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was performed at the time of the LTFU and compared to MRI data from placebo patients from a separate study.

Results: At entry into PRISMS, patients had a mean MS disease duration of 7 years since onset of disease. If one considers data from all 560 patients from the original PRISMS cohort, 56 % of patients progressed by 1 step on the EDSS scale (median time to 1-step progression of 5.4 years), 20 % reached EDSS 6.0 or higher, and 20 % were considered SPMS at LTFU. Drug therapy was well tolerated. Natural history series of patients seen at a comparable time-point post-onset show higher rates of progression and conversion to SPMS, with most series showing rates of conversion to SPMS, at 13 years post diagnosis, of approximately 35–50 %. BOD on T2 weighted MRI scans in the PRISMS LTFU cohort, was much less than predicted based on no/placebo-treated patients with a similar duration of disease.

Conclusions: Taken in the context of previously reported long-term safety data on Rebif®, these data support the sustained long-term favourable benefit-to-risk profile of this treatment (in doses up to 44 mcg tiw for up to 8 years). Case-matched comparisons between the PRISMS cohort and long-term natural history cohorts will be of interest.

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A comparison of the efficacy and tolerability of interferon-beta (IFNb) products used as initial or follow-up therapy for the treatment of relapsing multiple sclerosis: results from the QUASIMS Study

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Objective: To compare efficacy and tolerability of IFNbs used as initial or follow-up therapy for RRMS.

Background: IFNb products are the most frequently prescribed disease-modifying therapy for patients with RRMS. Several studies suggest these therapies have comparable efficacy. QUASIMS (Quality Assessment in Multiple Sclerosis Therapy) contains the largest cohort of MS patients assembled to compare available IFNb products in a wide range of clinical practice settings.

Methods: QUASIMS is a retrospective, open-label study and included 20 % of all IFNb recipients in Germany, Austria, and Switzerland. Patients received IFNb-1a 30 mcg IM 1x/w, IFNb-1a 22 or 44 mcg SC 3x/w, or IFNb-1b 250 mcg SC 3.5x/w. Patients had clinically definite RRMS, uninterrupted treatment for ≥ 2 years, and medical records documenting visits at baseline, 1, and 2 years. Preplanned outcomes: EDSS change, annualized relapse rate (RR), percentage of relapse-free patients, and reasons for therapy change. Efficacy analyses were adjusted for differences at baseline.

Results: Of 4754 enrolled patients, 3991 used IFNb as initial therapy (IFNb-1a IM 1469, IFNb-1b 1484, IFNb-1a 22 SC 784, and IFNb-1a 44 SC 254) and 662 patients used IFNb as follow-up therapy (IFNb-1a IM 224, IFNb-1b 182, IFNb-1a 22 SC 126, and IFNb-1a 44 SC 130). Initial Therapy: There were no differences among IFNbs at 1 or 2 years in mean RR or change in EDSS. The percentages of relapse-free and EDSS progression-free patients were also similar. Differences that were observed ($p < 0.008$) favored IFNb-1a IM. Follow-up (FU) Therapy: RR was higher and percentage of relapse-free patients lower for all products when used as FU. There were no differences in efficacy at 2 years between products except more IFNb-1a IM than IFNb-1a 44 SC patients were relapse free over 2 years ($p < 0.008$). Reasons for switching therapy differed across products, injection-site reactions were more frequent for SC IFNb-1a and 1b than IFNb-1a IM ($p < 0.008$).

Conclusions: Results of QUASIMS extend those of controlled clinical trials in MS to a wide range of clinical practice settings and complement the results of other open-label comparisons. Although some differences were observed among IFNbs used as initial therapy, efficacy among products was generally similar. Patients who received IFNb as FU therapy experienced less benefit than patients who received IFNb as initial therapy, suggesting there is no benefit for patients who switch from one IFNb to another.

