Results: 87 patients were initially included. 19 patients were excluded because of alternative or uncertain diagnosis. 68 patients (38 females) with a median age of 41.5 years (ranging from 2 to 82) were studied. Thrombophilia was detected in 17 patients (25%): 10 with prothrombin G20210A mutation, 3 with factor V Leyden, 2 had protein C deficiency and 5 had antiphospholipid antibodies. There was an infectious origin in 13 cases (19.2%) and a local factor for CVST was found in 12 (17.7%). Systemic disease was linked to CVST in 9 patients (13.2%), chemotherapy or hormone therapy in 9 (13.2%) and malignancy in 8 (11.8%). Venous thrombo-embolic disease was associated in 9 cases (13.2%). 7 women (18.4%) were contraceptive users and only one was in the puerperium (our centre has no obstetric wards). In 9 patients no etiologic factor for CVST was found. On admission, intracranial hypertension symptoms were reported in 56 (82.4%), focal deficits in 29 (42.7%) and seizures in 10 (14.7%). CVST was diagnosed with magnetic resonance image (MRI) in 53 patients (76.5%), computed tomography in 11 (16.2%) and 4 (5.9%) required angiography. In 44 cases (64.7%) thrombosis affected multiple sinuses, being superior sagittal sinus (35, 51.5%) and transverse sinus (42, 61.8%) the most frequently involved. During the course of the disease several complications occurred: seizures in 19 cases (27.9%), venous infarction in 32 (47%) and severe intracranial hypertension in 17 (25%). Surgical treatment (surgical drainage, decompressive craniectomy or ventricular drainage) was required in 24 cases (35.3%). Overall prognosis was favourable at three months (modified Rankin scale 0–2) in 52 (76.5%). 6 patients died, although only in 2 death was directly attributed to CVST.

Conclusion: We describe a large retrospective clinical series of CVST and analyse the clinical features, etiologic factors, diagnostic procedures, evolution and final outcome.

P493

Prospective study of transoesophageal echocardiogram-defined valvular strands in a hospital cohort with acute ischaemic stroke

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Background: Valvular strands (VS) identified in transoesophageal echocardiogram (TOE) are filiform material attached to the cardiac valve edges. Previous studies have found an independent association between valvular strands and risk of brain infarction, but most have been retrospective and failed to include data on brain imaging, stroke subtype and outcome.

Methods: This is a prospective study of patients admitted with acute ischemic stroke to a single institution over a defined time period. Recruited individuals undergo detailed history and neurological examination. The results of all stroke investigations are analysed, including TOE and laboratory tests to identify prothrombotic conditions in patients less than 60 years. All patients are followed up at 6 months to assess stroke outcome. Age-matched controls are identified from the TOE log book.

Results: We have recruited 50 patients to the study to date. Nineteen patients (19/50; 38%) underwent TOE, of whom 9 (9/19; 47.3%) had VS. Four patients had VS only on the mitral valve and two had VS only on the aortic valve. Three patients had VS on both mitral and aortic valves. Of the nine patients with VS, three had VS as the only potential cardiac source of emboli (CSOE) while 6 had other possible CSOE identified.

Conclusion: Our study shows that VS are present in up to half of the patients undergoing TOE as a part of their stroke work-up. We hope that our study will provide new data on the frequency of VS in patients with acute ischaemic stroke and their association with infarct topography, stroke subtype, prothrombotic susceptibility and clinical outcome over a defined time period.

P494

Recurrent stroke associated with sildenafil (Viagra™) and tadalafil (Cialis™) use

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Objectives: Sildenafil and tadalafil are one of the most frequently prescribed drugs for men with erectile dysfunction. Clinical trials of sildenafil and tadalafil have not shown an increased risk of stroke and myocardial infarction. However, postmarketing drug surveillance programs have mentioned strokes associated with their use, and case reports have been published.

Methods: We describe a 47-years-old man who have had two acute ischemic strokes in different vascular territories, in time distance of two years, both in close temporal association with sildenafil or tadalafil use.

Results: The first time, in the age of 45, he developed symptoms of right homonymous hemianopia during sexual intercourse after he took viagra. The brain magnetic resonance imaging (MRI) revealed ischemic lesion in left occipital lobe with reduction of cortical branches in P3 segment of left posterior cerebral artery. The second time, he became dysarthric immediate after sexual intercourse for which he had taken cialis. The brain MRI showed cortical fronto-temporal acute ischemic stroke in the territory of middle cerebral artery. Patient claimed that he had used these drugs solely in those two circumstances. Transthoracic echocardigraphy, carotid duplex and transcranial doppler ultrasonography was normal both times and the laboratory studies showed glucose intolerance and borderline elevation of cholesterol and low dense lipoproteins. He smoked two packs of cigarettes per day for the past 20 years. The genetic analysis documented that he was only heterozygous for the methylenetetrahydrofolate reductase (MTHFR) mutation with normal serum homocistein level. No hematological, coagulation nor inflammatory disorders were found.

Conclusion: This case report suggests that stroke is, although rare, real side effect of sildenafil and tadalafil use. Potential users should be

warned before taking it, especially if they have other stroke risk factors.

P495

Evaluation of factor V Leiden's role in ischaemic stroke among young adults in Iran

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Objectives: Several investigations have suggested different risk factors for ischemic stroke in young adults. In spite of extensive diagnostic studies, the primary cause remains unknown in some cases.Resistance to activated protein C (APC) is the most prevalent inherited risk factor for venous thromboembolism. Studies on factor V Leiden as the main cause of resistance to APC that has been done for clarifying the role of it in stroke are controversial. The current study is verifying the frequency and effect of factor V Leiden's mutation in ischemic stroke among young people in Iran.

Methods: This case-control study was performed during 14 months(September2007 to December2008) in Alzahra university hospital. After taking medical history and clinical investigations, 76 young adults (15–45 years) were included in the study. Twenty two patients with ischemic stroke (15 male, 7 female) and without classic stroke risk factors enrolled in the case group and 54 healthy young individuals(17 male, 37 female) were included in the control group. After filling consent form, 1 mL of their venous blood stream were obtained and sent to genetics department laboratory for DNA extraction, PCR and gel electrophoresis.

Results: No factor V Leiden mutation was found in the case group. There was one individual that was carrying the mutation as heterozygous. (Relative frequency = 1.85%)

Discussion: Based on our study, we concluded that in spite of determined role of factor V Leiden in venous thromboembolism, it might not be considered as an independent risk factor for ischemic stroke in Iranian individuals who are healthy regarding to other aspects.

This study was done with a research grant from Isfahan university of medical sciences.

P496

Opium addiction, a new independent risk factor for aneurysmal subarachnoid haemorrhage

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Background: Smoking is an independent risk factors for aneurismal subarachnoid haemorrhage (aSAH). However, there are rare report about the relation of opium addiction and aSAH. This study was undertaken to better clarify the risks associated with opium addiction and aSAH.

Methods: A case-control hospital-base study was done in Alzahra Hospital, Isfahan, Iran from 1 Jan 2006 to 1 Jan 2007. A total of 62 patients with aSAH and 731 matched control cases were included. Risk factors of SAH, including age, sex, cigarette smoking, history of hypertension (HTN), diabetes mellitus (DM) and inherited connective tissue disorders, hyperlipidemia (HLP), family history and also addiction to opium, alcohol or cocaine were evaluated. Logistic regression modeling was used to determine the Odd Ratio for aSAH.

Results: History of HTN, HLP, DM, family history of SAH and inherited connective tissue disorders were seen in 30 (48.3%), 8 (12.9%), 5 (8%), 1 (1.6%), 0 (0%). History of addiction to cigarette smoking, opium, alcohol, sympathomimetic drugs and cocaine was seen in 26 (33.3%), 16 (25.8%), 1 (1.6%), 1 (1.6%) respectively. The calculated Odd ratio for opium addiction was 2.27 (95% confidence interval [CI], 1.01–5.02) and for smoking 1.76 (95% CI, 0.99–3.12).

Conclusion: A positive association was found between opium addiction and aSAH. Similar to cigarette smoking, it seems opium addiction can be the important risk factor for aSAH. More cohort studies with larger sample size needs to confirm opium addiction as a new risk factor.

P497

Segmental left ventricular wall motion abnormality and the risk of ischaemic stroke

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Objectives: Left ventricular wall motion abnormality (LVWMA) is associated with increased risk of cardioembolic stroke. However, the association between segmental wall motion abnormality and stroke occurrence has not been fully evaluated. We aimed to evaluate the topographical effect of LVWMA on ischemic stroke.

Methods: We analyzed prospectively collected data on ischemic stroke patients with LVWMA demonstrated by 2D echocardiography from March 2007 to December 2008. LVWMA included acute or recent myocardial infarction, congestive heart failure with low ejection fraction, and dilated cardiomyopathy. Patients with other cardiac risk of thromboembolism including arrhythmia, valve disease, patent foramen ovale, and other miscellaneous disease were excluded. Patients with undermined causes according to TOAST classification were excluded. We divided myocardium of lateral ventricle (LV) into 17 segments according to the nomenclature introduced by American Heart Association. Wall motion abnormality was assessed according to the severity from 1 (normal) to 5 (aneurysmal change). Statistical analysis was performed using student t-test, Chi-test, and one-way ANOVA test.

Results: The study included 85 patients with LVWMA; 55 from cardioembolism (CE) group and 30 from non-CE (large artery atherosclerosis or small vessel occlusion) group according to TOAST classification. Compared to non-CE group, CE group had significantly lower mean ejection fraction (44.3 vs. 51.4%, $p < 0.01$). There was a trend to be higher mean severity score of LVWMA in CE group compared to non-CE group. In terms of the coronary artery territory, the frequency and severity of LVWMA were not statistically different between CE and non-CE groups. Among different LV regions, severity score of apical wall motion abnormality was higher in CE group compared to non-CE group ($p < 0.01$). Basal wall motion abnormality was more frequently observed in non-CE group than in CE group. In CE group, mean severity score was significantly higher in apical wall compared to middle and basal walls (1.89, 1.61, and 1.53 respectively, $p < 0.01$).

Conclusion: Apical wall of LV was more severely affected in cardioembolic stroke. In addition to ventricular dysfunction, severity of apical wall motion abnormality could play an important role in thromboembolism.

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P498

Stroke in young adults. A cohort from Argentina

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Background and purpose: Stroke in young adults (15–45 years old) is less frequent than in older populations and it has a different spectrum of etiologies. Young victims of stroke are usually previously healthy people and sometimes it leads to severe sequel in this group of active population with a long expectancy of life.
The purpose of this study is to analyze the characteristics of stroke in patients between 15-45 years admitted in our service.

Material and Methods: We retrospectively analyzed the total consecutive cerebrovascular events in young patients from the stroke data bank of our institution (January 2006 to January 2009). These patients were classified for analysis in two groups: I: age 15–35 and II: age 36–45 years-old. We analyzed demographic data, risk factors and stroke subtype (ischemic, intracerebral hemorrhage ICH and subarachnoid haemorrhage SAH). Etiology of ischemic strokes was established according to TOAST classification.
Data were analyzed using descriptive statistics with STATISTIX 7.0 using X2 for categorical variables. Significance was considered with $p < 0.05$.

Results: A total of 316 cerebrovascular events were registered in this period of time; 20 events (6.32%) ocurred in 18 young patients; mean age 36.4 (SD ±6.21), 13 were women (72.2%). Stroke subtypes were: ischemic 9 (50%), ICH 5 (27.8%) and SAH 4 (22.2%). According to the TOAST classification 70% of ischemic events were of undetermined cause; in 4 patients cerebral venous thrombosis was identified, (contraconceptive drugs intaken 2; preeclampsia 1).
Women predominated in both groups. Although ICH was more frequent in group I and ischemic stroke in group II, the difference was not statistically significant ($p = 0{,}15$) Fisher X2.

Conclusions: Prevalence of ischemic stroke in young people was low (3.47%) according to what is reported in the literature. In youngest patients (age < 35 years), ICH was the most frequent stroke subtype. Even when an extensive workout was performed to identify etiology of ischemic events, the proportion of undetermined cause was still high as it was seen in other series. There was a considerable proportion of cerebral venous thrombosis.
Although not frequent, cerebrovascular disease in young adults may have different etiologies than the older population; the effort must be guided to a best characterization of this population and their risk factors as well as to exclude the underlying cause and provide an adequate acute management and secondary prevention.

P499

Carotid plaques and homocysteine plasma levels: is there a real relationship?

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Background: Homocysteine has been proposed as a risk factor for atherosclerosis, mainly related with cardiovascular effects in young population. The association between plasma total homocysteine concentration and carotid atherosclerosis has not been thoroughly studied in high-risk populations with vascular disease. The aim of our study is to determine if there is a relationship between plasma total homocysteine levels and the number of carotid plaques.

Methods: Prospective observational study of consecutive patients admitted in the Stroke Unit between July-December 2007. All of them underwent carotid duplex. Variables: demographic data, vascular risk factors (arterial hypertension, diabetes, homocysteine plasma levels, smoking, dislypidemia...), previous treatments (antiaplatelets, anticoagulants, statins, ECA inhibitors...), number of carotid atheromatous plaques and carotid intima-media thickness.

Results: A total of 266 patients were included. Mean age was 65.9 ± 1 year. 59.1% were men. The mean of homocysteine plasma levels was 12.5 ± 0.5. 58.7% have previous arterial hypertension diagnosis, 19% had Diabetes. 79.2% were taking ECA inhibitors. The mean number of carotid plaques was 1.7 ± 0.1. Univariate analysis showed that the number of carotid plaques was related with previous arterial hypertension diagnosis ($p < 0.001$); diabetes ($p = 0.001$), dyslipidemia ($p = 0.004$) and higher homocisteyne plasma levels ($p < 0.001$). Multivariate analysis showed that higher levels of homocysteine were related independently with higher number of carotid plaques (OR: 7.334; CI: 1.908-28.187).

Conclusions: Homocysteine plasma levels are positively associated with the number of carotid atheromatous plaques in ischemic stroke patients of all ages, not only in young people. More studies should be done to determine its role in the development of carotid arteriosclerosis.

P500

Inflammatory markers and carotid atherosclerosis

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Objectives: Inflammation may have a crucial role in the pathogenesis of atherosclerosis. This hypothesis is supported by an increasing number of reports on the interaction between chronic infection, inflammation, and atherogenesis. The aim of our study is to study the association between inflammatory markers and different ultrasonographic markers of carotid atherosclerosis.

Methods: 160 patients with recent ischemic stroke were included and subjected to brain computed tomography, magnetic resonance imaging, carotid Duplex ultrasonography (to study intima media thickness, resistive index, stenosis and plaques) and inflammatory markers.

Results: The mean age of patients is 72.42 years, with more than half of the patients in the age group 70-89 years. As regard the ultrasonographic atherosclerotic markers we found that the mean intima media thickness is higher than normal in 66.25% of patients. The internal carotid artery resistive index, is increased in about 60% of patients. Both of the intima media thickness and the internal carotid artery resistive index are significantly associated with markers of inflammatory activity (fibrinogen, fibrin D-dimer concentration and C reactive protein). Carotid stenosis >50% is found in 54 internal carotid arteries, it is also significantly associated with inflammatory markers. We detected carotid plaques in 111 patients. Ulcerated plaques were found in 12.50% of patients and they are significantly associated with C reactive protein. We found also a significant association between symptomatic unstable carotid plaques and C reactive protein.

Conclusion: Extracranial carotid atherosclerosis is one of the major causes of stroke and ultrasonographic evaluation of carotid arteries is of great value for risk assesment, further management and secondary prevention of ischemic stroke patients. Inflammation may have a crucial role in the pathogenesis of atherosclerosis. Inflammatory markers may predict the risk of stroke even after adjusting of traditional risk factors and socioeconomic status. Assessment of inflammatory markers may be useful adjuncts in identifying those patients who are at a higher risk of developing vascular events, and in whom more aggressive treatments might be warranted. However, the

effects and cost implications of this treatment strategy are largely unknown.

P501

What is the association between hyperlipidaemia and cerebrovascular disease or stroke in Gwent/Wales

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Objectives: Dyslipidaemia as a risk factor of stroke is not fully understood. The aim of this study is to investigate whether Hyperlipidaemia (high LDL, low HDL and high Triglyceride) is a problem in stroke patients in Gwent and if dyslipidemia is correlated with stroke subtypes.

Methods: This is a retrospective Hospital-based study. Patient's case-notes in north and south of Gwent Healthcare NHS Trust were reviewed. Two groups were identified; a stroke group and a control group. Stroke diagnosis was proved by a CT brain examination. The control group are patients with falls, respiratory or gastrointestinal pathologies but have not had a stroke in the past or any other cardiovascular diseases. Lipid profiling for the patients has been done within the first 48 hours of admission of the patients to the hospital and 2–4 weeks after.

Results: There are 243 patients within the stroke group with 76% of them (184) had equal or above 3.5 mmol/L total cholesterol level. There are 243 persons within the control group with 164 had equal or above 3.5 mmol/L of cholesterol (89.6%). This difference in total cholesterol between the stroke patients group and the control is significant (p value = 0.000). There was no relationship between the type of stroke and whether the cholesterol level is high than 3.5 mmo/L or not.

There was insufficient evidence to conclude that the mean cholesterol level was different by the type of stroke ($F(4,235) = 0.637$. There was insufficient evidence to conclude that gender had an influence on the mean cholesterol level ($F(1,230) = 0.659$, $p = 0.42$.

Furthermore, there was insufficient evidence to suggest that an interaction effect between gender and type of stroke existed, ($F(4,230) = 0.706$,$p = 0.59$. It was found that 86.6% of the females had high cholesterol level compared to 75% of the male population. At 5% significance level, only the sex of the patient seems to have a significant relationship with the HDL and LDL cholesterol levels.

Using the multivariate Factorial Anova analysis of Variance, there is insufficient evidence to conclude that mean HDL and LDL levels are significantly different by type of stroke.(Wilks; Lymbda = 0.98,$p = 0.91$).

Conclusions: The high cholesterol is not a risk factor for stroke patients in Gwent. There is insufficient evidence to conclude that mean HDL and LDL levels are significantly different by type of stroke. Only the sex of the patient seems to have a significant relationship with the HDL and LDL cholesterol levels.

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P502

Gender differences in the clinical presentation and 6-month outcome of acute ischaemic stroke

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Objective: Stroke remains a major healthcare problem. In Ukraine stroke morbidity and mortality is one of the highest in Europe. Stroke is an important cause of death and disability in women as well as men. Some gender related differences has been reported in risk factors profile and outcome of ischemic stroke. The objective of this study was to verify and explain differences between men and women in the clinical presentation and outcome of ischemic stroke.

Methods: A total of 105 acute stroke patients discharged from Lutsk City Hospital (Western Ukraine) were evaluated for risk factors, clinical presentation, neurological deficit measured by NIHSS, 6-month survival, disability (Barthel Index) and handicap (Rankin scale). The patients were observed in the first day, at 14th day, 1 and 6 months.

Results: Overall, 55 (52, 38%) patients were males and 50 (47, 62%) females. Compared with males, female patients were slightly older (mean age 62, 12 ± 1, 99 vs. 59, 44 ± 1, 11 years, $p = 0.051$). History of hypertension ($p < 0.005$), diabetes mellitus ($p < 0.05$), obesity ($p < 0.005$), migraine ($p < 0.05$), myocardial infarction ($p < 0.05$) were significantly more frequent in female stroke patients. Alcohol abuse ($p < 0.005$), smoking ($p < 0.05$) severe neurological deficit ($p < 0.005$) were more frequent in male patients. No differences in glucose, total cholesterol, triglycerides, hsCRP levels and INR as well as education status were found. There were no sex differences in use of neuroimaging, antithrombotic therapy or consultation. At discharge from hospital, after controlling for all baseline and clinical variables, there were no sex differences in prediction for disability. Gender revealed a significant effect on survival: mortality rate was higher in female patients. Handicap at 6 month was similar in men and women.

Conclusions: We found that women with ischemic stroke had a worse prestroke condition. Both medical and social factors may significantly influence stroke outcome. There were no striking gender differences in stroke presentation or management of stroke. No significant gender effect was observed on 6-month survival.

P503

Hyperglycaemia and prognosis of stroke in nondiabetic and diabetic patients

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Objective: The aim of this investigation was to compare the characteristics and prognostic features of ischemic stroke in patients with type 2 diabetes and stress hyperglycemia, to determine predictors of in-hospital mortality in diabetic patients with ischemic stroke and the impact of the degree of hyperglycemia on the outcome and to examine the risk of stroke in patients with type2 diabetes.

Methods: We studied 675 patients with acute ischemic stroke (average age of patients 71.6 ± 24.6; 51.1% men, 48.4% women) admitted at "St. Grigor Lusavorich" Medical Center in a period from 1999 to 2002 years.

All patients were investigated according conventional protocol, neuroimaging has been done by CT scan. Stroke severity and dynamics of neurological and functional outcome were assessed by National Institutes of Health Stroke Scale and Barthel Scale.

Results: From all studied patients ($n = 675$) 44. 8% ($n = 297$) had a high level of glucose on admission. Among them 43.3% ($n = 117$) were diabetic patients and 60, 6% ($n = 180$) had no history of diabetes - stress hyperglycemia.

Mortality rate in normoglycemic patients was 38%, in diabetic patients—49% and in stress hyperglycemia patients—71%. High level of hyperglycemia was associated with increased risk of mortality within 30 days −57.1% ($n = 71$) in patients with stress hyperglycemia and 43.6% ($n = 55$) in diabetic patients.

Mortality risk was significantly higher in patients with high level of glucose on admission compared to normoglycemic patients (OR 3. 1),

in addition in group of stress hyperglycemia is higher than in diabetic patients group (OR 3. 6).
Analysis of lesion localization according to CT showed a prevalence of hemispheric strokes.
In group of patients with average age of 65–74 observed frequently co-morbidity with arterial hypertension, cardiac pathology.
Stroke severity and poor functional outcome directly correlates with combination of arterial hypertension and diabetes. For stress hyperglycemia this correlation was not significant.

Conclusions: Diabetes and stress-hyperglycemia associated with bad neurological and functional outcome. Risk of ischemic stroke in diabetic patients was three times higher compared to non diabetic patients. High level of glucose in blood on admission was associated with high rate of mortality and residual disability.

P504

Cerebral venous thrombosis in adults: a clinical study of 64 Iranian cases

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Background and Purpose: Our study purpose was to determine the clinical characteristics and etiologies of cerebral venous thrombosis in Tabriz.

Methods: We reviewed the records of all patients admitted with a documented diagnosis of cerebral venous sinus thrombosis from 2003 to 2006 in two major hospitals of Tabriz University of Medical Sciences were reviewed.

Results: Sixty-four patients (9 men, 55 women) aged I G to 80 years were identified. The relative frequency against arterial strokes was 1:26.31. Seventeen cases (27%) had a clinical picture of pseudommor cerebri. Twenty-eight women (51 % of (orate cases) had history of oral contraceptive pills (OCP) use. Nine cases were in postpartum period (16% of females). Other causes included surgical recovery period, antiphospholipid antibodies in 7, protein S deficiency in 4, systemic lupus erythematosus in 2, infections in 2, antithrombin III deficiency in 5.

Conclusions: In Tabriz. Adult cerebral venous thrombosis is not uncommon. Recent onset oral contraceptive use is the single most common etiology. Infection is no longer an important cause. Where as postpartum and post surgery cases were common. Patients with a clinical diagnosis of pseudotumor cerebri syndrome should undergo brain MRI and MRV before definite diagnosis and treatment.

P505

Childhood arterial ischaemic stroke in Egypt

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Objective: Arterial ischemic stroke (AIS) in childhood is a serious disorder about which little is published in Egypt. The aim of this study is to determine the epidemiology and outcome of AIS in Egyptian children.

Methods: Cases of childhood AIS, admitted to the Mataryia Teaching Hospital, Cairo, Egypt 2004–2008, were identified by medical record search. Information was collected on demographics, risk factors, arterial distribution, results of thrombophilic testing, management and outcome.

Results: During the 5 years of review 87 patients presented with 106 cases of AIS. Children less than 12 months of age represented greater than one third of all cases. Identifiable risk factors were present in 66% of cases with congenital heart disease the major risk factor. Thrombophilic testing was done for all cases with abnormalities present in 17% of cases. The estimated stroke-related mortality was 6.8%. Of the patients who survived and who had follow-up details available, 73% had a neurological deficit. 48 patients (55%) received anticoagulation. There was no statistically significant association between treatment with anticoagulation and normal neurological outcome.

Conclusion: AIS is over-represented in children less than 12 months of age and results in death or residual neurological impairment in the majority of cases. Further prospective studies are needed to identify risk factors for poor outcome. New prospective studies are needed to provide important information on clinical and laboratory based risk factors and to improve the outcome of childhood AIS.

P506

Clinical factors related to intracranial arterial stenosis in acute stroke patients

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Background: Intracranial arterial stenosis are common findings of stroke patients in Asia area. We reviewed stroke database to investigate clinical factors related to intracranial arterial stenosis, including carotid disease, and peripheral arterial disease which reflects advanced atherosclerosis.

Methods: Acute stroke patients at the National Health Insurance Corporation Ilsan Hospital from January 2005 to December 2007 with available transcranial Doppler(TCD) examination, carotid ultrasound and ankle-brachial indexes(ABI) formed the analysis cohorts. Retrospective review was performed.

Results: A total of 642 patients were included during that period, 212 patients with incomplete TCD study due to poor insonation windows were excluded(33%). According to TCD criteria, 3 groups of intracranial arterial stenosis are defined: 0 vessel stenosis is in 220 patients(51%), 1–2 vessels in 125 patients (29%), more than 3 vessels in 85 patients(20%). As the arterial number of intracranial stenosis increased, ABI is decreased ($p = 0.013$) and the size of carotid artery plaque is increased ($p = 0.011$). Among the risk factors, Diabetes, age, past stroke history are increased($p = 0.0000$, 0.006, 0.05) and HDL cholesterol showed tendency of decrease ($p = 0.033$). However hypertension, smoking, total cholesterol, LDL cholesterol, triglyceride and sex are not correlated with intracranial arterial stenosis.

Conclusions: Among the acute stroke patients, about a half of them have intracranial arterial stenosis and these patients tend to have higher burden of advanced atherosclerosis as evidenced by a higher prevalence of Diabetes, large sized plaques of carotid artery and peripheral arterial occlusive disease.

P507

Particularities of cerebrovascular impairment in obese patients with metabolic syndrome

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Objectives: 1. To detect the presence of carotid atherosclerosis in patients with metabolic syndrome (MetS). 2. To analyze the correlation between adiponectin serum levels and carotid atherosclerosis.

Methods: We studied a group of 116 obese patients (66 patients with MetS, 37 women and 29 men and 50 patients without MetS, 39 women and 11 men) referred to Elias University Hospital of Emergency between September 2007 to October 2008. We used a standard protocol of clinical and paraclinical investigations: determination of all components of MetS according to NCEP ATP III criteria, determination of adiponectin and leptin serum levels and measurement of common carotid intima media thickness (IMT) by Doppler ultrasonography method. Data obtained were analyzed using descriptive statistic methods.

Results: For all patients ($N = 116$), IMT values are correlated with age and fasting glucose serum levels. For patients younger than 40 years ($N = 53$), IMT values are correlated with waist circumference and total cholesterol serum levels. In the subgroup of women with MetS ($N = 10$), IMT values are also correlated with leptin serum levels, and in the subgroup of patients with MetS younger than 40 years ($N = 26$), IMT values are also correlated with waist circumference. IMT mean values were higher in the MetS group ($N = 66$) versus patients without MetS ($N = 50$), with statistical significance stronger for women ($p = 0.0358$) and age ($p < 0.0001$) Adiponectin mean values were lower in the MetS patients ($N = 23$) vs. patients without MetS ($N = 20$), with statistical significance stronger for women ($p = 0.0227$). We were not able to obtain any correlation between adiponectin serum levels and IMT values.

Conclusions:

1. In our study population IMT values are correlated with classic components of MetS (waist circumference, fasting glucose serum levels).
2. Current literature cites adiponectin to leptin ratio as having statistical significance in correlation with IMT, but in our study adiponectin serum levels were not correlated with IMT values. A possible explanation is that our study population was formed of obese patients, in whom adiponectin serum levels are lower than in non-obese patients.

P508

Stroke in Iran: a systematic review

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Objectives: To systematically review the stroke incidence, prevalence, risk factors, and outcome of stroke in Iran.

Methods: Publications on stoke were identified by searching the PubMed using the keywords: stroke, intracranial bleed, intracranial haemorrhage, brain infarction, neurological disorder, neurological disease and neurology, combined with epidemiology, incidence, prevalence, and with Iran, Iranian, Persian and Persia.

Results: Five hospital based-studies where identified. The annual incidence of first-ever stroke is 43.12/100,000 population/year. Two studies showed an annual incidence varies from 22.7 to 103.23 100,000 population for first ever and recurrent stroke. The annual incidence of young stroke (age 25–45) was 8 and 1.83/100,000 populations for children below age of 15. Stroke was reported to be slightly more common in females (range form 51–53%), but not in younger age-groups. The clinical series showed a mean age of stroke within the 7th decade. Only two studies reported all types of strokes while the other three included ischaemic stroke only. Ischaemic stroke was reported in 67.2–68.45% of all stroke patients while primary intracerebral haemorrhage in 23.9–28.4% and subarachnoid haemorrhage in 2.9–4.4%. One study reported that 54% of patients with ischaemic stroke had thrombotic event and 46% had an embolic one. Another study showed that 64% of patients with ischaemic stroke had territorial infarcts, 19.5% a small deep infarct and 4.6% a border zone territory infarct. Hypertension was the most frequent risk factor in stroke patients, being present in 54% of patients and cardiac causes in 54%, mainly rheumatic heart disease especially in young patients (34%).

Conclusion: The available data suggest that the unadjusted incidence of stroke in Iran is comparable to the figures from Arab Countries, higher than sub-Saharan Africa, but below the rate in developed countries and China. Stroke types and risk factors are similar to the western countries, except higher rate of rheumatic heart disease. No data is available about time trends in stroke incidence or long-term outcome. Well-designed community-based studies, fulfilling published quality criteria, are needed as a preparation to fighting this disabling condition in this part of the developing world.

Poster session 4

Child neurology

P509

Celiac disease-related antibodies in Italian epileptic children

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Objective: Conflicting results are reported on the association between epilepsy and celiac disease, an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Since contradictory findings can be due to the age and different genetic background of study populations, the low number of subjects analyzed, and the pre-selection of patients with specific types of epilepsy, we investigated the relationship between the two conditions in a large cohort of 272 unselected children with epilepsy compared to 300 healthy children coming from the same geographical area of North Italy.

Methods: We analyzed the frequency of immunoglobulin (Ig) G- and IgA-class antigliadin antibodies (IgG-AGA and IgA-AGA, respectively), and antitransglutaminase antibodies (IgG-tTG and IgA-tTG), as well as IgA-class antiendomysial antibodies (EMA) in 64 patients with idiopathic (either partial or generalized) epilepsy, 63 cryptogenic epilepsy, and 145 symptomatic epilepsy due to brain damage, cerebral malformation, metabolic disorder and degenerative disease.

Results: In our study cohort, the total number of samples from epileptic patients resulting positive for IgG-AGA was much higher than that from controls, while that with positive or borderline IgA-AGA was similar in the two groups. On the contrary, the prevalence of tTG-IgG and of tTG-IgA did not differ between patients and controls. The positive and borderline samples were both tested for the presence of CD-related antibodies with an alternative test and for the occurrence of EMA by immunofluorescence assay, but a concordant result between the diverse assays was found only in the case of positive samples. Only 5 out of the 272 epileptic patients showed evidence for antibodies surely related to CD (tTG and EMA). Finally, no patients showed isolated high IgA-tTG.

Conclusion: Due to the fact that AGA measurement has completely and justifiably fallen into disuse and the analysis with tTG antibodies is considered the most significant for clinical use, out data indicated that the prevalence of CD-related antibodies in epileptic children is comparable to that observed in age-matched controls of the same geographical area of North Italy, and consistent with what reported in a population screening study carried out in the general Italian population. In keeping with this

observation, Italian epileptic children should not be considered a group at risk for celiac disease.

P510

Clinically unsuspected multiple sclerosis in children: a long-term follow-up

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Clinically unsuspected multiple sclerosis is rarely seen in children in MRI examination performed with the other reasons.

In this study, three children with the age of diagnosis 7, 8, 15 years were reported in which multiple sclerosis was discovered unexpectedly at MRI. Two of the cases had history of epilepsy, one case were admitted because of pubertas precox. Initial MRIs were performed because of those reasons.Mean follow-up duration was longer than 5 years and all the other alternative diagnosis were eliminated in all cases. Repeat follow-up MRIs showed new T2 W or T1 W Gd-DTPA enhanced lesions. Oligoclonal bands were detected only one case.

In this study, diagnostic and treatment dilemmas and management principles of cases will be discussed.

P511

A case of a new leukoencephalopathy with brain-stem and spinal cord involvement

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Objective: Leukoencephalopaties are etiologically heterogenous neurological disorders of children. Many different forms have recently been identified especially on the basis of their radiological characteristics, according to which a differential diagnosis could be suggested. A new leukoencephalopathy with brain-stem and spinal cord involvement and lactate elevation (LBSL) has recently been defined based on characteristic abnormalities observed by magnetic resonance imaging (MRI) and spectroscopy (MRS).

Method: We identified a patient who had slowly progressive pyramidal, cerebellar and dorsal column dysfunction with a distinct white matter involvement on MRI. The patient is a girl, born in 1984 as the first of two sisters. Her initial motor-mental development was normal and her parents are healthy and non-consanguineous. At the age of 4, tremor was noted at her right leg while she was standing. Her arms were also affected and her gait deteriorated slowly within years. Recent neurological examination at the age of 18 revealed mild cerebellar dysarthria, hyperreflexia in the lower limbs, Babinsky's sign on the right, bilateral mild cerebellar signs. She has a very mild truncal ataxia and a severely impaired vibration sense on the legs. Laboratory studies were performed for the classical leukodystrophies, and the diseases for the inborn error of metabolism.

Results: MRI showed signal abnormalities in the periventricular- deep white matter, pyramidal tracts, superior and inferior cerebellar peduncles, intraparenchymal trajectories of the trigeminal nevre, and in dorsal columns of the spinal cord. MRS revealed increased lactate and decreased N-acetylaspartate in the white matter.

Conclusion: We have described an additional new patient with overall clinical and a distinct MRI pattern which is remarkable by the involvement of the specific trajectories of the brainstem which is compatible with LBSL. The demonstration of new cases will allow better delineation of clinical, radiological, and possibly, genetic features of this disorder.

P512

Behavioural change by music in patients with Rett syndrome

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Objectives: Rett syndrome is a childhood neurodevelopmental disorder characterized by stereotyped hand movement such as wringing. It usually caused by a mutation in the gene encoding MECP2 located on X chromosome (Xq28) and affects almost exclusively females. Patients with Rett syndrome typically have no verbal skills, and about 50% of patients are not ambulatory. However, they are reported to respond well to music in comparison with their physical and verbal disabilities. Therefore, change of their behavior and movement, especially stereotyped movement in response to music was studied.

Methods: A questionnaire was sent to all members of the Japan Rett syndrome association with the consent of the Ethics and Research committee in the association. It consisted of patients' reaction to music, their physical ability, and stereotyped movements. Patients were asked to check all that apply.

Results: The answer was obtained from 82 patients. All were female aged from 4 to 42 years (15.6 $\pm$ 8.9, mean $\pm$ standard deviation). Age of onset was 1.7 $\pm$ 1.0 years. Ambulatory patients with and without assistance were 34 and 22%, respectively. Stereotyped hand movements and body swinging were observed in 94 and 38%, respectively. Body swinging was observed back and forth in 32% and right and left in 23%. Major response to music was described as follows; smiling (94%), turning of the head to music (71%), vocalization (48%), and calming down (40%). Body swinging started with music in 51% and stopped in 15%. On the other hand, stereotyped hand movements started in 16% and stopped in 38%. Seizure was induced in 8.5%.

Conclusion: Patients with Rett syndrome actually had good response to music in their everyday life. Most of them seemed to be pleased with music. Stereotyped movements in body and hands changed oppositely in response to music. Different musical elements or separate neurological mechanisms might cause this contrary response. Body swinging could be induced by musical rhythm and stereotyped hand movements might be stopped by strong attention induced by music.

This study was supported in part by the Foundation of Chronic Disease adn Rehabilitation.

P513

Characteristics and aetiology of disturbed behaviour in multi-handicapped Egyptian children

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Objective: To describe the characteristics, proposed etiology, prevalence and types of different behavioral and emotional disturbances among multi handicapped Egyptian children.

Methods: a total of 3,800 consecutive multiply handicapped patients were retrospectively studied. Criteria for inclusion were regular follow-up period for at least 24 months. Types and prevalence

of behavioral disorders were correlated with the different forms of disabilities. Other factors associated with mental retardation such as degree of disability, etiology, correlation between degree of disability and percentage of behavior disorders; and types of behavioral disorders encountered were also analyzed.

Results: Follow-up ranged between 24 and 153 months (mean 61 months). Total group composed of 3800 multiply handicapped patients, of which 94% suffered from mental retardation, 25% suffered from cerebral palsy, 16% suffered from sensory deficits, and 29% suffered from epilepsy. The overall prevalence of behavioral disorders was 13% in the total group; ($n = 494$ patients with behavioral disorders included pervasive developmental disorders (190), attention deficits with (152) or without hyperkinesis (114) and disruptive behavior (253) disorders, those include 38 patients with pure disruptive behavior, all patients with ADHD, 2 patients with ADD, and 61 patients with PDD). It was 13.8% in mental retardation group; 4.3% in Cerebral palsy group; 3.8% in sensory deficits group; and 16.3% in epilepsy group. In mental retardation group 1.3% suffered from profound mental retardation, 5% suffered from severe mental retardation, 36.6% suffered from moderate mental retardation, and 57% suffered from mild mental retardation. Behavioral disorders are more prevalent in the moderately retarded group (18%). The proposed etiologies for disabilities were: Perinatal injury (41%); prenatal (37%); Postnatal (9.5%); and Indeterminate (12.5%).

Conclusions: behavioral disorders are not only very distressing to multiply handicapped patients and their families but also have a negative impact on their learning at school or other facility, peer relationships and social competence, so more attention should be paid to diagnose (detect and classify) and aggressively treat behavioral disorders by pharmacological, educational and environmental interventions.

P514

Alice in Wonderland-syndrome

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An extraordinary collection of symptoms present to the pediatric neuropsychiatrist, hiding behind it a wide set of differential diagnoses (e.g. temporal lobe epilepsy, pediatric migraine, Epstein-Barr viral infection, non-specific hyperpyrexia, etc.). A syndrome named for Lewis Carroll's "Alice's Adventures in Wonderland" (1865), characterized by body-image distortion and disordered perception of distances, size, shape and spatial relationships between objects. It can be considered "a rare manifestation of one of such more common diseases".

Objective: to define the syndrome, its etiology and pathophysiology in different diseases. Presenting two case reports. Methods: describing the symptomatology of the syndrome and the two cases, etiology and proposed pathogenesis.

Results: Two cases aged 9 and 6 years old, male, the first presented by illusions of size, shape, and color of objects, disturbed size of his head and left upper limb, and followed by throbbing headache. The second presented by disturbed body image, sense of time and spatial orientation. The first proved to be epileptic and the second due to typhoid fever.

Conclusion: Alice in wonderland syndrome is not an uncommon clinical picture. It may be underestimated diagnosis. Early diagnosis carries a good prognosis. "Alice's Adventures in Wonderland" is defined in patients with migraine, epilepsy, intoxication due to hallucinogenic drugs, schizophrenia, hyperpyrexia, Epstein-Barr viral infections, and other cerebral lesions.

P515

Risk factors for intraventricular haemorrhage in very low birth weight infants

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Objective: The purpose of this study was to determine the risk factors which predispose to the development of high grade IVH (grade 3 and 4) in very low birth weight infants.

Methods: In a retrospective case control clinical study files of all premature infants with birth weights less than1500grams admitted between April 2004 and Oct 2005 to the neonatal intensive care unit of Akbar Abadi hospital were reviewed. 39 infants with IVH grade 3 &4 were identified. A control group of 82 VlBW infants matched for gestational age and birth weight were selected. Prenatal data, delivery characteristics, neonatal course data and reports of cranial ultrasonography were carefully collected for both groups. Those variables that achieved significance ($p < .05$) in univariate analysis entered to multivariate logistic regression analysis.

Results: A total of 325 VLBW infants were evaluated. Mortality rate was 21.5%. Of the remaining the incidence of high grade IVH was 15.5%. Multivariate logistic analysis showed that following factors are associated with greater risk of high grade IVH occurrence; Lower gestational age (OR: 3.72; 95% CI: 1.65–8.38), birth weight (OR: 3.42; 95% CI: 1.65–8.38), Apgar score at 5 minute (OR:1.58; 95% CI:1.59–6.32), hyaline membrane disease (HMD, OR:3.16; 95% CI:1.42–7.45) and tocolytic therapy with magnesium sulfate (OR:4.40; 95% CI1.10–24.5).

Conclusions: Our results showed that maternal tocolytic therapy, mechanical ventilation, lower gestational age and birth weight, apnea hyaline membrane disease and low 5minute Apgar score increased the risk of major IVH.

P516

Excessive testing in emergent evaluation of children with first unprovoked seizure

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Backround: First afebrile seizure is one of the common causes of admission of children to emergency departments. A lot of tests usually are performed for these patients. The cost of such an evaluation is high and benefits are doubtful. We conducted this study in order to examine the results of the tests and find out what tests are necessary for children with first unprovoked seizure.

Methods: In a 7-year retrospective study files of 150 children aged between 1 month to 14 years admitted with first afebrile seizure to the pediatric ward of Rasool Akram hospital were reviewed. Reports of brain neuroimaging studies (Ct-scan & MRI) and laboratory tests were extracted.

Results: 150 patients with a mean age of 53 ± 48 months qualified for inclusion in the study. Of 150 children with first afebrile seizure, 143 (95%) had neuroimaging. 90% (128/143) had normal neuroimaging. Emergent computed tomography as initial study performed in 90% (128/143) and MRI in 10% (15/143) . Sixty patient had both MRI and Ct-scans. Clinically significant neuroimaging abnormality were reported in only 9.7% (14/143). There was a significant relation ($p < 0.001$) between focal seizures and abnormal neuroimaging. Children under 30 months of age were also more prone to have abnormal imaging ($p < 0.002$). Laboratory tests including complete blood count (CBC) and chemistry panel (Na, K, Ca, BUN, Cr) were performed for all. Only two patients were hypocalcemic, whom later diagnosed as having vitamin D resistant rickets.

Conclusions: The most important aspect of management after a first afebrie seizure is careful history taking and physical examination. Laboratory tests should be requested in very limited situations. Emergent brain Ct-scans are recommended in children with focal seizures, abnormal findings on physical examination, presence of any predisposing factors and those under 24 months of age.

P517

Congenital cataracts facial dysmorphism neuropathy in Serbian Romani patients

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Objectives: Congenital Cataracts Facial Dysmorphism Neuropathy (CCFDN, #604168) is a complex developmental disorder of autosomal recessive inheritance. Developmental abnormalities include congenital cataracts and microcorneae, primary hypomyelination of the peripheral nervous system, impaired physical growth, delayed early motor and intellectual development, mild facial dysmorphism and hypogonadism. CCFDN is genetically homogenous condition, where all the patients are homozygous for C > T transition 389 base pairs (bp) downstream of the exon 6/intron 6 junction of the Carboxi-Terminal Domain Phosphatase 1 (CTDP1, *604927) gene. The mutation alternates the splicing of CTDP1 pre-mRNA and causes the shift in reading frame and premature stop codon formation. The CCFDN mutation is particulary common among the endogamous Roma population Rudari, in whom the carrier rate is around 6–7%. In other Romani groups CCFDN mutation carrier rate accounts for ~1%. Here, we report three genetically confirmed CCFDN patients from Serbian Romani population.

Methods: DNA isolated from blood samples was used to PCR amplify a portion of CTDP1 surrounding the possible mutated region. 461 bp long PCR products were digested using Hin1II restriction endonuclease, and restriction products were separated in 2% agarose gels stained with ethidium bromide. c.863+389C>T transition abolishes Hin1II restriction site, so analysis of CCFDN patients on agarose gel shows one band of 461 bp instead of two bands of 221 and 240 bp.

Results: Three individuals of Romani ethnicity referred to mutation analysis based on clinical data and ethnic background were found to carry homozygous c.863+389C>T mutation in CTDP1, thus genetically confirmed as CCFDN patients.

Conclusion: Based on the latest registration data (year 2002), the Romani population in Serbia accounts for 108.000 individuals, but the real number is estimated to 400.000-450.000. Numbers indicate that the carrier rate of c.863 + 389C > T mutations in Serbian Romani people is around 0,3%, which is much less than expected. The reason probably lies in limited access to social- and healthcare, the common problem of Romani people, but also in the lack of awareness of this rare disorder among health care providers. CCFDN should be considered as the most likely diagnosis in children presenting demyelinating peripheral neuropathy and congenital cataracts, especially in patients with Romani ethnic background.

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P518

Absence epilepsy: generalised or partial seizure type?

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It is well known that absence epilepsy is a form of generalized epilepsy mainly affects children. Typical absence manifests as a sudden onset of staring without consciousness during 5-10 seconds. The EEG typically shows a 3 Hz spike/wave pattern. Neurologist sometimes see patients with absence whose EEG does not fit the typical absence pattern, but with focal epileptiform discharges; it makes us doubt that absence primary generalized seizure. The purpose of this study is to examine EEG abnormalities in children with typical absence clinical features.

Methods: we studied 28 children with typical simple absence seizures (just few seconds staring without consciousness) and complex absence seizures (staring with eyelid myoclonia, automatisms, changes in tone, face redness and so on); ranging in age from 4 to 17 (main age 10.73 ± 3.69). The investigation included interictal EEG, neurology status, neurovisualization (MRI or CT of brain).

Results: Family history was positive for epilepsy in 9 (32.2%) children; neurology status examination was intact in all children; neurovisualization showed asymmetric hydrocephaly in 1 (3.6%) children, retrocerebellar cyst in 2 (7.2%) children, 1 (3.6%) cyst in temporal the left lobe, 1 (3.6%) left arachnoidal cyst in lateral fissure, 1 (3.6%) dysmyelinated area in right parietal lobe.

EEG demonstrating only generalized spike/wave discharges of 3–4 Hz in 4 (14,3%) children.

Local epileptiform activity in 24 (85.7%) children: 7 in frontal lobe, 11 in temporal lobe, 6 in parietotemporal or centroparietal part.

Retrospectively in 10 (35.7%) children appeared partial seizure

Conclusion: This concept can be applied not only to the classical absence occurring in PGE but also to the rare cases of secondary bilateral synchrony with a primary frontal epileptogenic focus leading to true (though very slightly different) absences

P519

Autism and celiac disease: failure to validate the hypothesis that a link might exist

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Background: Autism is a heterogeneous condition and the possible pathogenic role of several different factor has been postulated. Previous studies reported the existence of a linkage between autism and celiac disease (CD). The aim of this study was to determine the association between autism and CD by anti-gliadin (AGA), anti-endomysial (AEA) and tissue transglutaminase (tTG) antibodies.

Materials and Methods: Thirty four consecutive autistic children (18 boys and 16 girls) aging 9.2 ± 4.1 years (range 4–16 years) and thirty four age- and sex- matched healthy anonymous blood donors (18 boys and 16 girls) aging 10.8 ± 4.0 years (range 4–16 years) were included. None of the patients and controls had symptoms (or positive family history) suggestive of specific gastrointestinal diseases.AGA and AEA antibodies (IgG and IgA) and IgA-tTG were detected by ELISA. Individuals with positive serology were offered duodenal biopsies.

Results: IgG-AGA was found in 4 (11.8%) patients and 2 (5.9%) controls ($p = 0.69$), while IgA-AGA was found in none of patients and controls. All patients presented normal values of IgG and IgA-AEA similar to control. There was no significant relationship between levels of AGA and AEA antibodies and the severity of autism in patients groups. The levels of IgA-tTG in four patients (but no controls) were in the borderline range ($P = 0.11$) and two of them were found to have mild villous changes with chronic inflammatory cells. However, characteristic histological features of CD were absent.

Conclusions: No evidence was found that children with autism were more likely than children without autism to have had celiac diseas.

Dementia/Higher function disorders

P520

B-type natriuretic peptide plasma levels are elevated in subcortical vascular dementia

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High levels of B-type natriuretic peptide (BNP), a serum marker of congestive heart failure, are associated with an increased risk for cognitive decline. However, no study has yet assessed this marker in different subtypes of dementia. We tested the hypothesis that BNP has a more significant association with vascular dementia than Alzheimer disease. Plasma BNP was measured in 15 patients with subcortical vascular dementia, in 19 Alzheimer patients without evidence of vascular co-morbidity, and in aged-matched controls. Compared to controls (28 ± 7 ng/L) BNP was elevated in subcortical vascular dementia (63 ± 17 ng/L; $p = 0.03$), but not in Alzheimer disease (36 ± 5 ng/L). In conclusion, subcortical vascular dementia is indeed associated with moderately elevated BNP levels, whereas this could not be shown for Alzheimer disease. Increased BNP levels probably reflect the larger cardiovascular burden in patients with subcortical vascular dementia.

P521

Cognitive function after transient topographical amnesia. MMSE: changes over the years

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Objective: The objective of this study was to assess whether transient topographical amnesia may constitute an early manifestation of visuospatial disorders and, therefore, to be useful as a predictive factor in patients at risk. To this purpose, we followed the clinical course of all consecutive patients who since 2001 were attended in the outpatient clinic of the Service of Neurology because of a transient spatial amnesia or disorientation episode.

Method: The study population included 42 patients, 12 men and 30 women, with a mean age of 67 years (range 44–90 years). Three of these patients showed cognitive impairment at the time of the initial consultation, with abnormal findings on Mini-Mental State Examination (MMSE) testing (scores between 11 and 22). Two patients had previously presented an ischemic stroke in the territory of the right posterior cerebral artery. Two other patients referred various episodes of topographical amnesia, suggesting 'jamais vu' epilepsy. These four patients had a total MMSE score between 28 and 30. One patient, since the age of 20, presented stereotyped, 'jamais vu' seizures of 1-min duration, and currently at the age of 82 scored 18 in the MMSE. The remaining patients did not show any neurological disorder, with MMSE scores ranging between 23 and 30.

Results: Over the follow-up of the patients, which ranged between 1 and 6 years, progression of cognitive impairment was documented in those patients who presented with initial cognitive impairment (3 out of 42). In the remaining 39 patients, moderate or severe cognitive impairment was found in 9, and mild cognitive impairment in 2 (length of follow-up between 2 and 3 years). The remaining patients (28 out of 42) are asymptomatic, with follow-up lengths of 1 year in 2 cases, 2 years in 4, 3 years in 7, and 4 or more years in 15.

Conclusion: In patients presenting an episode (or episodes) of transient topographical amnesia it is necessary to exclude the possibility of 'jamais vu' epileptic seizures or a previous stroke. Patients with transient topographical amnesia or transient spatial disorientation, without distinction between both terms, have a high probability of developing manifest cognitive impairment (in our series, 25% in a period of 3–4 years).
It is possible that a greater accuracy in the semiology of the event may add a more precise predictive value.
However, an analogy with transient global amnesia, in which the clinical course is almost always benign, cannot be established.