POSTER SESSIONS

Poster session 1

Neurobiology

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Mapping white matter tract changes in healthy ageing

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Background: With diffusion tensor imaging (DTI) an instrument is at hand to study features of physiological diffusion and subtle pathological conditions of white matter (WM) as changes of fiber coherence, density and myelination. Previous region of interest (ROI) studies pointed out age-related decline of anisotropy indices, especially in frontal WM, which was linked to the notion of a 'cognitive disconnection syndrome' [1].

Goal: We used a voxel-based approach to systematically investigate the regional preponderance of age-related decreases of fractional anisotropy (FA) and to control for varying raw data quality and global FA effects.

Methods: 42 healthy volunters without history of current or previous neurological or psychiatric illness (men/women: 22/22; 22–84 yrs, median 47.5 yrs) were investigated with DTI (spin echo EPI, TR/TE = 4200 ms/12 ms, 24 axial slices, matrix 128 × 128, 1.8752 × 3 mm^3, 1 mm gap; b = 880 mm^2/s [6 directions, 3 repeats] and b = 0 mm^2/s images). Affine and non-linear normalization of an average of two b0-images onto a standard T2-template (SPM'99) was performed. FA-maps were normalized accordingly and smoothed (Gaussian 8 mm). Regression models (FA-threshold 0.25; gender, mean FA of WM, signal to noise ratio (SNR) of WM included stepwise as covariates of no interest) were tested for negative age-FA-correlations (false discovery rate, $p < 0.05$, cluster size > 25).

Results: Large portions of WM in all lobes exhibited significant negative correlations with age. Gender had a minor covarying effect, whereas the inclusion of global mean FA value of each subject weakened global effects and revealed a regional pattern: Interrelations were stronger in the anterior WM portions with additional left-hemispherical prevalence. Among inter-hemispherical tracts the genu of the corpus callosum showed stronger age-association than mid and posterior parts. Focal accentuation was similar after correction for SNR of WM voxels as a measure of data quality.

Discussion: Age-related decline of FA in large portions of WM were demonstrable which is consistent with previous ROI and histogram analyses [2–5]. Changes in anterior WM tracts which are presumed to underly age-related cognitive decline deserve further investigation, especially correlation with cortical processes.

References

1. O'Sullivan, et al. (2001) Neurology
2. Pfefferbaum, et al. (2000) MRM
3. Pfefferbaum, et al. (2003) MRM
4. Abe O, et al. (2002) NBA
5. Rovaris, et al. (2003) Radiology

P194

Migration and differentiation of neural stem cells into NMD mice, an animal model of spinal muscular atrophy

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Neural stem cells may represent a therapeutic tool for neurodegenerative diseases since they can differentiate into neurons when grafted in CNS. However these cells remain undifferentiated or become mainly glial cells when transplanted into non-neurogenic regions of the CNS such as Spinal Cord.

Here we describe that in vitro expanded neurospheres are able to generate fully differentiated neurons with high efficiency into nmd (Ighmbp2 nmd-2J) mice, an animal model of Spinal Muscular Atrophy.

The nmd mutant mice express an autosomal recessive neurological disease with motor neuron degeneration. Behaviourally, these mice have a progressive paralysis and die by 3.5–4 weeks of age.

As a source of graft material, we used a neural stem cell-enriched population, expanded in vitro by neurosphere formation, that derived from

mice expressing the Green Fluorescent Protein (GFP) in all tissues and from Thy-1-YFP mice expressing a spectral GFP variant only in neurons.

Neurospheres were directly injected into lateral ventricle and into spinal cord (L1) of newborn nmd and wild-type mice. Transplanted cells migrate extensively in the brain hemispheres and over the rostrocaudal length of the spinal cord. Immunocytochemical analysis using the neuron-specific markers NeuN, TuJ1, NF, MAP2 revealed that most GFP positive cells acquired a neuronal phenotype one month after transplantation. Neuritis and spines on their processes indicated a functional maturation of these grafted cells.

We conclude that neural stem cells have an high neurogenic potential when transplanted into developing brain and in the presence of a neurodegenerative process such as in the nmd mice.