P522

Comprehension of complex instructions deteriorates with age and vascular morbidity

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Objective: Verbal comprehension is critical to the success of medical counselling. Here we tested how age, atrial fibrillation and other vascular risk factors affect the ability to understand complex instructions.

Methods: Verbal comprehension, cognitive functions, and vascular risk factors were assessed in 35 mid- and 39 late-life community—dwelling individuals (48–59 years and >59 years of age respectively). Verbal comprehension was assessed by a modified version of the Token Test (TT).

Results: In mid-life subjects education (standardized $\beta = 0.491$, $p = 0.003$) was the only predictor for TT performance. In late-life individuals it was age (standardized $\beta = -0.707$, $p < 0.001$), body mass index (standardized $\beta = -0.403$, $p = 0.007$) and the presence of atrial fibrillation (standardized $\beta = 0.374$, $p = 0.008$) that on multivariate analysis explained almost 40% of the variance of verbal comprehension.

Conclusion: These results indicate that ageing as well as vascular morbidity impair comprehension of complex instructions. Therefore medical counselling appropriate for mid-life individuals may be less successful in elderly people and particularly in those with vascular pathology.

P523

Is asymptomatic carotid artery stenosis really asymptomatic?

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Background and aims: Asymptomatic carotid artery stenosis (ACAS) contributes stenosis of one or both internal carotid arteries, without

cerebral ischemia related to it (transient ischemic attack, cerebral infarction, amaurosis fugax). Several studies showed that ACAS is not really asymptomatic and it is frequently associated with cognitive decline.
This study was aimed to analyze association between vascular risk factors, especially insulin resistance, and cognitive decline in 100 patients with ACAS and 50 age-, sex- and educational level healthy matched control subjects.

Methods: Insulin resistance was tested by homeostasis assessment model (HOMA IR), plasma insulin levels by radioimmunoassay, levels of total-, LDL-, HDL- cholesterol, triglycerides and plasminogen activator inhibitor-1 were measured. Carotid plaques characteristics and intima-media thickness (IMT) were determined by ultrasound system (ALOKA A 10, Japan). We used detailed neuropsychological testing to examine attention and concentration, memory, executive and visual-constructional functions, motor performance, language and speech. Study was prospective and all patients were followed-up for 2 years

Results: In comparison with controls, ACAS patients had significantly lower results on all neuropsychological tests at the beginning (F (1, 71) = 6, 37; $p < 0.001$), and after two years of follow-up, with further cognitive decline from the baseline(F (1, 71) = 71, 12; $p < 0.001$).Insulin resistance was significantly associated with memory, language and visuospatial disturbances (CC = -, 3891; $p < 0.001$) and carotid plaques characteristics with attention, executive and motor functions (CC = -,4662: $p < 0.001$).

Conclusion: ACAS is not asymptomatic, because it is associated with specific profile of cognitive impairment.Specific risk factors predict cognitive decline in certain neuropsychological domains, and this colud have important therapeutical implications.

P524

The Numbers Man

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Introduction: Gerstmann syndrome is a disorder of cognitive impairment that results from damage to the parietal lobe; most often due to trauma or stroke. It is characterized by dysgraphia, dyscalculia, left-right confusion and finger agnosia and not infrequently features dyslexia and aphasia.

Case presentation: A 55-year-old man was transferred for increasing shortness of breath and anaemia on the background of a history of childhood rheumatic fever, repaired corarctation of the aorta and aortic and mitral valve replacement. Echocardiogram demonstrated multiple mobile densities adherent to the prosthetic mitral valve and blood indices were consistent with mechanical hemolysis. On day two the patient developed the acute onset of the inability to read, do arithmetic or write in a comprehensible manner. He denied any other symptoms. An CT head demonstrated multiple infarcts of varying ages. MRI demonstrated an evolving acute infarct at the left frontoparietal junction.

The patient's cognitive deficits were striking, particularly in the context of his previous abilities. He'd had a particular facility with calculation such that his wife referred to him as a 'numbers man', able to perform complex arithmetic in his head. He was trained as a lawyer with a level of comfort with composing complex legal documents. Following this event, the patient had the onset of dyscalculia such that he was unable to perform even the simplest single-digit addition and subtraction. Furthermore, he was unable to read simple sentences or write single words or the most basic sentences [writing and arithmetic samples available]. He developed a kind of written perseveration such that he would be asked to write a word and subsequently every following word or sentence would begin with the same letter as that first word. He was otherwise entirely neurologically preserved.

Discussion: This syndrome was formally described and localized to the cerebral cortex in 1924 by the Austrian-born neurologist Joseph Gerstmann who was then Professor of Neuropsychiatry in Washington DC. There are relatively few published papers regarding this condition and this case is compelling in regards to the profound yet highly selective nature of the cognitive deficits. Furthermore, it provides an excellent correlation between clinical symptoms, objective measures of cognitive impairment and diagnostic imaging in lesion localization of a classically described syndrome.

P525

White-matter disruption associates with grey-matter atrophy in amnestic type mild cognitive impairment in Chinese Han

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Objectives: Amnestic type mild cognitive impairment (aMCI) has a high probability of evolving toward Alzheimer's disease (AD). White matter (WM) disruption and gray matter (GM) atrophy are commonly co-involved in the pathogenesis of AD. However, relatively little attention has been directed toward that WM disruption and GM atrophy are independent or related in aMCI.

Methods: The voxel-based diffusion tensor imaging and voxel-based morphometry were applied on the structural magnetic resonance images to evaluate the differences of whole-brain WM and GM changes between the thirty-two aMCI patients and thirty-one well-matched healthy controls, and correlations were further analyzed between WM disruption and GM atrophy in aMCI patients.

Results: Compared with healthy controls, aMCI subjects were associated not only with abnormalities in gray matter of memory-related areas, such as medial temporal lobe, temporo-parietal areas and frontal areas ($p < 0.001$, uncorrected), but also with concomitant abnormalities in cerebral white matter regions, such as left medial temporal lobe (mainly in parahippocampal gyrus), bilateral superior longitudinal fasciculus, right inferior longitudinal fasciculus, right inferior fronto-occipital (uncinate) fasciculus and right internal capsule ($p < 0.001$, uncorrected). Importantly, WM disruption was linearly related to adjacent and distant GM atrophy ($p < 0.05$).

Conclusion: The findings supported that multi-patterns of degeneration may co-act in the WM pathological process of aMCI patients. As aMCI is a putatively prodromal syndrome to AD, these data may assist with a better understanding of the essence of WM neuroimaing changes associated with the development of AD.

P526

Progressive Foix-Chavaney-Marie syndrome: a clinico-pathological investigation

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Objective: Progressive Foix- Chavaney–Marie syndrome (FCMS) known as the anterior operculum syndrome have been rarely reported

with pathological investigation. Here, we present a patient of progressive FCMS with clinico- pathological investigation.

Method and subject: The patient was a 74 year old right handed man who first noticed difficulty in speech and swallowing 1 year before. He could manifest only laborious, syllabic phonemes or short phrases, and the articulation was distorted which varied depending on the situation. Neurological examinations showed no abnormality in cranial nerves other than slight limitation of upward gaze bilaterally and slow movement of tongue without fibrillation. The motor and sensory systems were normal. We investigated the patient with MRI, 123IMP single photon emission computed tomography (SPECT) and manifested neuropsychological examinations including Western Aphasia Battery, WAIS-R, WMS-R and had kept the observation of the patient for 2 years until his death.

Results: The patient's facial and masseteric muscles seemed hypotonic with drooling. However, he could laugh and yawned normally with voices. The palatal and pharyngeal reflexes were normal unaccompanied with any pathological reflexes. MRI showed cortical atrophy in bilateral temporal lobes with scattering small ischemic lesions. 123IMP SPECT revealed decrease blood flow in the frontotemporal lobes predominantly in the left side. Neuropsychological examinations showed he had no aphasia, no dementia nor any other neuropsychological abnormality. He could communicate with writing. Following 6 months his speech impairment and dysphagia aggravated. Intubation fiberscope showed no abnormality. He also showed the elevation of tau protein of 548 pg/ml in cerebrospinal fluid. In additional 6 months, his writing ability had deteriorated to difficulty in communicating, and he also showed rigidity of extremities. He died of aspiration pneumonia 2 years after onset. Postmortem examination revealed neuronal degeneration with TDP-43-positive inclusions in the frontal, temporal and insular cortices, consistent with frontotemporal lobar degeneration with TDP inclusions (FTLD-TDP). In addition, moderate Alzheimer pathology (Braak stage IV-C) was also evident.

Conclusion: Progressive FCMS might be presumed to be classified a variant of FTLD-TDP overlapping of Alzheimer's disease.

P527

Dysfunction in mental rotation caused by arteriovenous malformation in left parietal lobe

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Objectives: Mental spatial transformations are a necessary and important component of daily life. They are classified into two types, object-based transformations and egocentric perspective transformations. Prior studies show that object-based functions in the right parietal cortex, and egocentric perspective in the left, although this is controversial. We will describe the clinical features of a patient with left parietal lobe damage and clarify the function of the left parietal lobe.

Case: A 39-year-old women patient underwent surgery for arteriovenous malformation (AVM) in the left occipital-parietal lobe, Brodmann fs Areas 18, 19, 39, 40 and 7. After excision, disorientation, memory disturbance, agraphia, direction disorder, dressing disorder and acalculia were found. Afterwards, these impairments improved gradually, but she noticed difficulty in using a computer, as well as doing several tasks simultaneously. Executive deficits and mental rotation dysfunction remained.

Methods: We tested the patient with standardized assessment tools for intelligence, memory, verbal ability and visuospatial perception and with the Shinjyuku west gate test for egocentric perspective transformation, as well as the F test and picture-rotating task for object-based transformation.

Results: She showed executive deficits, memory disturbance and agraphia for Kanji characters. She failed construct blocks test when the models were rotated. The *F* test asked for a correct F or reverse F when subject was rotated. She made only one error, but took time to answer when the letter was rotated from 150 to 250 degrees. The picture-rotating test was to mentally describe four subjects after rotated picture. This was a mental rotating test using a picture of a famous painting. The Shinjyuku west gate test was to mentally describe four buildings in front of the well-known train station. She felt that the Shinjyuku west gate test was more difficult than the picture-rotating test.

Conclusion: Mental transformation function is located in the left parietal lobe. Our findings suggested that the function of the left parietal lobe is more related to egocentric perspective transformation than object-based transformation.

P528

Inability of voluntary movement of left hand with lesion of corpus callosum

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Objectives: There are some patients who show an impairment of voluntary movements of the left hand, which cannot be ascribed to any motor and sensory deficits, or established symptoms such as ideational, ideomotor, or other minor apraxias. Established clinical classification of movement impairments cannot deserve describing every symptom. In order to reveal underlying mechanism of such symptom, we investigated a peculiar decrease or interruption of movements on the patient who complained that her left hand did not obey her command.

Patient and Method: The patient was a 69 year-old right-handed female, having suffered from cerebral infarction. She showed mild right hemiparesis, decreased position sense and tactile extinction on the left side. Grasp reflex was not observed. She showed mild aphasia. Ideational and ideomotor apraxia was not observed on both hands. Scores of Raven's Colored Progressive Matrices was 21/36. Magnetic Resonance Imaging methods revealed the old lesions in the right putamen, and left precentral gyrus, and new lesion (related to the last episode) on the posterior horn of lateral ventricle and trunk of corps callosum. The nature of her left hand's movement and action impairements were precisely examined on tasks of Optische Ataxie, ataxie optique, searching opposite hand's with eye closed, coordination of hand movements with and without objects, imitation of examiner's hand posture, and simple movements.

Results: There is no sign of imitation behavior, motor neglect, or alien hand sign. The nature of the impairments on the left hand were as follows; (1) delayed initiation, low amplitude, and slowing of movements, (2) which varies depending on situations, (3) inability to release objects of the left hand, when delivering objects from left hand to right hand. (4) intrusion of unexpected gestures such as smoothing down her hair.

Conclusion: The movement impairments of her left hand can be consistently regarded as disconnection syndromes due to damage of corpus callosum.

P529

Successful treatment of Wernicke encephalopathy after recurrent vomiting in a patient with pyloric sub-stenosis: description of the case and review of the literature

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Wernicke's encephalopathy is an acute or subacute syndrome characterised by a classical triad of symptoms: nystagmus and ophthalmoplegia, mental-status changes, and unsteadiness of stance and gait. The disorder results from a deficiency in vitamin B1 (thiamine), which in its biologically active form, thiamine pyrophosphate, is an essential coenzyme in several biochemical pathways in the brain. When patients with Wernicke's encephalopathy are inappropriately treated with low doses of thiamine, mortality rates averaged out at 20% and Korsakoff's Psychosis developed in about 85% of survivors. We report the case of a patient with neurological signs, neuropsychological assessment and magnetic resonance imaging (MRI) typical for Wernicke's encephalopathy but with no history of alcohol abuse. The patient suffered for about one week of severe and incoercible vomit. Using antiemetic drugs vomit stopped but soon after he started developing slowing of thinking and subtle characterial changes. Gait became unsteady in about ten days when he finally decided to see a doctor. Admitted to our clinic he was investigated for possible causes responsible for B1 deficiency. Hematological analysis, total body computed tomography and gastroscopy with biopsy were performed, showing a severe chronic gastropathy with a pyloric sub-stenosis, well documented causes of vitamine B1 malabsorption. Despite in Italy the dose of thiamine usually recommended for the treatment of Wernicke's encephalopathy is about 100 mg given intramuscularly daily for 3–5 days, our patient was treated with a much higher posology (5 times the advised one) (900 mg of thiamine given intramuscularly and 600 mg orally daily for the first 5 days and 900 mg intramuscularly daily for the following week) to avoid the development of the well known tardive consequences of B1 deficit. Even after just a week of treatment our patient experienced a great improvement of his neurological symptoms accompanied by a complete disappearance of MRI lesions. In our report we provide an update on the major advances in pathophysiology, prophylaxis, and management of this syndrome.

P530

Structural changes and atrophy of the principal brain white-matter tracts with aging: a diffusion tensor MRI tractography study

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Objective: To investigate the structural changes of the principal interhemispheric and within-hemispheric brain white matter (WM) pathways with aging. We also assessed the hypothesis of non-linearity in the WM structural and volume changes with age.

Methods: Brain DT MRI was acquired from 84 healthy volunteers (36 women and 48 men, mean age = 44 years, range = 13–70 years). DT MRI tractography was used to calculate the mean diffusivity (MD) and fractional anisotropy (FA) of the corpus callosum (CC), cingulum (CING), corticospinal tract (CST), fornix (FORN), uncinate fasciculus (UNC), inferior fronto-occipital fasciculus (IFO), and inferior longitudinal fasciculus (ILF). An index of atrophy was also estimated for each WM tract. To assess correlations between subjects' age and WM tracts MD, FA and volume changes, a second-order polynomial expansion was used considering DT MRI metrics as dependent variables of age.

Results: A liner correlation was found between subjects' age and average MD and FA in all WM fibre bundles, except for the CING and UNC where a significant linear correlation with age was found for FA, only. Moreover, the non-linear (quadratic) regression model better fitted MD increase and FA decrease in all WM tracts, except for FA in the CST. CING average MD correlated with subjects' age only using the quadratic model. A negative linear correlation was also found between age and volume changes in the CING, FORN and IFO, but with a better fitting using the quadratic model. CC volume changes correlated with subjects' age only using the quadratic model.

Conclusions: Structural changes and atrophy of WM fiber bundles with age are unevenly distributed across brain regions and involve WM tracts subserving either cognitive and motor performance. Such a variation is likely to be related to maturational aspects of the different WM regions.

P531

The anatomical localisation of the emotional expressions and regulations

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Objectives: Neurodegenerative diseases frequently affect brain regions that are important for emotional processing. However, to date, there are limited studies on the anatomical localization of the emotional expressions. Our study investigates the neuroanatomical correlates of the emotional expression in patients with neurodegenerative diseases with voxel-based morphometry (VBM) method.

Methods: The emotional expression was measured by the sum-up score of the six items of the emotional expression category in modified Manchester Behavior Questionnaire. Eighty nine patients with Alzheimer's disease, frontotemporal dementia (FTD), semantic dementia (SD), progressive non-fluent aphasia (PNFA), and corticobasal degeneration were evaluated. Total scores of the decreased and exaggerated emotional expressions were correlated with structural MRI gray matter volume using VBM.

Results: Voxels in the right and left insular were negatively correlated with decreased expressions of emotions. Similarly, those in the left inferior temporal gyri were negatively correlated with exaggerated expression of emotion ($p < 0.05$, corrected). These findings suggest that decreased tissue content in the right and left insular regions were associated with decreased emotions, and that of the left inferior temporal gyri is associated with exaggerated emotions.

Conclusion: The damage to the right or the left insular regions may lead to decreased expression of emotion. Reciprocal to these results, the damage to left inferior temporal gyri may lead to exaggerated expression of emotion. The regions discussed above likely play important roles in emotional processing. These results also suggest that both insular regions are important for the emotional perceptions and expressions, and that left inferior temporal regions are important for the inhibitory regulations of emotional expressions.

P532

Catecholaminergic antagonists infusion into the rat intraventricular area cause severe oxidative stress – Relevance for cognitive processes

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Objective: Impairments of cognitive performance have been observed in normal rats with β-adrenergic and D1-dopamine receptors blockade, suggesting that these receptors have a facilitator role in learning and memory processes. In the present study, we examined whether oxidative stress contributes to the memory deficits induced by β-adrenergic and D1-dopamine receptors blocked by means of pindolol and SCH 23390.

Methods: Male Wistar rats were divided into three groups: (1) sham-operated; (2) Pindolol; (3) SCH 23390. All drugs were stereotaxically injected in the rat intraventricular area. Rats were treated 12 days. Learning and memory tests began 2 weeks after the operation, and the ability of the rats to acquire the operant task was studied by means of Y-maze task and radial arm-maze task, respectively. We evaluated the antioxidant enzymes activity.

Results: Intrahippocampus injections of pindolol (10 μg/μl, 4.5 μl/site) and SCH 23390 (0.3 μg/μl, 4.5 μl/site) resulted in a significant impairment of both working and reference memory tested by means of radial arm-maze task, suggesting significant effects of spatial memory. Pindolol and SCH 23390 significantly decreased spontaneous alternation in Y-maze task, suggesting effects on spatial memory, especially on short-term memory. We observed that the levels of superoxide dismutase (SOD) and glutathione peroxidase (GPX) decreased in rats with β-adrenergic (βAR) and D1-dopamine (D1R) receptors blockade by means of pindolol (10 μg/μl, 4.5 μl/site) and SCH 23390 (0.3 μg/μl, 4.5 μl/site), respectively, and the level of malondialdehyde (MDA) increase in same rats, compared with sham-operated rats.

Conclusions: Learning and memory processes are coordinated with different brain regions. Since the oxidative damage may play a role in the aging process, including the associated decline, age-related impairment in spatial learning and memory may be alleviated by antioxidant treatment. Our results suggest that oxidative stress damage of the brain induced impairment in spatial memory of rats.

P533

Nicotine improves 6-OHDA induced impairment of memory and food reward in nucleus accumbens

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Objective: Although dopaminergic mechanisms have been implicated in motivational processes, their role in appetitive conditioning remains poorly understood. The present study investigated the effects of dopamine (DA) depleting lesions of the nucleus accumbens on performance in a radial arm maze task. Effects of nicotine (0.3 mg/kg, i.p.) were also examined in animals with nucleus accumbens lesioned, in order to determine the influence of nicotine on dopamine release in the nucleus accumbens.

Methods: Rats received bilateral infusions of either phosphate-buffered saline (shams) or 6-hydroxydopamine (lesions) directly into the nucleus accumbens. Two weeks later, a radial 8 arms maze task was used for memory assessment in male Wistar rats.
Nicotine (0.3 mg/kg, i.p.) was administrated 7 days after the last training in radial arm maze task and the test was repeated.

Results: The results indicate that nucleus accumbens lesions resulted in a significant impairment of both working and reference memory tested by means of radial arm-maze task, suggesting significant effects on spatial memory. Also the rat's motivation for food reward was extremely reduced.
Administration of nicotine (0.3 mg/kg, i.p.) significantly attenuated this impairment, by reducing both working and reference memory errors and augmenting food searching and intake.

Conclusions: These data are compatible with the hypothesis that nucleus accumbens dopamine serves to guide conditioned approach to appetitive cues. Since the facilitatory effects of nicotine was seen in the nucleus accumbens-lesion group, it is possible for nicotine to induce improvements on accumbal DA release, with effects on memory processes and food reward.

P534

Antibodies against GM1 and a-β peptide (1–40) in the serum of demented patients

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The ganglioside GM1, lipid raft component, has been associated with APP cleavage and plaque formation. In particular, GM1 is involved in amyloid β(Ab) formation, as well as Ab processing and has been shown to bind several Ab derivatives which appears to induce conformational changes in Ab, leading to oligomerization and translocation of the peptide outside of rafts to phosphatidylcholine-rich membrane regions. The concentrations of GM1 and GM2 are increased in the frontal cortex of AD brains, which may disrupt rafts and increase APP proteolysis and Ab production, and therefore affect cell function.

The aim of our study was to evaluate the levels of anti-GM1 IgM as well as of amyloid-b (1–40) in demented patients, correlating them with the type and the severity of dementia in relation to existent polyneuropathy.

We examined serum anti-GM1 IgM concentrations as well as the levels of plasma b-amyloid (1–40) in a total of 40 demented patients with a male to female ratio of 1:2.3 at a mean age of 70.4 years for females and 69.4 for males.
Out of the total number, 47% of the patients revealed increased values of anti-GM1. 50% of the patients suffered from vascular dementia. The most severely demented patients demonstrated MMSE score: 5-22/30 and revealed the most increased levels of anti-GM1 IgM (>34 EU/ml, with normal values <20 EU/ml). Patients with anti-GM1 IgM concentrations of 36.8 EU/ml revealed the highest levels of b-amyloid (1–40) (mean 207.5 pg/ml).

Our findings are indicative of a possible correlation between the levels of serum IgM anti-GM1, the concentrations of b-amyloid (1–40) and the severity of dementia, mainly the vascular type.

P535

Diagnosis of dementia and co-morbidities in a cohort of patients admitted to hospital for neurological acute symptoms

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Objectives: The aims of our study targeted to evaluate the frequency of dementia diagnosis and comorbidities in patients admitted in our

department of neurology after an initial presentation to the emergency room (ER).

Methods: We selected from our databases all the patients admitted in our department as emergencies in 2007 and diagnosed with dementia. We analyzed these patients in respect to sex, age, vascular risk factors, other comorbidities, results of regular blood sample investigations.

Results: In 2007, in our department were admitted through the ER 3124 patients. From these patients, 115 were diagnosed with dementia among other diseases when they were released (3.6%). The average age of demented patients was 75.91 years, 54.78% were men and 45.21% were women. A vast majority of these patients were diagnosed with cerebrovascular disease as well (78.26%). In concordance with this high incidence of vascular disease, the incidence of vascular risk factors and comorbidities was high: hypertension in 67.82%, dyslipidemia in 30.43%, atrial fibrillation in 24.34% and diabetes mellitus in 16.51% of the cases. Ischemic heart disease was present in an impressive proportion of the patients with dementia (41.73%) in contrast to other comorbidities, such as, for instance, chronic renal failure (2.60%). Anemia was a frequent finding (26.95%), and macrocytosis (27.82%) was more frequent than microcytosis (3.48%). In our group of patients, the most common type of dementia diagnosed was mixed dementia (vascular and neurodegenerative), in 65.21% of the cases, almost ten times more than 'pure' vascular dementia (6.95%). From the patients diagnosed with dementia, only 14.78% were diagnosed with dementia previous to their presentation to the ER.

Conclusion: Among the patients admitted in our neurological department for acute neurological symptoms, a small but significant proportion was diagnosed with dementia. Vascular risk factors and comorbidities were highly incident in these patients. Interestingly, only a minority of these patients was diagnosed with dementia before admission in the hospital for acute neurological complains.

P536

Potassium channel antibodies in one patient with reversible limbic encephalitis

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Objectives: Limbic encephalitis is more often considered as a paraneoplastic syndrome. However cases of autoimmune limbic encephalitis are reported in the literature. We report a case of limbic encephalitis with antibodies directed against voltage-gated potassium channels (VGKC antibodies).

Patient and method: A 68 year old woman with multinodular goitre and type II diabetes mellitus was admitted for acute confusional state in a context of hyponatremia and dysthyroidia. Correction of these metabolic disorders did not permit to reduce the symptoms. Additionally, the patient developed severe anterograde amnesia, non fluent dysphasia, insomnia and partial motor seizures.

Results: Resonance magnetic imaging of the brain revealed hyperintense signals on T2 weighted images confined to the left hippocampus which were in favour of a limbic encephalitis.
Investigations to find a paraneoplastic origin or a cancer were negative. Differential diagnosis like Herpes meningoencephalitis, Creutzfeld-Jakob disease and Hashimoto encephalitis has been excluded. Thus a VGKC antibodies dosage was performed and was positive at a level of 1250 pm. Intravenous corticosteroids 500 mg per day were given during 3 days, then oral prednisone 1 mg/kg per day. The patient also received two polyvalent immunoglobulins treatments (0,4 g/kg/day during 5 days). This treatment improved significantly amnesic, phasic impairments and behavioural symptoms.

Conclusion: Clinical characteristics of limbic encephalitis are the same in paraneoplastic or non paraneoplastic causes but prognosis is very different. Indeed, antineuronal antibodies are directed against intracellular antigens and cannot be reached by immunotherapy, whereas VGKC antibodies are directed against membrane antigens and can be reached by treatments. Immunotherapy is efficient in case of non paraneoplastic limbic encephalitis and these forms have usually a good prognosis. VGKC antibodies dosage has to be made in all limbic encephalitis.

P537

Intravenous immunoglobulin gammagard liquid contains anti-RAGE IgG and sLRP

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Background and objective: Baxter's Intravenous Immunoglobulin (IVIg) preparation γgard Liquid (GGL) has shown encouraging results in a phase II trial treating patients with mild Alzheimer's disease (AD) [Relkin et al, Neurobiol. Aging, 2008]. GGL, which is manufactured from large pools of human plasma donations, has been shown to contain amyloid-βconformer-specific IgG autoantibodies that could be involved in the beneficial effects observed in the phase II study (O'Nuallain et al. 2008). Here we asked the question whether GGL contains other antibodies and soluble proteins that can modulate the amyloid-βpathway apart from these naturally occurring anti-amyloid-βIgGs. In particular, we checked for the presence of antibodies against the receptor for advanced glycation end products (RAGE), a receptor involved in the amyloid-βinflux in the brain, and for the presence of soluble low density lipoprotein receptor-related protein (sLRP), a high-affinity amyloid-βbinding protein that can modulate amyloid-βefflux from the brain.

Materials and methods: We investigated 20 lots of GGL. We checked for the presence of anti-RAGE IgG by a direct ELISA using a synthetic peptide. sLRP was measured using plate-immobilized recombinant receptor-associated protein (RAP) to capture sLRP from the sample and we detected the bound sLRP with a monoclonal anti-LRP and an anti-mouse IgG peroxidase (Quinn et al. 1997). Furthermore, we ran inhibition studies to check the specificity of our assays.

Results: We detected naturally occurring anti-RAGE IgG in all GGL lots investigated and measured sLRP levels in the μg range (up to 40 μg/mL) with only moderate lot-to-lot variations among the different GGL lots. Inhibition with the RAGE peptide and RAP proved both assays to be specific.

Discussion and conclusion: Anti-RAGE antibodies present in GGL could block RAGE and inhibit the uptake of amyloid-βpeptide by the brain, whereas sLRP also present in GGL could lower the amyloid-βburden of the brain according to the sink hypothesis. The finding that GGL contains anti-RAGE IgG and sLRP broadens the possible mode of action of GGL in AD beyond the effects of anti-amyloid-βantibodies.

All authors are full time employees of Baxter Innovations GmbH, Vienna, Austria.

P538

Steroid-responsive Hashimoto encephalopathy mimicking Creutzfeld-Jakob disease

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Objectives: Hashimoto's encephalopathy is a rare neurological disorder with a heterogeneous group of neurological symptoms

associated with high titers of anti-thyroid antibodies. Clinical manifestations may include seizures, behavioral and psychiatric manifestations, movement disorders, and coma. Objective of this report is to describe a patient with this rare and controversial clinical syndrome.

Methods: A 66 year-old patient was admitted to our department after an acute onset, four days before admission, of confusion, speech and comprehension disturbances. Three days before admission, in the E.R. he had a generalized tonic-clonic seizure. Antiepileptic treatment was started. Two days before admission he developed fever (39.2°C). Lumbar puncture, serological, virological, bacteriological screening and neuroradiological exams were performed.

Results: Brain CT scan was non significant and EEG showed diffuse slow theta-delta activity. Lumbar puncture showed mild increase in proteins, with normal cell count and glycorrachia. Brain MRI showed unspecific cortical alterations in FLAIR images. Autoantibodies, virological, bacteriological and neoplastic screening were negative. Aphasia and confusion got worse and he developed rapidly progressive myoclonic jerks, visual hallucinations and aggressive behavior. Protein 14.3.3 was absent in CSF. Thyroid hormones FT3, FT4, TSH and anti-TPO antibodies were normal while anti-TG antibodies were present at high titer. He underwent thyroid echography and a diagnosis of euthyroid Hashimoto thyroiditis was made. Treatment with intravenous prednisone was started with fast improvement. On dismissal the patient had a normal behavior and was independent in self-care. He showed an improvement of aphasia, even though verbal fluency deficit persisted.

Conclusions: We describe an acute, rapidly progressive syndrome, mimicking Creutzfeld-Jackob disease, associated with euthyroid Hashimoto thyroiditis and significantly responsive to high dose intravenous prednisone. It is still not clear whether antithyroid antibodies are an epiphenomenon in some patients with encephalopathy or if the immune process has a pathogenic role. In our case, progressive clinical improvement after steroid treatment supports the latter hypothesis.

P539

Cognitive disorders in patients with hypothyroid encephalopathy

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Objectives: The decline of thyroid hormones contents in an organism is a tricker of the chain of pathological dysmetabolic processes which break the power processes in the cells and cause the destruction of neurons. These processes are fundamental in decreasing intellectual coefficient, which can be often seen at patients with primary hypothyroidism. This way, the purpose of our investigation was to study the features of cognitive dysfunction in patients with hypothyroid encephalopathy.

Methods: 258 patients with hypothyroid encephalopathy (HE) at the age 32–57 years old were examined by us. Also was examined the control group of 60 almost healthy people. Were used clinical-neurological, neuropsychological, neurophysiological methods of investigation.

Results: Practically all patients complained about the slowering of thinking, decline or memory and attention efficiency and the complication of memorizing. The estimation of the general cognitive productivity at patients with hypothyroidism on the mini-mental state examination (MMSE) scale revealed the subcompensated character of cognitive disorders (28-26 scores) at the initial stage HE, at the second stage of HE—distinct cognitive dysfunction (27–25 scores), at the third stage—meaningful cognitive decline (24–22 scores). The researches of the endogenous caused potentials at the first, second and third stage of HE defined the making of latent of the Ð300 peak longer then normal up to 9.7, 25 and 37% accordingly, that was the neurophysiologic correlate of cognitive infringements cortical type. Alongside with increasing cognitive disorders the reduction of ATF level on 8.1; 10.5 and 15.4% relating the normal one was observed at patients with I, II and III stages of HE. It testified about the break of energy capacity in the conditions of hypothyroidism.

Conclusion: Thus, the foundations for the reduction of intellectual capacity at patients with HE is an increasing energy shortage which causes the development of structurally-plastic and functional insufficiency of cerebrum cells. For the correction of these cognitive disorders alongside with recreation therapy at patients with hypothyroidism the medicines normalizing metabolic and power processes should be used.

P540

Atypical presentation and evolution of sporadic Creutzfeldt-Jakob disease

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Objectives: Creutzfeldt-Jakob Disease (CJD) is an uncommon neurodegenerative disease characterized by rapidly progressive onset of dementia, sometimes preceded or accompanied by other features as psychiatric or extrapiramidal symptoms, myoclonus or cerebellar disfunction. It is caused by abnormal proteins called prions that can be genetic, infectious or spontaneously acquired. The age of onset of most classic sporadic CJD (sCJD) is between 50 and 75, whereas non sporadic forms tend to have an earlier onset. We present a young patient affected with sCJD who developed atypical psychosis early in the course of the disease followed by status epilepticus, as has been reported in rare cases of CJD. Cerebral IRM was normal until late stages of the disease.

Methods: A 44 healthy year-old male presented with gait instability and dizzines for three months prior to admission, followed by psychotic symptoms and paranoic delirium. First neurological evaluation at Emergency Room did not reveal any neurological disease. The patient was admitted in a psychiatric hospital and neuroleptic treatment was started. Symptoms persisted and progressive loss of conscience and myoclonus appeared, so he was referred to our Hospital.

Results: Neurological examination revealed spontaneous opening of the eyes with bobbing movement, akinetic mutism and the presence of multifocal reflex myoclonus.

An EEG showed continuous epileptiform discharges, so antiepileptic drugs were started with no response. Blood sample analysis with autoantibodies, serologies against infectious agents, and paraneoplastic antibodies were normal. The examination of CSF revealed the presence of 14-3-3 protein. An MRI performed few weeks prior to death was strictly normal. The patient finally died five months after the onset of the disease. Necropsy study of the brain showed precipitation of protease-resistant prion protein (PrP) with a type I Western blot appearance. No deletions, insertions or point mutations were found in the 51-91 region of the PrP gene. Patient carried the Met/Met polymorphism for the Val position.

Conclusions: Sporadic Creutzfeldt-Jakob Disease can affect young people and must be considered in the differential diagnosis of an atypical psycosis.

A status epilepticus may develop in the course of this disease. Although typical lesions have been described in CJD, cerebral IRM can be normal until late stages of the disease.

P541

Neurosyphilis: a "new" old disease

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Introduction: The importance of investigating the aetiology of dementia lies in the possibility of treating reversible causes. The infective causes, namely neurosyphilis, are potentially treatable. The incidence of neurosyphilis manifested by slowly progressive cognitive and behavioural impairment (general paresis/dementia paralytica) fell with the advent of penicillin. Nonetheless, the recent increase in the reported cases, especially in HIV/AIDS population, justifies continued awareness for neurosyphilis, namely in the course of the diagnostic workup for dementia.

Clinical cases: The authors report the cases of two patients, both males in their forties, with long standing complaints of cognitive and behavioural impairment. During diagnostic investigation, a positive Rapid Plasma Reagin (RPR) test both in serum and Cerebrospinal Fluid (CSF) was detected, as well as elevated CSF protein level and cell count. The patients completed the penicillin treatment. There was improvement in both cases, but the patient with longer disease duration had to be institutionalised for behaviour changes.

Conclusion: Neurosyphilis has been considered a rare disease, and some recent dementia screening guidelines do not consider it obligatory in the initial serological workup. The presented cases aim to illustrate the main clinical characteristics of paretic neurosyphilis and also to increase the awareness of a potentially treatable disease, even in patients without risk factors. It should also be emphasized that the sooner the treatment institution, the better the clinical outcome.

P542

Antiphospholipid syndrome and systemic lupus erythematosus patients: what's new about cognitive involvement?

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Objectives: Systemic Lupus Erythematosus (SLE) and primary Antiphospholipid Syndrome (APS) patients display an increased risk of developing cognitive impairment as a consequence of central nervous system (CNS) involvement. In APS patients it has been often referred to multi-infarct dementia. Mild Cognitive Impairment (MCI) has been associated to antiphospholipid antibodies (aPL) in the absence of ischemia, but most of data are based on APS secondary to SLE, while PAPS are less investigated. In SLE, cognitive defects have been demonstrated in 6 to 66% of patients. Recently in SLE patients has been detected a new autoantibody directed to the glutamate receptor (anti-NMDA) able to induce neuronal cell apoptosis in vitro and cognitive dysfunction in mice even if a clear clinical association between these autoantibody and cognitive defects have not been demonstrated. Aim of the study was to analyze neuropsychological profile of APS and SLE patients to better characterize the pattern of APS and SLE cognitive involvement and to evaluate the possible association with autoantibody profile.

Methods: 26 consecutive patients referring to our clinics (7 PAPS and 19 SLE) underwent an extensive neuropsychological and psicodiagnostic assessment. Attention, executive functions, language, memory, visuo-spatial pianification, praxis and visual discrimination were investigated. Psychological status was assessed with: Symptom Checklist, Beck Depression Inventory, State-Trait Anxiety Inventory-Y and Short-Form Health Survey-36. Serological tests included ANA, ENA, anti-ribosomal P and anti-dsDNA ab, LA, anti-CL and anti-b2GP I ab and anti-NMDA ab.

Results: Qualitative and quantitative differences were detected in neuropsychological profiles between APS and LES patients with the former less impaired from the letter, even though not significantly in all cognitive domains. No association with anti-NMDA or anti-PL positivity was found neither with cognitive nor with psychological aspects. Depression, even if not significantly, was higher in LES patients.

Conclusion: Even if in our cohort there are not cases of full blown dementia, our study showed a high frequency of cognitive deficits of a single or few domains, thus suggesting a higher presence of MCI cases than supposed. Moreover SLE patients display a more diffuse cognitive involvement, while in APS ones there is presence of a preferential selective involvement of frontal functions. Clinical implications will be discussed.

P543

Playing table tennis with poor eyes, a case of posterior cortical atrophy

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We present a case of a 75-year old man with progressive visual complaints since 10 years. On examination he had prosopagnosia, simultanagnosia, dyscalculia, dysgraphia and severe problems with visuoconstructive tasks. His memory was normal. He had been misdiagnosed previously with occipital stroke of the right hemisphere. MRI of the brain showed marked posterior atrophy with an enlarged posterior horn of the lateral ventricle. Cerebral SPECT showed decreased perfusion in the occipital en posterior parietal regions. Posterior cortical atrophy is a neurodegenerative disease. After it was first described in 1988 over sixty cases have been described. Patients present with visual problems and intact primary visual functions. On examination complex visual disorders are found. Many patients present with (partial) Balint's syndrome or Gerstmann's syndrome or a combination of symptoms of both. Memory impairment is a late sign. It is a syndrome with a variable etiology. Alzheimer pathology is found inabout 50% of cases. Treatment as in Alzheimer's disease can be tried but evidence is lacking.

Preclinical neurobiology

P544

Expression of tight junction and drug efflux transporter proteins in a model of human blood-brain barrier

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Objectives: Brain endothelial cells are fundamental components of the blood-brain barrier (BBB) and are characterized by the presence of intercellular tight junctions (TJs). The structural integrity of TJs is

maintained by a number of integral proteins including claudins and occludin linked by other proteins such as zonula occludens (ZO) to the actin cytoskeleton. Moreover, several efflux transporters actively pump compounds out of the endothelial cells back into the blood reducing the exposure of central nervous system to delivered drugs. Although partial in vitro models of human BBB have been established, there is lack of models based on human brain endothelium cultures in the presence of human astroglial cells and there are no studies assessing TJ proteins as well as efflux transporters in in vitro human BBB models.

To address these issues, we analyzed the expression of two TJ and three efflux transporter proteins in an in vitro model of human BBB.

Methods: Human cerebral endothelial cells were isolated from microvessel fraction of glioma specimens obtained during neurosurgical operations. The astroglial cells obtained from the middle ring of the density gradient of the same tumor pool of the endothelial cells were seeded at the bottom compartment of a multiwell insert in the same culture medium of the endothelial cells. Transendothelial resistance (TEER) was measured and cell viability assessed by a MTT assay. Expression of occludin and ZO-1 as well as P -glycoprotein (P-gp) and multi-drug resistance proteins (MRP-1 and 2) was analyzed by ELISA and related gene transcripts assessed by RT-PCR.

Results: Higher TEER ($p < 0.0001$) as well as cell viability ($p = 0.007$) values were found in endothelial cultures in the presence of astroglial cells. There was a significant increase in expression of occludin ($p = 0.002$) and ZO-1 ($p = 0.0005$) by 13 and 25% respectively, in endothelial-glial co-cultures. Furthermore, there was a significant increase by 20% for P-gp ($p = 0.001$) and 9.4% for MRP2 ($p = 0.009$); by contrast, MRP-1 increased by 4% only. All related mRNA transcripts were found to be increased in the co-culture system.

Conclusions: This in vitro model of human BBB comprising adult endothelial and glial components, is suitable for studying the expression pattern of TJ and drug efflux transporter proteins and assessing the BBB protein changes in inflammatory and degenerative diseases of the central nervous system.

P545

Mesenchymal stem cell grafts in stroke: clinical and pathological benefits with important safety issues

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Objectives: Bone marrow stromal cells (BMSCs) have been attributed with significant effects after intra-arterial, intravenous and intrastriatal transplantation after ischemic cerebral stroke in rats. However, intraventricular (ICV) route of transplantation and migration of these cells into the parenchyma have not been studied in the middle cerebral artery occlusion (MCAO) model, so far.

Methods: Male adult Wistar rats ($n = 34$) were subjected to temporary MCAO. BrdU-labeled BMSCs (group A) or vehicle (group B) were ICV administered in both lateral ventricles 4 hours post reperfusion. Animals were clinically assessed (using the modified Neurological Stroke Scale, mNSS, and the Grid-walking test, GWT) at 6 hours and days 1, 3, 7, 14, 21, 40 and 60 post-MCAO. Pathology of the grafted cells, infarction and glia was studied on day 3 (acute phase) and day 60 (chronic phase) post-MCAO.

Results: A striking result was an impressive reduction of post-stroke mortality (group A: 5.8% and B: 33.3%, $p < 0.001$) by the BMSCs, accompanied by a significant improvement of the chronic mNSS score of group B animals ($p < 0.05$). GWT also improved in BMSCs transplanted animals (group A: -40.2 ± 38.3%; group B: 59.2 ± 18.4%) but failed to reach statistical significance. Pathology revealed migrating BMSCs in the parenchyma of the infarcted hemisphere at both phases, whereas no BMSC in the healthy side was detected, indicating a selective migration towards infarction. Hemispheric edema and middle line translocation were approximately 50% lower in group A compared to B ($p < 0.05$) on day 3, partially explaining the reduced mortality in the group. Astrocytic activation and scar were also found significantly lower ($p < 0.01$), while microglial activation was similar in both phases. Infarction volume, infarction cavity and hemispheric atrophy were lower in group A though not statisticaly significant. However, to our surprise and despite their beneficial effects, BMSCs also induced tumor-like fibroid masses within the ventricular system of the animals, even at 4-5 mm away from the injection site.

Conclusion: Our results indicate that ICV administration of BMSCs migrate into ischemic cerebral parenchyma, reduce lethal edema and astrocytic reactions and improve clinical scores. However, they should be handled with cautious since they form fibroid masses the consequences of which remain to be clarified.

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P546

Sublethal ischaemia enhances the expression of glucose transporter 3 in cultured astrocytes

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Objective: Astrocytes play an important role in the maintenance of intercellular communication through neural network in the central nervous system after ischemic insult to the brain. After brain ischemia, it is most important to restore the blood (glucose and oxygen) supply because neurons are extremely vulnerable to ischemic stress. The ATP-independent glucose transporter 1 and 3 (GLUT1, GLUT3) mediate glucose uptake in the brain cells, and astrocytes potentially express GLUT1 under physiological conditions. GLUT3 is primarily expressed in the membrane of neurons, but stressed neurons also express GLUT1 temporally when more glucose uptakes are necessary for supporting the neuronal activity. Enhanced GLUT1 activity contributes to the protection of neurons from death under pathological conditions such as hypoxia, ischemia, and situations in which mitochondrial respiration is suppressed. However, little studies have been performed on whether the activity of astrocytic GLUT1 changed after ischemic stress, and stressed astrocytes temporally express GLUT3 or not. This study demonstrated that sublethal ischemic stress enhanced the membrane expression of GLUT3.

Methods: Primary astrocytes were obtained from the cortical hemispheres of postnatal rats, and cells were maintained with a culture medium (CM) for 14 days. Ischemic condition was simulated by depriving cultures of oxygen and glucose (OGD), i.e., culture medium was replaced with the glucose-free buffer, and cultures were placed in an anaerobic chamber containing the de-oxygenation reagent. After sublethal OGD (sOGD), cultures were incubated with fresh CM (reperfusion). We defined 0 or 1 h reperfusion after sOGD as sOGD0 h or sOGDR1 h. The expression of GLUT1 and GLUT3 was evaluated by Western blot and fluorescence staining.

Results: The expression of the astrocytic GLUT1 was not changed in the sOGD0 h and sOGD1 h groups. In contrast, GLUT3 expression in cultured astrocytes was significantly enhanced after sOGD. The translocation of GLUT3 to the membrane was attenuated by treatment of cultures with an inhibitor of cAMP-activated protein kinase (AMPK) during sOGD.

Conclusion: The present study suggested that astrocytes promptly enhanced the GLUT3 expression under emergent situations such as ischemia, and glucose was imported quickly into astrocytes, possibly contributing to the protection of neurons as well as astrocytes themselves from ischemia-induced death.

P547

Long-term hypothermia using H2S greatly reduces infarct volume in aged rats after focal ischaemia

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In aged humans, stroke is a major cause of disability for which no neuroprotective measures are available. A viable alternative to conventional drug-based neuroprotective therapies is brain/body cooling, or hypothermia. In animal studies of focal ischemia, short-term hypothermia consistently reduces infarct size. Nevertheless, efficient neuroprotection requires long-term, regulated lowering of whole body temperature.

Focal cerebral ischemia was produced by reversible occlusion of the right middle cerebral artery in 17 month-old male Sprague Dawley rats. After stroke, the aged rats were exposed for 2 days to a mixture of air and a mild inhibitor of oxidative phosphorylation, hydrogen sulfide (H2S), which resulted in sustained, deep hypothermia (30.8 $\pm$ 0.7°C). Long-term hypothermia led to a 50% reduction in infarct size with a concomitant reduction in the number of phagocytic cells. At the transcription level, hypothermia caused a reduction in the mRNA coding for caspase 12, NF-kappa B and grp78 in the peri-infarcted region, suggesting an overall decrease in the transcriptional activity related to inflammation and apoptosis. By proteomics we identified Annexin 1 whose expression was increased in the infarcted area of hypothermic rats. Behaviorally, hypothermia was associated with better performance on tests that require complex sensorimotor skills, in the absence of obvious neurological deficits or physiological side-effects, in aged rats.

Conclusions: Prolonged, H2S-induced hypothermia is a simple and efficacious method to limit damage inflicted by stroke in aged rats.

P548

17 β-estradiol protects from mitochondrial and proteasome dysfunction induced by pesticides in human neuroblastoma cells

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Background and objectives: Epidemiological data indicate male gender and reduced fertile life length in women as risk factors for Parkinson's disease (PD), suggesting a neuroprotective role for estrogens. In vitro studies demonstrate indeed the ability of 17 β-estradiol to afford neuroprotection against neuronal damage caused by diverse neurotoxic stimuli. Exposure to rotenone and paraquat, through the inhibition of mitochondrial complex I activity and subsequent oxidative stress, provides classical models of PD both in vivo and in vitro. In the present study, we investigated the mechanisms underlying dopaminergic cell toxicity induced by various pesticides (paraquat, rotenone and 2,4-dichlorophenoxyacetic acid 2,4-D), and the possible protective effect of 17 β-estradiol.

Methods: The experiments were performed using a human dopaminergic neuroblastoma cell line (SH-SY5Y), which is also known to express estrogen receptors. SH-SY5Y cells were exposed to paraquat, rotenone and 2,4-D with or without pretreatment with 17 β-estradiol at various concentrations. We then evaluated mitochondrial function, ROS production, ATP levels, and proteasome activity.

Results: Exposure of SH-SY5Y cells to paraquat, rotenone and 2,4-D significantly reduced mitochondrial function, ATP production and proteasome activity in a dose and time-dependent manner. 17 β-estradiol increased basal proteasome activity in a concentration and time-dependent manner. Furthermore, pretreatment with 17 β-estradiol appeared to protect SH-SY5Y cells from pesticides-induced decrease of mitochondrial function and proteasome activity. This rescue effect was observed for both nM and uM 17 β-estradiol concentrations, suggesting that estrogen-mediated neuroprotection was probably mediated by both receptor-dependent and -independent mechanisms.

Conclusions: Our data identify mitochondrial and proteasome impairment as common mechanisms underlying dopaminergic cell toxicity induced by paraquat, rotenone and 2,4-D. Furthermore, our results indicate that estrogens exert protective effects against both these damages. This rescue effect is likely to occur through an indirect, estrogen receptor-mediated mechanism and through a direct, antioxidant effect.

P549

Neurological phenotype and reduced lifespan in heterozygous Tim23 knockout mice, the first mouse model of defective mitochondrial import

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The Tim23 protein is the key component of the mitochondrial import machinery. It locates to the inner mitochondrial membrane and its own import is dependent on the DDP1/TIM13 complex. Mutations in human DDP1 cause the Mohr-Tranebjaerg syndrome (MTS/DFN-1; OMIM #304700), which is one of the two known human diseases of the mitochondrial protein import machinery. We created a Tim23 knockout mouse from a gene trap embryonic stem cell clone. Homozygous Tim23 mice were not viable. Heterozygous F1 mutants showed a 50% reduction of Tim23 protein in Western blot, a neurological phenotype and a markedly reduced life span. Haploinsufficiency of the Tim23 mutation underlines the critical role of the mitochondrial import machinery for maintaining mitochondrial function.

P550

The effects of combined administration of AChE inhibitor and NMDAR antagonist on soluble A oligomers-induced arc expression

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Introduction: Alzheimer's disease (AD) is a progressive cognitive disorder of the elderly. One of the pathological hallmarks for AD is

extracellular accumulation of senile plaques composed of primarily aggregated β-amyloid (Aβ) peptide which is sufficient to disrupt synaptic transmission and thus leads to cognitive impairment. Recent studies also suggest that soluble Aβ-derived oligomers (ADDL) rather than Aβ fibrils are involved in the early memory loss cause by synaptic failures. Activity-regulated cytoskeleton-associated protein (Arc) is required for long-term memory formation. Alterations in the levels of Arc expression have been correlated with cognitive impairment during aging. ADDL have been demonstrated to be able to inhibit long-term potentiation (LTP), a cellular model of memory, and induce ectopic expression of Arc. In addition, deficits in brain cholinergic and glutamatergic neurotransmissions contribute to the cognitive impairments of AD. A combination of acetylcholinesterase (AChE) inhibitor and N-methyl-D-aspartate receptor (NMDAR) antagonist had been used to treat AD patients with improvements in cognitive functions. Although the cognitive impairment in AD caused by synaptic dysfunction and AChE inhibitor may work synergistically with NMDAR antagonist to enhance synaptic activity.

Objectives: An effort was made in this study to evaluate whether combined administration of AChE inhibitor and NMDAR antagonist could attenuate or prevent the effects of ADDL on Arc expression.

Methods: Primary neuronal cultures of neonatal rat's cerebral cortex and basal forebrain were used. Pretreatments of memantine (NMDAR antagonist) and/or galantamine (AChE inhibitor) were given for 30 min followed by ADDL treatment for 1 hr.