Further understanding of neural stem cell behaviour will have major advantages for stem cell therapy development.

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Human mesenchimal stem cells generate neurons after transplantation in developing mammalian brain

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The ability to isolate, proliferate, and genetically manipulate mesenchimal stem cells (MSc) is one of the major achievements in experimental biology. The multipotency of these cells has kindled numerous efforts to generate neural precursors in vitro. The controlled differentiation of MSc into neural cells provides experimental access to autologous transplantation in brain tissues and may eventually lead to alternative donor sources for CNS tissue reconstruction. In vivo reconstitution would be a more stringent test of the potential of MSc to acquire central nervous system fates. The limited self-renewal in the adult mammalian brain precludes the kind of ablation and reconstitution experiments used to study in vivo differentiation of hematopoietic progenitors. We have, therefore, used a different approach and introduced human MSc into the developing brain of mice. Previous studies have revealed that neurogenesis in the central nervous system (CNS) persists throughout life in many vertebrates, including humans. We used an in situ ibridization method (FISH) labelling human centromer to identify the human genome in host mice and specific RT-PCR and double-immunostaining for human products to determine the cell phenotype. Herein, we show that human MSc grafted into the 2 days old C57/BL mice cortex migrate into the host brain within the non-neurogenic region, the corpus callosum up to ~1–1.5 mm from the graft core, and showed differentiation into both neuronal and glial phenotypes. Most of injected MS cells expressing neuronal markers such neurofilament 160Kd and phenotypes remained close to the implantation site. Our results suggest that neuroepithelial precursors derived from human MS cells respond in vivo to guidance cues and signals that can direct their differentiation along multiple phenotypic pathways suggests that they can provide a powerful and virtually unlimited source of cells for experimental and clinical transplantation

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Altered expression of BDNF and obesity in mice deficient of the serotonin transporter

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Background: The association between brain serotonin (5-hydroxytryptamine; 5HT) levels and feeding behavior has been extensively studied. Low levels of 5HT lead to an upregulation of food intake in mice while central injection of 5HT can reduce food consumption. Brain derived neurotrophic factor (BDNF) is not only important in neurogenesis and neuronal plasticity, but is also involved in the regulation of feeding and energy balance. Furthermore, the increase of BDNF in certain brain areas during dietary restriction may explain the neuroprotective effects of fasting.

Aims: We observed that 5HT-transporter knockout mice (5HTT ko) become obese with ageing and investigated a possible correlation between the observed obesity in these mice and cerebral BDNF mRNA levels.

Materials and Methods: Twenty-two mice (11 wildtype (WT), 11 5HTT ko) were examined. Six mice of each group were put on a fasting regime overnight, while the rest of each group had access to food and water ad libitum. The BDNF mRNA levels in distinct brain areas including cortex, pons, thalamus and hypothalamus were investigated using quantitative Real-Time PCR.

Results: There was a significant increase in BDNF mRNA levels in the cortex of fasting WT (× 8) and 5HTT ko mice (× 12) compared to their littermates fed ad libitum ($p < 0.001$). The absolute levels of BDNF mRNA were higher in fasted WT than in fasted 5HTT ko mice ($p < 0.05$). In the thalamus there was only a slight increase in BDNF mRNA levels in fasted WT mice (n. s.), and 5HTT ko mice had no BDNF increase after fasting. The pons showed an inverse regulation: WT mice fed ad libitum had significantly higher amounts of BDNF mRNA than fasted ones (× 5; $p = 0.036$), while 5HTT ko mice showed a tendential increase in fasted individuals (× 2.3, n. s.). Overall, WT mice had higher pontine BDNF mRNA levels than 5HTT ko mice. Surprisingly, in the hypothalamus, which is regarded central to the regulation of feeding behavior, there was no change in BDNF mRNA levels in any genotype.