Results: Western blot showed that the levels of Arc protein increased significantly after ADDL treatments. Pretreatments of memantine alone or memantine combined with galantamine prevented ADDL-induced Arc expression. However, pretreatment of galantamine alone showed no effect on ADDL-induced Arc expression. These results revealed that memantine controlling the NMDAR gating and the subsequent glutamate excitotoxicity may have better therapeutic efficiency than that of galantamine.

Conclusions: According to these findings, the suggestion that combined therapy may increase the amount of acetylcholine for modulating the release of glutamate and may simultaneously prevent the glutamate excitotoxicity through NMDAR overactivation.

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Human adipose-derived multipotent stromal cells compensate neurological deficit in rats treated with 3-nitropropionic acid

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Introduction: Human adipose-derived multipotent stromal cells (hADMSCs) contain a number of stem cells and can be differentiated in several cellular lines including cells with neuronal phenotype in the presence of agents like retinoic acid, β-mercaptoethanol, BDNF, etc. 3-nitropropionic acid (3-NPA) is a well-known neurotoxin inducing an irreversible inhibition of mitochondrial succinate dehydrogenase. 3-NPA stimulates oxidative stress, which results in neurodegenerative process. It is known from literature that symptoms of 3-NPA toxicity are similar to those of Huntington disease. The aim of this study was to analyze the symptomatic relief and behavioral activity after stereotaxic inductions of hADMSCs, differentiated to neuronal phenotype by the administration of retinoic acid.

Materials and methods: Normal adult Wistar rats were used in experiments. Each experimental group contained 11 animals, 3-NPA treatment being performed during 5 days in a daily dose of 75 mg/kg. hADMSCs were cultured to 3-4th passage and then incubated with 10 mkM of retinoic acid for 6 days. Then hADMSCs were characterized for neuronal phenotype and stereotaxically transplanted to the rat's brain. The neurological parameters were measured every day before 3-NPA injection, whereas exploratory activity in "open field" test and formation of long-term memory in Morris-test were estimated at the first and last days of experiments.

Results and conclusion: hADMSCs after incubation with retinoic acid expressed neuronal markers such as nestin and GFAP. They also expressed NMDA receptors and all these facts are indications of the appearance of neuronal phenotype. 3-NPA treatment of rats developed significant neurotoxicity, which causes in motor disorders depending on 3-NPA dosage. 3-NPA treatment led to decrease in both horizontal and vertical activities in "open field" test. Morris test showed that rats after hADSC transplantation were more active and could faster find the platform in the water. So, we conclude that transplantation of hADSC, differentiated to neurons in the presence of retinoic acid in the rat's brains leads to ease neurodegeneration and increase behavioral activity.

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P552

Cholesterol regulates M-type K+ channels in sympathetic neurons

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M-type (KCNQ) potassium channels play an important role in regulation of action potential firing in neurons. Suppression of M current increase excitability and its enhancement can silence neurons. In the present study, we investigated the effect of cholesterol on M current in superior cervical ganglion (SCG) sympathetic neurons, using whole-cell patch clamp technique. Free cholesterol inhibited M current in a dose-dependent manner. Extent of inhibition induced by 10, 150, and 500 μM cholesterol was 19.0 ± 4.4 % ($n = 4$), 61.8 ± 3.9 % ($n = 4$), and 79.4 ± 4.8 % ($n = 3$), respectively. We investigated the involvement of phospholipase C in cholesterol mediated inhibition of M current. The cholesterol (150 μM)-mediated inhibition of M current was reduced to $32.8 \pm 2.65\%$ ($n = 6$) by edelfosine(1 μM), a phospholipase C inhibitor. However, cholesterol (150 μM) inhibited M currents whether or not intracellular Ca2+ was clamped (59.03% for 10 BAPTA vs. 36.25% for 0.1 EGTA, $p < 0.01$). Furthermore, cholesterol did not induce an increase of intracellular Ca in SCG neurons. We then examined the role of PKC in M current inhibition, and found that protein kinase C inhibitor, Calphostin C (1 μM) significantly blocked the inhibition of M current by 150 μM cholesterol ($7.7 \pm 6.5\%$, $n = 4$, p 0.01). We also tested whether direct activation of PKC by phobol ester inhibits M current. PDBu (1 μM), a PKC activator, significantly inhibited M current ($41 \pm 8.6\%$, $n = 4$), but an inactive analogue 4α-PDBu (1 μM) did not inhibit M current. We tested whether PKC can modulate M current through modulation of PIP2-channel interaction. Loading the cells with PIP2 (20 μM) significantly reduced

cholesterol-induced inhibition of M current. In the presence of PIP2, the inhibition of M current was 1.6 ± 3.2 % ($n = 4$, p 0.01). Furthermore, the inhibition of M current by direct application of phobol ester was also completely reversed in PIP2-loaded cells (9.9 ± 4.3%, $n = 7$). From these result, we suggest that the inhibition of M current by cholesterol in SCG neurons is via PLC and PKC activation. The decrease in PIP2-channel interaction is thought as a possible mechanism for PKC action in M current modulation.

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Nanoparticle mediated delivery of doxorubicin over the blood-brain barrier

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Generally, drug targeting to the brain could be achieved by going either "through" or "behind" the BBB. It was shown recently that the drugs normally unable to cross the BBB could be delivered to the brain after binding to the surface-modified polymeric nanoparticles (NPs). Further investigations provided evidence that the NP-based drug delivery systems possess a significant potential for brain targeting. The objective of this study was to develop a novel brain delivery system based on pegylated poly lactide-co-glycolide (PEG-PLGA) nanoparticles containing doxorubicin (DOX). DOX is a widely used antitumor antibiotic that has been shown to poorly cross the BBB because of the efflux transporters. To investigate the brain delivery property of the system, a lipophilic fluorescent dye, coumarin-6 was incorporated into the nanoparticle as a probe. DOX-NP loaded with coumarin-6 was quantitatively evaluated using an uptake experiment by a mouse brain endothelia cell line in vitro and its localization in brain tissue sections was visualized by fluorescence microscopy.

PEG-PLGA block copolymers were synthesizes and characterizes. Coumarin-6 loaded DOX-NPs were prepared. The mean diameter and zeta potential of the fluorescent DOX-NPs were determined. Mouse brain endothelial cell line (b End. 3 cells) were maintained in tissue cell culture dishes with streptomycin. The cells were incubated with fluorescent DOX-NP suspensions.. The fluorescent DOX-NPs has an average diameter of around 90–120 nm. The uptake of the particles by b End. 3 cells were depended on the incubation time, temperature, and nanoparticle concentration. The uptake amount at 37°C was much higher than that under 10°C. Fluorescent microscopy photographs of b End. 3 cells exposed to DOX-NPs at the concentration of 30 μg/ml demonstrated that the increase of fluorescent intensity in the cells correlated with increase in the time of incubation.

In-vitro and in-vivo results showed that DOX-NPs are a promising biocompatible brain drug delivery system with temperature, time, and concentration dependenence and an effective technique for brain drug delivery, especially for anti-cancer agents.

P554

Effects of angiotensin II, its receptor antagonists and captopril on cognitive functions and oxidative stress in rats

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Objective: The octapeptide hormone angiotensin II (Ang II) is produced in the mammalian brain. In addition to its well known central actions, such as increasing blood pressure and thirst, this peptide possesses interesting cognitive properties. Behavioral data obtained from rats have been difficult to interpret because of the diverse methodological approaches. Both stimulatory and inhibitory effects of Ang II on memory functions have been reported. There is also evidence that oxidative stress accompanies angiotensin II infusion, but the role of AT 1 versus AT 2 receptors on the generation of reactive oxygen species is not clear.

Methods: Losartan (AT 1 antagonist), PD 123177 (AT 2 antagonist), captopril (angiotensin converting enzyme-ACE inhibitor) and Ang II were administered by stereotaxic neurosurgery in the left cerebral ventricle. Passive avoidance and Y maze tasks were used for memory assessment.
We also assessed the levels of some enzymatic antioxidant defences like superoxide dismutase (SOD) and glutathione peroxidase (GPX), as well as lipid oxidation makers like MDA (malondialdehyde), from the temporal lobe, using chemiluminometric and spectrophotometric methods.

Results: In Y maze task the administration of losartan, PD 123177 and captopril resulted in an increase of short-term memory as evidenced by a significant increase of the spontaneous alternation, compared to sham operated group. Also, these 3 drugs caused a significant increase of step-through-latency in the passive avoidance task. The administration of angiotensin II induced a significant decrease in both spontaneous alternation and step-through-latency.
Alterations in the specific activity of the antioxidant enzymes (SOD and GPX) were found in the temporal lobe of angiotensin II treated rats, while the administration of losartan, PD 123177 and captopril resulted in an increase of these enzymes activity, compared to sham-operated group. Also the levels of MDA were found increase in angiotensin II treated rats

Conclusions: In conclusion, this study clearly demonstrates that inhibition of the RAS with either an ACE inhibitor or AT1/AT 2 blockers induces a significant facilitator effect on the cognitive functions and a substantial reduction in neuronal oxidative stress status. Therefore, the use of antihypertensive drugs, particularly ACE inhibitors and angiotensin receptor blockers, may be associated with a lower rate of cognitive decline in older adults and possibly in those with Alzheimer disease.

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Effects of paraventricular nucleus lesion on cognitive functions and oxidative stress

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Objectives: The stress response is mediated by the hypothalamo–pituitary–adrenal (HPA) system. Activity of the corticotropin-releasing hormone (CRH) neurons in the hypothalamic paraventricular nucleus (PVN) forms the basis of the activity of the HPA-axis. The current study was therefore designed to determine whether a unilateral 6-OHDA lesion of the PVN, which produce a marked decrease of brain noradrenaline and dopamine, leads to a deactivation of HPA-axis and affects the cognitive functions. Further, we were interested to know whether this lesion would result in an imbalance in oxidative stress levels of temporal brain area.

Methods: Male Wistar rats were subjected to right-unilateral 6-hydroxydopamine (6-OHDA) lesion of hypothalamic paraventricular nucleus or were sham lesioned. Behavioral tests (Y maze, radial arm maze and elevated plus maze) started 2 weeks after neurosurgery.
We also assessed the levels of some enzymatic antioxidant defences like superoxide dismutase (SOD) and glutathione peroxidase (GPX),

as well as lipid oxidation makers like MDA (malondialdehyde), from the temporal lobe, using chemiluminometric and spectrophotometric methods.

Results: Lesion of the PVN resulted in a significant impairment of short-term memory, explored by means of Y-maze task. Also, 6-OHDA lesion of the PVN induced a significant increase in the number of working and reference memory errors, explored by means of radial arm-maze, suggesting significant effects on spatial memory. In the elevated plus maze task sham-operated rats spent less time on the open arms that 6-OHDA lesioned rats, suggesting that 6-OHDA lesions significantly diminished anxiety state.
Alterations in the specific activity of the antioxidant enzymes (SOD and GPX) were found in temporal lobe of 6-OHDA lesioned rats compared to sham operated group. Also, MDA levels were significantly increased in the PVN lesioned rats, comparative with the control group.

Conclusions: These data indicate that PVN may have important implications in memory processes and oxidative stress status of the brain, with relevance for some neurodegenerative diseases, considering that during aging, the activation of the HPA system and CRH neurons in the PVN is affected, as in Alzheimer's disease and major depression.

P556
The cholinergic-catecholaminergic interaction in rat: cognitive processes and oxidative stress

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Objective: The cholinergic hypothesis of Alzheimer's disease (AD) has strongly influenced research on learning and memory over the last two decades. Furthermore, there are indications that other neurotransmitter systems affected by this disease may be involved in cognitive processes. Animal studies have suggested that catecholamines and acetylcholine may interact in learning and memory.
Also, a growing body of evidence suggests that an imbalance between free radical formation and destruction is involved in AD pathogenesis. The purpose of the present study was to investigate this interaction in a radial-arm-maze task, after coadministration of catecholamines and acetylcholine agonists.

Methods: We administrated pilocarpine (muscarinic receptors agonist, 8 mg/kg, i.p.), clonidine (α2 adrenergic agonist-0,5 mg/kg g.c., i.p.) and pergolide (unselective dopamine receptor agonist, 0.3 mg/kg, i.p.) in male Wistar rats, either singly or in combination. Also, we determined the specific activities of some antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPX), as well as lipid oxidation makers like MDA (malondialdehyde), from the temporal lobe, using chemiluminometric and spectrophotometric methods.

Results: Injection of pilocarpine, clonidine and pergolide each resulted in a significant stimulation of both working and reference memory tested by means of radial-arm-maze task, suggesting significant effects on spatial memory. Moreover, combined administration of all 3 agonist resulted in a synergistic stimulation of spatial memory. Regarding oxidative stress, the activities of SOD and GPX were increased in rats treated with cholinergic and catecholaminergic agonists. Also, MDA levels were significantly decreased in agonists treated rats, comparative with the control group.

Conclusions: These findings further support a role for the interaction between catecholamines and acetylcholine in the modulation of learning and memory processes. Also, oxidative stress may play a key role in some neuroprotective mechanism in the brain. These factors combine to build a case for the use of catecholaminergic and cholinergic agonists in early-stage dementia.

Neuro-ophthalmology

P557
Where is my armchair? A case of complete reversal of vision metamorphopsia in the saggital plane

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Objectives: To report a case of complete reversal of vision metamorphopsia (RVM) in the saggital plane with metamorphopsia of faces and visual hallucinations.

Methods: A 72 yo female complained from sudden abnormal visual perceptions. She referred that some furniture that was supposed to be located on the left side in her living room was now in the right side, and the same accounted for all rooms and objects in the house. Furthermore, the doors now opened from left-to-right and not from the usual right-to-left manner. She was able to recognize faces however all of them had "strange hair and long ears", like an elf face. She also referred visual hallucinations, essentially, small animals, in the left visual field. She was worried about these visual symptoms. Her past medical history was only remarkable for sinusal tachycardia related to anxiety and hypercholesterolemia.

Results: Neurological exam and computerize field analysis were normal. Routine biochemical and hematological laboratory tests were also normal. Brain MRI showed an acute infarct involving temporal, parietal and occipital cortex. AngioMRI revealed a 50% stenosis in the right internal carotid. Routine EEG was normal. Symptoms remain unchanged for two weeks and solved with oxcarbamazepine.

Conclusions: To our knowledge, RVM in the saggital plane has not been previously reported. Parietal and occipital cortex lesions that spare the optic radiations and the primary visual cortex, as in the patient reported here, have been related to RVM in the coronal plane. It is not known which mechanism determine the rotation plane of the vision metamorphopsia. The "elf-face" metamorphopsia has not been previously reported either and may be due to the involvement of the retrosplenial region since this area has been related to other types of faces metamorphopsia.

P558
3D gaze movements after midbrain lesions

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Objectives: Clinical studies have shown that lesions of the midbrain premotor nuclei of vertical eye movements (Interstitial Nucleus of Cajal and Rostral Interstitial nucleus of the Medial Longitudinal Fasciculus) cause not only eye movements deficits, such as vertical gaze palsy, but also cause a contralateral head tilt impairing the head posture while looking straight ahead (straight ahead position). In the present study, we investigate how acute rostral midbrain lesions affect not only the position of the eye and head when the gaze is directed straight ahead, but also after gaze movements in the periphery.

Methods: For the 3D eye movement recordings we used a dual search coil on the left eye (Skalar, Delft, The Netherlands). The 3D head movements were measured using two coils mounted on a head ring at a 90° angle between them. We measured six patients with acute midbrain lesions and nine healthy aged-matched control subjects. Subjects had 1) to perform head-free target directed saccades (head-free task) and 2) to point to the target with a head-mounted laser (head-

only task). We then fitted a second-order surface (Donders' surface) to the rotational head positions corresponding to periods of head fixation.

Results: All patients had a vertical gaze palsy and torsional deviations of vertical saccades or torsional nystagmus. Only two patients had a visible head tilt. In those patients the surface was shifted contralateral with respect to the lesion, but its shape was not altered. In patients that did not have a head tilt in the straight ahead position, Donders' head surfaces bent contralateral to the lesion, resuming a different form than the normal saddle-like one.

Conclusion: Our data show that quantitative analysis can demonstrate changes in gaze orientation in patients with midbrain lesions even outside the straight ahead position. These changes also suggest a role of the midbrain premotor nuclei in head control, as previously shown in non-human primates.

P559

Subclinical cardiac involvement in Leber's hereditary optic neuropathy

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Objectives: Leber's hereditary optic neuropathy (LHON) is a maternally transmitted disease resulting in acute or subacute central loss of vision. Three mitochondrial DNA (mtDNA) point mutations (at mtDNA positions 3460, 11778, and 14484) cause more than 90% of all LHON cases. Although LHON is relatively selective and mainly involves the retinal ganglion cells (RGCs), cardiac affection has been postulated. In order to asses the prevalence and clinical significance of the cardiac involvement, we systematically evaluated the electrocardiograms (ECGs) of 37 patients with LHON.

Methods: In order to address this question, we examined retrospectively the ECGs of 37 affected patients known to carry one of the three primary pathogenic mtDNA mutations: m.3460G > A, m.11778G > A and m.14484T > C.

Results: 37 patients from different pedigrees were examined. 30 patients carried the 11778 mtDNA mutation, only one the 14484 mutation and the remaining six carried the 3460 mtDNA mutation. 32 were male and five female. Mean age was 29.8 years (range 14–56). Mean duration of LHON symptoms was 24.6 months (2–59). Only one patient complained about having palpitations. All 3460-, all 14484- and 23 of 30 patients with the 11778-mutation, in total 32 out of 37, had abnormalities in the ECG. Among them were 10 (27%) having ST-segment abnormalities, 12 (32.4%) having left or right ventricular hypertrophy (LVH or RVH), 5 (13.5%) having bradycardia, 5 (13.5%) having an incomplete left or right branch blockage, 3 (8.1%) having p-wave abnormalities and one having multiple extra systoles.

Conclusion: 86% of the examined LHON patients showed ECG abnormalities. These results suggest that most LHON patients despite not complaining about cardiac symptoms show pathologic ECGs. Correlation of type of mutation, duration of optic symptoms and carrier status with cardiac disease requires further investigation. Nevertheless we propose that patients with LHON should routinely be screened for cardiac abnormalities.

P560

Cyclic oculomotor paralysis – The challenging diagnosis of paroxistic changes of the eye

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Background: Cyclic oculomotor paralysis is a very rare disorder of ocular motility in which the third nerve evidences paroxistic modifications, alternating between a spastic and a paralytic phase. Most cases have their onset before age 2.

Case report: A baby girl, first daughter of healthy parents had an uneventful gestation and labour. From the first week of age, parents noticed that occasionally she had unequal pupil size. When she was 6-months-old, together with the pupil change, parents noticed that the right lid would sometimes retract. This happened during sleep, eating and playing. At one year of age, the episodes would be more frequent, and sometimes the eye would look down and outward. She had a normal development, and no other changes were detected in general, neurological or ophthalmological examination. Brain MRI and EEG were normal. Now, 2 years of age, she maintains the cyclic phenomenon, independently of the occasion, slightly less frequent according to the parents: initially the right pupil dilates, then ptosis of the eyelid occurs, followed by abduction and infraversion of the eye. Afterwards lid retraction occurs, the eye returns to its position and pupil constricts. Frequent patching of the left eye was recommended to prevent amblyopia.

Discussion: Our patient presents the typical oculomotor cyclic spasms. However, unlike most of the reports in literature, she appears to have periods of normal oculomotor function. Of the 47 previous reports, only one was associated with neurologic lesion (supraclinoid aneurysm). In all the other the phenomenon persisted throughout life. Cyclic phenomena are rare in the nervous system, and the underlying mechanism of these cyclic spasms remains a mystery.

P561

The endocannabinoid CB1 receptor modulates retinal projection development

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In the adult brain, endocannabinoids (eCBs) exert an important neuromodulatory function by acting as retrograde messengers to regulate the function of many synapses. They operate mainly via their Gi/o protein coupled receptors CB1 and CB2. Both receptors negatively regulate adenylate cyclase, an enzyme synthesizing cAMP. Due to the presence of eCBs and their receptors at the fetal and early postnatal periods, it has been proposed that they might be involved in several developmental events, such as cell proliferation and migration, axon guidance and synaptogenesis. During development, retinal ganglion cells (RGCs) extend their axons toward their specific targets in the thalamus and the superior colliculus. RGC growth cone (GC) navigation is largely directed by guidance cues present in their environment. Recently, we showed that elevating intraocular cAMP levels accelerates RGC branch growth during early development. In the present study, we tested if an early postnatal modulation of the CB1 receptor activity would affect RGC axon development. We observed that during early postnatal development, the CB1 receptor is expressed along the visual pathway (the optic chiasm, the lateral geniculate nucleus and the superior colliculus). To investigate the effect of modulating the CB1 receptor activity on retinal projection development, hamsters received, at postnatal day 1, a unilateral intraocular injection of either an agonist (ACEA) or an inverse agonist (AM251) of the CB1 receptor. Compared with the saline, AM251 increased RGC axon growth whereas ACEA delayed their development. When retinal explants in culture were treated with AM251, GC surface area and GC filopodia number were increased significantly. On the other end, ACEA decreased these endpoints. The implication of the CB1R during retinogeniculate development was further investigated in the dLGN in adult CB1R−/− mice and their wild-type littermates. In adult CB1R deficient mice, the amount of territory occupied by contralateral projections is larger while the area occupied by ipsilateral projections remained similar to WT mice.

Our results demonstrate a significant overlap between contralateral and ipsilateral RGC projections in the dLGN in CB1R−/− mice. In conclusion, these results show for the first time the implication of the CB1 receptor during retinothalamic development.

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P562

Selective atrophy in the optic pathways in patients with Leber's hereditary optic neuropathy: a voxel-based morphometry MRI study

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Objectives: A selective loss of the smaller-caliber fibers of papillo-macular bundle of the optic nerve and of central vision characterize patients affected by Leber's hereditary optic neuropathy (LHON). Whether CNS involvement in these patients is limited to the optic nerve or, conversely, is more diffuse, is still a matter of debate. Aims of this study were a) to define the presence and distribution of brain gray matter (GM) and white matter (WM) loss in patients with LHON using voxel-based morphometry (VBM), and b) to assess their correlation with neuro-ophthalmologic measures, including optic coherence tomography (OCT).

Methods: Using a 3 Tesla scanner, dual-echo and fast-field echo scans were acquired from 12 LHON patients (mean age 31.2, range 20-46 years) and 12 age-sex matched controls (mean age 29.4, range = 23–45 years). VBM analysis was performed using SPM5 and an ANCOVA model, including age, gender and intracranial volume as nuisance variables.

Results: Average retinal nerve fiber layer (RNFL) thickness was significantly decreased in LHON patients. Compared with controls, LHON patients had significant clusters of locally reduced GM volume in the bilateral primary visual cortex (V1), the head of the left caudate nucleus, and the left precentral gyrus. Compared with controls, LHON patients had significant clusters of locally reduced WM volume in the chiasm, the optic tract, bilaterally, and in several areas located within the optic radiation (OR), bilaterally. V1 atrophy was significantly correlated with average and temporal RNFL thicknesses, while OR atrophy was significantly correlated with disease duration, and average and temporal RNFL thicknesses.

Conclusion: CNS involvement in patients with LHON is not limited to the anterior visual pathways, but extends posteriorly to the OR and V1, probably through trans-synaptic degeneration secondary to axonal damage in the retina and optic nerve. LHON might represent a valuable model to study the effect of axonal loss in the CNS.

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Visual pathways functional and structural abnormalities in patients with Leber's hereditary optic neuropathy

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Objectives: To define, using diffusion tensor (DT) tractography, the presence and distribution of structural damage along the visual pathways in patients with Leber's hereditary optic neuropathy (LHON) and their correlation with: (a) abnormalities of activations of the visual network, measured using functional magnetic resonance imaging (fMRI), and (b) clinical impairment, measured with clinical and optic coherence tomography (OCT).

Methods: We studied 5 patients affected by LHON and 10 sex- and age-matched healthy controls. Each subject underwent complete neuro-ophthalmological examination (including automated perimetry, OCT of retinal nerve fiber layer [RNFL] thickness measurement), structural MRI acquisition (including diffusion tensor MRI), and functional sequences in response to 5 different visual stimulations. SPM5 software was used to perform fMRI analyses, while tractography analysis was performed using FDT toolbox (FSL library).

Results: Optic nerve and chiasm atrophy were detected in all patients. The tractography analysis demonstrated abnormal DT MRI metrics in the right optic radiation and reduced fractional anisotropy (FA) values of the connection between the left lateral geniculate body and V5 in LHON patients, which were significantly correlated with OCT and RNFL measurements. In addition, patients had a significant reduction of V1 activation, bilaterally, and an increased activation of the right V5.

Conclusions: Optic nerve damage in LHON is likely to induce, through trans-synaptic degeneration, structural and functional changes of the retrochiasmal visual pathways from the optic radiation to the primary visual cortex. The activation of V5 in LHON patients could be interpreted as a possible compensatory mechanism secondary to V1 damage.

P564

Episodic diplopia associated with vascular third nerve compression

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Introduction: Ocular motor nerve dysfunctions were observed in single patients with vascular compression of the third nerve. One patient had clinical signs of a third nerve palsy and three patients suffered from episodic diplopia. In two of them, tonic deviation of the eye was observed and diagnosed as ocular neuromyotonia. We add another patient with episodic horizontal diplopia attributed to a vascular compression of the third nerve, which was successfully treated with lamotrigine.

Case report: A 58-year-old male reported a 1-year-history of episodes of horizontal diplopia. The mean frequency was one episode per week with a duration of up to 5 min. His wife observed several episodes. She described a transient marked esotropia of the left eye with an inability to abduct the eye beyond the midposition.
We were unable to observe a diplopic episode or to provoke an episode with sustained lateral gaze. Neurological and neuro-ophthalmological findings were normal as was direct current electro-oculography of horizontal eye movements (saccades, smooth pursuit, optokinetic nystagmus). MRI disclosed a contact of the left posterior cerebral artery with the third nerve exit zone. We assumed a neurovascular compression syndrome and started treatment with lamotrigine, which was followed by cessation of episodic diplopia at a dosage of 100 mg bid.

Conclusion: A causal relationship between the MRI-documented left-sided vascular third nerve compression and episodic diplopia seems likely. Transient esotropia of the left eye with an inability to abduct the eye beyond the midposition indicate activation of the left medial rectus muscle and episodic symptoms are characteristic features of vascular cranial nerve compression syndromes (e.g. trigeminal neuralgia, hemifacial spasm, obliquus superior myokymia, vestibular paroxysmia). Paroxysmal symptoms in neurovascular

compression syndromes are generally attributed to ephaptic neural transmissions between demyelinated axons in the segmental demyelinated portion of the nerve, where vascular compression occurs.

Anticonvulsive drugs may suppress ephaptic neural transmissions and were successfully applied in previously reported patients. Episodic tonic deviation of an eye as reported in our patient characterizes ocular neuromyotonia. Our observation further supports the hypothesis that "idiopathic" ocular neuromyotonia is due to vascular compression of one ocular motor nerve.

P565

Wernicke's encephalopathy after gastro-intestinal surgery for cancer: a retrospective clinical study

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Objectives: To report a retrospective clinical, laboratory and neuroradiological study of 10 patients who developed Wernicke's encephalopathy (WE) after gastro-intestinal surgery for cancer. Peculiar neurological features, causes of diagnostic failure or delay, vitamin supplementation and clinical outcome are discussed.

Methods: Ten patients (5 males and 5 females, aged from 49 to 76 years) with WE, developed after surgery for gastro-intestinal tract cancer, and without previous history of alcoholism, were included in the analysis. Diagnosis of WE was based on clinical, laboratory, neuroimaging findings and response to treatment with substitutive therapy. The following data were collected for each subject: personal history, type of malignancy and surgery, postoperative complications, duration of parenteral nutrition, glucose intake and antibiotic therapy, time between surgery and WE onset, neurological and clinical evaluation compared with neuroimaging (at onset and after vitamin supplementation), begin and dosage of substitutive therapy, outcome.

Results: The majority of patients reported a significant weight loss during the months preceding surgery. 80% of patients manifested WE after a time ranged between four and eight weeks. Mental-status changes and ocular motor impairment were noticed in all patients. Gait or trunk ataxia were evident in 60%. Photophobia, associated with miosis poor light response and signs of meningeal involvement were observed in 30% of cases. Total parenteral nutrition and glucose infusions were performed in all patients. All patients showed complications, including persistent vomiting (60%) and anaemia before (70%) and after surgery (30%). The four patients who died were more nutritionally compromised, even before the operation; mean age was higher; presentation of symptoms was various and atypical at the beginning and caused a delay of diagnosis and therapy. The other patients recovered in two-three weeks partially or completely. There was not correlation between kind of surgery and outcome.

Conclusions: Even if patients who undergo surgery for gastro-intestinal cancer may be considered at high risk of WE, the presence of atypical features, such as photophobia not previously described in WE, and the concurrence of complications altering consciousness may lead to diagnostic failure or delay, followed by poor outcome. Opportunity of preventing thiamine supplementation has to be clarified.

P566

Horizontal smooth pursuit adaptation in humans

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Background and objective: The smooth pursuit system is able to adapt to changes. Previous studies have documented adaptive capability in the smooth pursuit system using a double step of target speed in monkey and human subjects. These studies have demonstrated that significant adaptive changes of initial eye acceleration occur during double-step smooth pursuit paradigm. In this study, we evaluated normal ten healthy adults of smooth pursuit adaptation in onset latency, initial acceleration and gain of pursuit movement.

Methods: Adaptive changes of horizontal smooth pursuit were produced by double steps of target speed that step-up (10–30°/s) or step-down (25–5°/s). In the step-up paradigm, the target appeared at center and moved to the right or left 1° and then began moving at 10°/s for the first 100 ms and changed to 30°/s for the remainder of the trial. In the step-down paradigm, the target begins moving at 25°/s for the first 100 ms and then changes to 5°/s for the remainder of the trial. Smooth pursuit adaptation was evaluated during 100 trails for each adaptation paradigm. We conducted one set of adaptation paradigm consisted of step-up rightward, step-up leftward, step-down rightward, and step-down leftward in each subject.

Results: During early in adaptation (first 10 trials), the subjects used catch-up saccades after the target speed increased to maintain their eye on target. Later in adaptation (last 10 of 100 trials), the subjects followed the target smoothly even after the speed was increased or decreased to 20°/s. During later in period, onset latency, initial acceleration and gain of smooth pursuit after changing the speed of target were more improved than those of initial trial of adaptation period.

Conclusions: The results of this study show that significant changes in the smooth pursuit system after training using a target that moved in a double step ramp fashion of the subjects examined. We conclude that adaptive changes occurred in onset latency, initial acceleration and gain component of smooth pursuit movement by our training paradigms.

P567

Paralysis of upward gaze and eyelid retraction as isolated symptoms of mesodiencephalic junction infarction

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Objectives: Association of vertical gaze paralysis and eyelid retraction was described more than eighty years ago. Most of clinical descriptions available associate other symptoms and are due to extent lesions, so it has become difficult to determine its precise causal anatomic location.

Methods: A 50 year-old-woman without known cardiovascular risk factors presented with an acute onset of vertical diplopia, dizziness and drowsiness, with no associated paresthesia or weakness. On admission two hours after onset of symptoms, the patient was slightly drowsiness and vertical upgaze palsy, bilateral eyelid retraction and a mild gait ataxia were noticed. There was no nystagmus, and pupils were equal and reactive. A T1 Magnetic Resonance Imaging (MRI) of the brain revealed a low intensity 5 mm lesion with diffusion restriction, adjacent to left caudal side of third ventricle, suggesting acute infarction. MR angiography demonstrated patent vertebral and basilar arteries. Echocardiogram showed no lesions. The patient experienced a spontaneous partial improvement, and developed a compensating retrocolli.

Results: Few clinical case reports with eye movements' impairment due to discrete lesions, and modern experimental techniques, have increased our understanding of anatomic connections involved in vertical gaze. These structures are located at the mesodiencephalic

junction and include interstitial nucleus of Cajal, interstitial nucleus of the medial longitudinal fasciculus and posterior commissure. Unilateral or bilateral lesions involving these structures may produce vertical gaze palsies, commonly associating other ocular motility alterations, decreased level of consciousness, or memory disorders. Posterior commissure lies rostral to superior colliculi, at the junction of the aqueduct and third ventricle; its unilateral damage may lead to upward gaze paralysis and bilateral eyelid retraction (Collier's sign), though there are few descriptions of small vascular lesions involving its medial part.

Conclusion: We report a patient with isolated acute upgaze palsy and lid retraction in association with selective involvement of posterior commissure with no other clinical or radiological evidence of midbrain ischemia. Our report might provide further insight in the understanding of the control of vertical gaze.

P568

Orbital paraganglioma: a unique route to a rare destination. Case report

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Introduction: Paragangliomas are tumours of neural crest origin. Rare cranial locations of paragangliomas include the sella and parasellar regions. Orbital involvement is exceedingly rare; only a few reported cases are well-documented. Here we describe the unique case of a sellar paraganglioma - initially thought to be a pituitary macroadenoma - that extended into the orbit through the superior orbital fissure causing acute ocular symptoms.

Case description: A 63-year-old right handed male presented with acute proptosis, conjunctival vessel dilatation and chemosis of the left eye. Relevant past medical history included subtotal resection of a sellar/suprasellar/cavernous sinus lesion five years earlier; at the time the lesion was diagnosed as a non-functioning pituitary macroadenoma and treated with radiotherapy.

The preoperative MRI revealed a tumour involving the sella, suprasellar space and left cavernous sinus. Intriguingly, the lesion extended through the left superior orbital fissure into the orbit, exerting posterior pressure on the globe. Comparison with previous imaging showed that the only characteristic of the tumour that had changed since the radiotherapy was the growth through the superior orbital fissure into the orbit. The acute orbital symptoms were assumed to be caused by venous compression in the superior orbital fissure or at the orbital apex.

Considering that the sellar, suprasellar, and the majority of the cavernous sinus portions of the tumour were stable, the surgical plan was to resect only the new intraorbital portion and decompress the superior orbital fissure with the aim of preserving vision and extraocular movements. Using a transcranial approach, the superior orbital fissure was decompressed and the anterior 2/3 of the intraorbital portion of the tumour was removed in a circumferential fashion followed by intracapsular debulking of the posterior 1/3 at the orbital apex. Pathology was consistent with a paraganglioma. Six months later, postoperative visual acuity and extraocular movements remain unchanged compared to preoperative status.

Conclusion: We report here, for the first time, a sellar/cavernous sinus paraganglioma that extended into the orbit through the superior orbital fissure resulting in acute ocular symptoms. While an appropriate treatment paradigm has not been established, a review of all previously reported cases of sellar paragangliomas suggests radiotherapy is an important consideration.

P569

The line bisection task in the acute stage of hemianopia and neglect

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The line bisection task is a common clinical bedside tool for the assessment of spatial neglect and homonymous hemianopia (HH). While neglect patients show an ipsilesional deviation, hemianopic patients are usually known to displace their midline contralesionally towards the scotoma. Evidence for the "hemianopic line bisection error (LBE)" came from hemianopic patients in a chronic stage of brain damage (mostly occipital stroke). As it seems to represent a compensatory shift of attention the LBE may be absent in the acute stage. If so, is the line bisection task a reliable bedside tool to distinguish hemianopia from hemineglect in the acute stage of stroke?

We compared the line bisection task in hemianopic patients as well as hemineglect patients in their acute stage of stroke with healthy control subjects. At the bedside participants ($n = 21$) were instructed to bisect 6 lines (20 cm) equally distributed on a horizontal sheet of paper with a vertical dash. The LBE was expressed in % of total line length deviated from the centre with negative signs for leftward deviation. Controls bisected the lines very accurately (LBE $= 0.1\% \pm 0.3$, mean $\pm$ SEM). Patients with left spatial hemineglect showed a significant ipsilesional rightward deviation compared to controls ($15.3\% \pm 2.9$). Left and right hemianopic patients (LH, RH) showed a small but significant ipsilesional deviation towards their intact hemifield when compared to controls (LH: $1.4 \pm 0.5\%$, RH: $-2.0 \pm 1.2\%$). The ipsilesional deviation in LH patients was significantly smaller than in left hemineglect patients.

In summary, the LBE found in acute hemineglect patients replicates the findings of a distinct ipsilesional deviation in chronic neglect patients. Surprisingly, acute hemianopic patients showed a similar ipsilesional (though smaller) LBE but no typical deviation towards the scotoma like hemianopic patients in a chronic stage. Taking into account the presence of an ipsilesional deviation in both hemianopic and hemineglect patients in their acute stage of stroke, at that early time the line bisection task may be a less reliable tool to distinguish both conditions. We conclude that (1) the common "hemianopic line bisection error" may be absent in acute hemianopic patients and (2) a small ipsilesional deviation in the line bisection task does not necessarily refer to spatial neglect but may be an early finding in acute homonymous hemianopia.

P570

An unusual case of cavernous sinus syndrome

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Intracranial plasmacytoma is an uncommon manifestation of myeloma frequently associated with extension of a lesion affecting the clivus or skull base. There are rare case reports of myeloma presenting as an intracranial plasmacytoma and as cavernous sinus syndrome(CSS). CSS has been reported to be caused by myeloma in 5% of cases. We present three cases of myeloma with neuro-ophthalmology.

A 48-year-old woman presented with intermittent horizontal diplopia, right-sided retro-orbital pain and right abducens nerve palsy. Serum protein electrophoresis showed elevated IgG and free kappa light chains and skeletal survey showed lytic lesions. CT brain showed enhancing soft tissue mass causing bony destruction of clivus

and adjacent petrous temporal bone, MRI showed extension into the cavernous sinus. Bone marrow aspirate showed 65% plasma cells. She was treated with chemotherapy, palliative radiotherapy and stem cell transplant with good response.

A 64-year-old woman with established IgA myeloma presented with horizontal diplopia and left abducens nerve palsy. Investigations showed an IgA-lambda monoclonal band. CT brain showed enhancing lesions in the left cavernous sinus, frontal lobe and posterior fossa. CT body showed lytic lesions in pelvis when biopsied confirmed myeloma. She recommenced treatment but the disease was rapidly fatal.

Another 64-year-old woman with established IgA myeloma, presented with left eyelid drooping, right oculomotor nerve and right trigeminal nerve palsies consistent with a right-sided CSS. CT brain was unremarkable as was MRI brain and CSF analysis. She was treated with chemotherapy but the disease was rapidly fatal.

Although myeloma is thought to be a rare cause of CSS, these three patients all had clinical evidence and two had imaging evidence of a lesion within the cavernous sinus. Although we were unable to demonstrate a lesion with imaging in the third patient, the clinical signs could not have been caused by a lesion anywhere else. Two had a rapidly progressive course despite treatment with bortezomib, an established treatment. These three cases highlight the hitherto perhaps under-recognised occurrence of CSS caused by intracranial myeloma deposits. In two of the three patients the presentation with CSS was the first sign of disease recurrence and was followed by a steady deterioration and death despite aggressive treatment.

P571

The clinical characteristics and treatment outcome of post-traumatic BPPV

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Objectives: Head trauma is the most common cause of secondary form of benign paroxysmal positional vertigo (BPPV). However characteristics of post-traumatic BPPV (t-BPPV) have not been well evaluated. Therefore we reviewed the clinical presentation, response to treatment and short-term and long-term outcomes of t-BPPV.

Methods: We reviewed the clinical records of 779 consecutive patients with BPPV between 1999 and 2008 from Eulji BPPV Registry. Patients with onset of positional vertigo within 14 days of trauma were included in the t-BPPV group. Clinical presentation, response to treatment and short-term and long-term outcomes of patients with t-BPPV were compared with those with idiopathic BPPV (i-BPPV) who were similarly treated and followed up.

Results: Forty eight 6.16%) of 779 patients were diagnosed as t-BPPV. The mean age of t-BPPV was lower than those of i-BPPV (52.0 vs. 55.8). Female sex and posterior canal involvement was more frequent in both t-BPPV and i-BPPV groups. Bilateral involvement was more frequent in t-BPPV (4.2 vs. 0.8%). The cure rate at 1 week was not different in two groups (91.7% vs 92.3%). The mean follow up periods of t-BPPV and i-BPPV was 23.2 and 28.3 months each. Although short-term recurrence rate of t-BPPV at 3 months was higher (10.4%) than i-BPPV (4.8%), overall recurrence rate of t-BPPV (7 out of 48 patients, 14.6%) was lower than i-BPPV (29.4%). There was no recurrence in t-BPPV group after 9 months.

Conclusion: The age is younger and bilateral involvement is more common in t-BPPV group. Although t-BPPV recur more frequently within 3 months, long-term outcome of t-BPPV seems to be favorable.

Multiple sclerosis

P572

In vitro radionsensitivity in patients with multiple sclerosis

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Background and objectives: Multiple sclerosis (MS) is a clinically heterogeneous demyelinating disease leading to severe neurological disability. Based on the results of numerous studies, MS is presumably not caused by or associated with the inheritance of significant chromosomal abnormalities. On the other hand, it is well known that chromosomal aberrations are present at higher frequencies in cells of people with MS than in healthy controls. Experimental data suggest that exposure to mutagenic environmental factors is related with higher risk of MS. However, the significance of genetic factors in determining the clinical features of MS remains unknown.

The purpose of our study was to compare the spontaneous micronucleus formation and the micronucleus formation after radiation exposure of peripheral blood lymphocytes of relapsing-remitting (RR) patients and healthy controls (HC).

Methods: We investigated 15 patients with definite RRMS and 15 HC, matched for sex and age. Two blood samples were taken from every subject (one was left unirradiated and the other was exposed in vitro to 1,5 Gy). Afterwards two different lymphocytes cultures were prepared (from irradiated and unirradiated blood). Both cell cultures were stimulated with phytohemagglutinin. The radiosensitivity was estimated by means of cytokinesis blocked micronucleus test.

Results: No significant difference in the spontaneous micronucleus formation was observed between MS patients and HC. After radiation exposure the mean micronucleus value was significantly decreased in MS patients.

Conclusion: Our results reveal that MS patients have better repair capacity than healthy controls. We believe that this increased radioresistance could be a consequence of an adaptive lymphocytes activation triggered by oxidative stress. Further research involving larger sample sizes are needed to elucidate this question.

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P573

Peroxiredoxin II: an antioxidant with therapeutic potential in multiple sclerosis?

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Objectives: Numerous cellular components including lipids, proteins and nucleotides are damaged as a result of liberated reactive oxygen/nitrogen species in neurological diseases. The peroxiredoxin (prdx) family includes thiol-based antioxidant enzymes about which relatively little is known in the human brain. Prdx II is a potent, fast acting peroxidase with high activity against hydrogen peroxide. Decreased levels of prdx II have been associated with decreased expression and activity of glutathione peroxidase, another important brain antioxidant. More-

over, modification of prdx II proteins and the subsequent impairment of antioxidant activity may actively participate in the pathogenesis of Parkinson's disease. The aim of this study was to examine expression of prdx II in the human brain in multiple sclerosis (MS).

Methods: We investigated prdx II levels in human control ($n = 4$) and MS cerebral deep white matter ($n = 4$) and lesions ($n = 12$) by immunohistochemistry.

Results: Prdx II levels were increased in MS white matter compared with control tissues. However, in acute, inflammatory lesions there was a striking loss of prdx II. In subacute lesions prdx II levels were restored and this was markedly stronger in chronic lesions where astrocytes are the predominant cells.

Conclusion: There are marked changes in prdx II expression in MS that might be significant to the development and persistence of lesions. Further work will identify the cell types expressing prdx II in MS and elucidate the functional consequences of changes in prdx II expression or redox activity and subsequent anti-oxidant activity.

P574

Diffusion tensor imaging and MR tractography study of acute and chronic demyelinating plaques in patients with multiple sclerosis

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Objectives: We propose quantitative approach for differentiation acute and chronic demyelinating plaques in patients with MS using Diffusion Tensor Imaging (DTI) and MR tractography methods.

Methods: Two groups of patients were studied by conventional MRI and DTI on 1.5T SIGNA EXCITE (GE). The first group (PG) includes 43 patients (36–55 years) with relapsing-remising MS, and the second group (CG) includes 20 healthy subjects. Axial DTI of the brain using a single shot, multi slice spin-echo echo planar diffusion tensor pulse sequence with following parameters: TR/TE = 10000/83.6 ms were obtained. Using conventional MR images recorded before and after contrast injection (7.5 ml Gadovist 1,0 Mmol/ml, Bayer-Schering Pharma) the acute and chronic plaques were defined. The DT images were post processed and regions of interest (ROIs) were placed in acute and in chronic plaques. In addition, in the PG the ROIs were placed in the plaques and in the intact tissue of the ipsilateral hemisphere, and symmetrically, in the contralateral side of the brain on the plaque's level, and on the level of the intact tissue localization in the affected hemisphere. For comparison, in the CG ROIs positions were the same, as in the PG.

Results: From DT MR images the values of average fractional anisotropy (FA), and ADC coefficients were calculated. There were no significant differences between the ADC and FA values in the acute and chronic plaques ($p = 0.8053$ and $p = 0.2410$, respectively) or between the values in the intact brain tissue of both types of plaque ($p = 0.6973$, and $p = 0.1812$). The FA values in both acute and chronic plaques were significantly lower than the values in the intact tissue in the ipsilateral, and in the contralateral hemisphere, and in comparison with values, obtained for subjects of the CG. Also, the ADC values were significantly higher in the acute and chronic plaques compared to all regions of the intact tissue. The DTI was not able to detect differences between ADC and FA values in the acute and chronic demyelinating plaques in patients with MS.

Conclusion: Although the pathological findings in the demyelinating plaques are diverse, the comparison FA with ADC values in the acute and in the chronic plaques (black holes) provides us very useful diagnostic information for differentiation the type of MS. DTI characterizes both of MS-plaques as lesions, presenting higher ADC and lower FA values in comparison with intact brain tissue.

P575

Neuromyelitis optica complicating treatment of systemic lymphoma with rituximab

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Rituximab has recently shown promise as a treatment for neuromyelitis optica (NMO) or Devic's disease and is now the subject of clinical trials. We present the case of a 32 year old male who having previously been in good health was treated with Rituximab for B-cell non-Hodgkin's lymphoma and subsequently developed an aggressive form of NMO. The patient had received two cycles of chemotherapy both of which included Rituximab. He presented soon after remission of his lymphoma with a myelopathy and an area of longitudinal extensive transverse myelitis (LETM) was found in the cervical spine on magnetic resonance imaging (MRI). Extensive investigations, including NMO antibody testing, were negative. Following high dose steroids there was continued clinical progression and he was treated with radiotherapy for a presumed central nervous system (CNS) relapse of lymphoma. There was improvement in the LETM on MRI but continued clinical deterioration with the development of a profound bilateral optic neuritis (ON) producing blindness. Following the development of the ON the patient fulfilled the current diagnostic criteria for NMO despite the negative NMO antibody test, as there was an acute myelitis, an area of LETM on MRI and cerebral MRIs were repeatedly normal. A further course of high dose steroids followed by plasma exchange produced resolution in the cervical LETM on MRI but this was not associated with any clinical improvement. Despite reports of beneficial responses in NMO with Rituximab in this case there was concern treatment of the original lymphoma with Rituximab may have precipitated the episode of NMO. It is hypothesised that the immunomodulatory effects of Rituximab may have produced a clonal shift in B-cell antibody response resulting in NMO. This apparent potential of Rituximab to induce autoimmune CNS disease is of concern given the increasing use of Rituximab in a variety of disorders particularly haematological and rheumatological. Additionally if Rituximab is used increasingly in autoimmune CNS disorders then surveillance for such disease switching will be required.

P576

Decreased melatonin levels in multiple sclerosis relapse: comparison with clinical and cognitive scores

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Background: The role of melatonin in the course of multiple sclerosis (MS) could not be figured out to date.

Objective: Comparison of urine 6-sulphatoxymelatonin levels (aMT6 s; the major metabolite of melatonin), between MS patients and controls at time of hospitalization, and examining any possible correlation with clinical and cognitive scores.

Methods: Twenty eight clinically definite relapsing-remitting MS patients admitted with diagnosis of acute relapse were engaged in the study and beside clinical data, disability level using MS Functional Composite (MSFC), modified fatigue impact scale (MFIS), and expanded disability severity Score (EDSS) were recorded. Overnight aMT6 s levels were measured in urine. Control urines were collected from hospitalized patients with acute surgical problems.

Results: aMT6 s levels were significantly lower in MS group compared to controls; and significantly correlated with MSFC score,

but not EDSS. MFIS scores were shown to significantly correlate with MSFC scores.

Conclusion: Our results revealed that melatonin levels decrease in relapse phase MS patients, which correlates with disease severity in terms of MSFC score. The current data could suggest a role for possible dysregulation of melatonin production in the pathogenesis of MS. The possible significance of aMT6 s measurement for objective quantification of disease severity still to be further studied.

P577

Disruption of the default mode network in patients with primary progressive and secondary progressive multiple sclerosis

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Objective: The default mode network (DMN) is a set of brain regions, mainly located in the cingulum, frontal and parietal lobes, demonstrated to be consistently deactivate during active tasks and active in rest. A few studies suggested a disruption of part of the component of this network with aging and a more pronounced susceptibility to such a phenomenon in degenerative conditions. Aim of this study is to explore alterations inside the DMN in patients with primary progressive (PP) and secondary progressive (SP) multiple sclerosis (MS) and their correlation with disability.

Methods: Resting state (RS) functional MRI data were acquired from 33 SPMS patients, 23 PPMS patients and 25 matched controls. SPMS and PPMS patients were matched for age, sex, disease duration and disability. Independent component analysis (ICA) was used to decompose RS fMRI data into spatially independent maps and time courses using the GIFT software. This analysis produced 40 spatially independent maps, from which the DMN was identified. SPM2 was used to assess within- and between-groups activations (one-sample t test and ANOVA). Then, the average percentage signal change of DMN fluctuations inside each significant SPM cluster was compared between controls and patients.

Results: The DMN was clearly identified in the three groups of subjects studied. Compared to controls, both PPMS patients and SPMS patients had a significant decrease of fluctuations in the anterior portion of the cingulate cortex. In addition, SPMS patients also showed a decrease of fluctuations in the left inferior frontal gyrus. Abnormalities in the cingulate cortex were more pronounced in SPMS than in PPMS patients.

Conclusions: Disruption of the anterior components of the DMN might be among the factors responsible for the unfavourable clinical evolution of patients with progressive MS.

P578

Preservation of brain adaptive properties contributes to the clinical picture of benign multiple sclerosis

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Objective: The exhaustion of the brain adaptive properties over time has been postulated to be one of the mechanisms responsible for the accumulation of irreversible disability in patients with the progressive phenotypes of multiple sclerosis (MS). It is tempting to speculate that the long-term preservation of these properties might contribute to explain the more favorable clinical evolution of benign (B) MS. In this study, we investigated changes of activation of the motor network in patients with benign (B) multiple sclerosis (MS) in comparison with those with secondary progressive (SP) MS and healthy controls.