Conclusion: Dietary restriction leads to the expected increase of BDNF mRNA levels in the cortex of wildtype and 5HTT ko mice, but not to changes in the hypothalamus. Pontine BDNF mRNA levels show an inverse fasting regulation between genotypes. Studying the interrelation between cerebral 5-HT and BDNF in 5HTT ko mice may help to elucidate the central regulation underlying feeding and obesity.

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Study of putative pathways for central nervous system homing of systemically-injected neural precursor cells in mice affected with experimental autoimmune encephalomyelitis

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Selective mononuclear cell infiltration leading to demyelination and axonal damage occurs within the central nervous system (CNS) of patients with multiple sclerosis (MS). This process is mediated by interactions – at the blood-brain barrier (BBB) – of adhesion molecules and counter-receptors. In parallel, chemokines selectively attract inflammatory cells from periphery to the inflamed areas of the CNS, thus amplifying the inflammatory process. We have recently showed that adult neural precursor cells (NPCs) expressing VLA-4 and CD44 promote multifocal remyelination and functional recovery following intravenous or intrathecal injection in mice affected by a chronic form of experimental autoimmune encephalomyelitis (EAE), the animal model for MS. Here we analyze by a multidisciplinary approach the synergy occurring between cell adhesion molecules (CAM) and CAM receptors, chemokines and chemokine receptors modulating the selective homing of intravenously-injected therapeutic NPCs into the neural tissue during CNS autoimmune demyelination in rodents. Using immunocytochemistry, flow cytometry and real time PCR we found that undifferentiated adult mouse NPCs display highly strain-specific and time-regulated CAM (i. e., VLA-4, CD44, LFA-1, L-selectin, PSGL-1) and pro-inflammatory chemokine receptor (i. e., CCR1, CCR2, CCR3, CCR5, CCR7, CXCR3, CXCR4) patterns. When tested in a Boyden's chamber-based setting, pro-inflammatory chemokines, as RANTES and stromal-derived factor (SDF)-1, showed dose-dependent capacity to modulate NPC chemoattraction in vitro. Finally, intravital microscopy-based study of systemically-injected aNPC homing into brain microvasculature during LPS-induced subacute inflammation showed numerous aNPCs arresting in inflamed brain venules after injection into the carotid artery.

The expression of functional receptors, such as CAM and/or chemokine receptors might be therefore considered – if proved – as a prerequisite for optimizing the delivery of NPCs into inflamed CNS areas during autoimmune demyelination trough the blood compartment.

A clear understanding of those events involved in CNS-specific NPC engraftment, together with parallel studies of safety and clinical efficacy, are required to foresee any human future applicability in MS.

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entral dopamine depletion caused by MPTP administration augments actively induced experimental autoimmune encephalomyelitis in C57BL mice

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The central nervous system may play a role in the regulation of an immune response. Since experimental autoimmune encephalomyelitis (EAE) is an autoimmune disease with its effector phase in the CNS, we examined the role of central dopamine depletion in EAE pathogenesis. Dopamine depletion was obtained by treatment with 1-methyl-4phenyl-1,2,3,6-tetrahydropiridine (MPTP)(40 mg/kg). EAE was elicited by immunization with MOG 35–55 (150 *f*Yg) in CFA, supplemented with 4 mg/ml Mycobacterium

tuberculosis. Central nervous system depletion of dopamine, 7 days prior to EAE induction, caused earlier onset of the disease and augmented the clinical signs of EAE.In mice with injured dopaminergic system (group MPTP + EAE) onset of the symptoms was observed 15 days earlier than in mice not treated with MPTP (group EAE). In MPTP + EAE group two relapses were observed with a longer total time of clinical symptoms (9.8 vs 3.8 days) comparing to EAE group. Similarly, remission of symptoms in EAE group appeared earlier then in MPTP + EAE group (28^{th} day vs 38^{th} day). However, the disease index did not differ between the groups (2.16 vs 2.13).The MPTP-treated mice demonstrated also greater severity of histological lesions in the spinal cord, compared to EAE group.Histological analysis revealed stronger infiltration of inflammatory cells in the meninges and in perivascular space of the white matter of the lumbar spinal cord of MPTP + EAE mice. Our data showed, that EAE induction and progression was dependent on central dopamine level. It indicates that the nigrostriatal dopamine system is involved in regulation of immune response.