Methods: Using a 3T scanner, functional magnetic resonance imaging (fMRI) during the performance of a simple motor task was acquired from 17 BMS, 15 SPMS and 10 healthy volunteers (HV). BMS and SPMS patients were matched for age, sex, and disease duration. Analysis of activations was performed using SPM2 software. An Ancova model was used ($p < 0.05$, corrected for multiple comparison).

Results: Compared to HV, BMS patients had more significant activations of the left primary sensorimotor cortex (SMC), while SPMS patients had more significant activations of the left primary SMC, the left secondary sensorimotor cortex, the left infraparietal sulcus and the left inferior frontal gyrus (IFG), and several visual areas. Compared to HV and to BMS patients, SPMS patients had reduced activations of the left supplementary motor area and basal ganglia, and the right cerebellum. Finally, compared to BMS, SPMS patients had more significant activations of several areas in the frontal lobes, bilaterally and several visual areas.

Conclusions: The preservation of the mechanisms responsible for the overactivation of a given network might have a central role to explain the favorable clinical course of BMS.

P579

Cortical grey matter is spared in paediatric MS: a magnetisation transfer and diffusion tensor MRI study

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Objective: Contrary to what happens in adult-onset multiple sclerosis (MS), previous preliminary quantitative magnetic resonance imaging (MRI) studies showed only subtle changes in the normal-appearing brain tissues in patients with early-onset MS. Aim of this study was to evaluate the presence and extent of tissue damage in the brain normal appearing white matter (NAWM), gray matter (GM) and cervical cord from a large population of pediatric MS patients.

Methods: From 49 pediatric patients with relapsing-remitting MS and 15 sex- and age-matched healthy controls, brain dual-echo, brain pulsed gradient spin echo (PGSE) echo planar and brain and cervical cord 2D gradient echo with and without a saturation pulse sequences were acquired. Brain lesion volume (LV) was measured and cervical cord lesions were identified. Magnetization transfer ratio (MTR), mean diffusivity (MD) and fractional anisotropy (FA) maps were produced and the corresponding histograms of the NAWM and GM were derived. MTR histogram was also derived from cervical cord.

Results: In pediatric MS patients, mean brain T2 LV was 10.5 ml (range = 0.02–61.4 ml), average lesion MTR was 37.6% (SD = 2.6%), average lesion MD was 1.03 $mm^2/s \times 10\text{-}3$ (SD = 0.08), average lesion FA was 0.26 (SD = 0.02), and average number of cervical cord lesion was 1.2 (range = 0–7). Compared to healthy controls, pediatric MS patients had significantly increased average NAWM MD ($p = 0.02$) and decreased average NAWM FA ($p < 0.0001$). No diffusivity changes were found in the brain GM. No MTR changes were detected in the cervical cord. Age of disease onset was significantly correlated with average NAWM FA ($r = 0.54$, $p < 0.001$) and NAWM MD ($r = -0.45$, $p = 0.002$). Brain LV was significantly correlated with average NAWM FA ($r = -0.49$, $p = 0.001$).

Conclusions: This study confirms the paucity of the 'occult' CNS damage in pediatric MS patients. In these patients cortical GM is spared by the disease process, while NAWM changes are likely to be, at least partially, secondary to Wallerian degeneration of fibers passing through macroscopic lesions.

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P580

Deep grey matter T2 hypointensity in patients with paediatric multiple sclerosis

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Objective: To determine the presence of deep gray matter (GM) T2 hypointensity in patients with pediatric MS compared to healthy controls (HC) and their changes over a one year follow-up period.

Methods: Using a 1.5 Tesla scanner, a dual echo sequence was obtained from 46 pediatric MS patients (17 with clinically isolated syndromes suggestive [CIS] of MS and 29 with relapsing remitting MS, mean age = 14.7 years, range = 7–18; M/F = 19/27; median EDSS score = 1.0, range = 0–6.5) and 14 age-matched HC (mean age = 14.2, range = 10–20 years; M/F = 7/7). Eleven pediatric MS patients were reassessed clinically and with MRI imaging after one year. Normalized T2-intensity in the basal ganglia and thalamus was analyzed on each scan. Group comparisons were performed using regression models controlled for age and gender.

Results: At baseline, deep GM T2 intensity was similar between pediatric MS patients and HC in all the structures analyzed, except for left caudate nucleus ($p = 0.001$). At baseline, deep GM T2 intensity was similar between CIS and RR pediatric MS. After 1 year, T2 intensity in deep GM of pediatric MS remained stable.

Conclusions: In pediatric MS patients, deep GM is not completely spared from iron related changes. The relative preservation of these regions might be among the factors responsible for the more favourable clinical evolution, at least at short-medium term, of these patients.

P581

Deep grey matter T2 hypointensity in patients with clinically isolated syndromes suggestive of multiple sclerosis

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Objective: Gray matter (GM) magnetic resonance imaging (MRI) T2 hypointensity, a putative marker of iron deposition, is a frequent finding in patients with multiple sclerosis (MS). Aim of this study was to asses how early deep GM T2 hypointensity develops in MS, by studying patients with clinically isolated syndromes (CIS) suggestive of MS.

Methods: Forty-seven CIS patients (35 women and 12 men, mean [SD] age = 30.8 [6.9]years; median EDSS score [range] = 1 [0–4.5]) and 13 healthy control (HC) (9 women and 4 men; mean age [SD] = 32.54 [11.3] years), matched for age, were analysed for normalized T2-intensity in the basal ganglia and thalamus. Patients were assessed clinically at the time of MRI acquisition and after a median period of three years later.

Results: During the observation period, 38% of patients (n = 18) converted to definite MS. At baseline, only GM T2 intensity in the head of the left caudate nucleus was significantly reduced in CIS patients in comparison with HC ($p = 0.04$). At baseline, T2 intensity in the head of the left caudate nucleus was significantly lower in CIS patients with disease dissemination in space (DIS) ($p = 0.005$) than in CIS patients without DIS. Finally, baseline T2 intensity in the head of the left caudate nucleus was lower in patients that converted to clinically definite MS after three years ($p = 0.05$) than in patients that still remained CIS.

Conclusions: In CIS patients, deep GM is not spared from putative iron related changes, suggesting that neurodegeneration occurs early. Furthermore, GM iron deposition may represent a marker or mediator of an accelerating disease course.

P582

Contactin-2/Tag-1 directed autoimmunity is identified in multiple sclerosis patients and mediates grey matter pathology in animals

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Gray matter pathology is increasingly recognized as an important feature of multiple sclerosis (MS), but the nature of the immune response that targets the gray matter is poorly understood. Starting with a proteomics approach, we identified contactin-2/TAG-1 as a candidate autoantigen recognized by both autoantibodies and Th1/Th17 T cells in MS patients. Contactin-2 and its rat homologue TAG-1 (transiently-expressed axonal glycoprotein 1) are expressed by various neuronal populations and sequestered in the juxtaparanodal domain of myelinated axons both at the axonal and myelin side. The pathogenic significance of these autoimmune responses was then explored in experimental autoimmune encephalitis (EAE) models in the rat. Adoptive transfer of TAG-1 specific T-cells induced an encephalitis characterized by a preferential inflammation of gray matter of the spinal cord and cortex. Co-transfer of TAG-1 specific T cells with a myelin oligodendrocyte glycoprotein (MOG)-specific mAb generated focal perivascular demyelinating lesions in the cortex and extensive demyelination in spinal cord gray and white matter. This study identifies contactin-2 as a novel autoantigen targeted by T cells and autoantibodies in MS. Our findings suggest that a contactin-2 specific T cell response contributes to the development of gray matter pathology.

P583

Tactile-associated recruitment of cervical cord is altered in MS patients with fatigue

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Objectives: In multiple sclerosis (MS), fatigue is a rather common and troublesome symptom, which can notably compromise daily-life activities and be associated with impaired quality of life of these

patients. To investigate the pattern of tactile-associated cervical cord activations in relapsing-remitting (RR) MS patients with and without fatigue.

Methods: Cervical cord functional MRI (fMRI) was acquired from 20 healthy controls, 31 RRMS patients without fatigue (wf-RRMS), and 20 RRMS patients with fatigue (f-RRMS). Subjects were scanned when performing a sensory task, consisting of a tactile stimulation of the palm of the right (R) hand. Using a General Linear Model, statistical maps were generated for all subjects ($p = 0.05$). The presence of activity in the R and left (L), anterior and posterior cervical cord at different levels was assessed. The mean intensity signal change was computed for all activated voxels.

Results: Average cervical cord mean intensity change was 2.8% (standard deviation [SD] = 0.8) in controls, 3.22% (SD = 1.1) in wf-RRMS, and 2.93% (SD = 0.6) in f-RRMS ($p = 0.02$). Wf-RRMS had higher cord activity than controls ($p = 0.02$). Regional analysis showed that: a) controls had higher activity in the R than L cervical cord ($p = 0.004$) and in the posterior than anterior cord ($p = 0.022$), b) wf-RRMS had higher activity frequency in the posterior than anterior cord ($p = 0.005$), but not in L vs R, and c) in f-RRMS, no significant difference was found neither between R and L nor between anterior and posterior cord. Chi-square test showed higher occurrence of activity in wf-RRMS in L anterior C6 ($p = 0.004$) and R posterior C6/C7 ($p = 0.01$) than controls, while f-RRMS had higher occurrence of cord activity in R anterior C7/C8 ($p = 0.05$) and in L anterior C5/C6 ($p = 0.014$) than wf-RRMS.

Conclusions: An abnormal pattern of tactile-associated cervical cord activations occurs in RRMS patients. Fatigue is associated with reduction of cervical cord recruitment and loss of its lateralization.

P584

Decreased peripheral blood mononuclear cell neurotrophic factor expression in optic neuritis

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Objectives: Acute monosymptomatic Optic Neuritis (ON) is a common first manifestation of Multiple Sclerosis (MS). The pathogenesis of ON is similar to the pathogenesis of MS and involves a myelin antigen T-cell mediated autoimmune response, where inflammatory mechanisms contribute to axonal pathology as well as to demyelination. There is evidence that autoimmune cells in MS have neuroprotective properties mediated by the release of neuroprotective factors such as BDNF, NGF and GDNF. Recent studies have demonstrated higher levels of BDNF expression during relapse and in the recovery phase compared with values detected in the stable phase of the disease. The aim of the study was to investigate the BDNF and GDNF mRNA expression in peripheral blood from patients exhibiting a first episode of ON.

Materials and methods: In this study we included a group of untreated patients with acute ON ($n = 19$). The blood sample was collected within 4 weeks from the symptom onset. Neurological examination, Visual tests, VEP and MRI of the cerebrum were performed within a week from the referral to our clinic. We investigated the expression of BDNF and GDNF with Real time PCR in ON group and compared with a group of HC ($n = 19$) matched in age and sex. t-student parametric test was used to evaluate the statistical significance.

Results: Both neurotrophic factor gene expression was significantly reduced in ON patients compared to controls (1.77 fold; $p = 0.0069$ and 3.26 fold; $p = 0.0052$), for BDNF and GDNF, respectively.

Conclusion: Despite the finding that BDNF and GDNF expression from inflammatory cells is increased during MS relapses, our findings indicate that this may not be the case if first relapse is considered. Alternatively, the underlying immunopathology in ON may be different from that of established MS. Whatever the case might be, the absence of a neuroprotective potential of immune cells under these circumstances needs to be clarified.

P585

Susac's syndrome: clinical and therapeutical challenge

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Introduction: Susac's syndrome (SS) is a rare condition characterized by acute or subacute appearance of encephalopathy, visual and auditory defects. Microangiopathic changes in subcortical white matter, inner ear and retina are the pathological hallmarks of the disease. The clinical course is exacerbating-remitting with a tendency to stabilize over a period of years. Autoimmune aggression to endothelium is a possible pathogenetic mechanism. About 100 cases have been described and the therapeutic approach is poorly standardized.

Case report: A 34-year-old woman presented with a 7-day history of weakness, headache, confusion, nausea, paresthesias, and nonspecific visual disturbances. Brain MRI revealed multiple T2-hyperintensities in the subcortical white matter, corpus callosum, basal ganglia and thalami. Neuropsychological examination demonstrated mild dyscalculia and attentional deficits. CSF examination revealed moderately high protein and lymphocytic pleocytosis with normal glucose. Retinal fluoroangiography showed bilateral peripheral branch artery occlusions. Audiometric evaluation revealed low-frequency sensorineural hearing loss in the left ear. The triad of brain, retinal and cochlear involvement with microangiopathic signs was consistent with the diagnosis of SS. The patient underwent a 5-day course of IV methylprednisolone (IVMP) followed by IV immunoglobulins (IVIg) and tapering oral prednisone, with near-complete recovery. Aspirin and nimodipine were prescribed concurrently. 25 days later the patient presented an acute relapse with predominant consciousness disturbance. IVMP was repeated and followed by cyclophosphamide and IVIg, which are currently administered in a pulsed fashion. At 24 weeks from onset the patient has a normal neurological examination with persistence of stabilized bilateral visual field defects and bilateral hearing impairment. No other relapses were presented.

Conclusion: An aggressive therapeutic approach combining monthly pulses of cyclophosphamide, IVMP and IVIg seems to be effective in stabilizing the multiorgan involvement in SS. Although the long-term prognosis of SS is considered to be favourable, the risk of permanent neurological, visual and hearing damage warrants for vigorous treatment regimen at least in the first stages of disease.

Muscle disorders

P586

Sporadic late-onset nemaline myopathy in a patient with primary Sjögren's syndrome

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Objectives: Nemaline myopathy is a rare disorder defined by the presence of inclusions known as nemaline bodies or rods in muscle fibers. Adult forms are known as sporadic late-onset nemaline myopathies (SLONM). Some cases associated with monoclonal gammopathy or HIV infection are demonstrated, thus immunological disorders may be considered a role of the pathogenesis of SLONM. We experienced a patient with SLONM and Sjögren's syndrome (SS).

Methods: We present a case of SLONM previously diagnosed with primary SS and review the literature.

Results: A 58-year-old woman presented with progressive neck and proximal weakness of 2 years' duration. She also had dry eyes and dry mouth. Electromyography (EMG) showed myopathic motor unit potentials with fibrillation potentials and positive sharp waves (PSW) in the upper and lower limbs. Nerve conduction study was normal. The serum CK level was normal at 55 IU/l. Levels of IgG were mildly elevated (1701 mg/dl), but monoclonal gammopathy was absent. Anti SS-A/Ro antibody was elevated at 295 U/ml. A salivary gland biopsy revealed focal lymphocytic sialoadenitis with a focus score $\geq$1. Other collagen diseases were not evident. Thus, primary SS was diagnosed. A biopsy of the left quadriceps muscle was stained with hematoxylin and eosin, which revealed moderate variations in fiber size and no inflammatory cell infiltrate was present. Gomori trichrome staining revealed numerous rods in half of the muscle fibers. Fiber type proportions were normal and a few type 2C fibers were present. Many lobulated fibers present in the NADH-TR were often type 1 fibers. Electron microscopy revealed irregular accumulation of rods of which some appeared to originate from the Z discs. The patient was treated with predonisone, which improved the neck muscle weakness. Fibrillation potentials and PSW disappeared in EMG. However, residual weakness persisted in the proximal leg muscles.

Discussion: Many cases of SLONM associated immunological disorders such as HIV infection, monoclonal gammopathy, hypothyroidism, or dermatomyositis are reported, and some authors postulate a role of the immune system in the pathogenesis of this disorder. Our patient developed muscle weakness and sicca syndrome simultaneously, and presented clinical improvement with corticotherapy. [Conclusion] We consider that primary SS may play a role for causing nemaline changes in muscles. This is the first report of SLONM in a patient with primary SS.

P587

MELAS: clinical features, muscle biopsy and molecular genetics

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Objectives: MELAS is one of occurring mitochondrial diseases and is characterized by mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes. The aim of the study was to analyze a series of Brazilian patients suffering from MELAS.

Methods: Ten patients with MELAS were studied with correlation between clinical findings, laboratorial data, electrophysiology, histochemical and molecular features.

Results: The onset was before age 15 in 6 patients. Stroke-like episodes were present in all patients; other symptoms reported included vomiting, headache, seizures, weakness, dementia, hearing loss, short stature, ocular symptoms, ataxia and facial neuropathy. Blood lactate was increased in eight patients. Brain image studies revealed a stroke-like pattern in all patients, with unilateral lesions in six patients and bilateral lesions in four patients. Muscle biopsy showed ragged red fibers (RRF) in 90% of patients on modified Gomori-trichrome (MGT) and in 100% on succinate dehydrogenase (SDH) stains. Cytochrome c oxidase stain analysis indicated deficient activity in one patient and subsarcolemmal accumulation in seven patients. Strongly succinate dehydrogenase-reactive blood vessels (SSV) occurred in six patients. The molecular analysis of tRNALeu(UUR) gene by PCR/RLFP and direct sequencing showed the A3243G mutation on mtDNA in 4 patients.

Conclusions: The muscle biopsy often confirmed the MELAS diagnosis by presence of RRF on MGT and SDH stains, and by SSV in muscle biopsy specimens. Molecular analysis of tRNA-Leu(UUR) gene should not be the only diagnostic criteria for MELAS. Current concepts of clinical and laboratorial manifestation, brain images, histological features and molecular analysis were reviewed.

P588

A family of suspected Welander distal myopathy in Korea

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Background and objectives: Welander distal myopathy(WDM) is a late adult onset autosomal dominantly inherited disease, which is characterized by slowly progressive distal dominant weakness typically started in finger and wrist extensor. As the disease progress, symptoms spread to toe and ankle extensor, and proximal extremities, but the disease have relatively benign course with normal life expectancy. WDM was mainly reported in Sweden. However there was only one small family suspecting WDM in Korea. We report a family with eight patients with WDM.

Cases: Eight patients in a family suffered from muscle weakness and atrophy of hands. Pedigree shows autosomal dominant inheritance. The symptoms began in second or third decades and progressed slowly. Subjects with mild symptoms have finger extensor and wrist extensor weakness, where as more severe subjects have symptoms affecting distal hands muscles dominantly but motor weakness also involved feet and proximal limbs. All cases have normal intelligence and normal life span. Laboratory studies revealed slightly increased serum creatine kinase.(571 IU/L in severe one). Nerve conduction studies show generalized, moderate to severe decrement of compound motor action potentials amplitudes but normal conduction velocities. Electromyography studies show myopathic patterns.Muscle biopsy of extensor carpi muscles in 2 patients revealed degenerating fibers, variation of fiber size, and rimmed vacuoles on light microscope(LM), and intracytoplasmic and intranuclear filamentous inclusion on electron microscope(EM).

Conclusion: According to our and previous reported cases, we think that WDM is present in Korea.

P589

Atypical MELAS associated with the G12315A mutation in mitochondrial DNA: case report

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Introduction: Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) is typically presented in childhood. In 80% of those patients, the A3243G mutation in the transfer RNA (tRNA) of leucine (UUR) in mitochondrial DNA has been found. Herein, we report an atypical case of late-onset MELAS with unusual clinical features, including cerebellar ataxia and dementia. Genetic analysis demonstrated the G12315A mutation in the tRNA gene of leucine (CUN).

Case report: A 68-year-old woman was admitted to our hospital for evaluation of gait disturbance. The patient had been healthy until the age of 63, when bilateral hearing loss was noticed. After retirement at the age of 65, she became reclusive, then defective judgment and diabetes mellitus (DM) were pointed out at the age of 67. At 68 years old, the patient became apathetic and, untidy, and developed an unsteady gait. There was no particular past or family history of DM or neurological disorders. Neurological examination showed bilateral sensorineural deafness, truncal ataxia, limb ataxia, ataxic speech, and gait disturbance. Muscle strength in all extremities, ocular movements, and fundoscopy findings were normal. The score of Mini-mental state examination was 22/30, indicating dementia. Lactate was significantly elevated in both serum and cerebrospinal fluid. Brain CT findings showed moderate cerebral and cerebellar atrophy, with calcification in the bilateral pallidum and dentate gyrus on the cerebellum. There were no particular ischemic changes. Skeletal muscle pathology revealed ragged-red fibers. The late onset and clinical features were atypical for MELAS. Skeletal muscle total mitochondrial DNA analysis identified a heteroplasmic G to A point mutation in the tRNA gene of leucine (CUN) at position 12315. Only two reports have described the G12315A mutation in patients with chronic progressive external ophthalmoplegia (CPEO) with ragged-red fibers, with no such report in a MELAS patient.

Conclusion: This is the first report of a MELAS patient with the G12315A mutation. We concluded that the mutation is likely pathogenic, and may be responsible for MELAS as well as CPEO.

P590

Novel LMNA gene mutation in a patient with cardiac and skeletal muscle involvement

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Lamins A and C are type V intermediate filament proteins, which are components of the nuclear envelope. Lamins A and C are transcribed from a single gene, LMNA, which is encoded on chromosome 1q21.2–q21.3. 29. LMNA mutations are associated with several diseases, including Emery-Dreifuss muscular dystrophy (EDMD), limb-girdle muscular dystrophy type 1B (LGMD1B), dilated cardiomyopathies (DCM) with conduction disease (CMD1A), Charcot-Marie-Tooth type 2, Hutchinson-Gilford progeria syndrome, familial partial lipodystrophy, restrictive dermopathy and mandibuloacral dysplasia, along with various overlapping phenotypes and rare variants.

Objectives: We describe the case of a 58 years-old woman displaying dilated cardiomyopathy and skeletal muscle involvement, probably inherited as a dominant trait.

Methods: The subject underwent muscle biopsy and genetic analysis of LMNA gene (performed by PCR amplification and analysis with Denaturing High Pressure Liquid Chromatography), leading to identification of a novel, heterozygous frameshift duplication in position c.1102_1130 of exon 6, promoting the formation of a premature stop codon in the putative protein. The genetic analysis was, therefore, extended to the patient's son, which exhibited, since the age of 26, cardiac conduction disturbances, without skeletal muscle involvement. The same mutation was demonstrated.

Results: To our knowledge, this is the first report of a duplication in the LMNA gene. These data confirm previous observations describing a predominance of frameshift mutations in patients with adult-onset cardiac disease. In addition, variants in these patients were mostly located in coil 2B, as in our case. Since it has been previously shown that lamin hetero and homodimers can form via coil 2 interactions, we had hypothesized that mutations involving residues in this domain may affect dimer formation or higher levels of lamin assembly and that late onset phenotypes may arise through a loss of function mechanism secondary to haploinsufficiency.

Conclusion: Our observation further expands the type of LMNA mutations described in laminopathy patients, since a DNA duplication had not been identified before.

P591

A life-threatening case of β-enolase deficiency

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Objective: To describe clinical, biochemical and molecular data of a new patient with a metabolic myopathy due to muscle β-enolase deficiency.

Background: Muscle β-enolase deficiency is the last described defect of distal glycolysis. In 2001, Comi et al. firstly reported a benign case of a patient characterised by exercise intolerance, myalgias after physical exertion with no pigmenturia. His β-enolase enzyme residual activity was about 5% and he harboured a double heterozygous mutations in ENO3 gene.

Case report: We describe herein a 44-year-old man, born from consanguineous parents, who complained since his twenties, of several episodes characterised by intense myalgias, cramps, generalized muscle tenderness and marked presence of dark urines mainly mainly after intense muscle efforts. At age 42, he developed an acute renal insufficiency with anuria, muscle aches and generalized muscle weakness after a strong physical exercise. Because of a massive rhabdomyolisis (serum CK was 214,000 UI/l) and myoglobinuria he necessitated urgently many dialysis circles followed by a quite sudden restoration of renal function. After few weeks, ha had another episode of intense myalgias and referred to our Center: neurological examination was normal, EMG studies revealed a myopathic pattern. Vastus lateralis muscle biopsy showed increased myofiber size variability with several centralized nuclei with no lipid or glycogen accumulation.

Results: Biochemical studies evidenced normal activities of CPT II, AMP and glycolytic enzymes except for β-enolase that showed about 20% of residual activity (0.15 nmol/min/mg protein- n.v. 0.66 ± 0.1). Molecular genetic analysis of ENO3 gene revealed a missense homozygous mutation: a A452G transition in exon 7, changing an asparagine residue to serine at position 151 (N151S). The mutation affects a very conserved amino acid residue and is located in close proximity to the β-enolase catalytic site.

Conclusion: This case suggests a clinical heterogeneity of the β-enolase deficiency. In fact, the first case was definitely benign and sustained by a very low residual activity whereas the present case showed a higher enzyme activity but very life-threatening episodes from the clinical point of view. We can hypothesize that in patients with same biochemical deficiency, additional genetic or environmental factors may play a role in determining so different.

P592

Limb-girdle congenital myasthenic syndrome with tubular aggregates – Phenotypic clues for the entity

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Congenital myasthenic syndromes (CMS) are a clinically and genetically heterogeneous group of inherited muscle disorders caused by genetic defects that affect transmission at the neuromuscular junction (NMJ). The phenotype is of fatiguing weakness presenting usually from birth but later onset is also possible. Respiratory and bulbar weakness crises could be life threatening. Cases with no family history of the disorder could resemble myasthenia gravis and myopathic disorders. Lack of anti-AChR antibodies and no effect from immunosuppressive treatment could help in distinguishing CMS from myasthenia gravis. CMS may be classified according to the localization of the affected protein at the NMJ. To date recessive and less frequently dominant mutations in ten genes were identified as responsible for CMS. In the large Munich cohort of over 700 CMS families from all over the world about 50% have been genetically diagnosed in regard to the known genes. According to the genetic defect and protein involved some of the CMS could be successfully treated with specific and available pharmacological agents.

Limb-girdle myasthenia (LGM) is a known entity in the literature and recently DOK7 mutations have been identified as causing the disorder in some of the patients. Of the remaining, at least nine families have been published with LGM phenotype and characteristic tubular aggregates on muscle biopsy. We have characterized seven families with LGM in our cohort with known genes excluded by direct sequencing or linkage analysis. All of them show autosomal recessive inheritance pattern. The onset of the disease is between 2 and 12 years of age. All patients show proximal limb-girdle weakness and no ptosis, ophthalmoparesis, facial, bulbar or respiratory weakness. Creatin kinase levels are normal or slightly elevated. There is a clear decrement upon repetitive nerve stimulation. Muscle biopsies disclose tubular aggregates arising from the sarcoplasmic reticulum. The patients usually respond well to cholinesterase inhibitors. Genome wide scan will be performed in these families in order to identify the underlying genetic defect.

Optimal treatment, genetic counselling and elucidation of the pathomechanisms at the NMJ in CMS rely on the identification of novel genes involved in the disorder. Some of the approaches for this include candidate gene sequencing and linkage analysis. Referral of additional cases could promote further elucidating the precise entity.

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P593

Efficacy of repeated doses of intravenous immunoglobulin in patients with refractory myasthenia gravis

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Objectives: The efficasy of intravenous immunoglobulin therapy (IVIG) in the treatment of myasthenia gravis (MG) has been demonstrated by meny authors. Some of them recommended IVIG for execerbation of MG, while others for chronic forms of the disease.

Methods: We report the results of IVIG treatment in 75 patients with severe generalized MG (III b, IV a, and IV b according to MGFA classification) who were unresponsive to conventional therapy (anticholinesteras drugs, thymectomy and immunosuppressive drugs).

Results: All of the patients received a total dose og 2 g/kg during 5 consecutive days. This treatment was followed by single IVIG dose every 4–6 weeks. Each patient received additional immunosuppressive therapy which was stable during the first month of IVIG treatment. As a measure of treatment efficacy we have used changes in patients' functional status (expressed by mean disability score according to Besinger) and reduction of additional anticholinesterase and immunosupressive therapy. Early response to treatment (significant improvement within a 5–10 days of treatment), was registered in only 32 out of 75 (43%) patients. However, in most patients (69 out of 75; 92%) delayed improvement was noticed, and maintained up to six months. During the whole study period IVIG therapy allowed to reduce immunosuppressive drug dose in the majority of our patients. However, the combination of this therapy (corticosteroids and/or azatioprin or cyclosporine) and repeated doses of IVIG may account for the long duration of improvement. Mean disability score decreased from 12.3 to 5.7 at the end of the follow-up (6 months) period. None of the patients expressed any serious side effects.

Conclusion: Our data indicate that IVIG is a useful and well tolerated treatment, and we recommend it especially for patients with severe, refractory MG.

P594

IgD multiple myeloma paraproteinemia as a cause of myositis

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Objectives: A 48-years-old man was diagnosed a IgD-k multiple myeloma (MM) at age 38 years for which he successfully underwent chemotherapy and bone marrow transplant. He then developed a graft versus host disease (GVHD) whose manifestations included, three years later, a polymyositis, diagnosed at muscle biopsy and successfully treated with steroids. Few months after polymyositis remission, myeloma relapsed and the patient was treated with thalidomide for six years with good remission.

Soon after thalidomide suspension, MM relapsed again (serum IgD peak) and the patient came to our observation for a new onset of neuromuscular symptoms (distal lower limb hypopallaesthesia, proximal upper/lower limb hypotrophy, lower limb girdle hyposthenia, CK 485 U/L). He underwent both muscle and peripheral nerve biopsy to discriminate between myositis (paraproteinemia vs GVHD), amyloidosis and thalidomide toxicity.

Methods: Conventional histological/histochemical studies along with immunohistochemistry for HLA, MAC and IgD, were performed on skeletal muscle and peripheral nerve cryostat sections. CD8, CD4, CD19 and CD68 immunohistochemistry was performed on skeletal muscle only.

Results: The first muscle biopsy showed an inflammatory pattern with necrotic fibers, macrophagical invasion (CD68 positive), rare interstitial cellular infiltrates, widespread antiHLA positivity and negative antiMAC. Both the second muscle and the peripheral nerve biopsies confirmed the previously observed inflammatory aspects and showed an involvement of blood vessels (several perivascular cellular infiltrates in muscle, numerous dilated endoneurial capillaries, mild antiMAC positivity). Direct immunofluorescence for IgD showed diffuse positivity along the sarcolemma. Congo Red was negative in both biopsies.

Conclusions: IgD MM is a rare form of myeloma frequently associated with amyloidosis. Myositis is often described as expression of chronic GVHD, but not as a direct complication of MM. Second muscle biopsy revealed an inflammatory pattern with large amount of monoclonal proteins along the sarcolemma. Vessel inflammatory signs were also evident in peripheral nerve. This is the first case of concurrent polyneuropathy and myositis in IgD MM. We hypothesize that the neuro-myositis is caused by sarcolemmal deposits of IgD. The presence of these deposits correlates with high blood levels of monoclonal proteins. Immunohistochemistry for IgD and CD4 on the first muscle biopsy is underway.

P595

Clinical correlations of bind and blocking acetylcholine receptor antibodies in Myasthenia gravis

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Objectives: Myasthenia gravis (MG) is an autoimmune disease associated with antibodies directed to the postsynaptic acetylcholine receptor (AChR) at the neuromuscular junction. Autoantibodies against AChR and other muscle antigens can be used for the diagnosis of MG. Several serological tests are available for measuring AChR antibodies in the blood, including blocking, binding, and modulating antibodies. The purposes of this study is to compare the clinical severity of MG patients according to the AChR antibodies type.

Methods: This study was a retrospective analysis of antibodies type and medical records of 37 MG patients confirmed by serological test. The patients enrolled in the study had the both binding and blocking antibodies test and disease duration more than 2 years since diagnosis. Clinical severity was divided into mild and severe groups by Osserman's classification. Mild group included the patients who had ocular and mild generalized MG without bulbar muscle weakness. Severe group included the patients who had severe generalized MG with bulbar involvement and myasthenic crisis.

Results: We identified 28 patients that met our inclusion criteria. Eleven patients (39%) were men and 17 patients (61%) were women. Of the 28 patients, 13 patients had both the blocking and binding AChR antibodies (47%), 7 patients had the only binding antibodies (25%), and 8 patients had only blocking antibodies (28%). By defined clinical classification, mild and severe group included 16 and 12 patients, respectively. The patients of severe group showed both AChR antibodies in 11 patients and only binding antibody in one patient. All the patients with only blocking antibody were classified into mild group. Of the 28 patients, thymoma was found in six patients and five patients had both AChR antibodies.

Conclusion: AChR binding and AChR blocking antibodies were found with approximately the same frequency in 28 patients with MG. Patients with severe generalized MG or myasthenic crisis tended to have both the binding and blocking antibodies. Also, MG patients with thymoma showed similar tendency.

P596

McArdle's disease: a new mutation

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Objectives: McArdle's disease shows a prevalence of 1/100,000 inhabitants. More than 100 different mutations have been identified. A case with a new homozygous mutation will be described.

Methods: A 56 years old woman, originally from an 1,000 people population. Consanguineous parents. The women had eight brothers, five deceased in early infantile stage. She referred symptoms of fatigability and a mild and non-specific intermittent legs pain, with a mild decrease of proximal strength and atrophy of the elevator escapulae and of the quadriceps femoris muscles.

Results: LDH: 1.167.GOT:61.GPT:65.CPK:1,345 UI/l. Lactic acid profile and ammonium curve after exercise under ischemia: Maximum elevation of lactate of 2.18 mmol/l and one progressive elevation of ammonium up to 1,180 g/dl. Test of progressive effort: effort very reduced and inefficient energy. EMG: signs of proximal and distal moderate myopathy. Muscular biopsy: myophosphorilase activity obtained was null. In the study with electronic microscopy autophagic vacuoles are observed. In conclusion, Glycogen storage disease type V with autophagic vacuolar myopathy. PYGM gene molecular screening: protein M422 K, ADNc: c.1325 T > A homogozygous positive.

Conclusions: In patients with McArdle's disease the presence of ethnic and familiar particular mutations is frequent. We have found a new mutation in a patient with intolerance to exercise, with absence of the phenomenon of second wind.

Poster session 5

Cerebrovascular disorders: mechanisms and treatment

P597

MRI of cerebral ischaemia and chronic hyperperfusion after subarachnoid haemorrhage in rats

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Objectives: Subarachnoid haemorrhage (SAH) carries poor prognosis, which has been attributed to vasospasm related delayed cerebral ischemia. With MRI we have demonstrated that vasoconstriction, loss of cerebral blood flow (CBF) and ischemic tissue damage develop within 48 h after SAH in rats. Goal of the current study was to characterize the progression of tissue and perfusion changes in relation to outcome at chronic time-points after experimental SAH.

Methods: SAH was induced in 17 adult male Wistar rats by means of the endovascular filament method. MRI was conducted after 48 h

and 7 days, and included multislice T2- and diffusion-weighted MRI, dynamic susceptibility contrast-enhanced MRI, and pre- and post-contrast T1-weighted MRI. Maps of the T2, apparent diffusion coefficient (ADC), cerebral blood volume (CBV), CBF index (CBFi) and contrast induced T1-weighted signal change were calculated. MR parameters were measured in ipsi- and contralateral primary somatosensory fore- and hindlimb regions (S1) and caudate putamen (CPu) and statistically analyzed with a paired Student's t-test.

Results: Ten rats died before the first MRI scan at 48 h, and another 4 animals died before day 7. At 48 h SAH-induced brain lesions were characterized by areas of reduced ADC and prolonged T2 in large part of the ipsilateral somatosensory cortex and CPu. Relative T2 in ipsilateral S1 and CPu were $142 \pm 26\%$ and $132 \pm 31\%$, respectively (% of contralateral; $p < 0.05$). CBV and CBFi were increased in these regions; on average by more than 40% ($p < 0.05$). Also, there was significant contrast leakage in ipsilateral S1 and CPu. Three animals with significantly smaller ADC and T2 alterations in the lesioned area as compared to the other four animals, survived until day 7. In these animals, lesion T2 and ADC values had largely normalized, but CBV and CBFi remained elevated.

Conclusions: Experimental SAH was accompanied by a relatively high mortality rate. In animals that survived until at least 48 h post-SAH, ADC reduction and T2 prolongation in the MCA territory point toward cerebral ischemia. However, elevated CBV and CBFi suggest that perfusion loss occurs before this time-point. Animals with least signs of ischemia survived beyond 48 h. Our study corroborates the significant role of cerebral ischemia in outcome after SAH. Hyper-perfusion at later time-points may indicate that triple-H therapy in aneurysmal SAH patients can be detrimental.

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P598

Elevated neutrophil to lymphocyte ratio in ischaemic stroke patients compared with apparently healthy control subjects in Korean adults

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Background: The neutrophil/lymphocyte ratio (NLR) has recently been described as a predictor of mortality and morbidity in vascular disease, such as myocardial infarction and diabetes patients. We hypothesized that NLR might be elevated in ischemic stroke patients compared with healthy control subjects, and NLR might show different levels according to different subtypes of ischemic stroke.

Methods: In 446 patients in whom the presence of ischemic stroke was confirmed in brain MRI, serum white blood cell (WBC) count, neutrophil count (%) and lymphocyte count (%) were analyzed. Furthermore, NLR was calculated with neutrophil count divided by lymphocyte count. 409 Age and sex matched healthy control subjects with no underlying metabolic risk factors, were selected among the health screening program participants, and the analyses were performed in total of 855 subjects. The patients with ischemic stroke were divided into 5 groups according to TOAST classification, and all the subjects were divided into 3 groups according the tertiles of the leukocyte count tertiles.

Results: There were 182 women (40.8%) among the ischemic stroke patients. The subjects with ischemic stroke showed significantly increased mean values for WBC counts, neutrophil counts, NLR and decreased lymphocyte counts. When the parameters were compared according to the subtypes of ischemic stroke, mean values for neutrophil counts and NLR were significantly increased and mean lymphocyte counts were significantly decreased in subjects with CE and LAD type compared with SVO and TIA. When the predictability of each parameters were analyzed with the presence of ischemic stroke as the dependent variable, the highest tertile of NLR showed increased odds ratio for stroke compared with the lowest tertile of NLR (OR 5.025, $p < 0.01$).

Conclusions: NLR was elevated in patients with ischemic stroke compared with the healthy control subjects, and showed especially elevated levels in CE and LAD subtypes compared with SVO and TIA. NLR was the significant predictor for ischemic stroke, implying the possibility of peripheral inflammatory markers as the predictor for ischemic stroke.

P599

Can decreased glomerular filtration rate be a predictor of ICH after IV-tPA administration in patients with acute ischaemic stroke?

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Objectives: Persons with early stages of chronic kidney disease, defined by a decreased glomerular filtration rate (GFR), have an increased risk of cardiovascular disease. Recently, there was a report that decreased GFR influences platelet function, which might explain the increased risk of hemorrhagic stroke in a persions with decreased GFR. So, we aimed this study to elucidate that decreased GFR is a risk factor of Intracerebral hemorrhage (ICH) after thrombolytic therapy in patients with acute ischemic stroke.

Methods: Patient with acute stroke received IV tissue plasminogen activator (rt-PA) within 3 hours of symptom onset. ICH was defined as any parenchymal hemorrhage on CT with 72 hours after treatment. We calculated GFR of each patients and identified the known main predictors of ICH, such as age, clinical stroke severity, blood pressure (BP), blood glucose level, the presence of DM, hypertension, hyperlipidemia and stroke subtype.

Results: High systolic BP ($p = 0.046$), combined intra-arterial (IA) thrombolytics ($p = 0.031$), lower body weight ($p = 0.036$), and cardiogenic embolic stroke in TOAST classification ($p = 0.008$) were significantly related with ICH after IV-tPA. However, decreased GFR was not predictor of ICA after IV-tPA ($p = 0.185$).

Conclusion: It is not evident that decreased GFR influence the development of ICH after IV-tPA in patients with acute stroke.

P600

Reversible arterial occlusion in migraine-associated infarction

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Objectives: Migraine has been recognized as an independent risk factor in ischemic stroke. The pathophysiology of migraine-associated infarction remains elusive. Vasospasm had been considered to explain the aura associated with migraine and the rare cases of associated stroke. We present the two cases of migraine-associated infarction which involved the posterior cerebral arterial (PCA) territory.

Case Reports: A 30-year-old woman with a history of infrequent migraine with visual aura since childhood presented with moderate to

severe headache with nausea and vomiting. These headaches were typical of her previous migrainous episodes. Visual aura preceding headache had been for 30 min. It was beginning at the center and expanding to peripheral field. There was no family history of migraine. Visual field testing revealed a left homonymous hemianopsia. Initial brain MR imaging (MRI) showed increased signal on diffusion weighted image involving the right medial temporal and occipital lobes with corresponding decreased signal in apparent diffusion coefficient (ADC) values. MR angiography (MRA) of the brain showed total occlusion of the right PCA. Her headaches improved with NSAID and acetamoniphen. Antiplatelet and flunarizine were given for stroke and migraine prevention. Five-month follow-up MRA revealed recanalization of the occluded PCA.

A 50-year-old man with a history of intermittent throbbing, unilateral headache for 20 years. His migraines were characterized by visual aura, moderate to severe headache, nausea, and aggravating pain caused by physical activity, such as climbing stairs. 2 days prior to the admission there was dizziness preceding his migraine episode. He had right superior homonymous quadrantanopsis on confrontation test. Brain MRI performed on the first day of admission showed increased signal on Fluid Attenuated Inversion Recovery (FLAIR) and T2 weighted sequences involving the left medial temporal with hippocampus. MRA showed total occlusion of the left posterior cerebral artery. His symptoms had resolved during the next month. 43-day follow-up MRA depicted recanalization of the occluded PCA.

Conclusion: We report the two cases of migrainous infarction showing reversible arterial occlusion. Although vasospasm has been known to be the nature of arterial occlusion, the possibility of arterial dissection must be considered based on the angiographic finding of single artery involvement.

P601

Chronic subdural haematoma of adults and elderly admitted in a neurological unit: a retrospective study of 22 patients

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Chronic subdural haematoma (CSDH) a common disease of the elderly, has polymorphic clinical features and its diagnosis remains difficult in spite of abundant imaging methods. Although surgical intervention is accepted as the treatment of choice, patients are frequently admitted in neurological units and accurate data on these admissions are sparse. The aim of this retrospective study including 22 adults and elderly patients, admitted for symptomatic CSDH, from 2001 to 2005 in the neurological department of the Robert Ballanger Hospital, was to evaluate their risk factors, clinical presentation, radiological features, management and outcome. Characteristics of age, sex and history of trauma were similar to previous studies. It is interesting to note that 50% of our patients were on antiplatelet agents or anticoagulants, reflecting new trends of prescription and a greater co-morbidity, particularly of the intracranial pathologies. On CT scanning a fresh bleeding was found in 70% of patients and the CSDH was bilateral in 45% of the cases. Neurosurgical intervention was performed initially in 8 patients but 3 had to be reoperated. Fourteen patients were admitted without undergoing surgery, of whom 11 were given steroids and 3 had conservative management. In the steroid treated group, 2 patients eventually required a neurosurgical intervention. Almost half of our patients underwent surgery but 9 were treated only by corticosteroids suggesting that this is a good option in selected cases. At 1-year-follow-up, the outcome was excellent, only one patient, the oldest, had died. Nevertheless, one third of the patients still had mild motor and cognitive deficits or an epilepsy.

P602

About a stroke in possible POEMS syndrome

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Objectives: POEMS syndrome is a rare paraneoplastic disorder characterized by polyneuropathy, organomegaly, endocrinopathy, skin changes and plasma cell dyscrasia. Cases of arterial occlusions have been reported associated to POEMS but physiopathological mechanism remains debated.
We report a case of vertebro-basilar stroke in a man suffering of possible POEMS syndrome.

Case report: A 54-year old man presented with a one year history of sensorimotor demyelinating polyneuropathy associated to monoclonal IgA lambda protein. Initial investigations including skeleton radiography and bone marrow's histology were normal. He was admitted for sudden blurry vision, right facial and left hemiparesis. Brain Magnetic Resonance Imaging confirmed a vertebrobasilar stroke(involving bilateral cerebellum, pons, bilateral occipital regions and left thalamus). CT scan angiography showed a thrombus in the basilar artery, a left vertebral artery occlusion and a narrowing of the right one.
First imagery revealed also a C1's lytic mass infiltrating vertebral arteries. Vertebral biopsy diagnosed a plasmocytoma expressing IgA lamba type protein.
Clinical examination showed also lymphadenopathy, splenomegaly, livedo and acroscleriasis, mammary tension without gynecomastia. Monoclonal IgA lambda protein was found and low proteinuria without bence-jones protein. Other laboratory findings were normal including vascular endothelial growth factor(VEGF) level.

Results: Regarding stroke management the patient was initially treated by intravenous anti GPIIB-IIIA with clinical improvement(NIHSS score from 12 to 4)and partial arterial repermeabilisation. Cervical plasmocytoma was treated by radiotherapy.
According to international diagnosis criteria (Dispenzieri 2007), clinical history and paraclinic findings evocated a possible POEMS syndrome.

Conclusions: Arterial thromboses, including stroke, are associated to POEMS syndrome. Overproduction of proinflammatory cytokines, such as VEGF, seems to be implicated. In this case of possible POEMS, a compressive factor (vertebral mass infiltrating vertebral arteries) was present and precipitated the thrombotic phenomenon.
It is the first time that a compressive mechanism involving cervical plasmocytoma is described as the cause of a stroke. Moreover, this case emphasizes the importance of bone investigations in polyneuropathy associated to monoclonal protein.

P603

Results of intra-arterial treatments of acute ischaemic strokes at Henri Mondor hospital between 2005 and 2008

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Introduction: The intravenous thrombolysis transformed the assumption of responsibility of the ischemic stroke of less than 3 hours. In the event of failure or of late arrival at the hospital, a chemical and/or mechanical thrombolysis might be tried by intra-arterial way. We report the results of these endovascular procedures carried out to the hospital Henri Mondor between 2005 and 2008.

Material and methods: Occlusions of the middle cerebral artery (ACM) are compared with the group "control historical placebo" of study PROACT II (Prolyse in Acute Cerebral Thromboembolism II). Occlusions of the basilar trunk (BT) are compared with the group "intra arterial combined chemical thrombolyse" meta-analysis of Lindsberg.

Results: 31 patients underwent an intra-arterial procedure: 23 in carotidal territory and 8 for basilar artery occlusion. Were used: Rt-Pa (22%), abciximab (25%), mechanical thrombectomy (84%), angioplasty (59%) and intracranial stenting (16%), extra-cranial (25%). Carotid territory: 35% of the patients are independent in 3 months against 25% in the control group. The rate of recanalisation is 70% (18% in the group control, $p < 0.001$). The rate of intracranial symptomatic hemorrhage is 17% against 2% in the control group. Rate of death unchanged. TB: 37,5% of the patients are independent in 3 months against 24% by using the treatment of reference (chemical thrombolysis only), the rate of recanalisation is excellent (87,5% against 65% respectively).

Conclusion: The intra arterial procedures significantly increase the rate of recanalisation and tend to increase the independence of the patients in 3 months compared to the placebo group. We lack power to prove the superiority of mechanics on the chemical one. Patients must be well selected. In our series, an anticoagulant or antiplatelet treatment before stroke seems to support a better recovery at J90 without increasing the hemorrhagic risk. The association of the intravenous thrombolysis to the intra arterial procedure seems to be noxious. Autonomy in the event of occlusion of TB is dependent on the recanalisation.

P604

How frequently do young stroke patients require anticoagulation?

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Objectives: Young adults with ischemic stroke are more likely to have nonatherosclerotic etiologies for their stroke, including cardioembolic sources and hypercoagulable states. Some causes of stroke in young adults may require treatment with anticoagulation. We sought to determine the frequency of and etiologies for short-term and long-term anticoagulation use in young adults with stroke.

Methods: We reviewed the Young Stroke Registry maintained in our Comprehensive Stroke Center. Patients between the ages 16-50 were enrolled in the Registry with an ischemic stroke diagnosis. Demographics and premorbid risk factors were reviewed, use of antithrombotic agents before and after the stroke was recorded, and stroke etiology per the TOAST criteria was determined.

Results: 73 patients were available for analysis. The mean age was 38.0 years and there were 59% women. 18 patients (24.7%) were treated with short-term anticoagulation with warfarin (<6 months), with arterial dissection being the reason in one-third of these patients. Other reasons for short-term warfarin use included anticardiolipin antibody syndrome, protein C deficiency, and Snedddon's syndrome (one patient each). Four subjects (5.5%) were treated with long-term anticoagulation, with cardioembolic sources being present in all patients (three with cardiomyopathy, one with atrial fibrillation). The age range of the patients treated with long-term warfarin was 30-44 years (mean 35.8 years).

Conclusions: A significant proportion of young adults with stroke are treated with short-term anticoagulation but long-term anticoagulation is needed by few patients. This information can be useful for educating non-neurologists. Achieving compliance with warfarin for several decades is challenging. Therefore, reducing unnecessary anticoagulation can increase compliance and decrease the risk of major hemorrhagic events.

P605

Short-term outcome of patients with ischaemic stroke who did not receive intravenous TPA infusion in spite of their symptoms within 3 hours

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Objectives: Thrombolytic therapy of acute stroke (< 3hours) is the effective therapy for acute ischemic stroke. But yet, only a limited number of patients might be eligible for thrombolytic therapy because of narrow indications. The purpose of this study was to determine why stroke patients did not receive TPA therapy in spite of their symptoms within 3 hours.

Methods: the study was performed using prospective registry of ischemic stroke patients, together with a chart review at a general hospital from July 2007 to June 2008.

Results : of 309 stroke patients presenting to the our hospital, 278 (87.8%) were diagnosed with ischemic stroke and 12.2% with TIA. Twenty-one percent of patients with ischemic stroke (58/278) were admitted within 3 h of symptom onset and of these 30 (51.8%) patients did not receive IV TPA. The reasons for exclusion in this group of patients were mild stroke ($n = 23$), urgent time for TPA ($n = 2$), infarction with intracranial hemorrhage ($n = 2$), old age ($n = 1$), clinical improvement ($n = 1$), and no informed consent ($n = 1$). Of those patients who were considered too mild or were documented to have had significant improvement, 17% either progressive or dependent at hospital discharge or died during hospital admission.

Conclusion: Mild symptom was a major reason patients with ischemic stroke presenting within 3 hours did not receive TPA. Of patients with mild symptom, thirteen percent were progressive or dependent at hospital discharge. Treatment with TPA for these patients might be considered in selected cases.

P606

Two cases of early Wallerian degeneration detected only diffusion tensor image in stroke patient

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Background: Wallerian degeneration(WD) of the pyramidal tract after ischemic stroke is a well-know phenomenon. It is characterized by a highly stereotypical course, starting with disintegration of axonal structures within days after injury, followed by degradation of myelin along the affected tracts. It's important to detect WD because the extent of WD correlates with the motor deficit.

Conventional magnetic resonance imaging (MRI) detects signal intensity changes that vary during the time course of WD, but signal intensity changes are generally not detected until 4 weeks after stroke. We used diffusion tensor imaging (DTI) to assess WD within early stage after ischemic stroke. We describe here, two cases of ischemic stroke and compare with their conventional MRI and DTI within early stage after ischemic stroke onset.

Objectives, method and results: In case1, the patient with left MCA infarction was a 28-years-old female who presented with right side weakness with Broca's aphasia. In 3rd weeks after stroke onset, MRI showed left MCA infarction without WD. But we found WD using DTI. The same is true of the case2. 67-years-old female had

sudden onset right side central type facial palsy with dysarthria. The ischemic lesions were visible in corona radiate and putamen in MRI. We couldn't found WD in MRI, but just only DTI showed that within 1 day after ischemic stroke onset.

Conclusion: As our two cases, we detect WD of pyramidal tract within early stage after ischemic stroke onset only in DTI. In previous studies, evidence of severe pyramidal damage in the early phase after stroke would be of great value to assess the prognosis and rehabilitational potential of stroke patients Thus, DTI offers a way to detect severe degeneration of the pyramidal tract and may be a helpful tool in forecasting and monitoring recovery in patients with ischemic stroke.

P607

Long-term angiographic and clinical outcomes following stenting under flow reversal by proximal flow control technique for chronic total occlusions of the cervical carotid and vertebral arteries

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Objectives: Because there may be large amount of thrombi in chronic total occlusions (CTOs) of the cervical arteries, an expected risk associated with endovascular recanalization is high. The aim of the retrospective study was to investigate the feasibility, safety and effectiveness of stenting under flow reversal by proximal flow control for CTOs of the cervical carotid and vertebral arteries.

Methods: Included for analysis were patients (1) who were admitted to our institution from March 2005 to May 2007, (2) with recurrent TIAs, (3) modified Rankin scale of <2, (4) with angiographic total occlusion of the cervical carotid or vertebral arteries, (5) with estimated occlusion length of 150 mm or shorter in the affected arteries and (6) who underwent stenting for CTOs of the cervical arteries under flow reversal by proximal flow control technique. Procedural success, complications, one-year angiographic and clinical outcomes were investigated.

Results: During the study period, seven patients underwent stenting for cervical CTOs: carotid arteries in five cases and vertebral arteries in two cases. The median real occlusion length was approximately 26 mm (range from 10 mm to 38 mm). In all seven cases, CTOs were penetrated successfully with hard-type guidewires and dilated sufficiently with the stents. No complications occurred during the peri-procedural period, no TIAs have recurred for one year after stenting, and no restenosis occurred at one-year angiographic investigation.

Conclusion: Long-term angiographic and clinical outcomes were favorable. Stenting under flow reversal by proximal flow control for CTOs of the cervical carotid and vertebral arteries may be feasible, safe and effective in improving hemodynamic symptoms.

P608

Association of seropositivity to Helicobacter pylori with risk of acute ischaemic stroke

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Background: Helicobacter pylori has been associated pathogenetically with coronary atherosclerosis. Although stroke is pathogenetically related to coronary heart disease, data on relationship between chronic infection and acute ischemic stroke in Korea are lacking. Therefore, the author verify the relation of chronic H.pylori infection and risk of acute ischemic stroke, also chronic H.pylori infection and stroke subtypes.

Methods: From July 2004 to May 2005, 228 patients with acute ischemic stroke and 64 control subjects were enrolled in this study. All patients underwent stroke work-up including brain MRI, MRA, risk factor evaluation and subtype classification according to Trial of Org 10172 in acute stroke treatment (TOAST) criteria. IgG antibodies to *H. pylori* was measured by ELISA technique.

Results: There was tendency that H.pylori seropositivity in stroke (74%) was higher than that of controls (54%). And, chronic H.pylori infection was associated with a higher risk of acute ischemic stroke patient under 65(adjusted odds ratio, 2.608; 95% CI, 1.151–5.908) and caused by SVD (adjusted odds ratio, 2.762, 95% CI, 1.257–6.067).

Conclusion: This study shows that chronic H.pylori infection is associated with relatively young age acute ischemic stroke and SVD. Further studies are required to reveal whether chronic H.pylori infection is an independent risk factor for acute ischemic stroke.

P609

Intravenous tissue-type plasminogen activator therapy for ischaemic stroke: NIS stroke team experience November 2006 – February 2009

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Background: To present the preliminary experience of implementing intravenous thrombolytic therapy for acute ischaemic stroke in Stroke unite, Department of neurology, Clinical center Nis, South Serbia.

Methods: This prospective and observational study included 65 consecutive patients with an ischaemic stroke treated in our Stroke unit within 3 h from the onset of symptoms, between Novembar 2006. and January 2009. Patients were selected and treated in accordance with the American Heart Association guidelines. Primary safety and outcome variables were on MRI performed at 24–36 h, mortality and independence at 90 days. Intracranial and systemic haemorrhagic complications were recorded.

Results: 65 patients (35 men and 30 women) with a median age of 69 years ± 13.2 years (range 24–79) received thrombolytic treatment (approximately 3.4% of 910 patients with ischemic stroke). The median time from stroke onset to rt-PA therapy was 110 min (range 20–180) and from arrival in the emergency room to the start of thrombolysis 80 min. Baseline median NIHSS was 16 (range 4–44). 41 patients exhibited early clinical improvement, defined as a decrease in NIHSS score. Median NIHSS before discharge was 4.2 points. At 3 months, 80% (95% CI, 47, 9–64.1) of patients were functional independent. One patient developed a haemorrhage. 16.8% patients died within 3 months of stroke.

Conclusions: The use of intravenous t-PA by experienced neurologists in Stroke unites, is safe and it is associated with a favourable outcome, without excess risk, similar to that observed in clinical trials. Successful experience with this therapy depends on organization of the treating team and adherence to published guidelines.

P610

Newly developed method for the removal of hypertensive intracerebral haematoma

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Hypertensive intracerebral hematoma (ICH) account for approximately 78–85% of all form of nontraumatic intracerebral hemorrhage and is associated with a high mortality and morbidity. One of the objectives in providing assistance remains the development of new

minimally invasive methods and devices for the removal of hematoma.

We developed a minimally invasive method and device (patents of Russian Federation [1]65382; [1]2336030) for removal of intracerebral hematoma. The device—funnel cannula—which after the special markings introduced into the hematoma cavity.

This method has the following steps: (a) minimally invasive craniotomy, hole diameter about 2,5 centimeter, opening under local anesthesia is possible; (b) dura opening; (c) consequent punction of hematoma with special cannulas; (d) introducing of funnel cannula into the hematoma cavity; (e) removal of hematoma, secure hemostasis by electric coagulation is possible; (f) put of bone disc on its place.

We have performed this operation in 40 patients with hypertensive ICH (24 with putaminal hemorrhage, 12 with mix hemorrhage, 6 with subcortical hemorrhage).

The mean duration of operation was 46 min, the mean hematoma reduction rate was 89%, and no peri-operative hemorrhage with deterioration of symptoms and/or signs occurred. Therefore, we believe that minimally invasive hematoma evacuation with our surgical method may improve the prognosis in patents with hypertensive ICH.

P611

Systematic review and meta-analysis of currently available clinical evidence on migraine and patent foramen ovale percutaneous closure

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Background and Objectives: In recent years, a potential relationship between, migraine, stroke and patent foramen ovale (PFO) has emerged. We aimed to investigate the role of transcatheter closure of interatrial septal abnormalities on the occurrence of migraine.

Methods: BioMedCentral, Google Scholar and PubMed from January 2000 to December 2008 were systematically searched for pertinent clinical studies. Secondary sources were also used.
Secondary prevention studies of transcatheter closure for patent foramen ovale were required to include at least more than 10 patients followed for more than 6 months. The primary end-point was the rate of cured or significantly improved migraine after percutaneous PFO closure.

Results: After excluding 634 citations, we finally included a total of 14 studies for a total of 1,434 patients. Forty-two percent of the subjects included suffered from migraine, while most had a previous history of transient ischemic attack/stroke and were investigated retrospectively.
Quantitative synthesis showed that complete cure of migraine 47.7% (95% CI 30–66%), while resolution or significant improvement of migraine occurred in 76 % (95% C.I. 65.6–86.5 %) of cases.

Conclusions: Notwithstanding the limitations inherent in the primary studies, this systematic review suggests that a significant group of subjects with migraine, in particular if treated after a neurological event, may benefit from percutaneous closure of their interatrial septal defect. However, many questions remain un-solved.

P612

Magnesium and headache after aneurysmal subarachnoid haemorrhage

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Objectives: In patients with aneurysmal subarachnoid haemorrhage (SAH), headache typically is severe, and often requires treatment with opioids that have potentially harmful side effects. Magnesium has analgesic effects in several conditions, but whether it reduces headache after SAH is unknown. We hypothesized that patients with high magnesium levels due to magnesium treatment have less severe headache, and require less treatment with analgesics than patients with normal magnesium levels.

Methods: In a cohort of 108 patients with SAH included in the randomised Magnesium in Aneurysmal Subarachnoid Haemorrhage (MASH-II) trial, patients scored the severity of their headache on a ten-point scale until day 10 after the SAH. Patients with a decreased consciousness were excluded. Headache was treated according to a standardized protocol with acetaminophen, codeine, tramadol (a moderately strong synthetic opioid), and piritramide (a strong synthetic opioid). Serum magnesium levels were assessed every other day. Differences in mean headache scores between patients with mean high ($>$1.0 mmol/L) and normal ($\leq$1.0 mmol/L) magnesium levels were analyzed with a Student *t* test. Crude and adjusted odds ratios (OR) for the use of codeine, tramadol, and piritramide for patients with high versus normal magnesium levels were calculated with logistic regression.

Results: The 61 patients with high magnesium levels had statistically significant lower mean headache scores (4.1 $\pm$ 1.8) than the 47 patients with normal magnesium levels (4.9 $\pm$ 1.8), mean difference 0.8 (95% confidence interval (CI) 0.1-1.6). Fewer patients with high magnesium levels than patients with normal magnesium levels used tramadol (adjusted OR 0.3; 95% CI, 0.1–0.7) or piritramide (adjusted OR, 0.2; 95% CI, 0.1–0.5). There were no differences between the groups in the use of codeine.

Conclusion: In patients with SAH, elevated serum magnesium levels are associated with less severe headache and less frequent use of opioids. This is an important extra effect of magnesium therapy, when it proves to reduce poor outcome after SAH.

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Clinical neurophysiology

P613

Immersive virtual reality effects on balance and gait

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Objectives: the aim of this study was to investigate the effects on balance and gait induced by a completely immersive virtual reality (VR) with and without perturbation.

Methods: 10 healthy subjects were analyzed in different conditions: (a) standing posture (60 s) with eyes open, eyes closed, with the head mounted display, immersed in VR and immersed in perturbed VR; (b) standard gait, VR gait and perturbed VR gait.

Results: our results pointed out that immersive VR has no effects on balance during upright standing. Conversely postural activity was increased when the visual input was removed (eyes closed). Subjects immersed in the virtual environment walked slowly, with decreased cadence (−13%) and stride length (−28%) as well as increased base of support in terms of step width (+20%). The perturbation of the VR caused an interesting effect: many computed parameters, still away from the standard gait condition, improved if compared to the unperturbed VR condition.

Conclusions: analyzed subjects seem to trust visual information provided by VR. Walking in VR leads to gait instability, which is less pronounced in presence of perturbation, probably due to the reweight of sensory inputs. This study could represent the first step for clinical and rehabilitative applications of the proposed VR environment to neurological diseases.

P614

Evaluation of incidence and features of sacral area dysfunctions in Parkinson's disease and other extrapyramidal disorders

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Objectives: Prevalence of sacral area dysfunction (SAD) in extrapyramidal disorders (ED) and Parkinson disease (PD) is not known. While motor dysfunctions represent the main neurological complaint, bladder (urinary urgency and frequency), bowel (constipation) and sexual dysfunction, are usually underestimated by the pts. Moreover, whether these complaints are related to pathophysiology of disease itself or rather to pharmacological treatments is not clear.

Methods: We evaluated 40 pts (22 with PD and 18 with ED) (31 male, 19 female, age range 45-69 years old) average duration of illness 5 years, with clinical questionnaires for bowel (Wexner Score), International Index of Erectile Dysfunction IIEF-5 and Female sexual function Index, voiding diary. Motor dysfunction was assessed by the Hoehn andYahr and UPDRS and the cognitive functions by the mini-mental state examination (MMSE). The impact on quality of life was assessed by SF-36 and QoL. All were taking levodopa with/without dopamine agonists.
Urological and proctological causes of SAD as well as severe motor dysfunction were excluded (median Hoehn and Yahr stage was 3). The pts underwent a thorough neurophysiological evaluation of pelvic floor: somatosensory evoked potentials of pudendal nerves (SEPs), sacral reflexes (SR), electroneurography of pudendal nerves (ENG), electromyography of perineal muscles (EMG), sympathetic skin response (SSR), motor evoked potentials of pelvic floor (MEP).

Results: We found SAD in 90% of pts: most of them had not complained of symptoms during routine neurological assessment while neurophysiological assessment was more sensitive rather than scores and clinical evaluation in revealing altered motor and sensory pathway to pelvic area.
Spontaneous complaint of SAD in 12 % pts, 50% also with clinical score, and 90% with Neurophysiological alterations (SEPs were pathological in 87%, EMG in 65%, ENG in 37%, RS in 75%, SSR in 85%): these were correlated to the stage and duration of illness ($p < 0.01$)

Conclusions: Neurophysiological assessment of the pelvic floor is able to reveal subclinical abnormalities in most pts with ED: who usually do not complain of SAD until later stages of disease, when SAD are so severe to determine great impact on their quality of life. Clinical questionnaires are more effective than neurological examination alone in revealing pts with SAD, but are less sensitive than neurophysiological assessment, which is able to detect SAD even in preclinical stages.

P615

Neurophysiological involvement differs between secondary and primary progressive forms of multiple sclerosis

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Objectives: Visual evoked potentials (VEPs) may be considered useful for diagnostic purposes and to monitor burden and progression of the disease in patients with multiple sclerosis (MS). The aim of our study is to search for differences in the pattern of VEPs abnormalities in the primary (PPMS) and secondary (SPMS) progressive forms of the disease.

Methods: We consecutively analyzed VEPs records in 103 patients affected by progressive MS followed at our centre (55 M, 48 F, mean age 47 ± 10.34; SPMS 49, PPMS 54; mean EDSS 4.8 ± 1.53), who also underwent clinical assessment. Among SPMS patients, 18 had clinical history of optic neuritis (ON) in a single eye and 2 in both eyes.

Results: Visual impairment was worse in SPMS compared with PPMS even when excluding patients with previous ON ($p < 0.0001$). Absent P100 to 30' was found in 29 (29.5%) eyes in SPMS patients, of which 9 with history of NO (50% of total NORB), and in 10 (9.4%) eyes of PPSM patients (chi square 13.4; $p < 0.0003$). The higher prevalence of absent responses in SPMS compared with PPMS was present also after excluding eyes with previous history of optic neuritis in SPMS (26.3%; chi square 9.2; p 0.0025). Similar results were found concerning check-size 15' (Chi-square 9.0; $p = 0.0017$). No significant group difference was found concerning absolute latencies or amplitude of recorded responses. However, when classifying VEPs according to a 4 graded conventional score (from normal to absent responses), SPMS scored higher compared with PPMS both concerning patients ($p = 0.037$) and eyes ($p = 0.006$), the latter tendency remained also after excluding eyes with previous ON ($p = 0.05$).

Conclusion: Consistently with previous literature, the frequency of P100 absence is significantly greater in SPSM patients than in PPSM patients. Moreover, VEPs abnormalities are more severe in SP compared with PP MS patients, also after correcting for previous ON. This finding is consistent with milder visual impairment and a lower retinal fiber axonal loss in PPMS compared with SPMS, although the degree of demyelination along the visual pathway, as measured by VEPs latencies, is similar in the two groups. Taken together, this evidence may suggest a different underlying pathological substrate in the two forms of the disease, with a more prominent conduction block/axonal loss from longer demyelinating lesions in SPMS, and more scattered and shorter lesions, with less axonal involvement, in PPMS patients.

P616

Abnormal calf reflexes at standard tibial nerve SEPs may indicate pyramidal involvement in multiple sclerosis

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Objective: Occasionally, we observe a muscle response in the popliteal derivation at standard tibial nerve somatosensory evoked potential (SEPs) compatible with a spinal reflex. The aim of our study was to assess whether such responses are related to a clinical and/or

neurophysiological evidence of pyramidal tract damage in a cohort of patients with multiple sclerosis (MS).

Methods: We retrospectively analyzed data from 352 MS patients (135 M, 217 F; age 37.81 ± 11.59; 274 relapsing-remitting, 52 secondary progressive, 27 primary progressive), undergoing clinical assessment and motor (MEPs) and somatosensory (SEPs) evoked potentials to the four limbs.

Results: A reflex popliteal response at tibial nerve SEPs (latency 41.9 + 5.9 ms), was found in 46 (13%) patients, 21 (34.42%) of them with normal SEPs. Patients with such reflex had higher EDSS (3.78 + 1.45 vs. 2.89 + 1.80), pyramidal FS (2.67 + 0.87 vs. 1.91 + 1.14), central conduction time at motor evoked potentials (MEP) to the upper (11.6 + 6.7 vs. 9.1 + 4.4) and lower limb (23.7 + 6.9 vs. 20.7 + 7.3), central conduction time to upper limb SEPs (7.2 + 2.0 vs. 6.5 + 1.8) and latency of cortical potential (P40) to lower limb SEPs (46.3 + 5.7 vs. 42.6 + 5.6) compared with patients without such response ($p < 0.025$, unpaired t test). Pyramidal deficits (FS > 1) were present in 40 (86.9%) out of these 46 patients, and in 157 (51.3%) of patients without (Chi square:20.6; $p < 0.0001$). Lower limbs with calf reflex were more likely to have abnormal MEPs, (62.29% vs 37.70%; Chi square 7.5, $p = 0.006$) although such reflex was present in 23 (6%) lower limbs with normal MEPs.

Conclusions: Reflex responses to calf muscles may be found at standard SEPs to ankle tibial nerve stimulation. They may be considered as a possible indicator of pyramidal dysfunction, sometimes evident only at clinical examination and not at standard MEPs. Although less sensitive compared with MEPs, calf muscle reflexes could represent the only neurophysiological evidence of pyramidal involvement in patients undergoing standard motor and somatosensory EPs. Therefore, careful attention should be paid to the presence of EMG reflex responses at popliteal derivation, normally used only for the assessment of peripheral conduction.

P617

Deficient high-acceleration vestibular function in polyneuropathic patients

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Background: Unsteadiness during standing and walking is a frequent complaint of patients with polyneuropathy (PNP).

Objective: To determine whether balance disorders in PNP-patients may be caused by reduced proprioceptive input from the feet alone or whether impaired vestibular input, resulting from involvement of the vestibular nerve, can be an additional factor. Methods: 37 patients (age: 65 years ± 12 SD; 12 women) with electro-diagnostically confirmed PNP (predominantly axonal: 18; predominantly demyelinating: 19) underwent horizontal search-coil head-impulse testing, which assesses the high-acceleration vestibulo-ocular reflex (VOR).

Results: Relative to a healthy comparison group, the gains (eye velocity divided by head velocity) of the horizontal VOR were reduced in 27 of 37 patients (unilateral: 13; bilateral: 14). The percentages of patients with unilateral or bilateral VOR deficits were not significantly different between patients with axonal or demyelinating PNP.

Conclusions: Two thirds of patients with axonal or demyelinating PNP showed unilateral ($\sim$ 50 %) or bilateral ($\sim$ 50 %) gain reductions of the horizontal high-acceleration VOR. This finding suggests that, in many patients with PNP, the neuropathic process includes the vestibular nerve. Such information is highly relevant for subsequent physical therapy, since vestibular exercise improves balance control and reduces disability.

P618

The value of sensory nerve conduction study in acute inflammatory demyelinating polyneuropathy

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Background and objectives: Acute Inflammatory Demyelinating Polyneuropathy (AIDP) is the most common cause of acute and severe generalized peripheral neuropathic weakness. The prompt diagnosis of AIDP is needed to initiate early treatment. Although nerve conduction studies (NCSs) are important ancillary diagnostic aid, the importance of sensory NCSs have been overlooked relatively. We undertook this study to evaluate the sensory NCS abnormalities including sensory sparing patterns in AIDP and to establish possible predictors of AIDP when compared to other neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP) and axonal neuropathy (AN).

Methods: We evaluated sensory NCS data from 45 consecutive patients of AIDP. Sensory sparing patterns and modified sensory ratios of the sural, median, and ulnar SNAPs (sensory nerve action potentials) of AIDP patients were included in an analysis. Sensory NCS findings including all potential sensory sparing patterns and modified sensory ratio were compared to patients with AN and CIDP patients. Logistic regression models for modified sensory ratio (sural SNAPs/[median + ulnar SNAPs / 2]) were conducted.

Results: In AIDP, 31 patients (68.9%) had low-amplitude or absent SNAPs in the upper extremity. The sural nerve frequently showed normal NCS findings (81.5%) compared to the median and ulnar nerves. The reverse pattern was seen in AN and CIDP, in which the sural nerves showed more or similar abnormalities than the median and ulnar nerves. A sural sparing patterns were more frequently seen in AIDP group ($p < 0.05$). The modified sensory ratio was higher in AIDP compared to CIDP and AN groups and was an independent predictor for AIDP patients as compared to the CIDP group (OR = 2.68, CI = 1.67-9.12; $p < 0.05$) and AN group (OR = 8.10, CI = 2.01-21.19, $p = 0.001$).

Conclusion: Our study showed the modified sensory ratio discriminate the AIDP from CIDP and AN. This patterns of sensory NCS including sural sparing patterns and modified sensory ratio may be useful in contributing to the electrodiagnosis of AIDP.

P619

Longitudinal evaluation of axonal regeneration in mouse after nerve crush: a stimulated single-fibre electromyography study

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Objectives: Animal models to study nerve regeneration, such as the sciatic nerve compression, are well characterized from the histological point of view. However, neurophysiological measurements of axonal regeneration still need a gold standard method. In this study we want to explore whether the association of classical neurophysiological tests and stimulated single-fiber electromyography (SFEMG) may contribute to better describe axonal regeneration occurring after experimental nerve injury.

Methods: 15 8-week-old C57 Bl/6 mice underwent unilateral sciatic nerve crush at the ischiatic notch. 5 mice at each time point, 7, 14 and 42 days post-injury (p.i.), were randomly studied. At each time point, compound motor action potential (CMAP) of footpad muscle by stimulation of sciatic nerve, jitter of single fiber potential (measured as mean consecutive difference, MCD) and fiber density (FD) in calf muscle were analyzed. Mice were then sacrificed to evaluate the amount of pathological damage and ongoing regeneration.

Results: At day 7 p.i., footpad muscle was still lacking, while both MCD and FD significantly increased in comparison to baseline; at day 14 p.i., low-amplitude CMAP appeared, together with further increases of MCD and FD as well. At the third time-point (42 days p.i.), CMAP amplitude further recovered without still achieving baseline values; in the meantime, both MCD and FD persisted elevated.

Conclusion: These results point out that neurophysiological tests, longitudinally performed, may provide a consistent quantitative measure to monitor axonal regeneration (and functional recovery) following nerve injury. CMAP amplitude may be regarded as a global estimate of the number of active motor units, while SFEMG variables (MCD and FD) measure impaired safety factor of neuromuscular endplates as well as density of sprouts of regeneration. Further studies are necessary to standardize the method; however, combined analysis of CMAP and SFEMG represents a surrogate marker for in vivo monitoring of axon regeneration after nerve injury.

P620

Clinical usefulness of a new peroneal nerve orthodromic sensory conduction technique in patients with foot drop

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Objective: to evaluate the clinical usefulness of a new neurophysiological tool in the investigation of foot drop causes.

Background: standard electrophysiological assessment, including electroneurography (ENG) and electromyography (EMG), is usually sufficient to establish a correct differential diagnosis between a peroneal neuropathy at fibular head (FH) and L5 radiculopathy presenting with foot drop however, may not solve always a definite localization of the site of lesion, particularly, in presence of a severe muscular atrophy, a pure demyelinating lesion at FH and lastly in pure axonal loss. Therefore, we assessed a new simple and reliable technique to better investigate the orthodromic sensory conduction of superficial peronel nerve (SPN) and deep peroneal nerve (DPN) across FH [1].

Methods: electrophysiological tests were performed on 25 consecutive patients with clinical evidence of foot drop. In all patients motor conduction velocities (MCV) of common peroneal nerve SPN and DPN were obtained. Besides, antidromic SPN conduction according to Liverson and Ma's technique and orthodromic sensory conduction (SCV) of SPN and DPN across FH were found out. Needle EMG of L4-L5-S1 territories was performed.

Results: 13 patients presented L5 radiculopathy confirmed with neuroradiological images while the others 12 showed peroneal neuropathy at FH. In patients with L5 radiculopathy, amplitude and MCV across FH were normal, however sometimes MCV could not be recorded because of severe muscular atrophy. Instead, the orthodromic conduction study was normal in all cases, ruling out peroneal neuropathy at FH. EMG confirmed the extent of radiculopathy.

In patients with peroneal neuropathy MCV revealed abnormalities across FH even if sometimes MCV could not be performed consequently the severe muscular atrophy. Similarly, the orthodromic conduction studies showed reduction of amplitude and CV across FH or absence of responses.

Conclusions: This new reliable technique may be useful to rule out peroneal neuropathy at FH in patients with L5 radiculopathy. The test evidenced itself consistent with standard electrophysiological investigation in foot drop patients, therefore it is reliable also in those cases where the classical approach may not solve a correct differential diagnosis referring to severe muscular atrophy and slight motor impairment.

Reference:

C.Marchini et al (2009) Peroneal nerve orthodromic sensory conduction technique: normative data. Neurol Sci (in press)

P621

Carpal tunnel syndrome: electrophysiologic diagnosis

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Objectives: To consider, in patients clinically suspected of having CTS, which the best electrodiagnostic tests (EDX) to confirm the diagnosis are by evaluating sensitivity (S) and specificity (SP) scores and positive/negative predictive values (PPV, NPV).

Design: Retrospective, transversal and observational study with a view of solving a problem of comparison. The diagnostic effectivity of each of these tests was compared to the median palm-wrist test (gold standard).

Material and methods: Tests carried out in the Clinical Neurophysiology Unit of German Hospital and Buenos Aires San Martin School of Medicine Hospital involving 2,200 patients, in whom various pathologies were assessed. In 135/2200 (6%) patients with clinical signs of CTS, the following tests were done: Median Mixed Nerve Conduction in the Palm-Wrist segment (MMNCPW). Median Sensory Nerve Conduction in the Wrist-I, II, III and IV digit (MSNCI, MSNCII, MSNCIII, MSNCIV). Differences in latencies: wrist-I digit segment for the median and radial nerves and wrist-IV digit segment for the median and ulnar nerves. Median Motor Nerve Conduction (MMNC) and Terminal Latency Index (TLI). Sensory Distoproximal Ratio (SDR): evaluation of the ratio of antidromic median sensory nerve conduction velocity from the III digit to the palm compared to the palm-wrist segment. Combined Sensory Index (CSI): the sum of the median-ulnar ring finger antidromic difference (ring-diff), the median-radial thumb antidromic difference (t-diff) and the median-ulnar midpalmar orthodromic difference (palm-diff).

Results: 102 (75%) were female, 33 (25%) male, 41 (30%) bilateral, 94 (70%) unilateral, 79 (45%) right handed and 33 (18%) left handed. MMNC: S 74.5%, SP 87%, PPV 96.2%, NPV 43.5%. TLI: S 65.8%, SP 74.1%, PPV 87.7%, NPV 43.5%. T-diff: S 82.3%, SP 61.1%, PPV 80%, NPV 64.7%. Ring-diff: S 74.07%, SP 75%, PPV 83.3%, NPV 63.1%. Palm-diff: S 82.4%, SP 80.6%, PPV 91.04%, NPV 65.7%. SDR: S 47.05%, SP 91.8%, PPV 91.4%, NPV 48.5%. CSI: S 100%, SP 100%, PPV 100%, NPV 100%.

Conclusions: We found CSI an accurate and reliable method for diagnosing carpal tunnel syndrome, being superior as regards sensitivity and specificity to the other techniques used in this study.

P622

Clinical and electrophysiological findings in idiopathic tarsal tunnel syndrome

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Objective: Tarsal tunnel syndrome (TTS) is an entrapment neuropathy of the tibial nerve. This was a retrospective study to evaluate clinical and electrophysiological characteristics of idiopathic TTS.

Methods: We reviewed the medical and electrophysiological records of consecutive patients with foot sensory symptoms. Inclusion of patients was based on clinical findings suggestive of TTS. Among them, patients with any other possible causes of sensory symptoms were excluded. Control data were obtained from 19 age-matched people with no sensory symptoms or signs. Routine motor and sensory nerve conduction study including medial plantar nerve (MPN) using surface electrodes were performed.

Result: Twenty one patients (13 women, 8 men, 9 unilateral, 12 bilateral) were enrolled to have idiopathic TTS (total 31 feet). Tinel's sign was positive in 16 feet (51.6 %) of TTS and four feet (10.5%) in control group. The statistically significant electrophysiological parameter was difference of sensory conduction velocity (SCV) between sural nerve and MPN. Amplitude and SCV of MPN were not significantly different between idiopathic TTS feet and controls.

Conclusion: Bilateral idiopathic TTS was more common than unilateral. Tinel's sign and difference of SCV between sural nerve and MPN may be helpful for the diagnosis of idiopathic TTS.

P623

Sympathetic skin responses evoked by muscle contraction

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Introduction: Voluntary muscle contraction is accompanied by an increase in sympathetic nerve activity. However, such an activation is not always paralleling with responses at the sweat gland level. The sympathetic skin response (SSR) is a simple and non-invasive method of autonomic assessment that reflects a synchronized activity of the sweat glands. The aim of our study was to examine the possible relationship between isometric muscle contraction (IC) and changes in the SSR.

Methods: In 11 healthy right-handed volunteers, we recorded the SSR from the palm of the hand induced by contralateral triceps IC (mSSR) of variable intensities and durations. We measured the latency, duration, amplitude, waveform and habituation index (HI) of the mSSR, in comparison to the SSR induced by supramaximal electrical stimulation (eSSR) of the brachial plexus at the axillae.

Results: A single mSSR was always present at a mean latency of 1.34 ± 0.5 s after the onset of IC. Response amplitude, but not latency or duration, correlated positively with the intensity of IC ($r = 0.67$; $p < 0.001$). The latency was shorter, the duration was longer and the HI was reduced in the mSSR in comparison to the eSSRs (ANOVA; $p < 0.05$ for all comparisons).

Conclusions: The mSSR is likely generated endogenously together with the motor commands since inputs from muscle afferents cannot account for response onset. This, together with its low level of habituation, underscores the possibilities of physiological and clinical studies using the mSSR, especially in the assessment of autonomic function in patients with nerve afferent problems.

P624

Taste and flavour increase cerebral blood flow during chewing

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Purpose: It is a known fact that the senses of taste and smell are conveyed to the brain through receptors that respond to chemical stimuli. It is also known that changes in cerebral blood flow (CBF) reflect neuronal activity in the brain. Thus, alteration of taste and smell stimuli may have some effect on neuronal activity. The study was conducted to examine whether sweetness and flavors in food can influence CBF during gum chewing.

Method: Twenty-four healthy dentate subjects (12 men and women, mean 27.0 ± 2.8 years old) participated in the study. CBF was assessed after at least four hours of having meals. A transcranial Doppler ultrasonography system (Multi Dop-T, DWL) was used to measure blood flow velocity of the left and right middle cerebral arteries (MCAs) which pass 80% of the blood in the cerebral hemispheres. It is known that olfactory sense stimulation is treated in front-orbital area, therefore near-infrared spectrophotometry was used to evaluate changes in the tissue hemoglobin level in the left and right frontal regions. Subjects were instructed to chew a piece of gum (for 5 min) at a rate of 1 Hz. Consecutive CBF monitoring was performed at rest before (5 min), during, and after gum chewing (5 min) with 10-min or more intervals between the monitoring. Test foods were (1) lemon-flavored sucrose gum, (2) unflavored sucrose gum, and (3) unflavored unsweetened gum, adjusted for hardness. These three types of gum were given to subjects in random order.

Difference in CBF before gum chewing (at the baseline) and that during 5-min gum chewing was determined from measurement data and the effect of different sweetness and flavors of tested gum on CBF was examined by Friedman's test and Bonferroni's correction.

Result: Blood flow velocity in the bilateral MCAs significantly increased during gum chewing compared with the baseline independent of sweetness or flavors and decreased immediately after chewing. Frontal CBF also increased during and after gum chewing compared with that of the baseline on both sides. Comparing these three types of gum, the lemon-flavored sucrose chewing gum induced significantly higher CBF than those of the other two types, while the unflavored sweet gum and the unflavored, unsweetened gum caused no significant change in CBF.

Conclusion: Our results suggested that influence of smell stimulation on CBF was stronger than that of sweetness.

P625

Assessment of minimal hepatic encephalopathy in cirrhotic patients treated with probiotics

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Objectives: The predominant strategies for minimal hepatic encephalopathy(MHE) diagnosis are psychometric tests. The aim of this study was to assess the reliability of trail making test(TMT) for practical use in evaluation of MHE in patients with probiotic treatment.

Methods: A cohort of 30 outpatients,sex ratio M/W = 9/21,age between 39–49 years old, middle education, with nonalcoholic end

stage liver diseases, Child-Pugh A (score 5 to 6 points) and stage 0 for hepatic encephalopathy according to West-Haven criteria, were enrolled in this study. They had psychological evaluation with psychometric test TMT, with separate assessment of TMT part A and B,setting as cut-off values for part A :78 seconds and for part B: 273 s. We divided our patients in 2 groups. First group with 15 patients received usual treatment for liver disease plus probiotics as a mixture of lactobacillus acidophilus $750x10^6$ and lactobacillus bifidus 250×10^6 living organisms, once a day at lunch time for 3 months. The second group with 15 patients received only usual medication for liver disease. None of the patients received medication that could modify encephalopathy in one way or another (lactulose, antibiotics, analgesics), or having TIPS. After finishing 3 months of treatment we repeated hepatological, neurological and psychological evaluation.

Results: The group with probiotic treatment had a significant reduction of time necessary to complete TMT-B from baseline mean time = 329 ± 25,06 seconds to final mean time = 302.2 ± 13.29 s ($p < 0.01$). The second group who didn't receive probiotics showed a slightly increasing of mean time necessary to complete TMT-B: from baseline 315.13 ± 20.20 to 323.4 ± 24.54 s ($p > 0.01$). TMT-A for the group with probiotics result in baseline time 43.33 ± 4.68 s, final time 41.4 ± 5.34; the group without probiotics baseline time: 43.46 ± 4.96 s and final time: 42.73 ± 5.47, both displaying times under cut-off line,since first administration of test. No significant differences were noted related to sex or age of the patients.

Conclusions: Our study showed that TMT part B is more sensitive and therefore more reliable in detecting changes related to MHE in this cohort of patients. Data related to TMT part A showed values under cut-off line, constantly situated in normal range area. According to psychological evaluation,TMT part B, treatment with probiotics improved neurocognitive abilities in Child A cirrhotic patients.

P626
Diagnostic value of α band frequency in EEG of Alzheimer patients

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Objectives: Digital EEG pattern specific for Alzheimer disease is not studied yet.

Methods: Resting EEG (10–20 electrode montage) was recorded by the use of "Brainscan" system in 150 persons divided in three groups: I 50 healthy 20–55 year old volunteers, II - 50 healthy 55–75 year old volunteers, III 50 patients with mild Alzheimer disease (2.5 ± 0.6 years of anamnesis). Psychic and somatic status of examined were studied accurately. For checking up α rhythm frequency after Furie's reversal transformation and elimination of β-θ- and δ- rhythms periodmetric analysis performed for single "pure" α rhythm (8–13.5 Hz). Finally mean frequency in frontal and occipital regions in EEG of all subjects compared.

Results: Significant distinction between a healthy subjects and Alzheimer patients has proved to be changed spatial—frequency α rhythm structure. High-frequency α rhythm is dominant in the occipital zone and low- frequency α rhythm prevails in the frontal one of a healthy subjects. The Alzheimer patients show the opposite relationship: the frontal α frequency is higher than in occipital zone. This phenomenon named the "inversion". It can be revealed only by mean of digital EEG, visually—no, because the difference between frontal and occipital mean frequency may be less than 0.01 Hz. It is necessary to remark that α rhythm inversion concerns only frequency without any concomitant alterations in regularity, amplitude or index.

The inversion discovered in 90% cases of Alzheimer disease, while among healthy persons of 20-55 years—in 2%, among healthy persons elder than 55 years—7%.

According CT investigation results any isolated occipital or frontal lobe pathology not found. Therefore α frequency spatial inversion is stipulated by violations of rhythm generator's function which is located in thalamic nuclei. The inversion mean EEG quality decline and determined by disharmony between thalamic and anterior α rhythm generators.

Conclusion: In EEG-pattern of Alzheimer disease inversion may be considerate as diagnostic sign. Compared to previous studies dedicated to α rhythm characteristics this was the first investigation that illustrated the α frequency profile sensitivity in revealing organic brain damage in Alzheimer patients. Future studies should evaluate the clinical usefulness of this approach in early differential diagnosis, disease staging, and therapy monitoring.

P627
Comparison of quantitative EEGs between frontotemporal dementia, Alzheimer's disease and age-adjusted controls

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Objective: To examine quantitative EEG (qEEG) abnormalities in frontotemporal dementia (FTD) and compare with Alzheimer's disease (AD) and age-adjusted controls.

Method: We studied three groups, matched with respect to demographic variables: 26 patients affected by AD, 25 patients with FTD and 28 normal subjects. We performed spectral analysis, calculating relative power within delta, theta, α and βband.

Results: in comparison with controls, FTD and AD patients show a widespread and increased theta activity, AD patients show an increased delta power in occipital regions and a decreased α activity in posterior regions. Moreover in AD patients we observed an increased theta and delta activity and a decreased α activity in posterior regions compared with FTD patients.

Conclusion: FTD patients reveal qEEG abnormalities compared with controls and a different pattern of qEEG changes than AD patients. These results suggest that QEEG may be helpful in FTD diagnosis and in distinguishing subjects with AD from subjects with FTD

P628
Visual-evoked potentials and macular degeneration

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Objectives: The object of this research is to evaluate the correlation of intermittent light (ILVEP) and pattern reversal visual evoked potentials (PRVEP) with the visual acuity (VA), size, volume and central retinal thickness (CRT) of choroidal neo-vascular lesions in patients with age-related macular degeneration (MD).

Methods: We studied 26 eyes of elderly patients with MD by ILVEP and PRVEP.

The subjects were placed in a dark room 1 meter facing a checkerboard screen with a 60 degree pattern. Electrodes were pasted at Oz (active), Fz (reference) and Fpz (ground). Pattern reversal occurred at a rate of 1.9 Hz. The average latencies of 100 VEPs were calculated for each eye separately with the other eye patched
The same procedure was performed using intermittent light stimulation eminating from googles placed over the subjects eyes.
The VA was recorded for each eye using early treatment diabetic retinopathy charts (ETDRS) along with the size of the neo-vascular lesion as determined by fluorescence angiography and the CRT and volume on optical coherence tomography.

Results: The latencies of the first positive wave for the ILVEP (P1) and PRVEP (P100) tests were compared with: the vision on the ETDRS, lesion size, macular volume, and CRT for each eye separately.
The mean latency of P1 of the ILVEP was 86 + 43 ms.
The mean latency of P100 of the PRVEP was 165 + 41.5 ms.
The mean CRT was 248 + 88.5 mm.
The mean lesion size was 16.8 + 18.9 mm^2 .
The mean lesion volume was 7.2 mm^3 + 1.4 mm^3.
There was no statistically significant correlation between P1 latency of ILVEP and vision, lesion size, macular volume, or CRT.
Furthermore, no statistically significant correlation could be found between the P100 latency of PRVEP and CRT or lesion volume.
On the other hand, a definite statistically significant correlation was obtained between P100 latency of PRVEP with VA ($p = 0.005$) and lesion size ($p = 0.019$).
This is further confirmed by the fact that no statistical correlation could be found between the PRVEP latencies and lesion characteristics in the non-diseased eye of the same patients.

Conclusion: We conclude from this study that there is a statistically significant correlation between P100 latency of the PRVEP with VA and lesion size, but not with lesion volume or CRT. Furthermore, the ILVEP test has no value in patients with macular degeneration as it does not correlate neither with visual acuity nor with the characteristics of the macular lesion.

P629

Alexithymia and changes of skin potential level during mental arithmetic task

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Objectives: Alexithymia is a difficulty in describing own state. Changes in skin potential level (SPL) is a negative electric potential in the palmar surface. It can be used for assessment of the state of arousal (Leiderman 1963). We examined relationships between individual levels of alexithymia and the changes of SPL during mental arithmetic task.

Methods: 21 healthy volunteers (10 males, 11 females, 19-23 y.o.) took part in the study. All volunteers were assessed for alexithymia using 20-points Toronto Alexithymia Scale (TAS-20) (Haviland 1996). The arithmetic task consisted of repetitive multiplying of different two-digit numbers in high temp during 9 minutes. SPL was recorded continuously before, during and after the task for 28 min in total. For assessment of mood and arousal changes subject filled in Lang's Self Assessment Manikin, SAM (Bradley 1994) four times during experiment: before SPL recording, immediately pre-onset and post-offset of the task, and after the end of the record.

Results: The arousal level was elevated at the beginning of recording and post-offset of the stimulation and gradually decreased after. After the end of the task mood had a tendency to decrease and did not normalize after the end of the record. SPL decreased before and increased after the onset of the task. The SPL recovered after the task at the end of 9 minute post-offset rest. Persons with higher level of alexithymia demonstrated faster recovery of pre-test SPL values after the task. There was also a trend to the relationship of alexithymia with greater SPL during the task.

Conclusions: Alexythymia is related to the faster relaxation after metal load that can be explained by the lack of attention to the assessment of ones own performance during preceding task.

Extrapyramidal disorders: movement disorders

P630

The clinical profile and radiological features of clinically diagnosed PSP-P patients in India

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Background: A proportion of pathologically diagnosed cases of Progressive Supranuclear Palsy do not develop the classic features, prove difficult to diagnose during life and are considered as atypical PSP. PSP-P is a distinct variant of PSP and is different from classical Richardson Syndrome and Parkinson's disease. There are few clinical reports of this disorder and none from South Asia. No radiological measurement details exist so far in literature to the best of our knowledge. Recognition of these features may further help segregate these patients from parkinsonian syndromes for diagnostic, therapeutic and prognostic determination.

Objective

1. To study the clinical profile demographics of clinically diagnosed PSP-P patients in India.
2. To describe the radiological characteristics of PSP-P and to compare it with preexistent data on PSP and PD.

Methods: The study included 10 patients of PSP-P. Details of history, with detailed neuropsychiatric evaluation and brain MRI were obtained. All the findings were recorded and analyzed for variations from existing PSP data. Patients of PSP-P were identified based on previously described clinical profiles. MRI midsaggital sections were taken and midbrain area and the ratio of the area of the midbrain to the area of pons were measured.

Results: All 10 patients had insidious onset asymmetric tremor, with a relatively slowly progressive course. Nuchal dystonia was present. There was vertical gaze palsy with restriction of upward gaze rather than downgaze restriction in all our patients (in contrast to reports of PSP-P in Western literature). Recurrent falls were not present early in the course of the disease, and were either absent or only occasional. Response to treatment was better than PSP, with a moderately good therapeutic response to levodopa, and was often sustained for several years in some cases. The midbrain area and midbrain to pons ratio in these patients were different from those of Steele Richardson syndrome and Parkinsonian patients reported in literature.

Conclusion: PSP-P is a distinct clinical entity with characteristic clinical features and radiological correlates that qualify for consideration of a defined diagnostic criterion with clinico radiological correlation.

P631

Clinical features and remission of idiopathic cervical dystonia in the treatment of Botulinum toxin

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Objective: Previous studies on Idiopathic Cervical Dystonia (ICD) have shown a favorite effect of Botulinum toxin (BTX) in ICD. BTX for ICD had been approved since 2001 in Japan, however there are only a few articles on BTX treatment for ICD. We had the study on the effect of BTX for ICD.

Subjects and methods: The subjects enrolled was sixty patients with ICD (30 males and 30 females, mean age: 50.6 ± 15.2 year-old, mean age of disease onset:45.1 ± 14.6 year-old, the severity of disease was 9.9 ± 4.4 points by Tsui score). The BTX used was BOTOX®. BTX was injected into target muscles under EMG guidance. The disease severity was evaluated by Tsui score.

Results: The mean dose of BTX was 94.6 ± 36.2 unit at first time and then had been increased within 240 unit each treatment. The average dose of BTX was from 150 unit to 200 unit at each treatment. Among of sixty patients, remission was observed in eighteen patients (30%). For further analysis, we divided three types of groups according to head deviation: one-way head deviation (simple form) group and a combination of two or three-way head deviation (complex form) group. Among 60 patients, there were ten patients with simple form, 26 patients with two-way deviation and 24 patients with three-way deviation. The most common component is head rotation both in simple and complex forms, followed by head tilt in complex forms. Combination of head tilt observed was about 50% in patients with two-way deviation and then up to 100% in three-way deviation. The disease severity was 6.2 ± 2.4 in simple group, 9.5 ± 4.0 in two-way deviation patients and 12.1 ± 4.3 in three-way deviation patients. The disease duration was significantly longer 11.8 ± 7.3 years in patients with simple form than that (3.8 ± 4.9 years) in two-way head deviation. There was no remission case in simple form, however eleven cases (42%) with remission observed in two-way head deviation group. The most common of clinical type of head deviation in remission group was a combination of two-way head deviation.

Conclusions: The specific clinical features of remission are younger, a combination of two-way head deviation and early start of BTX. Two-way head deviation is better than simple form in remission. Clinical aspect of simple from is significantly older, longer disease duration and lower scores of Tsui than complex forms, however, there is significantly less remission case in simple form than complex forms.

P632

Iron accumulation in the basal ganglia, movement disorders and hypoceruloplasminemia: a new nosographic entity?

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Introductions: For a long time abnormalities in ceruloplasmin (Cp) synthesis have been associated with disorders of copper metabolism, like Wilson's disease. Moreover Cp is also a multi-copper ferroxidase that plays a relevant role in the iron metabolism, as in an autosomal recessive neurodegenerative disease called Aceruloplasminemia. We describe five patients with movement disorders, iron brain overload and low ceruplasmin serum.

Patients and methods: In five sporadic patients (four men and one woman-mean age 63), evaluated for involuntary movements (chorea, dystonia) and bradikinesia in our Clinic between 2004 and 2006; several investigations were indicative of altered iron metabolism. They all underwent to routine laboratory tests, 24-hour urinary copper levels, serum ceruloplasmin and copper, iron and ferritine levels, immunological assessment, pharyngeal tampon, anti-streptococcal antibodies and genetic assessment for Huntington disease, Hallervorden Spatz PANK2+ and spinocerebellar ataxia. Brain and abdomen Magnetic resonance imaging (MRI), neuropsicological tests and oculistic assessment (to esclude Kayser–Fleischer ring, optic atrophy and retinite pigmentosa) were also performed.

Results: In all the patients there were low ceruloplasmin serum with normal cupruria and an abnormal T2 hypointensity of the basal ganglia due to iron deposition. No alteration in oculist evaluation and in abdomen MRI were found. Two patients had also high ferritine serum levels. In all of them the genetic assessments were negative and a descriptive diagnosis was made: "hipercinetic or akinetic rigid syndrome associated with iron deposition".

Conclusions: We exclude neurodegenerative diseases like Hallervorden Spatz PANK2+ , Huntington disease, Neuroferritinopathy and Wilson's disease, and hypothesize that the presence of progressive extrapyramidal symptoms in these patients is suspectable of altered iron metabolism, due to an "hypoceruloplasminemia". It's reported in literature cases of multiple system atrophy and cerebellar ataxia with hypoceruloplasminemia, indicative of some relationship between Cp and the pathogenesis of movement disorders.
The antioxidant role of Cp may play a role in neurodegeneration, most notably in the basal ganglia diseases, where it could be the background of a new nosographic entity.

P633

Rapid onset dystonia-parkinsonism complex after delivery: case report

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Objective: Rapid onset dystonia-parkinsonism complex (RPD) is a rare, autosomal dominant movement disorder with reduced penetrance, abrupt onset over hours to weeks, with stabilization within 30-60 days, prominent bulbar dystonia along with signs of parkinsonism and/or identifiable triggers. We report a patient with apparently sporadic genetically proved RDP with childbirth as a trigger event in disease appearance.

Methods: Diagnostic tests in presented patient focused on excluding secondary dystonia, likewise Wilson's disease. Furthermore, brain MRI, SPECT of the brain—DAT scan and genetic analysis were performed.

Results: A 32 year-old woman admitted at our outpatients ward complaining of speech disturbances, problems with swallowing and gait difficulties. Her symptoms had appeared after delivery and had developed over the course of few hours and progressed in the following week. Over the two-years period of follow-up there was no progression of initial symptoms. Her clinical picture included severe dysarthria, dysphagia, drooling, orolingual dystonia with sardonic smile, hypobradikinesia of the right limbs and intermittent dystonia of the right foot while walking. She underwent 6 months levodopa trial (400 mg daily) without any response, and also was treated with

baclofen (up to 75 mg daily) and amantadine unsuccessfully. MRI and DAT scan showed no abnormalities.

Conclusion: There was no benefit of levodopa in treatment of our patient which is in accordance to the literature, despite the fact that in some patients CSF homovanilic acid is reduced. The interesting remark is appearing of symptoms after delivery of the second child

P634

Idiopathic basal ganglia calcification (Fahr disease) in Serbian family

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Introduction: Fahr disease or idiopathic basal ganglia calcification (IBGC) is a very rare neurodegenerative syndrome that is associated with a variety of movement disorders and neurobehavioral and cognitive manifestations. Despite numerous clinical, pathological, and biochemical investigations, its etiology remains unknown.

Objectives: To present a Serbian family with IBGC.

Methods and results: We have identified three members of one family (father, daughter and son) with probable autosomal dominantly inherited IBGC. All of them had positive CT findings but completely different clinical presentation. The proband, 56 years old woman, had mild orobuccal dyskinesias and mild choreoathetoid movements of both hands, and almost not paying attention on her symptoms, in the contrast with marked symmetric calcified areas in basal ganglia, thalamus, dentate nucleus, periventricular white matter on CT. We excluded all secondary causes of calcification in her case. Her 58 years old brother had very similar distribution of calcification on CT, but different clinical presentation with isolated gait freezing as only clinical sign. Father, 88 years old, who was asymptomatic, also showed calcification of the basal ganglia on CT, suggesting an autosomal dominant inheritance.

We performed neurological, neuropsychological and psychiatric assessments, CT, HMPAO-SPECT and DaT-SPECT imaging, transcranial parenchimal and doppler sonography, EEG, EMNG, visual, auditive, sensor and motor evoked potential in our three patients, in order to show wide spectrum of abnormalities in IBGC and heterogeneity in clinical presentation in the same family (video presentation also available).

P635

The pattern of grey matter and white matter atrophy in patients with Parkinson's disease and depression: a voxel-based morphometry study

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Objective: Depression is a frequent neuropsychiatric feature of Parkinson disease (PD). However, the pathophysiology of depression in PD is still poorly understood. In this study, we investigated in vivo the regional pattern of grey (GM) and white matter (WM) atrophy in patients clinically diagnosed as PD with (PD-Dep) and without depression (PD-NDep).

Methods: Thirty-nine PD patients (age 66 years $\pm$ 8 standard deviation [SD], men 25, Unified Parkinson Disease Rating Scale III [UPDRS III] 20.4 $\pm$ 7.3 SD) were diagnosed based on clinical consensus criteria. Depression was diagnosed on the basis of DSM IV criteria. Hamilton rating scale for depression (HAMD) was administered to all patients. Using the Statistical Paramentric Mapping (SPM5) and the recent Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) method, voxel-based morphometry (VBM) was used to assess GM and WM atrophy in PD patients and 26 age and sex-matched healthy controls (age 63 years $\pm$ 7 SD, men 14).