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Creatine increases lifespan in mice

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Introduction: Aging and neurodegenerative diseases have neuropathological features in common, for example impairment of energy metabolism and free radical damage. Even under physiological conditions mitochondrial energy production is a main source for the generation of reactive oxygen species (ROS). The natural compound creatine (Cr) – part of a mitochondrial energy buffer and transport system – has a potentially ameliorating effect on ROS-associated damage. Indeed, Cr was highly neuroprotective in several animal models of neurodegenerative diseases, e. g. Huntington's and Parkinson's disease. If neurodegeneration and aging have similar underlying pathological processes and if Cr helps in the former, then it might help in the latter as well. We therefore conducted a mouse trial on the effect of oral Cr on aging.

Materials and methods: 120 C57Bl/6 mice (1 year old) received either Cr-enriched (1 %, n = 60) or equicaloric (n = 60) food pellets. 83 mice were allowed to reach their natural end of life, the remaining 37 underwent neurological phenotyping (SHIRPA protocol, rotarod, grip strength) and a behavioral screen. Additionally, 10 mice (5 Cr, 5 placebo) were sacrificed under standardized conditions after 1 year of treatment for RNA expression profiling.

Results: Mice treated with Cr lived longer than controls (613 ± 84 vs. 563 ± 95 days, $p < 0.02$). Cr mice also had significant lower serum lactate (3.23 ± 0.29 vs. 4.11 ± 0.21 mmol/l) and a better performance in the object recognition test. Neurological phenotyping revealed no group differences. Expression profiling showed significant upregulation (2.7 fold, $p < 0.01$) of inter-alpha-trypsin inhibitor (IATI), which is an endogenous serine protease inhibitor.

Discussion: So far, only caloric restriction has been shown to increase longevity in laboratory animals. In this study we were able to show a similar effect of Cr in healthy, aged mice (+ 10 %). The effect might have been even more pronounced if Cr had been started earlier in life. Cr can principally exert its effects via several different mechanisms: (i) energy donor, (ii) anti-apoptotic, (iii) anti-oxidative, and (iv) anti-excitotoxic. The better memory performance of the Cr animals raises hope, that Cr improves not only lifespan, but also quality of life. The relevance of the upregulation of IATI, which has anti-neoplastic and anti-inflammatory properties, is an interesting finding and deserves further investigation.

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New abnormalities in the CSF of vitamin B12-deficient patients

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Chronic cobalamin (Cbl) deficiency causes subacute combined degeneration (SCD) characterized by central and peripheral myelinolysis associated not only with an increased production of methylmalonic acid and homocysteine (tHCYS) but by the locally increased production of a myelinolytic agent as TNF-a combined with the locally decreased production of the neurotrophic agent EGF. As previously reported by us, the imbalance between neurotoxic and neurotrophic agents in the CNS and CSF of Cbl-deficient (Cbl-D) rats was corrected by Cbl replacement treatment, as well as the myelinolytic lesions in CNS and PNS. Furthermore, the increased TNF-a and the decreased EGF levels had been observed in sera of patients with severe Cbl-D. We measured the CSF levels of Cbl, tHCYS, TNF-a and EGF in 14 Cbl-D patients with SCD and 40 controls with other neurological disorders without Cbl-D. CSF Cbl and EGF levels were tested by radioimmunoassay, tHCYS by fluorescence polarization immunoassay, TNF-a by solid phase enzyme immunometric assay. All SCD patients had also haematological abnormalities typical of a severe Cbl-D status. The criteria to include the SCD patients were: 1) symptoms and signs of central myelopathy or peripheral neuropathy in accordance with the classical neurological SCD picture; 2) electrophysiological confirmation based on abnormal results on nerve conduction studies performed in at least four nerves of upper and lower limbs (including both sensory and motor studies) and somatosensory evoked potential of median and tibial nerves. SCD patients had a significant decrease of Cbl levels ($p < 0.005$) concomitantly with a significant increase of tHCYS ($p = 0.0001$) than CSF controls (r: –0.588; $p = 0.027$). We also found a CSF TNF-a levels significantly increase ($p < 0.002$) and the CSF EGF levels decrease ($p < 0.0001$) in the same patients than in CSF controls. Moreover the mean TNF-a levels in patients with central and peripheral SCD manifestations was higher than the SCD patients with central involvement only as well the decrease of EGF levels. We propose the determination of TNF-a and EGF levels in the CSF of patients with involvement of CNS and PNS without unknown cause in order to identify Cbl-D patients easly treatable with replacement therapy.