Results: Fourteen patients were considered depressed. No UPDRS III difference was found beween patients group. The mean HAMD score was 21.7 in PD-Dep and 8.7 in PD-Ndep patients ($p < 0.001$). Compared to controls, both PD-NDep and PD-Dep patients showed regions of GM loss in the bilateral dorsolateral and orbitofrontal cortices, in the right caudate nucleus, hippocampus, anterior cingulate gyrus, and in the left angular gyrus. No significant difference in GM atrophy was found between PD-NDep and PD-Dep subjects. No significant WM loss was found in PD-NDep patients compared with both the other groups. When comparing PD-Dep with controls and PD-NDep patients, WM atrophy was found in the right orbitofrontal region, anterior cingulum and inferior temporal regions. Moreover, in all PD patients HAMD score was significantly correlated with orbitofrontal WM atrophy.

Conclusions: The general pattern of GM atrophy appears to be similar in PD-NDep and PD-Dep patients, suggesting that GM loss may not be associated with depression in PD. On the other side, WM appears to be affected in PD-Dep patients only, suggesting that orbitofrontal and cingulate WM atrophy may play an important role in the pathophysiology of depression in PD. These findings are consistent with the hypothesis that depression in PD may result from a disconnection between the orbitofrontal cortex and the lymbic system.

P636

Cognitive impairment in multiple system atrophy

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Background: Multiple system atrophy (MSA) can be divided into two groups according to clinical and pathological findings; MSA-P type and MSA-C type. A few studies demonstrated some cognitive impairment in MSA but a well designed study including a large number of patients has rarely been performed. Furthermore, a direct comparison in neuropsychological assessment between MSA-P and MSA-C type has not been reported.

Objectives: The aim of this study is to compare the neuropsychological findings between MSA-P and MSA-C type. We also compared the neuropsychological findings between MSA and Parkinson's disease (PD).

Method: Four subject groups (28 patients with MSA-P, 20 MSA-C, 50 PD, 35 healthy control) participated in this study. They were all matched for age, education periods and disease duration. All subjects were evaluated using the Seoul Neuropsychological Screening battery (SNSB). Detailed clinical history, motor examination and clinical disability were also obtained. Statistical analysis was performed with Mann Whitney test and chi-square test.

Results: There were no significant differences in neuropsychological test between MSA-P and MSA-C type. However, the patterns of cognitive impairments were somewhat different between the two groups. Compared to the control and PD groups, patients with MSA-P type showed lower score in MMSE, naming test, repetition, visual memory test, and patients with MSA-C type in frontal executive function such as go-no-go, alternating square and triangle and luria loop test. The performance of MSA patients was

significantly impaired in most items compared to the control and PD groups.

Conclusion: There were somewhat different patterns in neuropsychological tests between MSA-P and MSA-C type if specifically looked in. In contrast to the previous studies, patients with MSA showed worse performance compared to PD patients.

P637

Huntington's disease in a cohort from Argentina

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Objectives: To characterize clinical and epidemiological features of a cohort of patients with Huntington's disease (HD) from Argentina and compare this sample with HD patients from other world regions. Background: HD is a neurodegenerative disorder with a wide variation in the clinical presentation and prevalence among different ethnic groups.

Material and methods: We evaluated 29 non-institutionalized HD patients from 26 families. All patients but 2 were symptomatic. Gender, ethnicity, education, affected parent, age of onset and CAG repeat length were carefully analyzed. Twenty-seven patients were genotyped for CAG repeat length.

Results: Our sample comprised 14 females, mean age 48.71 $\pm$ 14.07 years (range 23–72) and 15 males, mean age 51.33 $\pm$ 14.03 years (range 23–72). The mean age at onset of HD was 42.78 $\pm$ 12.01 years (range 22–66), with 41.54 $\pm$ 9.89 years (range 23–58) for females and 49.93 $\pm$ 13.97 years (range 22–66) for males. High school, college and university education was completed in 31.01% of the individuals, respectively. Motor and psychiatric symptoms at onset occurred at the same percentage (44.83%). Western Europe ancestry was identified in 79.3% of patients. Expanded HD alleles varied from 36 to 55 repeats (mean. 44 $\pm$ 3.78); normal alleles ranged from 15 to 24 repeats (mean 18.75 $\pm$ 2.22). Ten cases showed a paternal transmission. The mean size of the expanded CAG repeat was non-significant for paternal or maternal transmission (mean: 44.52 $\pm$ 5.46 vs.43.20 $\pm$ 2.66). There was a negative correlation between the number of CAG repeats and the age at onset of the disease r = -0.7017 (Pearson correlation coefficient), $r^2 = 49.24\%$.

Conclusions: Clinical and genetic characteristics of this sample were similar to those reported in Western European countries and North America but different than those of other South American populations. Although non-extensive epidemiological data of HD are available in Argentina, these findings agree with the genetic structure of the Argentinean population (80.2% European).

P638

Bilateral globus pallidus stimulation in Westphal variant of Huntington's disease: a case report

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Background: Westphal variant of Huntington disease (HD) is characterized by dystonia, rigidity, bradykinesia, unsteady gait and cognitive impairment. Patients usually show the first symptoms before age 20 and carry an expansion of more than 60 CAG repeats in Huntingtin gene. Deep brain stimulation (DBS) is an effective treatment for several conditions characterized by involuntary movements such as essential tremor, Parkinson's disease, and dystonia. Its application is expanding rapidly. DBS in HD has been anecdotally described with some improvement in choreic component. No data exist about DBS in Westphal variant of HD.

Case report: A 28-year old man with a 14-year history of genetically confirmed HD and clinical characteristics consistent with Westphal variant showed a progressive disabling course with dystonia of the trunk and limbs, difficulty in walking and in movement, myoclonus of upper limbs, dysarthria, dysphagia, and cognitive impairment. He was currently treated with sodium valproate, benzodiazepines and pramipexole. The patient underwent bilateral implantation of quadripolar electrodes (model 3387; Medtronic®) in the posterior internal globus pallidus (GPi) under microelectrode guidance. A dual channel programmable pulse generator (KINETRA; Medtronic®) was implanted subcutaneously 1 week later.

Results: Immediately after the DBS electrode implantation complete spontaneous suppression of myoclonus was observed together with improvement of trunk and limb dystonia and rigidity, fluidity of walking and ocular movements. After starting GPi stimulation at progressively higher frequencies mild dystonia and myoclonus reappeared. The Unified Huntington's Disease Rating Scale (UHDRS) scores for the motor and behavioural subsets changed respectively from 73 and 7 preoperatively to 60 and 7 after implantation (stimulus off) and to 40 and 2 after stimulation (1 V, 70 Hz) at 2 weeks from surgery. Drug treatment was continued without changes throughout the evaluation.

Conclusions: GPi stimulation induced significant favourable motor effects in our patient with Westphal HD. Both lesional and stimulus-related components are presumably responsible for the improvement observed.

P639

Fatal case of hemiballistic movements emerging one month after intracerebral haemorrhage concomitant with benign hemichorea

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Introduction: Hemiballism is a rare hyperkinetic movement disorder that presents with unilateral flinging movements of the limbs. Movements are involuntary, of wide amplitude, and irregular. The most characteristic finding in hemiballism is a lesion of the contralateral subthalamic nucleus, usually of vascular origin. Hemiballism often coexists with hemichoreic movements and can smoothly change into hemichorea (hemichorea/hemiballism).

Case report: A 62- year-old women with hypertension was admitted to a local hospital after an acute onset of hemichoreic movements of the left side of her body. On admission the patient had hypertension crisis. During hospitalisation she was diagnosed with adult-onset diabetes mellitus. Computed tomography of the head (CT) revealed a hemorrhagic lesion in the right temporo-parietal region (nucleus caudatus and lenticularis). The hemichoreic movements disappeared quickly as a result of benzodiazepine treatment, and she was discharged completely free from hyperkinetic movements. The patient was admitted again to the hospital after 1 month with unexpected recurrence of intense involuntary movements characterized as hemiballism. Surprisingly CT showed no new focal lesions in the brain, but only a resolution of the previously documented hemorrhagic focus. Treatment with neuroleptic and benzodiazepine drugs did not soften extrapyramidal movements. The patient was transferred to the Department of Neurology of Wroclaw

Medical University with severe hemiballism of the left side of the body. Patient condition deteriorated during hospitalisation. Three days later the movements became hemichoreic, after next five days disappeared. Disturbances of consciousness intensified. She developed high fever, severe anaemia, renal and hepatic failure, hyperglycaemia and electrolyte imbalance. Despite resuscitation the patient died after another few days.

Discussion: We report rare fatal case of intense hemiballism, that revealed only whole month after intracerebral haemorrhage (right nucleus caudatus and lenticularis). Haemorrhagic stroke was followed by transient, benign left hemichorea disappearing in a few days. Abrupt hemiballism was not connected with a new vascular lesion in the patient's brain (CT showed only a resolution of the previously documented hemorrhagic focus). Severe movement disorder could have been also related to metabolic disturbances - newly diagnosed adult-onset diabetes mellitus with non-ketotic hyperglycaemia.

P640

Evoked potentials in patients with Wilson's disease

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Background: Wilson's disease is an inherited disorder of copper metabolism presenting with a variety of symptoms but commonly as a liver or neuropsychiatric disease. Abnormal evoked responses are constantly found among patients with neurological manifestation and sometimes in patients with hepatic presentation or in presymptomatic siblings suggesting that evoked potentials can be used in the assessment of the subclinical nervous system involvement in Wilson's disease

Patients and methods: Visual evoked potentials (VEP) were performed in 36 and brainstem auditory evoked potentials (BAEP) were done in 37 Wilson's disease patients. The diagnosis of Wilson's disease was based on the clinical symptoms and laboratory findings and confirmed by identification of the two disease-causing mutations in ATP7B.

Results: BAEP were abnormal in 26 out of 28 patients with neurological manifestation of Wilson's disease. The latencies of III and V waves and interpeak III–V and I–V latencies were significantly prolonged in patients with neurologic manifestation compared with healthy controls and patients with hepatic manifestation. The latter had normal BAEP. VEP were abnormal in 81% of our patients. Abnormal VEP were recorded in 6 out of 7 patients with hepatic presentation. The values of N75, P100 and N145 latencies were significantly longer in patients than in healthy controls.

Conclusion: BAEP are frequently abnormal in patients with neurological presentation of Wilson's disease. Even without clinical and neuroimaging evidence of nervous system involvement, there is subclinical dysfunction of brainstem auditory pathways. In contrast to previously published studies, VEP are more frequently abnormal in Wilson's disease patients. Prolonged P100 latency was found in 85% of the patients with hepatic presentation suggesting frequent subclinical involvement of the visual pathways.

P641

Transcranial brain sonography in differential diagnosis of Parkinson's disease and atypical parkinsonian syndromes

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Background: Clinically differentiating Parkinson's disease (PD) from various degenerative forms of atypical parkinsonism (ATP) (progressive supranuclear palsy, PSP; multiple system atrophy, MSA; corticobasal degeneration) may be quite challenging. The use of transcranial brain sonography (TCS) has been proved as sensitive and reliable in detecting basal ganglia (BG) alterations as well as the third and lateral ventricles changes which may be helpful in differentiating PD from ATP.

Objective: to evaluate the value of the TCS in differentiating PD from ATP in a group of consecutive patients with PD, PSP, and parkinson variant of MSA (MSAp).

Methods: The study comprised 214 patients with sporadic parkinsonism and 50 healthy age-matched controls. TCS was performed in a previously described manner, by an examiner who was blinded to the clinical data.

Results: Moderate or marked substantia nigra (SN) hyperechogenicity on one or both sides was found in 89.5% PD, 18.75% PSP and 16.7% MSAp patients, and in 8.3% of normal healthy subjects. The findings of normal SN echogenicity indicated the clinical diagnosis of ATP (sensitivity: 82%, specificity: 89%, PPV: 72%, NPV: 94%). The combination of the SN hyperechogenicity with any other TCS finding did not improve the sensitivity or specificity of differentiation between PD and ATP. Third-ventricle (TV) dilatation of more than 10 mm was found in 87.5% of PSP patients, and was less frequent in controls, PD and MSAp. Estimates of this parameter as a discriminative measure showed that PSP might be discriminated from controls, PD and MSAp (PPV of 87, 68, 87%, respectively). Hyperechogenicity of the lenticular nucleus (LN) was found in 19% PD, 72% PSP and 78% MSAp patients. Echogenicity of thalami and caudate nuclei were not significantly different between groups and did not contribute to discrimination between them. The combination of LN hyperechogenicity and normal SN echogenicity discriminated ATP from PD with the PPV of 91%. The TV dilatation in combination with LN hyperechogenicity differentiated ATP from PD, and PSP from PD, with a PPV of 92% and 91%, respectively. If these two parameters were combined with normal SN echogenicity these predicitivities reached 100%.

Conclusion: TCS is an easy to implement, non-invasive, and inexpensive technique that could help in the differential diagnosis of parkinsonian syndromes. The routine use of TCS in the clinic could enable disease-specific therapy to be started earlier.

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P642

Receptor cardiac scintigraphy with 123I-metaiodobenzilguanidine (MIBG) for differential diagnosis between idopatic Parkinson's disease and atypical parkinsonism in patients with extra-pyramidal and dysautonomic disorders

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Objectives: Aim of the study is operate a differential diagnosis between idiopatic Parkinson (IPD) and atypical Parkinsonisms such as multisistemic atrophy (MSA) and progressive supranuclear palsy (PSP) in patients with extrapyramidal disturbances and disautonomic disorders.

Methods: Examined 13 Caucasian patients, with extrapyramidal disturbances such as tremor or bradykinesia and one or more disautonomic disorders such orthostatic hypotension, nicturia, sphynteric and REM-sleep disturbances. The pharmacological tests with L-DOPA and insufficient Apomorphine performed in all patients showed little or no response. Computerized Tomography (CT) and a 1.5 magnetic resonance imaging (MRI), scans gave aspecific results, absence of previous focal symptoms and/or signs of cerebral vascular disease (CVD). DATSCAN cerebral SPECT showed a miscellaneous damage degree of nigro-striatal dopaminergic pathway.
At the final diagnostic stage, 4 patients were considered with possible IPD, whereas the remaining 9 suspected of atypical Parkinsonism. Patients were therefore assessed through scintigraphy to glide down cardiac in front projection on the thorax with acquisitions to 1 and 3 h from the 123I-metaiodobenzilguanidine (MIBG) injection. In 3 patients a 4-h cardiac SPECT has been acquired also. The diagnostic judgment was formulated based on the visual and semiquantitative analysis by means of calculation of the ratio advanced heart/mediastinal space (H/M) (cut-off $\geq$ 1.7).

Results: Out of 13 examined patients, 4 suspected IPD, showed a deficit of the fixation of the radiopharmaceutical left ventricular wall, and the ratio value H/M has turned out inferior to the cut-off which confirmed the previous diagnosis. Out of 9 patients suspected of atypical Parkinsonism, 8 showed scintigrafic pattern normal with advanced ratio H/M to 1.7; in a single patient the diagnosis was inconclusive because both the pattern visual and the borderline of the ratio have not allowed an univocal interpretation, also because of an abnormal increase of the pulmonary captation that has altered the value background activity. SPECT scans in 3 patients have not influenced meaningfully the diagnostic judgment.

Conclusion: The receptor scintigraphy with MIBG has demonstrated a valid support for the differential diagnosis between IPD and Parkinsonisms in patients with scintigrafic evidence of nigro-striatal damage, no meaningful pharmacological and radiological tests and concomitant disautonomic deficit.

P643

Face emotions recognition in spinocerebellar ataxia patients

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Objectives: Recognition of other's emotional states is fundamental for a regular social behaviour. So far only few studies have assumed that cerebellum is also involved in the emotional processing. We know that cerebellum is implicated in cognitive functions with a peculiar pattern of impairment in patients with cerebellar lesions defined as Cerebellar Cognitive Affective Syndrome, including frontal, attentional, linguistic, visuospatial, mnestic, affective and social disturbance.
Spinocerebellar ataxias (SCA) are a group of heterogeneous degenerative pathologies involving cerebellum and his connections. Garrard et al. (2008) demonstrated that SCA patients are not impaired on tasks requiring emotional processing, but on Theory of Mind (ToM) tasks, suggesting that social cognition can be fractionated into functionally independent subsystems.
In the present study we assessed the ability to identify facial expressions of emotions in a group of SCA patients to better understand the role of cerebellum in the emotional processes.

Methods: Twenty patients, affected by SCA (9 SCA2, 5 SCA6, 2 SCA7, 4 SCA8), were recruited in our Ataxia Center.
To assess recognition of facial emotions we used the Ekman 60 Faces Test for basic emotions, that used photographs displaying happiness, sadness, disgust, fear, surprise or anger. For social emotions we used the Tamietto 50-faces displaying flirtatiousness, admiration, arrogance, guilt or neutral. Twenty healthy subjects age and education-matched were enrolled as a control group. Participants were required to choose the label that best describes the emotion displayed by each face.

Results: We found an impairment in basic emotions recognition in patients, the worse performance was in sadness recognition. We did not find any differences between SCA's subgroups. A greater impairment has been observed in the social emotions recognition. Negative emotions (arrogance, guilt) recognition was more affected and SCA2, SCA7 had the worse scores.

Conclusion: The deficit in emotions recognition among SCA patients could be partially explained by their executive or attentional deficit linked to the cerebellar degeneration. The worse recognition in social emotions could be justified by their greater complexity and consequent heavier mental processing demand. The alternative hypothesis is that cerebellum is involved not only in ToM, but also in other aspects of the social cognition more focused on somatomotor processing.

P644

Growth hormone and insulin-like growth factor-I and cognitive function in Huntington's disease

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Background: Neuroendocrine alterations in Huntington Disease (HD) were reported in recent different studies. Previously we demonstrated an increase in basal plasma of GH and IGF1 levels. Current suggestions point out the possible influence of the somatotropic axis in cognitive deficits seen with aging, in adults with growth hormone deficiency and in neurodegenerative disease, such as in Alzheimer disease. However, data on GH/IGF-1 axis and cognition in HD is scarce.

Objectives: The aim of our study was to investigate the longitudinal relation between somatotropic hormonal disturbances in Huntington's disease and the cognitive deficits.

Methods: The studied population consisted of 109 genetically documented HD, aged between 21-85 years. We determined fasting blood levels of total IGF1, GH and IGFBP3 plasma concentration at

baseline. The Unified Huntington Disease Rate Score (UHDRS) cognitive was used to assess cognitive impairment at both baseline and follow-up period. The mean of follow-up period was 1.2 ± 1.2 years.

Results: By using mixed linear models analysis we found that higher plasma concentration of IGF1, and IGF1/IGFBP3 ratio as well as GH in male was significantly associated with more cognitive decline.

Conclusion: Our findings suggest that the systemic resistance to IGF-1 in HD may contribute to the progressive decline of the cognitive function.

P645

The pattern of cognitive impairment associated with the motor subtype in Parkinson's disease

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Objectives: Previous studies found over-representation of a postural instability and gait difficulty (PIGD) motor subtype in Parkinson's disease with dementia (PD-D).

Methods: There were 120 patients with Parkinson's disease (PD) included in this study. All patients were evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) and neuropsychological tests. On the basis of, the criteria for dementia (DSM-IV) and the results of the neuropsychological assessments, the patients were divided into three groups: non-demented (PD-ND), mild cognitive impairment (PD-MCI) and dementia (PD-D). In addition, patients were also grouped into two phenotypes, tremor or postural instability gait difficulty (PIGD)-predominant groups based on the UPDRS components. We also analyzed clinical characteristics and subtypes of disease. In addition, the relationship of the cognitive impairments and the parkinsonian motor handicaps was evaluated.

Results: There was a significant relationship between cognitive impairment and the motor subtypes; the PIGD group had a higher prevalence of PD-D than did the other group. In addition, there were significant correlations between the general cognitive functions and motor handicaps, especially those with axial symptoms. Multiple logistic regression analysis showed that the motor subtype was independently associated with the cognitive decline in PD.

Conclusion: These findings support that cognitive decline in patients with PD is associated with specific motor subtype in PD; this might be explained by the involvements on nondopaminergic pathways. These results have implications for clinical management of PD with regard to the motor symptoms and cognition.

Neuro-oncology

P646

Subtentorial involvement in secondary brain lymphoma

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Case Report: We present the case of a 51-year old man with a medical history of retroperitoneal non-Hodgkin large B-cell lymphoma, treated with 8 cycles of chemotherapy (CHOP), declared as complete remission by the hematologist at the final evaluation (including a whole body PET examination). The patient was addressed to our department 2 months later for right palpebral ptosis, swallowing difficulties and behavioral changes. On physical examination the patient had bilateral IIIrd nerves palsy, gait and limb ataxia, bilateral pyramidal signs. Brain MRI showed bilateral brainstem and thalamic lesions with gadolinium enhancement. Lumbar puncture founded decreased chlorides (627,7 mg/dl) and CSF flowcytometry assay detected large mononuclear B cells with the CD5 + CD20 + CD45 phenotype. HIV antibodies were negative. A diagnosis of secondary brain lymphoma with midbrain involvement was made based on patient history, clinical and paraclinical findings. The patient was treated initially with corticosteroids, with short lasting response, followed by intrathecal cytarabine with almost complete neurological remission. Unfortunately, he died aproximatively 4 months later.

Discussion: The particularity of our case is bilaterally midbrain involvement.

Central nervous system involvement with secondary malignant lymphoma is a rare complication observed in the management of patients with hematological malignancy. Most studies report direct involvement of the neuraxis at one time during the course of the disease (2 to 10 percent of patients with aggressive NHL). 90% of CNS lymphomas are supratentorial, commonly affecting frontal and parietal lobes, deep grey nuclei, corpus callosum and clustering around ventricles and gray matter/white matter junction. Lesions are often multiple. Spinal cord and leptomeninges are more frequently affected in secondary CNS lymphoma and are associated with considerable morbidity and mortality. Subtentorial lesions in CNS lymphoma are very rare.

Repeated CSF examination, brain biopsy, 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET) and thallium-201 single photon emission computed tomography (Tl-SPECT) can help to diagnose CNS lymphoma. Response to steroids and radiation therapy is often spectacular but short lasting. Long-term survival is poor (mean survival time 4-6 months).

P647

Anti-NMDA receptor encephalitis without tumour association: a case report

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Objectives: Anti-NMDA receptor encephalitis is a recently described disorder that often associates with ovarian teratoma. We report a new case without tumor association.

Methods: A 22-year-old woman was admitted to Psychiatry for one month history of apathy, fatigue, auditory hallucinations and paranoid thoughts. Her symptoms worsened, with mutism, unconsciousness and central hypoventilation requiring ventilatory support. MRI of the brain revealed T2 and FLAIR hyperintensities in medial temporal lobes, right caudate, pons and middle cerebellar peduncles. In EEG generalized epileptic discharges. CSF with 30 lymphocytes/mcl and oligoclonal bands. Studies for infections, collagen-vascular autoimmune disorders, thyroid autoimmunity, paraneoplastic and VGKC antibodies negative. Antibodies to NR1/NR2 heteromers of NMDA receptor were identified in CSF. No tumor in body CT and transvaginal ultrasound. She received corticosteroids and IVIG with initial improvement two weeks after. MRI hyperintensities resolved and mesial temporal atrophy developed. Progressive improvement of memory deficits and episodes of agitation and disorientation. Three

months after symptom presentation, inversion of sleep patterns and regressive behaviour; four months later she had resumed her studies without relapses or residual deficits.

Results: In 2005 a new antibody-associated encephalitis with prominent psychiatric symptoms, hypoventilation and ovarian teratoma was described. Target autoantigen was found to be NR1/NR2 heteromers of NMDA receptor. A recent series of 100 patients has established clinical features, tumor association and response to treatment. Most patients presented with psychiatric symptoms or memory problems and developed seizures, decline of consciousness, diskynesias, autonomic instability or central hypoventilation. 60% of patients had a tumor, usually ovarian teratoma. All patients had abnormal EEG findings and most CSF lymphocytic pleocytosis. In 50 % of patients brain MRI showed hyperintensities on T2 or FLAIR sequences in one or several brain regions. Despite severity of the disorder, 75% of patients recovered or were left with mild deficits.

Conclusion: We report a new case of anti-NMDA receptor encephalitis with extensive MRI lesions, lack of underlying tumor, and excellent outcome despite severity of the symptoms. Given that prompt diagnosis and treatment are usually effective, physicians should keep a high index of suspicion for this recently characterized disorder.

P648

Factors released from lung tumour cells alter adhesion molecule expression and increase activation of human cerebral endothelial cells

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Objectives: To examine whether factors released from cultured lung tumour cells alter expression of the adhesion molecules inter-cellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and endothelial selectin (E-selectin) and the endothelial cell activation marker endoglin (CD105) in cerebral endothelial cells (ECs). This system was used as an in-vitro model of lung tumour metastasis to the brain.

Methods: Two different lung tumour cell lines A549 (adenocarcinoma) and SK-MES (squamous cell carcinoma) were cultured in a defined basal medium (DMEM-BS) and the factors released by the tumour cells were collected (conditioned medium (CM)). Human cerebral microvascular endothelial cells (HCMEC-D3) were seeded on 96 well plates, treated with CM or DMEM-BS for 4 and 24 h and adhesion molecule expression (ICAM-1, VCAM-1 and E-selectin) and CD105 expression analysed by ELISA. Results were analysed by the Mann-Whitney test.

Results: Compared to control levels (100%) SK-MES CM significantly increased ICAM-1 expression after 24 h to $122.5 \pm 6.8\%$ ($p = 0.037$, $n = 3$) and VCAM-1 expression after 4 and 24 h to 169.99 ± 91.35 and $142.11 \pm 44.04\%$ respectively ($p = 0.037$, $n = 3$). E-selectin expression was increased after 4 h activation with A549 and SK-MES CM to $120.99 \pm 11.26\%$ and $117.25 \pm 10.74\%$ respectively ($p = 0.002$, $n = 6$).
CD105 expression after 4 h was 131.06 ± 19.29 and $126.44 \pm 10.86\%$ ($p = 0.014$, $n = 4$) versus control (100%) for A549 and SK-MES CM respectively. At 24 h, CD105 expression was $215.24 \pm 17.8\%$ and $195.28 \pm 20.3\%$ ($p = 0.014$, $n = 4$) versus controls (100%) for A549 and SK-MES CM respectively.

Conclusions: Proteins/factors released from the two different lung tumour cell lines significantly alter adhesion molecule expression of cerebral ECs. These factors also activate and significantly increase CD105 expression of cerebral ECs. In conclusion, factors released from lung tumour cells significantly influence the cellular phenotype of cerebral endothelial cells.

P649

2 cases with leptomeningeal carcinomatosis in gastric cancer

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Leptomeningeal carcinomatosis (LC) is a neurologic complication of cancer. Although LC is common seen in patients with leukemia,breast cancer and lung cancer, LC is an uncommon complication of gastric cancer.
We aimed to present 2 cases of leptomeningeal carcinomatosis in gastric carsinoma.

Case1: A 62-year-old male admitted to our outpatient clinic with headache, vertigo, nausea and vomitting. He was diagnosed with advanced gastric adenocarcinoma 6 months ago. On his neurological examination, he had trunk ataxia.Cerebellar tests were bilaterally abnormal. He had no neck stiffness or other meningeal irritation signs. Brain MRI showed meningeal contrast enhanced in infratrentorial space. Analyses of cerebrospinal fluid showed malignant epithelial cells and signet ring cell types. The patient died within 2 weeks.

Case 2: A 65-year-old male patient with advanced gastric adenocarcinoma suffered from diplopia and headache for 1 month. He had third nerve plasy on the left side and minimal hemiparasis on the right side. Contrast enhanced brain MRI was normal. Analyses of cerebrospinal fluid showed signet ring cells. The patient deteriorated within 2 week and died.
LC is an uncommon complication of gastric cancer. The physicians should be alert with regard to LC in the presence of unexplained neurologic symptoms in the patients with gastric cancer. Cerebrospinal fluid analyses are necessary when brain MRI is normal.

P650

Reflex sympathetic dystrophy in patient with neurofibromatosis type I

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Introduction: The neurofibromatosis type 1 is an autossomal dominant disorder, that can cause multiple clinical manifestation. Diagnosis of neurofibromatosis is based on clinical criteria. Neurologic compression structure may be an important sign of this disease.
The diagnostic criteria for neurofibromatosis type 1, according to the consensus held by the National Institutes of Health (NIH) in 1986, must include two or more of the following findings: (1) six or more café-au-lait spots on the skin, larger than 5 millimeters (mm) across in children or 15 mm across in adolescents and adults; (2) two or more neurofibromas of any type, or one or more plexiform neurofibroma; (3) freckling under the arms or in the groin area; (4) optic nerve glioma; (5) two or more Lisch nodules (iris hamartomas); (6) a distinctive bony lesion, such as sphenoid dysplasia or thinning of a long bone and (7) first degree relative diagnosed with neurofibromatosis type 1.

Case report: A 39-year-old man, white, smoker, was admitted to our hospital presenting a lack of strength and pain throughout the left

upper limb about six months. The previously healthy patient, denied the use of chronic medications, neither surgical procedures in the past. On physical examination, it were identificated neurofibromas, the largest located in the left lumbar region and right upper limb. The patient also had axillary freckles, more than six caféau-lait spots in the back, and Lisch nodules in the iris. Therefore, fillding in the diagnostic criteria for the Neurofibromatosis type I.

The left upper limb was in dystonia position with internal rotation of the arm and flexion of wrist sustained. The hand was sweating, swelling and blushing.

It was performed MRI of the brain which was normal. The MRI of the cervical spine showed diffuse increase in the volume and intensity of intra-medullary signal in T2 weighted sequences in the segment between C3 and T2, especially on the left side.

The patient was referred for neurosurgical group, which opted for a conservative treatment in view of the imminent risks of performing biopsy of the lesion and the small possibility of complete resection of the tumor. Currently, he is being followed in outpatient using steroids and antihypertensive treatment.

Conclusion: Neurofibromatosis patients should be monitored regularly and compressive symptoms should be precociously investigated.

P651

Radiation-induced aneurysm

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Introduction: Radiation injuries on the vascular system are well recognized, occurring most frequently as small vessel thrombo-oclusive phenomena. Radiation induced intracranial aneurysms are rare, but with potentially fatal complications. We report a case of a left middle cerebral artery aneurysm, in a patient irradiated to an ipsilateral oligoastrocytoma 8 years before. Clinical aspects and etiopathogenesis are discussed, supported by literature review.

Case report: A 36-year-old female, without past medical history, had a first seizure and diagnostic brain CT scan revealed a calcified lesion with subacute haemorrhagic component, at the left half of the suprasellar cistern. Angiography excluded aneurysms and the brain MRI identified an intra-axial calcified fronto-uncal-hypothalamic lesion, extending to the suprasellar cistern. After seven years of follow-up, slow progression lead to a biopsy of the lesion that revealed an Oligoastrocytoma grade II (WHO). A year later, due to clinical worsening, patient was submitted to surgery, with extensive tumour excision, confirming the previous histology. Subsequent radiotherapy was performed, with subtotal remission. The patient remained stable with epilepsy controlled by carbamazapine and mild right pyramidal syndrome. Eight years after radiotherapy, due to new onset of headache and right facial paresis, a brain MRI was performed and showed a left frontal subarachnoid haemorrhage, not contiguous with the tumour. Angio-TC scan revealed a left middle cerebral artery aneurysm with 5 millimetres. Embolization was performed without complications.

Conclusion: Radiation induced intracranial aneurysms are rare, with only 25 cases reported in the literature. These aneurysms occurred a mean of 8.5 years after treatment, but the causal relationship is sometimes difficult to prove. In our patient the relation between the two conditions is supported by aneurysm location at the irradiated area and by its absence at the previous pre-radiotherapy angiography. We highlight the importance of attempting the diagnosis of these aneurysms that may have important therapeutic and prognostic implications.

P652

POEMS syndrome and report of a case with headache and papilloedema as presenting symptoms

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POEMS syndrome is a multi systemic disease related to localized plasmacell dyscrasia that is associated with an over production of inflammatory cytokins.The diagnosis of POEMS syndrome requires the presence of polyneuropathy and monoclonal plasmacell disorder as well as fulfillment of at last one other major criterion and one minor criteria.

Case presentation: History: A 52 year old woman was admitted to the hospital because of slowly progressive muscle weakness and paresthesia in distal upper and lower limbs from 2 years ago.The patient has been well until 2 years earlier,when she experienced severe headache and then she was hospitalized and undergone diagnostic work up for headache and papiledema and she was discharged by diagnosis of IIH.The results of brain MRV and MRI has been unremarkable.After 2 months she developed distal paresthesia and becoming progressively week untle admission. She also noted skin hyperpigmentation, diffuse skin thickening and weight loss of 15 kg over past 2 years.

Physical exam:we found spleenomegaly,diffuse skin thickening and hyperpigmentation,temporal wasting,bilateral papiledema,severe symmetrical limb weakness predominantly in distal legs,generalized areflexia and distal sensory impairment of limbs.

Bone x ray result: A mixed lytic and sclerotic lesion in Rt humerus.

CT scan of thorax: Pleural effusion.

CT scan of abdomen: Spleenomegaly.

Laboratory: Increased IgG monoclonal Ab, elevated TSH level with decreased level of both T3 and T4,and increased protein in CSF analysis.

Bone marrow biopsy: plasmocyte infilteration(8%)

EDX evaluation:Frank decrease of CMAP&SNAP amplitude with markedly slowed conduction velocities in upper limbs and absent distal CMAP&SNAP in the lower limbs.

With diagnosis of POEMS syndrome the patient treated with prednisone and melphalan.

Conclusion: POEMS syndrome usually present with polyneuropathy or organomegaly .in our case the presenting symptom was headache which in other center was evaluated for CVT and finally she was treated with diagnosis of IIH,and then other sign and symptoms of POEMS syndrome was gradually appeared.We have not found any report of this syndrome with such presentation in literature review .We suggest that this syndrome should be keep in mind because it could be presented with various features and with early diagnosis and treatment more recent papers indicate median survival time exceeds 10 years.

P653

Unusual presentation of pineal cyst: case report

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Introduction: Pineal parenchymal tumors are rare and the majority are malignant. Glial cysts of the pineal gland are benign and mostly asymptomatic incidental lesions found in the brain MRI or at autopsy examinations. In rare cases pineal cysts become symptomatic and require surgical intervention. Symptomatic glial cysts may be clinically and radiologically indistinguishable from cystic neoplasms of the pineal region. The most frequent presenting symptoms are due to

increased intracranial pressure (90%), followed by Parinaud syndrome or diplopia (50%).

Case report: We report the case of a 60 years old woman, who presented acute onset of transient vertical diplopia and paraesthesia on the left side. At neurological examination she presented mild sensitive and also motor hemisyndrome but no visual disturbances. The clinical history included previous diagnosis of ophthalmic migraine (characterized only by visual symptoms but no headache) and estrogenic substitution therapy for menopause.
She was admitted to our Stroke Unit and immediately performed a brain MRI with AngioMRI sequences. The MRI images showed a voluminous cystic lesion of the pineal region, with no obstructive hydrocephalus and without gadolinium enhancement, but with mild compression on the superior colliculi and pulvinar, mainly on the right side. There were no coagulation abnormalities at the thrombophylic screening; the Eco-Color-Doppler didn't detect any atheromasic disease at the epi-aortic vessels. AngioMRI confirmed that the brain circulation was normal. There were no detected cardiac abnormalities at the echocardiogram. The neurological symptoms didn't recover.

Discussion: Only limited clinical data regarding pineal cystic lesions behaviour are available. We hypothesize that, in our Patient, the mild left hemisyndrome, so as the "hemicrania episodes" are due to the compression related to the voluminous pineal cystic lesion. In our knowledge this is an unusual presentation of pineal lesion.

P654
A mismatch? Brain in the donor and heart in the recipient

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Objective: Although much progress has been made in the treatment of heart failure, both from a medical and a surgical point of view, only heart transplant has revolutionized survival of these patients when there are no other therapeutic options. It is a fact that not much attention has been given to the state of the donor brains, which are frequently candidates of transplantation after an intracranial hemorrhage, head trauma or suicide. Intracerebral lesions can alter cardiovascular and autonomic function. Besides, the evidence that intracerebral lesions can create cardiac lesions and result in cardiac arrhythmias even in the absence of significant coronary atherosclerosis is substantial.

Case: 12 year old female patient who had dilated cardiomyopathy underwent heart transplantation. Her follow-up under immunosuppressive therapy was normal without any evidence of organ rejection. On the postoperative 10th day, she had cardiopulmonry arrest after severe bradycardia and was not able to be resuscitated. Her myocardial autopsy was normal. Her cardiac donor was a young otherwise healthy male except with a brain tumour. In the hurricane during organ resection after brain death, the latest situation of his brain and the pathology of the tumour was unpredictable.

Discussion: It has been known that the brain influences the heart. Intracerebral lesions can cause a wide range of cardiac disturbances and even sudden death. Organ transplantation is a matter of time and every second is valuable for the recipient. But the donor who had been accepted as brain death, is mostly disregarded after being searched for any infectious agent. We can not exclude that these intracerebral lesions may have further promoted myocardial injury in a denervate state with myocardial hypersensitivity to catecholamine. To our knowledge, studies in guiding the clinician determining the conclusion of considering the patient as a heart donor with a severe brain pathology are lacking.

P655
Antiproliferative effect of helianthine on human glioblastoma cells in vitro

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Objectives: A major focus of modern brain cancer research has been to explore the potential of target therapy to combat malignant gliomas disease. In this study we investigated the effect of three compounds belonging dye chemical class (Methyl Red, Methyl Yellow and Methyl Orange) for their ability to inhibit glioblastoma cell growth in vitro. Antitumor efficacy of the compounds was evaluated in two glioblastoma cell lines GB18 and GB38.

Methods: The antiproliferative effect of Methyl Red, Methyl Yellow and Methyl Orange (Helianthine) was examined using MTT assay. The proteins expression and tyrosine phosphorylation were determined through immunoprecipitation and Western Blotting.

Results: Our results showed that the anionic Helianthine, with a sulfonyl charge, induced cytotoxicity in both GB cell lines while Methyl Red and Methyl Yellow were not cytotoxic. As receptor tyrosine kinases seem to have a major role in oncogenic signaling, the effect of Helianthine on EGFR, IGF-1R and their common intracellular signalling via PI3-K and ERK1/2 was also analysed. The treatment with Helianthine blocked EGFR and IGF-1R activity; EGFR inactivation preceding IGF-1R inactivation in both cell lines. In 18 GB cell lines, Helianthine treatment blocked ERK1/2 phosphorylation but did not affect PI3 K activity. On the opposite, treatment with Helianthine reduced PI3 K phosphorylation but induced very slight inactivation of ERK1/2 in 38 GB cells. Both PI3 K and ERK1/2 inactivation by Helianthine coincide with IGF-1R inactivation in GB cells. The inactivation of the protein kinases was irreversible in 18 GB cells, while in 38 GB cells, the level of phosphorylation of the protein kinases was reverted within 8 h.The cell death was accompanied by the degradation of PARP in GB cells without affecting BCL2 expression in the GB cells.

Conclusions: Here we found that of the dye molecules tested, only Helianthine have cytotoxic effect on GB cells and the treatment with Helianthyne downregulated EGFR and IGF-1R activity and their intracellular signal proteins in GB cells. The cell death was accompanied by the degradation of PARP without affecting BCL2 expression in the GB cells.

P656
Oculomotor palsy after paraganglioma excision and positioning of an autologous bypass graft

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Paragangliomas are rare carotid body tumors that arise at the bifurcation of the common carotid artery, they are normally benign and have slow growth rates. Surgical resection is generally recommended, but entails an inherent risk of injury of cranial nerves such as the hypoglossal, the

vagus, the glossopharyngeal, the spinal accessory and the facial nerve, shortly after the surgical treatment. A 28-year-old woman with no previous clinical history developed in two months a laterocervical mass. She underwent a neck ultrasonography and, then, a cervical computed tomography (CT) and an angiography that showed a vascularized mass at the left carotid bulb interpreted as a large carotid body chemodectoma (Shamblin classification III). She underwent a complete resection of the chemodectoma and part of the internal carotid artery with legation of the external carotid artery and a carotid-carotid graft bypass in an inverted saphenous vein. She was discharged with just a slight Horner syndrome determining mild left blepharoptosis and miosis. The bioptic findings confirmed the lesion was an infiltrating paraganglioma.

Two weeks later the patient developed sudden diplopia and a worsening of the left blepharoptosis. Ophthalmological examination revealed midriasis and blepharoptosis of the left eye associated to a mild medial and inferior rectus muscle paresis. Carotid Ultrasound Doppler sonography and carotid angio CT showed a complete occlusion of the internal carotid bypass with a trombosis extending till the carotid siphon. The patient underwent transcranial echo Doppler and intracranial magnetic resonance angiography which showed a left internal carotid occlusion and a good intracerebral blood flow compensation by the Willis circle.

These clinical findings were considered due to a partial third cranial nerve palsy on a plausible inflammatory genesis.

Peripheral neuropathy

P657

Clinicopathological and genetic study of CMT2

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Background: Charcot-Marie-Tooth neuropathy (CMT) is a heterogeneous group of disorders of the peripheral nervous system with a broad spectrum of clinical severity and different pattern of inheritance. Genetic defects underlying most major forms of hereditary neuropathies are now known. Genetic studies have revealed the following gene mutations as the causes CMT2; MFN2, KIF1B, RAB7, GARS, NEFL, HSPB1, MPZ, HSPB8 for CMT2 (autosomal dominant axonal form); LMNA, GDAP1 for AR-CMT2 (autosomal recessive axonal form);

Objective: The main objective of this study was to investigate the clinicopathological and genetic aspects of autosomal dominant (AD) and autosomal recessive (AR) CMT 2 in a small cohort of Turkish patients.

Methods: Thirty-three patients were studied clinically and electrophysiologically. We have also analysed all the known genes for these patients and only 8 underwent sural nerve biopsy.

Results: Of the thirty-three, 22 had autosomal recessive inheritance, only 9 were autosomal dominant and 2 were considered as isolated cases. Interesting associated clinical features in some patients besides the classical CMT phenotype were optic atrophy, hoarseness, deafness, tremor, cyphoscoliosis and calf hypertrophy. Median motor nerve conduction velocity was greater than 38 m/s in all except one. Sural nerve biopsies were compatible with an axonal neuropathy with demyelinating features in some. Genetic analysis showed one MFN2, one HSPB1, two GDAP1 and two NFL mutations.

Conclusions: In this small cohort, we found a mutation in only 18 % of families. This situation contrasts with that in CMT1, where PMP22 duplication is responsible for the great majority of cases. Our findings confirm the marked genetic heterogeneity of CMT2. Low mutation rate in general, mentioned in previous papers also indicate that new loci and genes might be responsible.

P658

Peripheral neuropathy and VIII cranial nerve involvement in Fabry disease

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Introduction: Fabry disease (FD) is an X linked lysosomal storage disease caused by deficiency of the -galactosidase A. The characterization of peripheral nerve dysfunction and VIII cranial nerve (CN) involvement in FD is important for its early recognition.

Objective: To assess the clinical and neurophysiological features of the peripheral neuropathy and VIII CN associated with FD.

Methods: We prospectively examined 38 consecutive adults with FD (17 males, 21 females; mean age: 35.63 years, range 19-73).
Each patient was assessed clinically and by nerve conduction studies (NCS) and quantitative sensory testing (QST); including cold, warm, vibratory, cold-pain, and heat-pain detection thresholds in one hand and one foot. The results of the QST for patients with FD were compared with 16 healthy individuals (mean age, 29.3 years) using the Mann–Whitney U-test
Neuro otologic symptoms and signs were evaluated in 20 consecutive patients with FD using Horizontal Head Thrust Test, conventional calorics., Vestibular Evoked Myogenic Potentials (VEMP's)., pure tone audiometry with speech discrimination and Brainstem Auditory Evoked Potentials.

Results: All the patients had symptoms or signs of FD, the most frequent was acroparaesthesia. The group of patients had significantly ($p < 0.05$) elevated their mean CDT and WDT (hand and foot), CP and HP (foot), VDT (hand and foot) compared with our controls Among the group with FD 92.1% presented abnormal QST, within this subgroup 73.68% showed increased CDT, 65.78% had altered WDT. NCS, were normal. Neuro-otologic manifestations: 3 patients were asymptomatic. Short spontaneous spells of vertigo were reported by 16 patients (80%). and hearing loss or tinnitus was referred by 80% of the population.
Neuro otologic involvement was peripheral in 15 and central in 1. The main finding was that in 15 subjects there was a lack of neural or vascular pattern in the involvement of the peripheral labyrinth.

Conclusions: We identified symptoms of neuropathy in both heterozygous and hemzygous patients. The neuropathy predominantly affects A-delta and C small fibers. QST is the most sensitive neurophysiological tool for the diagnosis of peripheral neuropathy in FD. Neuro-otologic involvement is frequent in FD affecting the vestibular-cochlear labyrinth in the majority of patients.

P659

Clinical phenotype of Transthyretin Val107 familial amyloid polyneuropathies is marked by rapid and severe tetraparesia

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Objectives: Met30 is the most common Transthyretin (TTR) mutation associated with familial amyloid polyneuropathies (FAP). We report the clinical phenotype and evolution before liver transplant (LT) of FAP associated with the rare Val107 TTR mutation (Val107-TTR).

Methods: Retrospective review of patients with Val107-TTR mutation and nerve biopsy proven amyloidosis over a 21-year period. We assessed delay between onset and first neurological exam, initial

symptoms and course of the neuropathy. Clinical evaluation included Modified Norris score (MNS) (normal = 75), walking disability score (normal = 0 to wheelchair bound = 5), MRC score, autonomic dysfunction and cardiac evaluation.

Results: Twelve patients were reviewed, including 7 from 5 different west indian families. Mean age at onset was 63 year (51.9-71.6); male-female ratio was 11:1. Mean delay to first neurological examination was 26 months (5–70). Initial complaints were paresthesiae in the limbs in 8 patients (67%) and muscle weakness in 4 (33%). Only 4 (33%) had early autonomic symptoms (dizziness, erectile dysfunction or diarrhea).

At first examination, 8 patients (67%) had developed pain, 10 (83%) had weakness of the limbs which was distal but also proximal in half of them (42%). All patients had distal symmetrical sensory loss. Nine patients (75%) lost body weight (mean 13 kg). Cardiac impairment was found in 11 patients (92%). Ten had ventricular hypertrophy, and 2 an ejection fraction below 60%.

During follow-up, most patients developed severe tetraparesia with both proximal (mean MRC = 3) and distal (mean MRC = 2) impairment and severe walking disability: 11 (92%) required a cane (Rankin = 4) after a mean interval of 33 months (2-93), and 8 (67%) became wheelchair bound after a mean interval of 52 months (25–106). The mean MNS was initially extremely severe at 56 (33–74) and eventually decreased to 27 after a mean of 32 months (7–76) of evolution. Eleven patients (92%) developed autonomic dysfunction which was severe in 3, including diarrhea/constipation ($n = 9$; 75%), sexual impotence ($n = 8$; 67%) and postural hypotension ($n = 7$; 58%). Four patients eventually required permanent cardiac pacing. Five of the 8 patients without LT died after a median interval of 6 years.

Conclusion: Val107-TTR-FAPs is a rapidly paralyzing neuropathy leading to severe walking disability and a diffuse tetraparesia. Compared to portuguese Met30 TTR-FAP, patients have more severe motor impairment but less autonomic dysfunction.

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Chronic inflammatory demyelinationg polyradiculoneuropathy with and without diabetes mellitus – A retrospective hospital-based study

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Background: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is characterized by relapsing or progressive dysfunction of the motor and/or sensory fibers of the peripheral nervous system due to inflammatory demyelination. Secondary axonal degeneration is important for permanent disability. CIDP is important to recognize as it is potentially treatable. CIDP associated with diabetes mellitus (DM) has been recognized.

Aim: To study the clinical, electrophysiological and cerebrospinal fluid (CSF) characteristics of Hong Kong Chinese patients with CIDP; and compare between CIDP patients with and without DM.

Methods: Patients followed in our neurology clinic who fulfilled the diagnostic criteria for CIDP of the Ad Hoc Subcommittee of the American Academy of Neurology AIDS task force and had disease duration of at least 1 year were studied. All patients had standardized electrophysiological studies for diagnosis and progress monitor.

A total of 27 CIDP patients were studied. Their mean onset age was 57.9 years (range 23– 80), and 17 were males. Their mean disease duration was 7.1 years (range 1–18 years). Three patients had monoclonal gammopathy. Six patients (22.2%) had relapsing disease. Nine patients (33.3%) had DM (all type 2 DM) with a mean duration of 6.1 years (range 1-20 years) between DM diagnosis and CIDP symptom onset. The mean HbA1c value at CIDP onset was 7.7% (range 6.0–15.1%). Their mean CSF protein level was 1.7 g/L and all had acellular CSF. Their mean onset and worst modified neuropathy impairment score (NIS) were 35.3 and 63.0 respectively. The mean number of conduction blocks (over 4 limbs on standard electrophysiological studies) was 3.8 (range 0–8). 86.7% patients responded to plasmapheresis, 83.3% responded to oral corticosteroids and 83.3% responded to intravenous immunoglobulins (response defined as significant improvement). Three patients (11%) died, 2 of these 3 had monoclonal bands. Among the survivors, clinical outcome was satisfactory in 85% patients who remained ADL independent at latest follow-up, while 15% were ADL partially dependent. 61% of patients required immunosuppressant therapy upon latest follow-up. There is no significant difference in any clinical, electrophysiological and CSF parameters between patients with and without DM.

Conclusion: One third of our CIDP patients had type 2 DM. There is no difference in clinical, electrophysiological and CSF characterisitics between CIDP patients with and without DM.

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Diagnostic utility of high-resolution sonography in ulnar neuropathy

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Objectives: High-resolution ultrasonography (HRU) has repeatedly shown itself as an accurate and cost effective tool in the diagnosis of nerve injury. We investigate the value of HRU in the diagnosis and localization of ulnar nerve injuries (UNI). We correlated nerve cross-sectional area (CSA) with electrophysiological parameters, and identified the ultrasonographic findings of nerve abnormalities which were not localizable with electrophysiology.

Methods: Forty-three patients with clinical ulnar nerve palsy were recruited. All underwent nerve conduction studies (NCS). 26 of them underwent EMG. Ulnar neuropathy at elbow was diagnosed as per the AANEM criteria.

These patients then underwent HRU of the ulnar nerve using a 12 MHz linear array transducer. The nerve cross-sectional area was calculated at the sulcus ulnaris, 3 cm below and 5 cm above the elbow. Based on our laboratory normative data, a cross-sectional area more than 0.10 cm was considered enlarged.

Results: In 25 of the UL in our sample, NCS was able to localize ulnar neuropathy to the elbow. There were 12 UL with abnormal NCS findings but the injury was not localizable by NCS or EMG. In these cases, HRU helped to localize the injury to the elbow in 7 of them and to other parts of the upper limb in 5. Furthermore, HRU was able to demonstrate causative underlying scar tissue in 1 case and abnormal vasculature in another.

In 10 cases, NCS findings were normal but EMG findings were abnormal. In 3 of these cases, EMG was able to localise the abnormality- in 2 cases to the elbow and in 1 case distally. HRU showed this to be at the Guyon's canal. In 7 of these 10 cases with normal NCS, EMG was unable to localise the injury. HRU then localized 4 of them to the elbow and 2 of them to sites elsewhere - one at the site of an old distal radius fracture and another at the Guyon's canal.

In patients with UN at the elbow, there was negative correlation between CSA and NCS parameters distally, namely sensory nerve action potential, dorsal cut nerve peak latency and motor conduction velocity (MCV) below the elbow. ($p < 0.05$)

Conclusion: HRU is a useful diagnostic tool for ulnar neuropathy when standard electrophysiology proves to be inconclusive despite

the presence of clinical symptoms. This is especially so in cases of focal ulnar nerve injury secondary to entrapment, trauma or any other focal pathology at locations besides the elbow. HRU can also provide additional information about the pathology of the nerve injury.

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Mononeuritis multiplex affecting cranial nerves as a clinical manifestation of neurosarcoidosis

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Objectives: Sarcoidosis is a multi-system disease of unknown origin. Neurological symptoms are rare (around 5–10%) and diagnosis in the absence of systemic involvement is difficult. We present a case of neurosarcoidosis presenting as mononeuritis multiplex with cranial nerve involvement.

Methods: A 57-year-old female with idiopathic anterior uveitis presented with bilateral sequential peripheral facial palsy, with partial response to corticosteroids. In the following months bilateral trigeminal neuropathy, palatal palsy, bilateral spinal and hypoglossal neuropathy concurred. She also showed signs of bilateral ulnar and median neruopathy and partial involvement of radial, peroneal, tibialis and sural nerves, as well as neuropathic radicular pain at C8-dermatome and both legs.

Results: bilateral facial nerve enhancement and neurophysiologic study showed facial cranial neuropathy and axonal and demyelinating motor sensitive neuropathy with predominant involvement of lower limbs. The results of the following tests were normal: serum and cerebrospinal fluid angiotensin-converting enzyme, immunological and microbiological tests, computer tomography of thorax, abdomen and pelvis, gallium-67 γgraphy, bronchoscope and bronchoalveolar lavage. A skin, muscle and nerve biopsy showed multiples non-caseating epitheloid granulomata in the three tissues. The patient symptoms notably improved after a course of high dose corticosteroid.

Conclusion: Neurosarcodosis may present as mononeuritis multiplex, with cranial nerve involvement in absence of other neurological features. Cranial nerves enhancement in magnetic resonance can support diagnosis. Nerve biopsy can provide diagnosis when no other systems are envolved.

P663

Multifocal motor neuropathy: analysis of prognostic factors

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Objective: Multifocal motor neuropathy (MMN) is a disorder characterized by asymmetric weakness and conduction blocks(CB). Aims of the study were: (1) to define relevance of clinical (age of onset, gender, duration of illness at first evaluation, muscle involvement in UE/LE, serum anti-GM1 IgM) and electrophysiological features (CB) as predictive factors of prognosis and quality of life; (2) to compare long-term prognosis between IVIg treated and untreated patients (3) to characterize HLA class I and II distribution.

Methods: We studied 25 defined MMN (17 males and 5 females) enrolled between 1991 and 2008. Mean age of onset was 42 years,(range 21–64), mean duration of follow up was 6,8 years (range 8 months to 17 years), duration of illness at first evaluation was 2 years (range 10 months-8 years). Ten patients had GM1 IgM antibodies. Twenty patients received periodic IVIg, with frequency and dosage based on response to early courses. Five patients were untreated. All patients were assessed by MRC for muscle strength in 24 muscles of upper and of lower limbs (maximal sumscore 120), INCAT Overall Disability Sum Score (ODSS), Rankin disability scale. Nerve conduction was performed initially and periodically during follow up. Quality of life was tested by SF-36 Questionnaire. Typing of HLA class I (-A and -B)and class II (DRB1 alleles) was performed in 15 MMN patients and in 3528 controls.

Results: (1) There was a significant correlations ($p < 0.05$) between proximal muscles involvement at onset and worsening of MRC, ODSS, RANKIN and quality of life scales during the follow up. (2) Twenty patients (80%) had at least one CB in motor nerves at onset: there was a positive correlation between number of CBs and improvement of quality of life after therapy ($p < 0.05$). 3) A moderate disability (Rankin > 3) was reached after a mean of 5.4 years in untreated and after 7.7 years in treated patients. Treatment also reduced probability of reaching disability (Rankin > 3) from 20 to 6% after 3 years and from 50 to 30% after 5 years. No other significant correlation was observed including HLA-A, -B (class I) and HLA-DRB1 alleles (class II) antigen distribution.

Conclusion: Proximal weakness, the number of nerve with CB and IVIg therapy have an impact on the prognosis of patients with MMN.

P664

Atypical presentation of acute inflammatory polyradiculoneuropathy in patient with multiple myeloma after allogeneic stem cell transplantation

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Objective: We report the case of a caucasian male affected by multiple myeloma who developed an acute polyradicoloneuropathy with atypical onset.

Case report: A 44-years-old man was admitted to our hospital for the acute development of a selective palatal palsy with increasing rinolalia.
The patient had diagnosed as having multiple myeloma at the age of 40 years. He was treated with two autologous stem cells transplantation and then with allogenic transplantation at the age of 43 years. Subsequently he had started Cyclosporine immunosuppressive therapy and some months later he had developed a drug related neurotoxicity with seizures, so that antiepileptic therapy was started. The first neurological examination did not show involvement of the other cranial nerves, nor muscle weakness and nor sensibility impairment; deep tender reflexes were normal. After three days, the clinical picture showed progressive bilateral facial weakness, dysphagia, lower limb hyposthenia. On the fourth hospital day, the patient developed respiratory failure and he needed tracheotomy and invasive ventilation. Electrodiagnostic studies and cerebral fluid examination were suggestive of acute demyelinating polyradicoloneuropathy. Moreover the sierological tests for gangliosides GQ1b antibodies were negative. He was treated with a five day course of intravenous immunoglobuline (0,4 g/kg/die), with following progressive improvement of symptoms.

Conclusion: Our case is suggestive of an overlap between Miller Fisher and a Guillain Barrè syndrome, given the prominent

orofaringeal palsy without ophthalmoplegia, as a possible post allogenic transplant complication in multiple myeloma, through a pathway of cross-reaction.

P665
Central nervous system involvement in POEMS syndrome

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Patient: We describe the case of a 44-years-old woman diagnosed with POEMS syndrome on the basis of contemporaneous presence of sensorimotor demyelinating polyneuropathy, IgA λ monoclonal gammopathy, pleural and pericardial effusions, ankle oedema, slightly reduced folic acid and vitamin B12, selective glomerular proteinuria and bone lesions.
Cerebrospinal fluid (CSF) examination revealed multiple oligoclonal bands (OB) with increased IgG level (6.97 mg/dl; n.v. 0.60-3.80); OB were not present in the serum. Brain and cord MRI scan showed multiple T2-hyperintense lesions in the frontal, temporal and parietal white matter with no gadolinium enhancement suggestive for a demyelinating disease.

Results: Central nervous system involvement is not usually described in POEMS syndrome and the underlying mechanisms are poorly understood.
VEGF, a cytokine inducing angiogenesis and microvascular hyperpermeability, is upregulated in POEMS syndrome as well as in the multiple sclerosis (MS) plaques and it is supposed to play a role in both diseases. Therefore, a role of VEGF in determining CNS myelin involvement in POEMS syndrome may be hypothesized.

Conclusions: Our study suggests that CNS damage could be more frequent than we know and should induce to more extensively look for it in patients with POEMS syndrome.

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P666
Cardiovascular autonomic evaluation in patients with idiopathic painful small fibre neuropathy

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The idiopathic painful small fiber neuropathies (IPSFN) result from a variety of causal conditions. Are prevalent in some diseases such as diabetes and amyloidosis. Changes in sensory and autonomic system, especially cardiovascular, are frequently seen. These latter, often, are only discovered when faced with specific autonomic tests, object of this study.

Patients and methods: 50 autonomic cardiovascular evaluations in patients with painful small fiber neuropathy established without question, so idiopathic (IPSFN) were analyzed. Many of these patients did not report complaints suggestive of cardiovascular autonomic involvement. After clinical examination cardiovascular autonomic tests was applied, such as respiratory sinus arrhythmia, passive tilt test, hand grip and the Valsalva maneuver. Were excluded from the study patients who had glucose intolerance or metabolic syndrome, diabetes, deficiency of vitamin B12, peripheral or central nervous system infections, collagen diseases, cancer, drug use against the autonomic system and also patients with heart disease of any origin.

Results: From 50 patients with IPSFN, 19 (38%) had abnormal tests. The average age was 47.9 ($\pm$22.1) years of age in group of patients with abnormal tests. The male was prevalent with 12 (63%) individuals affected. Only two patients were black. No patient had compromised parasympathetic cardiovascular evident in the test of respiratory sinus arrhythmia. The test with the largest number of changes was the passive tilt test, revealing change in 58% (11) of cases. During the Valsalva maneuver there was no increase in blood pressure in Phase IV of testing in 53% (10) of cases. In the test of static force 42% (8) of the patients showed no increase in blood pressure after five minutes of voluntary muscle contraction.

Conclusion: To know the intensity of autonomic dysfunction results in better and more appropriate therapeutic orientation, as well as contribute pending the prognosis for specific groups of patients. Our study emphasizes the importance of proper investigation in patients with cardiovascular autonomic IPSFN ahead of the results of prevalent sympathetic cardiovascular autonomic involvement in the study group.

P667
Long-term follow-up of proximal diabetic neuropathy in a cohort of 15 patients

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Objectives: Long-term prognosis of Proximal Diabetic Neuropathy (PDN) is not known. We aimed to obtain follow up evolution of our patients seen between 1996 and 2008.

Methods: We reviewed the clinical files of 15 patients with PDN followed-up for at least 12 months. All patients underwent comprehensive neurological and electrophysiological examination, laboratory testing, CSF analysis and a neuromuscular biopsy. Lumbar imaging was normal for all patients. We assessed functional disability using the modified Rankin score (0–6) and a walking disability score (WDS: normal = 0 to wheelchair = 5) and neuropathic pain using the visual analogue scale (VAS, range 0–10).

Results: There were ten men and five women (mean age 64 years (55–73y)). All had type 2 diabetes, including 3 requiring insulin, and 5 with poor glycemic control (HbA1c > 8%). Neuropathic pain was the first and main symptom in all but 2 patients who presented inaugural paresis. Severe pain (VAS > 7) preventing sleep occurred in 8 patients (53%). Early severe weakness developed in the painful territory (mean MRC = 2). It affected proximal lower limb (LL) in 10 patients (66%), predominantly distal LL in 3 and both proximal and distal in 2. Two patients reported also thoracic pain. Initial symptoms were bilateral in 8 cases. Five patients developed severe walking impairment (WDS 4-5). Nerve biopsy showed mixed axonal and demyelinating pattern with

inflammation in 7 cases. Nine patients received high dose oral corticosteroids. Two received IVIg, one both treatments. The 3 milder cases had no specific treatment.
Mean follow up was 4 years. Four patients experienced an exacerbation of their pain, needing an increase in steroid dosage. No paresis recurrence occurred. Three patients died (included one from diabetes complication). At their last examination, 8 patients presented no paresis, in the others the mean MRC had improved from 2 to 3.5. Eleven patients (73%) were able to walk without assistance. Final disability was low or moderate (Rankin score 0 to 3) for 11 patients and severe in two (Rankin 4). Despite an initial improvement under treatment, neuropathic pain remained the main complaint for 8 patients (VAS 2 to 6). Even with analgesic intake, persistent disabling pain occurred in two cases (VAS 4-6).

Conclusion: Most of PDN patients recover a good degree of autonomy. Persistent and disabling pain is a frequent, sometimes hardly relieved. Relapse of motor deficit was not observed during follow up.

P668

High level of serum tau protein in a patient with multifocal motor neuropathy

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Objectives: Tau protein-localized primarily in the axon of neurons - is one of the most widely distributed microtubule-associated proteins. Elevated CSF total-tau (t-tau) levels have been found in CNS and PNS disorders such as Alzheimer's disease, Creutzfeldt-Jacob disease, encephalitis, stroke, multiple sclerosis and Guillain-Barrè syndrome (GBS) [1, 2]. Increased serum t-tau was detected in a study looking for markers of axonal damage in acute ischemic stroke [3]. We aimed to optimise an ELISA test for a dementia study.

Methods: Serum t-tau was measured in patients with several peripheral and central neurological disorders using a commercially-available sandwich ELISA kit from Innogenetics®.

Results: We repeatedly found a very high serum t-tau level (1250 pg/ml) in one of 6 patients with MMN, but not in sera of patients with amyotrophic lateral sclerosis, GBS, inclusion body myositis or chronic inflammatory demyelinating polyneuropathy.

Conclusion: So far no link has been described between MMN and tau pathology. It is therefore unclear, whether this finding is purely incidental or reflects axonal degeneration in this patient.

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P669

Hereditary neuropathy with liability to pressure palsies: report of two clinically severe cases

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Objectives: To report two patients with genetically confirmed diagnosis of Hereditary Neuropathy with liability to Pressure Palsies (HNPP) presenting with severe forms of polyneuropathy. HNPP is an autosomal dominant disorder typically characterized by recurrent, painless, monofocal palsies. However, it displays marked clinical variability ranging from asymptomatic family members to a rare form of slowly progressive generalized polyneuropathy.

Methods: We reviewed the clinical files of two patients with severe polyneuropathy of onset in infancy with molecular confirmation of a 1.5-Mb deletion on chromosome 17p11.2.

Results: First clinical case: 30 year-old woman with normal birth and psychomotor development in the first year. At age 2 she begins displaying difficulty in gait with frequent falls and inversion of the right foot. Several orthopedic surgeries were performed without clinical benefit. At four year-old she notices lack of strength distally in the upper limbs. Early electrophysiologic studies report a non-specific sensitive-motor polyneuropathy. Genetic evaluation of gene 17p11.2 showed the typical pattern of HNPP. At present time she presents severe tetraparesis of distal predominance, with complete distal algic hypoesthesia and impairment of gait. Distal nerve conduction studies show absence of motor and sensory response in the upper and lower limbs.

Second clinical case: 32 year-old woman who reports gait difficulty with fatigue and frequent falls at 3 year-old. At age 5 she performed achilles tendon lengthening tenotomy. Nerve biopsy was inconclusive and electrophysiologic studies revealed non-specific sensitive-motor polyneuropathy. She had a slowly progressive evolution and, at age 26, HNPP was finally diagnosed based on genetic evaluation. Presently she has severe tetraparesis with marked muscle atrophy, generalized in the lower limbs and distally in the upper limbs, as well as distal algic and palesthesic hiposthesia. Family members do not show genetic or electrophysiological features of the disease.

Conclusions: HNPP has a wide spectrum of clinical presentations. Genetic analysis allows to identify rare and severe presentations of this disorder, much different from its usual mild symptoms. Therefore, it should be considered as a differential diagnosis of gait impairment of early onset.

P670

Nonexertional heat stroke in a patient with familial amyloid polyneuropathy

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Introduction: Heat stroke is a medical emergency, presenting with hyperthermia, dry and warm skin and central nervous system manifestations such as coma, seizures or delirium. Autonomic dysfunction, an important manifestation of familial amyloid polineuropathy, is a risk factor for this condition, as it impairs thermoregulation.

Clinical case: Fifty-year old Portuguese woman, with a history of heart block and a pace-maker implantation in the previous year. The diagnostic workup of the heart block, in the context of a positive family history, had revealed a transthyretin mutation (Val30Met), and the diagnosis of familial amyloid polyneuropathy was established. She was admitted in the Emergency Department on a hot summer day, in a coma (grade 4 in the Glasgow Coma Scale), intubated, spontaneously breathing and hemodynamically stable. The patient had been found unconscious inside her car, without any known precipitants. Axillary temperature was 107.6 F (42°C) and there were signs of tongue bitting. Neurological examination showed no meningeal signs or focal deficits. Brainstem reflexes were intact.

The blood tests were compatible with a disseminated intravascular coagulation and revealed a slight increase in the urea and creatinine. The urine test was positive for blood. The blood smear revealed botryoide neutrophils.

The brain CT-scan and MRI were normal and the EEG showed diffuse slowing of the basal rhythm, with no paroxysmal activity. Treatment with peripheral cooling measures, intravenous fluids, heparin and platelet concentrates was initiated with a favourable clinical response. The patient recovered consciousness eighteen hours after admission and gradually improved.

Conclusions: Heat stroke is a possible clinical manifestation of autonomic failure in patients with familial amyloid polyneuropathy. Prompt recognition of the diagnosis is of paramount importance. These patients should be allerted to take protective measures in order to avoid heat stroke.

P671

Guillain-Barré syndrome and dengue fever are not associated

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Objectives: There are some occasional case reports of the association of dengue fever and the Guillain-Barrã syndrome (GBS). Also dengue fever has been reported to be associated with higher incidence of GBS on the basis of a population study during an epidemic outbreak of the disease in Cuba. This study was designed to look for an association between GBS and dengue fever in Ribeirão Preto, São Paulo, Brazil where a dengue fever epidemic outbreak occurred in 1990 and 1991.

Methods: The medical records of all hospitalized GBS patients in the city from 1987 to 1997 and those from of all dengue cases in 1990 and 1991 were revised.

Results: An average incidence of 1.06 GBS cases per 100,000 inhabitants, varying from 0.24 to 1.91 per 100,000, was found along the study. There was no seasonal preponderance. The incidence of GBS was 1.58/100.000 (7 cases) in 1990 and 0.69/100.000 inhabitants (3 cases) in 1991. A precedent infection was observed in 65,7% of GBS cases, mainly upper airway infections (UAI) and diarrhea. In none of these cases dengue was present, even in 1990 and 1991, when its incidence was 546.9/100.000 and 56.7/100.000, respectively.

Conclusions: We conclude that in Ribeirão Preto, dengue fever is not associated with GBS syndrome as was registered in Cuba. The association of dengue fever and GBS could depend on the genetic background of the population or to occur on the basis of isolated cases.

P672

The role of tumour necrosis factor α as a marker in chronic inflammatory demyelinating polyradiculoneuropathy

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Objectives: Tumour necrosis factor α (TNF-a) secreted by the autoreactive T-cells and activated macrophages may play a role in the pathogenesis of demyelination and the breakdown of the blood nerve barrier in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). We aimed to study the role of TNF-a as a specific marker in a heterogeneous group of CIDP patients.

Methods: the serum level of TNF-a was measured by ELISA technique in a group of 60 CIDP patients, 32 (53.3%) patients have idiopathic CIDP and 28 (46.7%) patients have concurrent diseases with CIDP. Eighteen (30%) patients have CIDP and diabetes mellitus CIDP-DM, 10(16.7%) have CIDP and hepatitis; and 10 (16.7%) have CIDP and collagen diseases. We correlated the TNF-a serum levels of those patients with the corresponding Neuropathy Impairment Scores (NIS) and we measured also the serum level of TNF-a in 20 healthy controls matching in age and sex.

Results: The mean of TNF-a levels was 50.13 pg/ml ± SD 41.24 in patients while in controls it was 12.5 pg/ml ± SD 6.19. Fourty-four patients (73.3%) had high level of TNF-a (above the cut-off level 31.7 pg/ml).There was no correlation between TNF-a serum levels and the corresponding NIS ($P > 0.05$). Patients with DM or collagen diseases showed a statistically significant higher mean value of TNF-a than those without diabetes or collagen diseases ($p < 0.05$) while, there was no statistical significant difference between mean value of TNF-a in cases with or without hepatitis ($p > 0.05$).

Conclusion: The serum levels of TNF-a in CIDP patients were statistically high compared to those of controls but not correlated to the NIS. Also, the mean value of TNF-a was statistically higher in the presence of DM or collagen diseases suggesting that this marker is not so much specific for CIDP but it may be an indicator for the cumulative effect of the various immune inflammatory responses in concurrent diseases with CIDP.

P673

The role of matrix metalloproteinase 9 in chronic inflammatory demyelinating polyradiculoneuropathy

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Objectives: Matrix metalloproteinase 9 (MMP9) plays a role in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) pathogenesis as it helps activated T-cells to cross blood nerve barrier and it is able to degrade the myelin basic protein. We aimed to study the dignostic value of MMP9 in nerve biopsy of a heterogeneous group of CIDP patients correlating its mean value with the corresponding Neuropathy Impairment Scores (NIS) of those patients and with the presence and absence of concurrent diseases.

Methods: Sural nerve biopsies were taken from 60 CIDP patients, 32 (53.3%) patients have idiopathic CIDP and 28 (46.7%) patients have concurrent diseases with CIDP. Eighteen (30%) patients have CIDP and diabetes mellitus, 10(16.7%) have CIDP and hepatitis; and 10 (16.7%) have CIDP and collagen diseases. Immunohistochemical study for epineurial MMP9 expression was performed. For statistical analysis, the number of epineurial blood vessels showing positive endothelial staining for MMP-9 were counted and given as number per total epineurial blood vessels within the same nerve cross section making it a percentage.

Results: Positive immunohistochemical staining of epineurial blood vessels for MMP9 was present in 58 out of 60 patients. Its mean percentage was 4.81% ± SD 4.69. There was no correlation between positive MMP9 immunoreactive vessels percentage and corresponding total NIS. There was no statistical significant difference between mean percentage of positive MMP9 immunoreactive vessels in diabetics and non diabetics, in cases with or without collagen diseases and in cases with or without hepatitis ($P > 0.05$).

Conclusion: The immunohistochemical study of MMP9 in sural nerve tissue added more value for the nerve biopsy as a diagnostic tool in CIDP although it is not correlated to the NIS or the concurrent diseases.

P674

Sural nerve biopsy findings in chronic inflammatory demyelinating polyradiculneuropathy with diabetes mellitus, collagen diseases and hepatitis

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Objectives: Diabetes mellitus, collagen diseases and hepatitis (B or C) are known concurrent diseases with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). In this study, we investigated the role of electron microscopic examination of sural nerve biopsy in differentiating between idiopathic CIDP and CIDP with these concurrent diseases.

Methods: Sural nerve biopsies were taken from 60 patients with CIDP; 32 (53.3%) patients have idiopathic CIDP and 28 (46.7%) patients have concurrent diseases with CIDP. Eighteen (30%) patients have CIDP and diabetes mellitus (CIDP-DM), 10(16.7%) have CIDP and hepatitis; and 10 (16.7%) have CIDP and collagen diseases. Sural nerve tissues were processed for electron microscopic examination and the following pathological findings were reported in each specimen: the degree of demyelination, axonal degeneration, endoneurial fibrosis, inflammatory cells, oedema, regenerating clusters, Schwann cell proliferation, onion bulb formation and thick walled blood vessels.

Results: Axonal degeneration was present in 100% of biopsies from CIDP patients with concurrent diseases while present in 93.8% of those with idiopathic CIDP. Oedema was present in 81.3% of biopsies of patients with idiopathic CIDP while seen only in 55.6% of those with CIDP-DM patients ($p < 0.05$). Thick walled blood vessels were seen in 88.9% of biopsies of CIDP-DM patients and in 100% of those of patients with collagen diseases and hepatitis while present only in 56.3% of those with idiopathic CIDP patients ($p < 0.05$).

Conclusion: There is statistically significant lower rate of edema in CIDP-DM patients and statistically significant higher rate of thick walled blood vessels in CIDP-DM, collagen diseases and hepatitis compared to the same findings in idiopathic CIDP.

Multiple sclerosis

P675

Progranulin genetic variability in primary progressive multiple sclerosis

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Objective: To test whether progranulin gene (GRN) variants contribute to Primary Progressive Multiple Sclerosis (PP-MS), disease subtype with prominent axonal degeneration. To determine progranulin levels in Cerebrospinal Fluid (CSF) from MS patients as compared with age-matched controls.

Methods: 239 patients with PP-MS and 289 age-matched controls were tested for association of GRN with risk for PP-MS. Five common variants (rs2879096, rs3785817, rs4792938, rs9897526 and rs5848) tagging about 100% of the GRN SNPs in the HapMap database with an $r^2 > 0.80$, were genotyped by allelic discrimination using an ABI PRISM 7000 instrument (ABI). Progranulin CSF levels were measured in 37 MS patients and 26 controls using ELISA. Haploview and Sigma Stat softwares were used to test for association and to compare progranulin levels.

Results: No significant differences were found between MS-PP patients and controls according to single markers distribution. Rs2879096, rs3785817 and rs4792938 were found to be in strong LD and the rare CGG haplotype was found to be associated with the disease ($p = 0.021$). No differences between patients and controls were found in CSF progranulin levels (5.87 ± 0.28 vs. 6.22 ± 0.39 ng/ml, $p > 0.05$), even stratifying according to gender or the subtype of MS.

Conclusion: Our results do not support a major role for GRN in the genetic etiology of PP- MS. Nevertheless, the CGG haplotype is likely associated with the disease, supporting a role of progranulin in neurodegeneration. Considering CSF progranulin levels no differences were found in between patients and controls, although, given the small population analyzed, further studies are needed to confirm these preliminary data.

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Why (and how) to detect neuropsychiatric symptoms in early stages of multiple sclerosis?

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Objective: Most common neuropsychiatric symptoms in multiple sclerosis (MS) are depression (40-60%) and anxiety (90%), but some other psychiatric symptoms may imitate them. Effective treatment in MS should be managed according to these symptoms in commorbid psychiatric disorders and MS patients must often accept and tolerate these symptoms. The most frequently used scales in all MS patients are Beck inventories II. for depression (BDI II) and for anxiety (BAI II). However, SCL-90 covering all psychiatric symptoms typical for early stages of MS is not so frequently used for interferrention with dissability in MS and wrong positive findings. The aim of this study was: 1/ to explore a range of anxiety and depression 2/ to estimate a difference between positive results of depression and anxiety from Beck inventories II.and SCL-90.

Patients and methods: Patients with clinically definite relapsing-remitting MS according to McDonald's criteria, with disease duration shorter than 7 years and treated by IFN βor glatirameracetate and concomitant peroral imunosupression more than 1 year were included. In the included patients BDI II, BAI II., SCL-90, MMSE were evaluated and neurological examination with EDSS evaluation was provided. Patients with higher EDSS than 3.0, actually in relaps and with lower MMSE 25 were excluded. In 20 patients (15 males and 25 females) frequency of anxiety, depression were evaluated and results from Beck inventories and SCL-90 were compared.

Results: Prevalence of depression according BDI II was 35% and according to SCL-90 was 30%, by both scales 27%. High prevalence of anxiety was detected by BAI II 65%, however by SCL-90 only 62 % all of them aslo referred anxiety according BAI II and independently on depression. But there were difference in results between Beck inventories and SCL-90 for depression was found.

Conclusion: Physicians can use SCL-90 as a diagnostic tool for MS patients in early stages with lower physical and cognitive disability, but together with BDI. SCL -90 contains almost all neuropsychiatric somatic symptoms, which may be associated with MS in early stages. For diagnosis a "more cognitive than somatic" depression is better to use a BDI. The most common neuropsychiatric symptom associated with MS is anxiety, that may manifest also without depression.

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Psychopathology in multiple sclerosis: coping strategies, representation of the disease, locus of control and social support

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Objectives: Uncertainty as for the future, an entourage sometimes not very present, can cause an erroneous representation of the disease among MS patients and an inadequate adaptation causing of the disorders of mood.
Does this study aim at highlighting which variables mediating are most likely to explain the importance of incidence and prevalence of the depressive and anxious symptoms in MS?

Methods: 45 MS patients, 34 women and 11 men, old from 21 to 65 years (mean age = 45 years ± 11.65) with one mean duration of 9 years (±7) and an average score EDSS of 3.5 (±2.3), were evaluated with 6 self-questionnaires : a locus of control scale (MHLC), a social support scale (SSQ), a coping strategies scale (WCC), a representation of the disease scale (IPQ-R), an anxiety scale (STAI) and a depression scale (BDI-II).

Results: Problem-focused coping were negatively correlated with depression (r = -0.349, $p = 0.01$) and anxiety (state: $r = -0.410$, $p = 0.0048$; feature: r = -0.458, $p = 0.0013$). Emotion-focused coping were positively correlated with depression (r = 0.580, $p = 0.0001$) and anxiety (feature : $r = 0.554$, $p = 0.0001$). In addition, positive representations of the disease were positively correlated with problem-focused coping (r = 0.316, $p = 0.0338$).

Conclusion: The more MS patients perceive their family circle like available, the more they use social support-focused coping and problem-focused coping. As for the belief in the effectiveness of the treatments, as well as a good comprehension of the disease, these positive representations lead the patients to use problem-focused coping strategies.
Representations of the disease influence coping strategies and psychological adjustments. They are capital to take into account, for better treating anxiety and depression in MS.

P678

Validation of the Fatigue Impact Scale in Hungarian patients with multiple sclerosis

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Objectives: Fatigue is one of the most common disabling complaints in patients with multiple sclerosis (MS), with prevalence rates from 53 to 92% depending on the definitions used. The aims of our study were to test the validity, test-retest reliability and internal consistency of the Hungarian version of Fatigue Impact Scale (FIS). To evaluate the multidimensional aspect of fatigue, several scales have been developed. The FIS is a commonly used fatigue scale in both clinical and experimental studies. It is a multidimensional scale measuring the physical, cognitive and social effects of fatigue. It comprises 40 questions, of which 10 is related to cognitive, 10 to physical, and 20 to social subscales. Each question scores between 1 and 4, changing from minimal to severe degrees. The maximum total score is 160.

Patients and methods: In the first application 111 patients affecting MS and 85 healthy controls (HC) were included. On average 3 months later, in the second application 99 of the 111 MS patients and 79 of the 85 HC filled in the FIS and the Beck Depression Inventory (BDI).

Results: The total FIS score and subscale scores were different statistically between MS patients and healthy controls in both first and second FIS applications ($p < 0.001$, cognitive subscale $p = 0.004$). The BDI score was higher in MS patients than healthy volunteers (first application: 11.9 ± 8.8 and 7.0 ± 7.0; second application: 12.2 ± 9.5 and 6.8 ± 7.5; $p < 0.001$). To assess the test-retest reliability, the scores of two FIS applications did not differ statistically neither in the MS group or the HC group (cognitive: $p = 0.360$, $t =$; physical: $p = 0.781$; social: $p = 0.111$; total: $p = 0.130$ and cognitive: $p = 0.860$; physical: $p = 0.135$; social: $p = 0.422$; total: $p = 0.724$). The internal consistency of the questionnaire (Cronbach's α value) were 0.968 for cognitive, 0.976 for physical, 0.976 for social and 0.988 for total FIS scores ($p < 0.001$).

Conclusion: Similar to the results of the previous studies (Turkish, Swedish), the Hungarian version of the FIS is valid and reliable. It satisfies the condition to be an expert tool for the assessment of the effects of fatigue in the Hungarian MS population.

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MS and neuropsychiatric symptoms: an emotional adjustment?

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Purpose: Multiple sclerosis (MS) patients and team members have to deal with emotional, cognitive, social and with the effects of the demielinization plaques and with the uncertain course of the disease. These aspects might influence the psychiatric symptoms express by these patients. In healthy population neuropsychiatric symptoms are also present. The aim of the present study is to characterize these symptoms among MS patients when compared with healthy controls.

Methods: We evaluated 68 MS patients at least 6 months after clinical diagnosis and 30 age/gender matched healthy controls. The MS group (age 37 ± 9.3, EDSS 3 ± 2.7, years of clinical diagnosis 8.2 ± 5.9) was diagnosed according to McDonald diagnostic criteria (McDonald 2003). The MS protocol included the MSQuest (an anamnesis questionnaire), SintomsCheckList-90 scale was used as a screening tool for neuropsychiatric symptoms (a cut point of 1.5 was considered significant for all items). All subjects were interviewed and evaluated by a trained psychologist, in a one hour consultation.

Results: Most of patients had their diagnosis between 30 and 40 years. Relapsing-remitting form was diagnosed in 72% of patients. Global Severity Index (GSI) was 1.4 ± 0.5 for MS patients and 0.8 ± 0.3 for the healthy controls. Considering depression, the score was considered significant for MS patients (1.6 ± 0.7) and no significance for the controls (0.7 ± 0.5). Obsessive compulsive symptoms were significantly present in MS (1.8 ± 0.4) when compared to controls (1.1 ± 0.5). Anxiety symptoms in MS patients had a mean of 1.2 ± 0.6, in healthy controls was 0.6 ± 0.3. Thoughts of death in MS had a mean of 1 ± 0.8 and 0.7 ± 0.8 in the control group. Both groups showed significant results for eating and sleeping items.

Discussion: Healthy population also has neuropsychiatric symptoms in their daily bases. Depressive and obsessive compulsive symptoms were significantly present in the MS patients when compared to the controls. Eating and sleeping disorders are present in both groups, neither associated nor representative to the disease. The exacerbation of these neuropsychiatric symptoms might be associated

to MS and to its mechanisms. Their exacerbation may also be associated to disease variables and not to an emotional adjustment to the disease. Future research is needed.

P680

How do multiple sclerosis patients perform on immunoactive treatment?

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Objective: The introduction of immunoactive treatment was a breakthrough in management of multiple sclerosis. This treatment has beneficial effects on MRI and clinical disease activity but only partial effects on clinical progression. It has not been established how this treatment effect translates into quality of life (QoL) of multiple sclerosis patients. The aim of the study was to assess the quality of life (QoL) of MS patients on different immunoactive treatment (immunomodulation, immunosupression, and steroid treatment).

Methods: 173 patients with a diagnosis of clinically definite MS according to McDonald's criteria were included into the study (M/F = 52/121; mean age: 36.9 ± 8.9; mean disease duration: 8.9 ± 6.6 years; mean EDSS: 4.34 ± 1.84) as well as 86 healthy control patients (M/F = 40/46; mean age:38.4 ± 11.1). 43 patients were on immunomodulation (mean EDSS: 3.36 ± 1.67), 49 patients were on immunosupression (mean EDSS: 5.10 ± 1.57), 46 received steroid treatment (mean EDSS: 4.16 ± 1.79) while 35 patients were not subjected to immunoactive therapy (mean EDSS: 4.70 ± 1.95). All subjects were assessed on MMSE, Beck Depression Inventory, Fatigue Severity Scale, World Health Organization Quality of Life Instrument and in EDSS.

Results: The best QoL was observed in patients on immunomodulation, the worst in patients on immunosupression ($p < 0.05$). The highest level of depressive symptoms was found in patients on steroid treatment, the lowest in patients on immunomodulation ($p < 0.05$). The highest intensity of fatigue was observed in MS subgroup obtaining immunosupressive therapy, the lowest in patients on steroid treatment. No correlation was found between depression and fatigue in investigated group of MS patients.

Conclusions: Immunomodulation seems to be beneficial in terms of quality of life of MS patients. Although, better QoL of patients receiving this treatment can be also influenced by their better functional state compared to patients on immunosuppresion.
Higher level of fatigue in MS patients on immunosupression should be explained by more advanced brain tissue damage (with axonal damage involvement), rather than side effects of immunosuppressive therapy. Higher risk of depressive symptoms in patients treated with steroids is a well known phenomenon and previously described side effect. Interestingly, our study does not support the hypothesis of higher intensity of depression in patients treated with interferon.

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Clinical, neuroimaging and electrophysiological correlates of brain atrophy in multiple sclerosis

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Objective: This study aims to search for a correlation between transcranial magnetic stimulation (TMS) evoked motor potentials (MEPs), expanded disability status scale (EDSS), corpus callosum (CC) atrophy in MS patients.

Background: MS is a chronic progressive inflammatory demyelinating disease and axonal degeneration is recognized as the cause of disability and disease progression. The most common localizations for MS plaques are periventricular white matter, internal capsule, pons, brachium pontis, CC, optic nerves and the spinal cord. CC is a major white matter bundle which plays an important role in functional inter-hemispheric integration, communicating cognitive information through interconnections between the hemispheres.

Design/Methods: Study group consisted of 79 clinically definite MS patients (51 female [64.6%], mean age 35.33 ± 7.67 years) and 50 controls (25 female [50%], mean age 35.04 ± 8.81 years). Routine neurological examination was performed and EDSS scores were evaluated. Patients were stimulated by TMS and MEPs were recorded. Absent values, decrease in amplitude, prolongation in latency and CMCT were considered as abnormal. Patients and controls were screened with MRI for CC volumes. CC atrophy was defined as volume 2 standard deviations lower than the mean volume of the controls.

Results: Evaluation of the patients revealed 60 patients (%75) as relapsing remitting MS, 19 patients (%25) as secondary progressive MS. The CC volumes revealed that 31 patients (39.2%) had CC atrophy. EDSS evaluation revealed 60 (75%) patients had EDSS $\leq$ 4, 19 (25%) patients had EDSS $>$ 4. 24 (40%) patients with EDSS $\leq$ 4 had CC atrophy, 7 (37%) patients with EDSS $>$ 4 had CC atrophy. Patient group with CC atrophy had 83% abnormal cranial amplitudes evaluated by MEPs.

Conclusions/Relevance: Progressive phase of MS is clinically marked by motor disability and cognitive dysfunction resulting from axonal loss and brain atrophy. In our study no correlation between EDSS and CC atrophy was found. This finding may indicate that CC atrophy might develop at the early disease stages, even before high EDSS scores. Our results indicate that MEPs correlate significantly with disease disability. Further studies with advanced neuroimaging methods are needed to explain the relationship between brain atrophy and clinical correlates of the disease.

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Oral delivery of DNA-chitosan nanoparticles for induction of antigen-specific tolerance in EAE: a potential therapeutic strategy for multiple sclerosis

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Objective: To determine if oral gene delivery of MBP-chitosan nanoparticles results in immune tolerance and neurological recovery of mice with experimental allergic encephalitis.

Methods: Elaboration of chitosan-DNA nanoparticles with the MBP gene and Lac Z reporter gene were examined for enzymatic and pH degradation, similar to the degradation process of fed antigens delivered by the gastro-intestinal tract. Animals were immunized against myelin basic protein (MBP) and a group of animals were fed with chitosan-DNA nanoparticles. Verification of transgene expression was done by administering chitosan-DNA nanoparticles with a transgene for Lac Z as a reporter gene. Confirmation of generation of systemic immune tolerance in previously immunized mice against MBP was made by quantification of TLR expression through RT-PCR in intestinal tissue and by histological analysis of inflammatory responses in the CNS as well as evaluation of myelin integrity.

Results: Chitosan-DNA nanoparticles were resistant to pH and enzymatic degradation. Mice fed with chitosan-DNA nanoparticles with Lac Z as a reporter gene showed transgene expression in intestinal epithelia that lasted at least for 7 days after administering one dose of chitosan-DNA nanoparticles containing 10 ug of genetic material. EAE mice fed with chitosan-DNA-MBP transgene developed systemic immune tolerance against MBP as shown by TLRs down-regulation at the intestinal level after gene delivery; decreased in inflammatory plaques in the CNS and recovery in myelin integrity after receiving 3 doses of chitosan-DNA MBP at 28, 35 and 42 das after immunization. Immunized control animals showed increasing inflammatory infiltrates in the CNS as well as lost of myelin integrity.

Conclusion: Transgene expression of a natural folded antigen at gastrointestinal mucosa for a period of 3 weeks should be able to down-regulate or delete an antigen specific immune response. In contrast antigen feeding regimens have not shown therapeutic benefits since the antigen is almost completely destroyed in the gastro-intestinal tract and the system is not able to delete a previous immune response. Chitosan-DNA nanoparticles may improve the clinical deficits and autoimmunity in animals previously sensitized against those antigens. In the case of MS, induction of immune tolerance by expression of neuroantigens at the mucosal level might be therapeutic and disrupt the ongoing autoimmune inflammation allowing regeneration of tissues.

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Effectiveness of an information aid for newly-diagnosed MS patients: the SIMS trial

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Background: People with MS express a desire for more information about their disease, and to be involved in decisions about their care.

Objectives: To assess the effectiveness, in terms of patient knowledge and satisfaction with the information received, of a structured add-on information interview, given within 15 days of communicating an MS diagnosis.

Design and setting: The SIMS-Trial (ISRCTN81072971) is a multicenter (six Italian MS centers), phase III, prospective, randomized, allocation-concealed, controlled trial comparing the study intervention with usual practice in 120 newly-diagnosed people with MS.

Study Intervention: Add-on interview conducted by trained neurologists, during which information about MS is presented with the aid of a specifically designed CD. The information is tailored to individual needs; the patient is also given a booklet containing all the information provided.

Control intervention: Current practice at each center as regards communication of MS diagnosis.

Trial outcomes. Primary endpoints, assessed one and six months after diagnosis disclosure, are knowledge and satisfaction with diagnosis communication as determined by the "MS Knowledge Questionnaire" and by the instrument "Comunicazione medico-paziente nella Sclerosi Multipla" (revised). Secondary endpoints are changes in the Hospital Anxiety and Depression Scale, and in the Control Preference Scale. Attrition, number of consultations and number of visits to the MS center over the study period are also examined.

Results: The SIMS-Trial is conducted according to the Good Clinical Practice Guidelines of the EU (ICH Topic E 6 [R1] - Guideline for GCP). The investigators' meeting took place in February 2008, and by September 2008 the study protocol was approved by the Ethics Committees at all participating centers. One-hundred fourty patients have been screened and 84 randomized so far. Two patients have withdrawn from the study, and three refused the informing interview. Detailed baseline data and preliminary results will be presented.

Study supported by: Fondazione Italiana Sclerosi Multipla (Grant n. 2007/R/19 to A. Solari).

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Development of an information aid for newly-diagnosed MS patients

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Background: Patient information aids are increasingly regarded as important components of clinical practice. They improve sense of control, adaptive coping, and enable shared decision making with healthcare professionals. There is little evidence of their successful implementation in the MS field.

Objective: An information aid for newly-diagnosed MS patients was developed consisting of a CD and a booklet. The objective was to provide unbiased, high-quality information about MS intended to supplement rather than replace patient-practitioner interaction (Elwyn 2006).

Methods and results: The information aid was produced using information from three sources: focus groups with patients and clinicians (Solari 2007), multidisciplinary expert opinion, and a comprehensive literature review.

The CD contains an introduction followed by a menu of headings: MS insights; The diagnosis; What happens after diagnosis; Therapies; Emotions; Having a child; FAQs; Glossary. Animations and aids are used throughout the CD. A speaker illustrates the entire presentation. Emotions are also presented as an eight-minute video. Navigation through the CD is determined by the user and is traced electronically, and time spent on each topic is recorded. Links to the glossary are present from all pertinent points on the program.

The booklet has eight chapters (90 pages), a glossary (36 pages), and a section for notes. The chapters match the CD topics in title and information provided.

Conclusions: The information aid is now being compared to usual practice in an ongoing Italian multicenter phase III prospective, randomized, allocation-concealed, controlled trial (SIMS-Trial; ISRCTN81072971). A qualitative study (SIMS-Qual), nested within the trial, will be also performed to scrutinize the experience of participants, by means of in-depth interviews with purposively sampled patients, and a focus group of health professionals. Integrating quantitative and qualitative research methods will help us maximizing our ability to interpret results according to empirical evidence.

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Targeted therapy of relapsing-remitting multiple sclerosis with interferon β-1b: results of a Polish multi-centre survey

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Objectives: In Poland reimbursement hurdles limit the use of immunomodulatory therapies in multiple sclerosis (MS). Treatment entry criteria of the National Health Fund (NHF) narrow target group of patients compared to approved drug indications, in order to direct therapy to the subset that might benefit most from disease modifying treatment. We aimed to follow-up patients treated with interferon β-1b according to the NHF inclusion criteria, to evaluate treatment efficacy as compared to observed in randomised clinical trials (RCTs).

Methods: Treatment naïve patients with relapsing form of MS, scheduled for therapy with interferon β-1b (Bferon, Bayer Schering Pharma) in the MS Therapeutic Programme, were followed over the period of up to 2 years in the routine practice setting. All patients must have experienced at least two relapses during the previous 2 years and get at least 23 points in the NHF-specific scale (range 3–28), which comprises: age, disease duration, Expanded Disability Status Scale (EDSS) score and annualised relapse rate. NHF scale favours patients aged <40 years, with disease duration < 3 yrs, EDSS score <2 and annualized relapse rate 3–4/years. Responders to treatment were defined as relapse-free and progression-free patients. Further efficacy endpoints included annualised relapse rate and change of EDSS score. The prescribed dose of Bferon was 250 mcg subcutaneously every other day.

Results: Between 9/2005 and 12/2006, 248 patients were enrolled in 24 centres throughout Poland. Mean age was 30.1 ± 7.7 years (range 16–65 yrs). Median disease duration in studied cohort was 1.5 years (range 0.6–3.5 years) with vast majority of patients (85%) having EDSS score less than 2. Patients were observed for a mean period of 1.63 ± 0.59 year (range 0–3 years). The proportion of responders to treatment was 66.2% and 46.3% at 1 and 2 years respectively. Annualised relapse rate decreased significantly from 1.09 ± 0.5 before treatment to 0.53 ± 0.83 at 2 yrs ($p < 0.0001$). EDSS stabilised (score change ≤ 0.5) in 70.6% and 66% patients at 1 and 2 years, respectively. Improvement in EDSS (by at least 1.0) was seen in 14.2% and 17.4% patients at 1 and 2 years, respectively. Out of 5.6% (14/248) patients who dropped out, 5 withdrew because of disease progression and 2 for drug intolerance.

Conclusions: Our efficacy data are consistent with reports from RCTs. Narrowing of treatment inclusion criteria vs approved Bferon indications does not result in improved clinical outcome.

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Autologous haematopoietic stem cell transplantation as a treatment modality for progressive multiple sclerosis

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High dose immunosuppression and autologous haematopoietic stem cell transplantation (AHSCT) is a new and promising therapy for multiple sclerosis (MS) patients. In accordance with Guidelines of AHSCT in MS (Comi et al. 2000) to assess risk/benefit ratio of AHSCT in MS it is mandatory to collect further data. We aimed to study outcomes in progressive MS patients after early (EDSS 1.5–3.0), conventional (3.5–6.5) and salvage (7.0–8.0) AHSCT.

94 patients with MS (secondary progressive, 59; primary progressive, 25; progressive-relapsing, 10) were included in this study (mean age −33.7, range: 17–54; male/female, 43/51). BEAM ($n = 49$) or BEAM-modified ($n = 45$) conditioning was used. Seventy six patients underwent conventional, 11 patients—early and 7 patients—salvage AHSCT. Median EDSS at base-line was 5.5 (range 1.5–8.0). The mean follow-up duration was 20 months (range 6-114 months). Neurological evaluation was performed at baseline, at discharge, at 3, 6, 9, 12 months, and every 6 months thereafter; MRI - at baseline, at 6, 12 months, and later once a year.

Transplantation procedure was well tolerated by the patients with no transplant-related deaths. The efficacy analysis was performed in 61 patients who had had follow-up for at least 9 months. At 6 months post transplant the following distribution of patients according to clinical response was observed: 31 patients achieved an objective improvement of neurological symptoms; 30 patients had disease stabilization. Among the patients after conventional AHSCT there were 48% patients with improvement and 52% with stabilization; after early AHSCT—71% with improvement and 29% with stabilization; after salvage AHSCT—33% with improvement and 67% with stabilization. In 1 year post-transplant 2 patients relapsed (both - conventional AHSCT); in 2 years post-transplant 3 patients had disease progression (all conventional AHSCT). All other patients experienced either improvement or stabilization throughout the follow-up.

MRI analysis before AHSCT revealed Gd + lesions in 27 out of 75 patients. No active, new or enlarging lesions were registered after AHSCT in patients without disease progression.

This study provides ample evidence in support of safety and benefits of AHSCT in progressive MS patients. The data obtained points to the feasibility of early, conventional, and salvage AHSCT in progressive MS patients.

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Cognitive training in multiple sclerosis: an fMRI study

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Objectives: Studies on the efficacy of cognitive training in multiple sclerosis (MS) have provided conflicting results, due to patients' clinical heterogeneity, the use of tasks not specific for the trained function, and poor neuropsychological outcome measures. We investigated the effectiveness of a PC administered intensive neuropsychological training of attention and executive functions in clinically stable relapsing-remitting MS patients with low disability and its correlation with brain activation changes during functional magnetic resonance imaging (fMRI).

Methods: Among 80 RRMS patients screened, 11 patients were included as they had z scores < 1.5 SD in both Paced Auditory Serial Addition Test (PASAT) and Winsconsin Card Sorting Test (WCST). Other inclusion criteria were normal vision, normal right-hand motor function, and absence of psychiatric symptoms or therapies. Patients underwent an extensive neuropsychological evaluation (PASAT, WCST, verbal fluencies, Selective Reminding Test, Symbol Digit Modality Test, Divided attention reaction times, MSQoL and MADRS), and fMRI (Stroop interference test) at baseline and at the end of the cognitive training period. Six patients had attention and executive functions rehabilitation (3 hours weekly for 3 months by means of Rehacom ® Divided Attention and Plan a Day software).

Results: At baseline, the two groups had similar clinical and neuropsychological characteristics. At follow up, the rehabilitated group had a significant improvement at PASAT ($p = 0.02$), WCST ($p = 0.04$), phonemic fluency ($p = 0.03$), divided attention ($p = 0.03$), MSQOL ($p = 0.02$). The not rehabilitated patients did not improve in any test. At follow up, fMRI showed between-group differences in Stroop congruent (rehabilitated group with greater activation in BA10, precuneus and S2) and incongruent (rehabilitated group with greater activation in cingulum and BA10) conditions. Between-group and time interaction showed a significantly greater activation in the rehabilitated group in left BA10, left M1, cingulate cortex, and right S2.

Conclusions: Specific cognitive training has a significant effect in mildly-disabled RRMS patients with poor attention and information processing abilities, whose neural correlate seems to be a greater cortical activation of brain structures, such as the cingulum and the prefrontal cortex.

P688

Efficacy, safety and tolerability of natalizumab in Turkish multiple sclerosis patients with high disease activity: a hospital-based cohort at a university faculty of medicine, multiple sclerosis unit, Istanbul

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Natalizumab is a monoclonal IgG antibody against α-4 integrin, able to significantly reduce relapse rate, disability progression and lesion development in relapsing remitting multiple sclerosis (RRMS).

Natalizumab has been available in Turkey since May 2007, it can only be administered to patients with two or more relapses on disease modifying treatment (DMT) in the previous year with the special permission of the ministry of health.

The objective of this study was to analyse efficacy, safety and tolerability data in our patients with RRMS treated by natalizumab from May 2007 to January 2009.

Since May 2007, 38 patients with high disease activity RRMS were included in the study, Expanded Disability Status Scale(EDSS) score before and every 3 months of treatment,relapse rate in 1 year before the initiation of treatment, and number of relapses every 3 months of treatment with natalizumab, were recorded in each patients.

There were 22 women (57.8%) and 16 men (42.2%) (F:M ratio: 1.3/1) in this cohort. Age of patients at January 2009 were mean 34.2. Age at MS onset was 24.8. Mean duration of disease was 8.5 years . Mean duration of treatment with natalizumab was 9.3 months (range 2 to 20 months). At January 2009, 37 patients have been receiving natalizumab. Median annual relapse rate 1 year before natalizumab treatment was 2.6. Mean EDSS score at the initiation of the treatment was 4.1. One patient developed brainstem relapse3 months after the initiation of natalizumab treatment, and he stopped the therapy. In other two patients, clinical relapses occurring within 48 h after the first dose of natalizumab were observed and they completely improved after five days intravenous methyl prednisolon therapy. Mean EDSS score at 9.3 months of natalizumab therapy was 2.9.In 20 patients, EDSS was stabilized, and it improved at least 1.0 point at 6 months of treatment in18 patients..We did not see any side and adverse effects during the treatment period.

Natalizumab appears to be effective, safe and tolerable during our observation period in MS patients with high disease activity as the annual relapse rate dropped from 2.60 to 0.08 and this relapse rate was lesser than the 0.26 reported in the AFFIRM study after the first treatment year. Mean EDSS score dropped from 4.1 to 2.9 at the 9.3 months of natalizumab treatment These results seem very positive but should be confirmed on long-term,prospective further studies.

P689

Sexual dysfunction in women with multiple sclerosis

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Objectives: sexual dysfunction (SD) is frequently observed in multiple sclerosis (MS)patients, in 30-80% of cases [1]. However its extent is not well defined as the frequency of SD is usually not compared with that of healthy subjects. Our study has been carried out in order to estimate the frequency and characteristics of SD in women with MS, compared with a control group.

Subjects and methods: female sex function Index (FSFI), sexual distress scale (SDS), and Beck Depression Inventory (BDI) were administered to 60 consecutive ambulatory definite MS women(age 18–55 years), and to a control group of 60 healthy females.

Results: MS cohort: mean age 38.0 ± 6.9 years, mean disease duration 9.8 ± 6.3 years, mean EDSS 1.9 ± 1.4. The mean age of controls was 37.7 ± 6.2 years. Social, educational and marital characteristics were similar in the two groups.
In MS patients (controls in brackets) the mean FSFI score was 25.7 ± 6.9 (27.6 ± 6.5). The score of subscale of desire was 3.5 ± 1.1 (3.4 ± 1.0), of that of arousal 4.1 ± 1.7 (4.3 ± 1.4), of lubrication 4.5 ± 2.0 (5.0 ± 1.4), of orgasm 4.5 ± 1.9 (4.7 ± 1.5), of satisfaction 4.6 ± 1.6 (4.9 ± 1.3), of pain 4.7 ± 2.0 (5.3 ± 1.3). The difference between the two cohorts was significant only for the subscale of pain. The SDS score was 9.7 ± 11.6 (8.6 ± 6.9) (ns). When data were analysed separately in 3 subgroups according to disease duration ($<$ 5ys, 5-10 ys, $>$ 10 ys), FSFI score resulted statistically lower in MS compared to controls for subjects with a disease

duration > 10 years. In these subjects a statistically significant correlation was found between FSFI and BDI.

Conclusions: FSFI is an useful self-report measure of female sexual function (2); it includes 19 items evaluating desire (2 items), arousal (4 items), lubrication (4 items), orgasm (3 items), satisfaction (3 items), and pain (3 items). For each item, 0 corresponds to lack of funtion,5 to its higher level. In our study the scores of healthy subjects were similar to normative data of the American population [2].
The scores of FSFI in MS were not statistically different from those of healthy subjects, except for pain scale. SD measured by means of FSFI and SDS was not a major complaint in our MS cohort, with a low mean disability. However SD was frequent, and statistically correlated with depression, in females with a long disease duration.

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P690

Natalizumab in paediatric multiple sclerosis: preliminary data of 17 patients

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Background: Natalizumab has a strong effect in reducing relapse rate and disease progression in multiple sclerosis (MS). Two recent studies described a beneficial effect in one [1] and three cases [2] with paediatric MS. Natalizumab was safe and well tolerated in a cohort of 38 subjects with juvenile Crohn's disease [3]. About 1/3 of paediatric MS cases do not respond to IFNB or Glatiramer Acetate. These patients can be candidated to a second line treatment.
We report here the preliminary results of 16 cases treated with Natalizumab before 18 years of age.

Subjects and methods: demographic and clinical data were collected using a standardised form. Subjects were treated with Natalizumab if affected by definite MS, experienced a relapsing course with at least 2 relapses in the previous 2 years and/or incomplete recovery in spite of treatment with IFNB or GA, or experienced a relapsing course with a recent severe relapse and an incomplete recovery. Patients and parents gave their informed consent to the treatment.

Results: 17 patients (11 girls) were included, mean age at onset 12.4 ± 2.6 years, mean age at treatment with Natalizumab 14.2 ± 3.1 years. Brain/spinal cord MRI showed Gd + activity in the previous year in all subjects, and it was active in 11 subjects before starting the treatment.
At present the mean follow up duration is 7 months, lasting more than 12 months in 4 cases. The treatment was well tolerated in all subjects, 1 complained of diarrhoea, another one of headache. Only one relapse was recorded, 1 month after the therapy was started. The mean EDSS score decreased from 2.6 to 2.0.

Comment: Natalizumab is a promising treatment for RR-MS patients with paediatric age who do not respond to usual immunomodulatory treatment. We have started a cooperative follow up study to assess long term safety, tolerability and clinical effectiveness.

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P691

A profile of a population from a Real-World Observational Study compared to the baseline patient characteristics of a recent phase III trial (BEYOND) in relapsing-remitting multiple sclerosis patients: baseline patient characteristics in ROBUST

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Objective: To describe baseline patient characteristics of relapsing-remitting multiple sclerosis (RRMS) patients from a real-world observational study and those from a recent phase III clinical trial in multiple sclerosis (MS).

Methods: The Real-World Bseron® Outcomes Study (ROBUST) is a twelve-month, US prospective, observational, open-label, single-arm, multi-center outcomes study of Interferon β-1b given every other day for RRMS. Patient outcomes were reported both by patients and by physicians directly via a web-based data capture tool. A total of 226 patients, including a small fraction ($n = 17$) with clinically isolated syndrome (CIS), were enrolled across 52 neurologists' sites. Descriptive statistics were generated for demographic and baseline variables in ROBUST, and the results for the RRMS patients ($n = 209$) are compared to those of the BEYOND population ($n = 2244$).

Results: Compared to the baseline characteristics of the population in BEYOND, the ROBUST RRMS population is more female (79 vs. 70%), more racially diverse (87 vs. 91% white), older (mean age 42.5 vs. 35.7 years; mean age at onset 33.6 vs. 31.0 years), and similar in duration of MS disease (5.1 vs. 5.2 years). The comparisons in EDSS scores in ROBUST RRMS population versus that in BEYOND are: comparable overall mean EDSS (2.55 vs. 2.3); EDSS ≤1: 24 vs. 14%; 1.5 to 3: 49% vs. 61%; 3.5 to 5: 17% vs. 25%, EDSS > 5: 11 vs. < 0.1%, respectively, with 8% EDSS = 6 vs. excluded EDSS > 5.5. ROBUST had relatively more RRMS patients with only one relapse in the past year (67% vs. 54%) but fewer with two (23% vs. 37%) and a similar percentage with three or more (10 vs. 9%).

Conclusion: Since real-world observational studies, such as ROBUST, generally have broader inclusion criteria, their participants typically constitute a more heterogeneous population than those in controlled clinical trials. The profile of the former can serve as a good benchmark against which MS clinical trials can enroll subjects and assess the ability to generalize their results.

The ROBUST study was funded by Bayer HealthCare Pharmaceuticals, Inc.

P692

Complementary and alternative medicine use by multiple sclerosis patients in Spain

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Background: The use of complementary and alternative medicine (CAM) is frequent in patients with chronic diseases. CAM is expensive and not harmless. Some european studies have found high rates of CAM use in patients with multiple sclerosis (MS).

Objective: The goal of this study was to examine the frequency and characteristics of complementary and alternative medicine (CAM) use among patients with multiple sclerosis (MS) in the region of Madrid and to explore the reasons for use and perceived effectiveness of these therapies.

Methods: In order to collect sociodemographic and disease related variables as well as aspects of CAM utilization, 368 outdoor MS patients from eight different hospitals in Madrid (Spain) were examined with a cross-sectional survey. The investigation was completed by data of the neurological examination. Factors evaluated for their association with CAM use included: age, gender, disease severity, disease-modifying drugs (DMT) use, MS duration, MS type, education level, EDSS and costs.

Results: At the time of investigation 30.2 % of the MS patients reported that they were currently using one or more CAMs. Most of the used therapies were chosen as a complement and not as alternative therapy (17%). Phytotherapy (40,6%), relaxation techniques (14,2 %), and acupuncture (11.3 %) were the most commonly used CAMs. When evaluating the efficacy of CAM, patients reported improvement in 81,5 %, no influence in 17,5% and worsening in 1 % of the cases. 7% of the CAM therapies were accompanied by minor side effects. The mean annual cost of regular CAM use was 2,600 € pro patient. Multiple regression analysis revealed that users of CAM were more severely affected by the MS than non-users. Patients with secondary progressive MS were on CAM more often than other MS types. CAM use was more likely among participants with higher level of education.

Conclusions: MS patients in Madrid used CAMs, overall as a complement therapy but the use is less than in other european countries. Patients spend a considerable amount of money on regular CAM use. Disease factors such as severity and MS type play an important role in their use.

P694

Natalizumab-induced freedom from disease activity after failure to previous therapy in relapsing-remitting multiple sclerosis

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Objectives: To analyze the efficacy of natalizumab after switching relapsing-remitting multiple sclerosis (RRMS) patients from other disease modifying treatments (DMTs).

Background: Natalizumab (Tysabri) is a monoclonal antibody directed against VLA4 that was recently approved for the treatment of RRMS. Due to safety concerns, the use should be restricted to highly active patients and/or patients with insufficient response to other DMTs. The pivotal trials were not designed to examine the effect of natalizumab as an escalation monotherapy.

Methods: Prospective, open label, observational study. All patients initiating natalizumab had experienced at least 1 relapse in the previous year under DMTs and had at least 1 Gd-enhancing lesion on their brain MRI. Previous treatment with interferon-β(IFN-β) or glatiramer acetate (GA) were stopped at least one week and azathioprine or mitoxantrone at least 3 months before switching. The minimum therapy duration with natalizumab was 6 months for all patients. 21 RRMS patients were included in this analysis. The mean age of the patients was 25.5 yo with mean disease duration of 6.8 years. All patients were under IFN-β(17) or GA (4) during at least the previous year before starting natalizumab therapy. Four patients had also received azathioprine and 1 patient mitoxantrone.

Results: The mean relapse rate in the previous year was 2.15 (1–4), the mean EDSS at baseline was 3.3 (1,0-6.0), the mean number of Gd + lesions at baseline 2.58 (1–6). Under tysabri treatment the annualized relapse rate dropped to 0.20. Eleven patients improved their EDSS (0.,5 to 1.5 steps down), others remained stable at 6 months. The mean number of Gd + T1 lesions dropped to 0.,23 and the mean number of new T2 lesions was 0.25 on the control MRI at 6 months. 55% of patients were free from disease activity, i.e. had no relapses, no EDSS progression, no new T2 lesion and no Gd + T1 lesions after 6 months of Tysabri. 5 patients experienced minor adverse events (1 zona, 2 flu-like symptoms, 1 gastroenteritis, 1 allergic reaction).

Conclusion: Natalizumab was well tolerated and safe as escalation therapy when previous DMTs had failed to control disease progression in this group of highly active RRMS patients. These results suggest comparable efficacy to the phase III AFFIRM trial of natalizumab when the drug is used in a context of breakthrough disease. Although data from preliminary analyses are promising, long term investigations are warranted.

P695

The timed 100-meter walk test: an easy-to-use sensitive tool to detect and evaluate restricted walking capacities in multiple sclerosis

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Objectives: The primary aim of this study was to develop a quantitative ambulation test that correlates with the maximal walking distance in multiple sclerosis (MS) patients.

Background: The timed 25-foot walk (T25FW) weakly correlates with overall walking capacities of MS patients. We developed the timed 100-meter walk test (T100T), which besides reflecting speed may be more sensitive to other walking parameters such as gait and spasticity-related fatigue.

Methods: In the T100T, the patient is instructed to walk as fast as possible on a distance of 100 meters. Eighty-eight MS patients with an EDSS score from 0 to 5.5 and 60 normal controls performed the T100T and the T25FW. In addition, 30 normal controls and 30 patients performed the tests twice.

Results: T25FW (R2 = 0.79) and T100T ($R^2 = 0.89$) correlated with the nonlinear distribution of EDSS scores. The correlation

between T100T and T25FW values was high ($r^2 = 0.81$) for the low (0–3.0) and high (3.5–5.5) scores of EDSS. The intra-class correlations were excellent and similar for both tests. The range of T100T values in MS patients (40.4–114.7 s) was 10-fold wider than that of the T25FW (3.0–9.1 s). The univariate distribution analyses demonstrated that abnormal T100T values appear to be more sensitive than T25FW to predict walking limitations. Finally, the correlation with the reported and/or actual maximal walking distance without aid and rest was significantly better for T100T.

Conclusions : The T100T proves to be superior to the T25FW in terms of discriminatory power for the detection and evaluation of restricted walking capacities in MS. The T100T should be of interest for clinical trials studying disability worsening and improvement across the spectrum of EDSS. It may provide more sensitive measure for ambulation change in quantifying progressive MS pathology.

Biogen Idec, Inc. provided statistical analysis support.

P696

Cognitive aspects in relapsing-remitting multiple sclerosis patients treated with immunomodulant drugs: 24-month follow-up of the ITACA study

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Background: Multiple sclerosis (MS) is the leading cause of disability in young adults and its progression, involving cognitive and physical aspects, may influence both the Quality of Life (QoL) and the affective status.

Aim: To evaluate long-term effects of different first-line Disease Modifying Therapies (GA or IFNs) on cognitive functions, affective status, fatigue and QoL in patients with relapsing remitting multiple sclerosis (RRMS) over a 24-month period.

Method: Observational, longitudinal, multicentre, Italian study. The study was designed to follow-up a cohort of MS patients treated with immunomodulant drugs for 2 years. The patients underwent a comprehensive neuropsychological and neurological evaluation in the designed time. MS Quality of life/54 items, Montgomery Asberg Depression Rating Scale and Fatigue Severity Scale were administered too. We defined as "mild" cognitive impairment the failure in 1 or 2 tests in the cognitive domain and as "severe" the failure in at least 3 tests. 51% (314) of the patients were treated with GA and 49% (307) with IFNs.

Results: 752 patients were enrolled by 79 Italian Centres (397 patients were treated with GA and 355 patients with IFNs). 130 patients (17%) dropped out. In the cohort of the 622 subjects who completed the 24-month follow-up, 57% showed at baseline cognitive impairment (40% "mild" and 17% "severe"). At the 24-month cognitive impairment was detected in 43% of the patients: 31% had "mild" and 12% "severe" cognitive impairment. Cognitive impairment did not progress in both IFNs and GA groups. A significant correlation between cognitive impairment and EDSS scores was observed both at baseline and at follow-up ($p < 0.05$). Both at baseline and at 24-month follow-up patients with a "severe" cognitive impairment complained of a mean higher level of fatigue and of depressive symptoms, compared to patients with "mild" or no cognitive impairment. No difference was found between baseline and follow-up in self-perceived QoL.

Conclusions: The prevalence of cognitive impairment in our group of RRMS is remarkable. Subjects with "severe" cognitive impairment are more likely to suffer both from a more severe depressive symptomatology and physical disability compared to those with no or "mild" cognitive impairment. Subjects treated with both INFs or GA did not show progression of cognitive impairment.

P697

In vivo monitoring of neuroprotection by glatiramer acetate in patients with relapsing-remitting multiple sclerosis

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Objectives: Apart from its (TH2) immunomodulatory effects, glatiramer acetate (GA) is suggested by recent in vitro and animal model studies to be neuroprotective by stimulating neurotrophin secretion in the CNS. The clinical evaluation of these neuroprotective properties is not proven yet.

Methods: In this prospective two-year pilot trial, therapy-naïve patients with relapsing-remitting MS have been enrolled. Patients were either treated with standard GA therapy or received no treatment (patient's decision). Neurological examination and diagnostic work-up (including different serum parameters and FACS analysis) were done every three months; neuropsychological testing, brain MRI, and evoked potentials (EP) were performed yearly.

Results: 22 patients have been enrolled; 15 received GA therapy, 7 patients had no immunomodulatory treatment. Baseline characteristics (including mean age, disease duration, number of relapses and EDSS; visually, sensory and motor EP) were similar in both groups. Neuropsychological testing (including verbal and figural memory, attention, executive functions, quality of life (QoL) and fatigue) revealed a significant better short-term memory and a better QoL at baseline in patients without treatment. MRI exhibited no differences in the T2 lesion load whereas the number of contrast-enhancing lesions (CEL) was higher in the GA group at baseline. Until 1st of February 2009 20 patients (91%) have completed one year follow-up. Mean EDSS and number of relapses did not differ between the investigated groups at any time. After one year the T2 lesion load as was well as the number of CEL were similar in both groups. There were no significant differences in EP findings at year one. After 3 months of GA therapy serum MOG and MBP IgG levels significantly increased, but decreased again in the further course of therapy. No differences were found in the number of T-, B- and NK-cells as well as BDNF-labeled T-cells and -monocytes as measured by FACS. Serum BDNF levels determined by ELISA were comparable between both groups.

Conclusion: To our best knowledge, this is the first multimodal approach to monitor neuroprotection of GA in a prospective clinical trial. A one-year interim analysis revealed no significant differences between the GA-treated and the untreated group. However, given the delayed therapeutic effect of GA and the longterm MS disease course, the one-year interim analysis may be a too short timepoint to measure neuroprotection.

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P698

Delivery technology for multiple sclerosis therapy: an international, multi-centre, single-arm, open-label, 12-week, phase IIIb trial of a new electronic device for subcutaneous injection of interferon β-1a

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Objective: Poor adherence to disease-modifying drugs (DMDs) for multiple sclerosis (MS) may lead to suboptimal treatment outcomes. All current DMDs for MS require frequent parenteral administration, which can cause difficulties for some patients and may impact on adherence to therapy. Developments in injection-device technology may encourage adherence to treatment regimens. A new electronic multi-dose autoinjector device has been developed for subcutaneous (sc) administration of interferon (IFN) β-1a. To maximize comfort, the device allows adjustment of injection depth and speed, and to enhance convenience it provides the patient with visual and auditory cues during the injection process. It also records information on dosing history. The suitability of this device for self-injection is being evaluated in an ongoing study in patients with relapsing MS. Secondary study objectives are to evaluate: the incidence of injection-site reactions; patient satisfaction with use; and patients' and trainers' impressions of device characteristics.

Methods: This is an international, multicentre, single-arm, open-label, 12-week, Phase IIIb study. Patients, enrolled are aged 18–65 years with relapsing MS (McDonald criteria) and disease durations of ≥ 3 months, and had received IFN β-1a 44 mcg sc three times weekly (tiw), consistently for ≥ 6 weeks prior to screening. Exclusion criteria include regular injection of any other medication during the screening and study periods, and any physical/visual impairment that would preclude proper use of the device. At baseline, patients are trained in the use of the new device. Patients receive IFN β-1a, 44 mcg sc tiw, for 12 weeks. Assessments are performed at baseline and weeks 2, 4, 8 and 12.

Results: The primary endpoint is the proportion of patients rating the device as 'very suitable' or 'suitable' for self-injection of sc IFN β-1a 44 mcg sc tiw at week 12. Secondary endpoints include the incidence of pre-defined injection-site reactions; various subscale scores on the MS Treatment Concern Questionnaire; and overall evaluation of the device based on a user trial questionnaire.

Conclusion: This study will evaluate the suitability of a new electronic device for self-injection of sc IFN β-1a 44 mcg sc tiw in patients with relapsing MS. Improvements in delivery technology may encourage patients to adhere to treatment.

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P699

Understanding and meeting the injection device needs of patients with multiple sclerosis

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Objective: Frequent, chronic injection of disease-modifying drugs for multiple sclerosis (MS) is challenging for some patients, and poor adherence may lead to suboptimal treatment outcomes. New injection methods may help to improve treatment adherence. The aim of this study was to survey patients' experience with current injection methods and their reactions to the RebiSmartTM, a new, electronic, autoinjector device for subcutaneous (sc) interferon (IFN) β-1a.

Methods: Patients (18–65 years) with relapsing MS, receiving sc or intramuscular IFN β-1a, IFN β-1b, or glatiramer acetate for ≥ 2 months undertook a self-administered online interview. Patients were questioned on their current injection method and, following a description of features and injection procedure, their impressions of the new device.

Results: Of 422 patients, 186 (44%) were using autoinjector devices, 183 (43%) were using pre-filled syringes, and 53 (13%) were using syringes and vials. Approximately one-third of patients received assistance with injection. Reasons (both physical and psychological) for not self-injecting included needle phobia and not trusting oneself to inject correctly. On a scale of 0 (not at all satisfied with current injection method) to 10 (very satisfied), mean score was 6.7; 40% of patients scored 8–10. Scores were highest for patients using autoinjectors. When patients were asked to rate the appeal of the new device, this was also scored from 0 (not at all appealing) to 10 (very appealing). Mean score was 7.7; 65% of patients scored 8–10. Scores did not differ by current injection method. Most respondents (96%) identified benefits of the new device; the ability to tailor injection settings (39%) and dosing log (38%) were most common.

Conclusion: Key barriers to self-injection in patients with relapsing MS are needle phobia and fear of incorrect injection. Patients reacted favourably to the electronic autoinjection device, citing features such as the dosing log as particularly beneficial. A simple, reliable injection device may reduce needle anxiety and concerns over technique, inspiring greater patient confidence in self-injection. Such encouragement, combined with dose-monitoring ability, may improve treatment adherence.

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P700

Rapid and sustained efficacy with cladribine tablet treatment in relapsing-remitting multiple sclerosis (RRMS): results from the CLARITY study, a 96-week, phase III, double-blind, placebo-controlled trial

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Objectives: Cladribine tablets are in development for the treatment of multiple sclerosis. Cladribine is a pro-drug, and activation in specific cell types provides targeted and sustained immunomodulation, permitting the investigation of an oral short-course annual treatment. Here we investigated the time course of efficacy onset for cladribine tablets relative to placebo, from the CLARITY (CLAdRIbine tablets Treating multiple sclerosis orallY) study in patients with RRMS.

Methods: RRMS patients (McDonald criteria; EDSS: 0–5.5) were randomised (1:1:1) to one of two cladribine tablet regimens (total dosage of 5.25 or 3.5 mg/kg) or matching placebo. Cladribine tablets were administered in short courses (once daily for 4–5 days) in 4 or 2 consecutive months during the first 48 weeks and for 2 consecutive months at the start of the second 48 weeks. Efficacy endpoints included the annualised qualifying relapse rate (primary), the proportion of relapse-free patients, and MRI activity measures vs.

placebo (active T1-Gd + , active T2, and combined unique [CU] lesions per patient per scan).

Results: The ITT population comprised 456, 433 and 437 patients randomised to 5.25 mg/kg, 3.5 mg/kg or placebo groups, respectively. Annualised qualifying relapsed rates in the 5.25 and 3.5 mg/kg groups demonstrated numerical differences vs. placebo as early as 4 weeks (0.27 and 0.23 vs. 0.42), with differences achieving statistical significance in the 3.5 mg/kg group at 12 weeks (0.27 and 0.20* vs. 0.49) and in both the 5.25 and 3.5 mg/kg groups at 16 weeks (0.21* and 0.19* vs. 0.44, respectively); efficacy was then sustained through to 96 weeks (0.15* and 0.14* vs. 0.33). A similar early and sustained treatment effect was observed on the proportion of patients relapse-free vs. placebo. For MRI activity measures, significant treatment benefits were evident on the first MRI assessment at 24 weeks (mean number of CU active lesions per patient per scan: 0.38* and 0.49* vs. 1.91 in the 5.25 and 3.5 mg/kg vs. placebo groups, respectively) and maintained through to 96 weeks. Further correlations between clinical and MRI parameters will be presented.

Conclusions: Treatment with cladribine tablets resulted in rapid and sustained improvements in clinical and MRI outcomes. Together with the observed favourable tolerability and safety results (reported elsewhere), these results suggest that annual short-course treatment with cladribine tablets may provide an important new option in MS therapy.

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General neurology

P701

Has substitutive treatment any efficacy in traumatic brain injury patients with GH deficit?

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Objective: Patients with severe traumatic brain injury (TBI) frequently show cognitive sequelae, fatigue and impaired quality of life (QoL). Several recent studies have shown that pituitary deficits are frequent, including growth hormone deficit (GHD). GHD patients without TBI also have fatigue, impaired QoL and cognitive disorders, which can be improved by substitutive treatment. Here, we analyzed the effectiveness of substitutive treatment in TBI patients.

Methods: TBI patients who complained after one year of fatigue and cognitive disorders had systematic assessment of pituitary functions (with stimulation tests), physical and cognitive (attention, memory, executive functions) disorders and QoL (QOLIBRI scale). All hormonal deficits were supplemented, including GHD. Control of cognitive assessment and QoL was performed one year later. Results obtained in a group of 17 GHD patients were compared with those of an equivalent group (age, education level and TBI severity) of non-GHD patients.

Results: Most cognitive parameters improved, but without between-group difference. More definite improvement was found in GHD patients for the QOLIBRI scale subtests: personal factors assessed by the patient (group x session interaction: $p = 0.037$) and family ($p = 0.065$), physical factors assessed by the patient ($p = 0.092$) and intellectual factors evaluated by the family ($p = 0.071$). Only 2/17 patients wished to discontinue treatment after one year.

Conclusion: In TBI GHD patients, substitutive treatment can contribute to better improvement in QoL, but not to better performance in cognitive tasks. These contrasted results must be confirmed in a larger group of patients.

P702

McCune-Albright syndrome and neurology: a case report

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Introduction: McCune-Albright syndrome (MAS) has a clinical spectrum of fibrous dysplasia of bone (FD), caféau-lait skin spots and precocious puberty (PP). Recently, the syndrome has been enlarged to include malignancies and endocrinopathies such as thyroid disease, acromegaly, Cushing syndrome and hypersecretion of growth hormone (GH). Optic and vestibulocochlear nerve involvement has been reported in the literature. It is a rare disease with estimated prevalence between 1/100,000 and 1/1,000,000. FD can involve a single or multiple skeletal sites and presents with a limp and/or pain, and, occasionally, a pathologic fracture. MAS is due to mutations in the gene encoding the Gs protein α subunit coupling 7-transmembrane-domain receptors to adenylate cyclase, leading to constitutive adenylate cyclase activation and cAMP overproduction. We report an adult case of MAS with predominant megalocephaly, multiple bilateral compressions of all the cranial nerves with the exception of olfactory and hypoglossal nerves.

Methods: The 40-year-old female patient initially diagnosed at the age of 4, based on fibrous dysplasia of several bones and three caféau-lait skin spots, in the course of the disease she presented with PP and abnormal hypersecretion of GH. Multiple bone malformations gradually appeared mainly in the proximal limb bones. 14 years later on, she has a cranium diameter 3 times bigger than the average. She underwent multiple surgical operations to neutralize the skeletal malformations. On the age of 20, an atonic ulcer in the lower peroneal region emerged.

Results: One year prior to hospitalization she developed gait disorder, severe optic decrement, dysphagia, pharyngeal weakened muscles, bilateral hypacousia, bilateral trigeminal sensory loss and nasal quality of speech with dysphonia. Pyramidal tracts were intact. On admission to our clinic, she was practically blind. Severe neuropathic trigeminal pain and impairment of consciousness level were added. She died after 10 days due to irreversible bone compression of the brainstem.

Conclusions: MAS is a rare disease with no optimal treatment. Neurosurgical decompression and orthopaedic operations are contraindicated especially in adulthood due to increased bleeding tendency and impaired calcium metabolism. Surgery is only helpful to prevent fracture deformities in childhood and adolescence. The clinical Neurologist may only offer palliative therapy.

P703

A rare disorder of retinal, cochlear and cerebral vasculopathy

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Objective: In this abstract we would like to report a case-series presented with Susac syndrome and further review their clinical presentations, ophthalmologic, neurologic and cochlea-vestibular findings, radiologic characteristics and treatment options.

Background: Susac syndrome is a rare disorder characterized by a clinical triad of subacute encephalopathy, visual loss secondary to retinal artery occlusion, and sensorineural hearing loss. Etiology is unknown but involvement of autoimmune vasculitic mechanisms is believed to result in a microangiopathy affecting the arterioles of the brain, retina, and cochlea. Demonstration of retinal arteriolar occlusions, sensorineural hearing loss and increased signal intensities in the white and gray matter on T2 weighted brain magnetic resonance imaging facilitate the diagnosis.

Design/Methods: The cases included 3 females between the ages 25–46 years with sudden vision loss on presentation. The patients were referred to departments of neurology and ophthalmology for their symptoms and were treated with high dose intravenous corticosteroids. The differential diagnoses for the patients included multiple sclerosis, systemic lupus erythematosus, Behçet's syndrome, sarcoidosis, tuberculosis, syphilis and lymphoma.

Results: Subsequently patients developed recurrent visual and hearing problems, muscle weakness and immunosuppression treatment was initiated with the diagnosis of Susac Syndrome.

Conclusions/Relevance: The first Susac syndrome in Turkey was described in 2006 and our abstract aims to expand this case report by reporting a case series of this rare disease in Turkey. Early recognition of this disease is crucial for the initiation of early treatment with systemic immunosuppression to prevent the development of neurologic, ophthalmologic and auditory impairment.

P704

Leptomeningeal metastasis: a single-centre prospective study

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Objective: We evaluated symptoms, signs, results of cerebrospinal fluid (CSF) examinations, duration from primary cancer to diagnosis of leptomeningeal metastasis (LM) and mean survival time.

Background: Recently, LM has increased in frequency as patients live longer and neuro-imaging studies improve.

Materials and methods: We prospectively collected 31 patients with LM confirmed by CSF cytology who had visited Kosin University Gospel Hospital, Busan, Korea. All patients were evaluated considering three anatomic areas; brain, the cranial nerves and the spinal roots. Brain and spinal magnetic resonance imgages were checked. Tumor markers such as carcinoembrionic antigen (CEA) were checked from serum and CSF.

Results: 19 men and 12 women were diagnosed as LM. Mean age at diagnosis was 56 years. Primary cancer sites were stomach (11, 35%) and then lung (9, 29%), lymphoma (3, 9%), breast (3, 9%), esophagus (2, 6%), cervix and common bile duct (each 1, 3%). Symptoms included headache (21/31, 67%), mental change (9, 29%), nausea/vomiting (6, 19%), dysarthria (4, 13%) and weakness due to spinal lesion (4, 13%). Common signs of LM were presented with abnormal mental state (10/31, 32%), papilledema (5, 16%), seizure (5, 16%) and nuchal rigidity (3, 9%). 26 patients (83%) had increased CSF pressure over 16 cmH20, 23 (74%) showed increased white cells count over 5/mm^3, 22 (70%) had increased protein over 50 mg/dL and 18 (58%) had decreased glucose level below 40 mg/dL. 12 patients among those had adenocarcinoma showed increased CEA over 5 ng/mL. Mean time from primary cancer to LM was 17 months. Mean survival duration after diagnosis was 1.5 months.

Conclusions: It is important to know symptoms, signs, neurological deficits and CSF results of LM in patients. Based on this study, we found that the most common symptoms were headache and mental changes. It is helpful to diagnose if we meet increased pressure, cells, protein and CEA and decreased glucose from the CSF study of patients suspected with LM.

P705

Relevance vector machine: consciousness classifier applied to cerebral metabolism data of vegetative and locked-in patients

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Objectives: The vegetative state (VS) is a devastating condition where patients awaken from their coma but fail to show any behavioral sign of consciousness. Locked-in syndrome (LIS) patients also awaken from their coma and are unable to show any motor response to command (except for small eye movements or blinks) but recover full consciousness of self and environment[1]. Clinical practice shows that recognizing unambiguous signs of conscious perception in such patients can be very challenging. This difficulty is reflected in the frequent misdiagnoses [2].

Methods: We here aimed to disentangle vegetative from LIS patients by teaching a "machine" to discriminate consciousness, using [18F]fluorodeoxyglucose-positron emission tomography scans obtained in healthy controls and patients in a VS. The user-independent classifier was tested on brain scans obtained in patients with LIS. Data consisted of PET scans from 37 control subjects, 10 VS and 6 LIS patients. We used a sparse probabilistic Bayesian learning framework called "Relevance Vector Machine" (RVM) [3] to classify the scans. The trained RVM classifier, applied on an input scan, returns a probability value (p-value) of being in one class or the other: "conscious" (1) or not (0).

Results: Training on the control and VS groups was assessed with a leave-one-out cross-validation procedure, leading to 100% classification accuracy. The control images obtained a mean p-value of .99 (min .91) and the VS images, .07 (max .37). When applied on the LIS images, all these patients were classified as "conscious" with a mean p-value of .95 (min .85).

Conclusion: We could train an automated classifier on cerebral metabolism scans distinguishing between normal consciousness and VS. Moreover, when applied on a third group of data (LIS), all patients had a strong probability of being correctly classified as similar to the controls,. Therefore automated RVM classification of cerebral metabolic images obtained in coma survivors could become a useful clinical tool for the automated PET based diagnosis of altered states of consciousness.

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P706

Neurological soft signs in Behcet's disease

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Objective: Patients with Behcet's disease have an excess of minor neurological abnormalities (neurological soft signs). Our objectives are; (a) to investigate the neurological soft signs (NSS) in Behcet's disease (BD) patients,who had no neurological symptoms, by using neurological evaluation scale (NES).
(b) To evaluate the effect of silent infarction on NES scores in BD patients.

Methods: 36 Behcet's disease patients without neurological symptoms and 36 healthy control were included in the study. NSS were assessed with the Neurological Evaluation Scale (NES). Cranial magnetic resonance imaging was conducted to determine the silent cerebral infarcts.

Results: Patients with BD had significantly higher scores overall and on each subscale (except for subscale "others") of NES than control groups. Tandem walk, adventitious overflow, tremor, graphestesia, fist edge palm test, Ozeretski test, finger thumb opposite, mirror movements, extinction, synkinesis, convergence, finger nose test, glabellar reflex, grasp reflex, suck reflex were also significantly higher in patients with BD than healthy control group. There were no significant differences in the total NES scores, total subscale scores and each of the NES items between BD patients with silent infarction and without .

Conclusion: Early diagnosis of neurological involvement in BD is important and NES is an useful instrument for detecting subclinical neurological involvement in BD patients.

P707

Diffusion-weighted imaging, diffusion-tensor imaging and tractography for dummies

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Objectives: Since the first Magnetic Resonance Imaging (MRI) scanner was built in 1977, many new techniques has been introduced. Most textbooks on MRI describe the techniques using mathematical and physical constructs that are not easily accessible to doctors. This poster describes the basis and use of three new techniques, diffusion weighted imaging (DWI), diffusion tensor imaging (DTI) and tractography in non-technical terms.

Methods: The fundamental nuclear property of "spin" is described to explain the concept of nuclear magnetic resonance. The use of resonance coupled with magnetic field gradients and intrinsic tissue properties (T1 relaxation, T2 relaxation) to generate the image is then conceptualised. Special sequences to generate images sensitive to the diffusion of water molecules (diffusion weighted imaging) are illustrated. Finally an extension of this technique, diffusion tensor imaging, is reviewed. This can be applied to determine the integrity of white matter and non-invasively track white matter connections within the brain (tractography).

Results: DWI generates images whose contrast depends on the degree of diffusion of water. Restricted diffusion leads to a bright signal on DWI and can be used to identify ischaemic tissue early in stroke within the window for thrombolysis. ADC ("apparent diffusion coefficient") maps demonstrate the degree of diffusion with brighter areas having greater diffusion. Thus ischaemic areas appear dark. DTI extends this concept to look at the directionality of diffusion. Water preferentially diffuses along the long axis of white matter tracts, so diffusion is anisotropic (unequal in different directions). Mean diffusivity (MD) measures the overall degree of diffusion in all directions, whilst fractional anisotropy (FA) quantifies how anisotropic diffusion is. White matter has greater FA and this measure can be used to assess myelin integrity. FA falls in damage and changes are seen in a number of conditions. By using the predominant direction of diffusion within each voxel on the scan, adjacent voxels can be linked to map out white matter connections within the brain (tractography). This can be used in neurosurgical planning, such as tumour surgery.

Conclusions: The basic concepts of DWI, DTI and tractography can be easily understood conceptually without complex mathematics. These techniques have been illustrated along with application to a number of diverse areas (stroke, tumour surgery, MS, schizophrenia).

P708

Central facial palsy revisited: a clinical-radiological study in ischaemic stroke

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Objectives: Central facial palsy affects usually voluntary movements of the lower face contralateral to the affected hemisphere. This pattern is classically attributed to bilateral cortico-nuclear projections to the motoneurones innervating the upper facial muscles and solely contralateral projections to the motoneurones innervating the lower facial muscles. Recently an alternative model has been proposed based on the existence of multiple representations of face movements in the frontal cortex. The objective of the present study is to investigate this model in humans by correlating the distribution of weakness in single facial movements with different vascular territories in stroke patients.

Methods: We assessed consecutive stroke patients over a one-year period in our clinic. Five facial movements were assessed by comparing the affected side with the contralateral side: forehead elevation, eyelid closure, upper lip and nose elevation, lip closure, lower lip depression. The site of the ischemic lesion was classified, according to the Alberta Stroke Program Early CT Score (ASPECTS) on head CT scans obtained after at least 3 days from onset. Patients with history or radiological evidence of previous ischemic stroke, patients with hemorrhage and non collaborative patients were excluded. Subsequently only patients with facial weakness were included for statistical analysis.

Results: 134 patients were considered. Sixteen were excluded for inadequate compliance, 54 were excluded for the presence of previous ischemic episodes. Of the 64 remaining patients, 29 had facial weakness and were finally included in the analysis. The results showed that weakness in eyelid closure was strongly associated with anterior cerebral artery stroke and that weakness of lip elevation, lip closure and lip depression was significantly associated with middle cerebral artery stroke. Weakness in forehead elevation was observed for stroke in both anterior and medial artery territories.

Conclusion: Our results support the hypothesis of multiple representations of facial movements in different vascular territories. Facial palsy associated with middle cerebral artery stroke selectively spares eyelid closure. On the other hand, anterior cerebral artery infarction can cause isolated weakness of eyelid closure.

P709

Primary CNS lymphoma: the new great imitator

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Primary central nervous system lymphoma is a rare and often difficult disease to diagnose. The authors report an atypical case.

Fifty-six years old caucasian male, previously healthy, with family history of Leyden disease and a trip to Mozambique three years before. The patient presented with insidious onset of vespertine asthenia, anorexia with weight loss, sleep cycle inversion and nocturnal holocranial headache. There was no nausea, vomit or fever. Normal physical and neurological examination. Blood tests revealed slightly elevated erythrocyte sedimentation rate, C-reactive protein and ferritin and high IgE. Viral, bacteriological and parasitological tests were all negative. CSF cytobiochemistry was unremarkable and viral, parasitological and bacterial tests were all negative. Tumor markers and onconeural antibodies were negative as well. CNS imaging showed multiple areas of distinct heterogeneous signal supra- and infratentorial, cortical and subcortical, with restriction to diffusion, without swelling and no contrast enhancing suggesting embolic lesions with pethequial component. An embolic source was excluded by transesophageal echocardiogram and carotid and vertebral triplex scan. A supra-aortic angiogram was also performed and showed no vascular lesions. A body CT scan, a PET scan and an upper endoscopy did not evidence occult neoplastic disease. Clinical deterioration occurred with obnubilation, dysphasia, left hemiparesis and cerebellar ataxia. A neuroimaging guided stereotactic biopsy was conducted and, keeping in mind the hypothesis of paraneoplastic encephalitis the patient initiated intravenous immunoglobulin and corticosteroid with little clinical and no imagiological improvement Histology and immunocytochemistry revealed a histiocyte infiltrate with a few lymphocytes (with no microorganisms), oedema of vascular endothelium and rare small aggregates of large atypical cells in blood clots, expressing CD45, CD20, MUM1 and Ki67, thus suggesting a large B-cell non-Hodgkin lymphoma.

This case illustrates the diagnostic challenge that this entity still poses in spite of the increasing advances in diagnostic workup.

P710

Cerebral amyloid angiopathy presenting as non-haemorrhagic reversible leukoencephalopathy

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Introduction: Although intracerebral hemorrhage is the most commonly recognized clinical manifestation of cerebral amyloid angiopathy (CAA), recent clinical reports had described a distinct presentation with acute/subacute cognitive decline, seizures, T2-hyperintense MRI lesions and pathologic evidence of inflammation of CAA-affected vessels.

Case report: A 70-year-old man was admitted to our department in February 2007 with cognitive and behavioural disturbances with a 2-months progressive and fluctuant course. Five months before he started to have complex partial seizures. Neurological examination revealed an apraxic gait and the neuropsychological evaluation revealed significantly episodic verbal memory impairment, executive functions disorder (impulsivity, reduced verbal fluency and abstract reasoning disturbance) and minor impairment of visuospatial construction. Cranial MRI showed large confluent white-matter lesions, hyperintense on T2-weighted images and hypointense on T1-weighted images, with no gadolinium enhancement, involving primarily both fronto-temporal lobes. Diffusion-weighted sequences showed increased ADC consistent with vasogenic oedema. Gradient-echo weighted images demonstrated multiple scattered cortical/subcortical microbleeds. EEG showed slow background activity and left fronto-temporal continuous slowing. CSF examination was unremarkable except for positive oligoclonal bands. APOE genotype was E3/E4.

Brain biopsy obtained from right frontal region revealed abundant amyloid deposition within leptomeningeal, cortical and subcortical vessel walls associated with perivascular lymphohistiocitary inflammatory infiltrate.

After several months, during the diagnostic workup, the patient presented spontaneous clinical improvement and 6-months later MRI showed almost complete resolution of the white matter abnormalities.

Conclusion: Nonhemorrhagic reversible leukoencephalopathy represents an unusual presentation of CAA and has been associated with pathologic evidence of vascular inflammation of CAA-affected vessels, as in our patient. Probably, this inflammation represents an immune response to the vascular deposits of β-amyloid (AB). Clinical course is variable, most cases being monophasic but it can also be a relapsing disorder requiring long term immunosuppressive therapy.

CAA-related inflammation may represent a distinct disease subtype with implications for clinical practice and ongoing immunotherapeutic approaches to Alzheimer disease.

P711

Adult acute idiopathic demyelinating relapsing-remitting brainstem encephalomyelitis. Longitudinal clinical, radiological and treatment considerations

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Background and objective: So far, no criteria for differentiation between monophasic Acute Disseminated Encephalomyelitis (ADEM) and a first episode of Multiple Sclerosis (CIS) have been established. Differential diagnosis may have prognostic and therapeutic implications. ADEM affects the white matter in spinal cord as well as in cerebrum simultaneously, and it is mandatory to exclude autoimmune and infectious diseases. Nowadays, It is still impossible to predict which patients will suffer from recurrent bouts (ADEM RR) and which treatments are the most effective. We present the clinical, radiological findings, and treatment approach of a patient with 6 years of follow-up.

Clinical Features: 21-year-old woman admitted to the hospital for presenting vomiting and hypoalgesia in lower limbs, subsequently double vision, dysphagia, dysarthria, hypophonia, respiratory insufficiency that needed intensive care unit treatment, propioceptive ataxia and paraparesis with cervical sensory level.

Results and MRI findings: Cranial and spinal cord MRI revealed large lesions in brainstem and cervico-dorsal spinal cord, both enhancing with gadolinium contrast. CSF showed pleiocytosis, high level of proteins and normal glucose. An infectious or systemic origin was excluded. Patient was treated with intravenously Glucocorticoids (GC), which improved symptoms and MRI partially. After two months of clinical stability, spinal symptoms reappeared with the same characteristics, improving with GC again. Azathioprine was then added. After 4 years without symptoms, spinal and brainstem symptoms relapsed, leading to the use of GC and plasmapheresis.

Three months later, a new spinal recurrence led to the introduction of Mycophenolate Mofetil. At the time this abstract was written, patient has been asymptomatic for the last 10 months with bilateral horizontal nistagmus and metameric trunk dysesthesia as only secuelae.

Conclusion: Adult idiopathic ADEM-RR is an uncommon disease in which little is known about its natural history, prognosis and treatment. Our observation suggests that chronic immunosuppressive treatment is sometimes needed. A better knowledge of the pathogenesis of this entity will probably help to find a better therapeutic approach.

P712

Recurrent hyponatremia as presentation of a Rathke's cleft cyst

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Rathke's cleft cyst (RCC) is an embryologic remnant of the Rathke's pouch, a stomodeal ectoderm' invagination, commonly intrasellar. It is usually an incidental finding at necropsy or neuroimaging studies. Symptomatic cysts are described in adults (40–60 years), with female predominance, manifesting with headaches, endocrinologic and visual disorders. The late onset and the presentation of hypopituitarism with recurrent hyponatremias in the present case, are unusual in RCC.

A 74 year old man was admitted because persistent vomiting and general weakness for a month. Recurrent hyponatremias responsive to fluid restriction in previous hospital admissions were recorded. He denied fever, headache, sensory, sphincter or radicular symptoms, although admitted recent loss of libido. The patient became confused, disoriented, with drowsiness. Clinical exam revealed moderate paraparesis, generalized hyporreflexia, and impossible gait.

Severe hyponatremias (to 114 mEq/l) with low serum osmolality were detected. No findings were obtained after blood, cerebrospinal fluid and extensive systemic studies, except a lumbosacral radiculopathy of degenerative origin. Suspecting an endocrinologic disorder, hormone levels were determined and hypopituitarism with adrenal insufficiency diagnosed (cortisol of 28'4 nmol/L), together with deficit of LH and inappropriate secretion of antidiuretic hormone (ADH). Cranial magnetic resonance image showed a T1-hypointense and T2-hyperintense intrasellar cyst mass (25 × 18 mm) with suprasellar extension, compressing the pituitary. After steroid therapy, the evolution was excellent with clinic and biochemical recovery. Surgery was disestimated.

Hyponatremia is a frequent electrolyte disturbance, aetiologically diverse, that courses with digestive symptoms, confusion and consciousness's disorder, and may be fatal. Steroid deficit and increase of ADH are both pathophysiological mechanisms of hyponatremia in hypopituitarism. In elderly with hypopituitarism, stress situations may precipitate an acute adrenal dysfunction and hyponatremia, because the decrease of ACTH receptors in adrenal cortex and the failure of endogenous cortisol to suppress ADH. We remark the need of high clinical suspicion when not explained hyponatremia, especially in elderly, is diagnosed. Hormonal study and pituitary neuroimaging are essential to starting early therapy avoiding fatal consequences.

P713

Diagnosing and managing some complications of intracerebral dermoid cysts

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Background: Intracerebral dermoid cysts are rare congenital tumors. They can long remain asymptomatic but possible complications are various and may be fatal.

Objectives: To illustrate some of the potential complications of dermoid cysts, understand the physiopathogenesis, and to discuss the most appropriate treatment of the cyst and the associated symptoms.

Methods: We report the case of a 23-year-old patient who was initially admitted into the neurology department for a 2-month history of progressive headache. He was rapidly diagnosed with a dermoid cyst located in the paramedial region of the right frontal lobe. Two weeks later, he presented a sudden neurological deficit associating diplopia, vertical oculomotor palsy and right facial palsy. And extensive and repeated neuroradiological workup was performed, including early MRI scans, MR angiography of intracranial and cervical arteries, and transcranial doppler (TCD). Subsequently, CT angiography and a control TCD were also performed. Cardiological explorations, blood and CSF testing were associated .

Results: MRI scans (DWI, T1-W, FLAIR) showed a cerebral infarct of the left thalamus. Multifocal hypersignals on T1-weighted images accounted for fatty droplets disseminated in the subarachnoid spaces. The diagnosis of chemical meningitis due to the rupture ot the cyst was confirmed by CSF analysis. Intracranial velocities were fast on TCD. There was no radiological argument for an intracranial vasculitis nor for a mass effect of the tumor on the vessels. All other investigations were normal.

Conclusion: In this case, a progressive headache and an acute deficit caused by a cerebral infarction followed the rupture of a dermoid cyst.

Most likely the cerebral infarct is explained by transient vasospasm of intracranial arteries remote from the tumor location. This phenomenon is linked to the widespread chemical aggression secondary to the rupture of the cyst into the subarachnoid spaces. Given the rarity of this clinical picture, there is no consensus concerning the management of such patients and decisions are discussed individually. In our case, size and localization of the tumor did not allow a surgical resection. The patient was prescribed corticosteroid medication (3 days of intravenous 250 mg bolus of methylprednisolone, and oral prednisone 1 mg/kg/d with progressive decrease over 3 months), and lifetime antiaggregant medication.

P714

Rheumatoid meningitis as a rare extra-articular manifestation of rheumatoid arthritis

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Introduction: Rheumatoid meningitis (RM) is a rare but lethal extra-articular manifestation in elderly patients with longstanding seropositive rheumatoid arthritis (RA). Since 1954, only 25 histopathologically proven cases have been reported.

Case report: A 64-year-old woman with a 10-year history of RA was admitted with recurrent episodes of dysarthria as well as left-sided hemihypesthesia and impaired coordination lasting up to ten minutes. Physical examination between these episodes revealed no neurological deficits and

only mild synovitis involving the joints of both hands and feet. Laboratory data demonstrated an inflammatory reaction with elevated ESR (56 mm/h). Rheumatoid factor and anti-CCP antibodies were detected, whereas ANCA and ANA were negative. Examination of cerebrospinal fluid (CSF) demonstrated a mononuclear pleocytosis (142cells/mm^3), repeated culture and cytology were negative. Despite intensive microbiological examinations no infectious agents could be detected. MRI showed abnormal gadolinium-enhancement in the meninges in the right frontal lobe with sulcal effacement and areas of hyperintensity in the underlying cortex. Brain biopsy demonstrated a chronic active leptomenigitis with granulomatous reaction, multifocal necrosis and meningeal vasculitis. Biopsy cultures were negative. Based on clinical and laboratory findings diagnosis of RM was made. Under the initial treatment with corticosteroids and azathioprin (150 mg q.d.) over an 8-month period the patient's condition deteriorated. Treatment was changed to monthly intravenous infusions of cyclophosphamide 600 mg/m^2. After 9 months again progression was observed. Therefore, infliximab was applied intravenously at a dosage of 5 mg/kg at weeks 0, 2, 6, then every eight weeks thereafter in combination with subcutaneous methotrexate (MTX) (15 mg q.w.) leading to an stabilization of the patient's condition.

Conclusion: RM should be considered as a possible diagnosis even during an inactive state of systemic arthritis due to RA. Pathologic examination reveals three abnormal patterns: rheumatoid nodules, vasculitis involving the meninges, the brain and the spinal cord, and nonspecific meningeal inflammation. Although there have been several reports of successful treatment with immunosuppressants, there are no established treatment regimes for RM to date. Our patient was refractory to corticosteroids, azathioprin and cyclophosphamide. Her disease stabilized with infliximab in combination with MTX.

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