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Embryonic stem cell-derived peripheral nervous system cell fates – a source for tissue repair

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Embryonic stem cell derived neural precursors (ESNPs) have the capacity to differentiate into a variety of neuronal and glial subtypes. As a first step towards the use of ES cells in the treatment of peripheral nervous system (PNS) disorders we studied the capacity of FGF2-dependent ESNPs to give rise to neural crest derivatives.

Upon growth factor withdrawal-induced differentiation, 10 ± 2 % of the cells were found to coexpress peripherin and the neuronal marker beta-III tubulin. Up to 2 % of the peripherin-positive neurons displayed immunoreactivity for Brn-3a, a marker combination typically observed in peripheral sensory neurons and its precursors. 3 ± 0.4 % of the peripherin-immunoreactive neurons expressed the proneural transcription factor MASH1, indicating putative peripheral autonomic neurons. Other neural crest derivatives detected, included myofibroblastic cells expressing nestin and smooth muscle actin as well as P0- and p75-positive Schwann cells. We next investigated whether bone morphogenetic proteins (BMPs) promote the differentiation of neural crest phenotypes. ESNPs exposed to 10 ng/ml BMP-2 showed a clear decrease in neuronal differentiation. At the same time, the fraction of peripherin-positive neurons increased from 21 ± 4 % to 64 ± 5 %. BMP-2 also lead to an increase of P0/p75-positive Schwann cell phenotypes. Depending on the cell density, BMP selectively promoted the elaboration of SMA/nestin-positive myofibroblastic cells or GFAP-positive astrocytes. First transplantation studies in organotypic gut cultures indicate that ES cell-derived neural precursors survive and incorporate in an in vitro modell of colon aganglionosis.

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Effects of levetiracetam on the production of nitric oxide (NO) induced by administration of NMDA in the rat cerebellum

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Nitric oxide (NO) is a free radical gas playing a critical role in diverse signal transduction processes in the central nervous system. It is established that the increase of NO concentrations in the cerebellum induced by administration of NMDA follows a biphasic scheme. Recently, it was shown that levetiracetam increases the production of NO in the brain.

In the present study we analysed the effects of the pre-administration of levetiracetam on the production of nitric oxide (NO) using intra-cerebellar microdialysis in rats. In addition, we tested the hypothesis that DNQX, an AMPA antagonist, increases the production of NO following a pre-treatment with levetiracetam.

Microdialysis was performed in male Wistar rats. A microdialysis probe (CMA 12, CMA, Sweden) was inserted in left cerebellar nuclei (AP: –11.6 mm, L: + 2.3 mm, D: –5 mm). NO production was mesured using a two step assay method (colorimetric determination-Griess reaction, Active Motif, Belgium). Perfusion of the probe was performed at a rate of 2

microl/min (dialysates collected every twenty minutes; volumes: 40 microl). The protocol was composed of 3 steps: (1) pre-administration of levetiracetam (2 doses: 3.6 microgr and 36 microgr), (2) infusion of Ringer, (3) administration of NMDA locally during 80 minutes (10 mmol). In one group of rats, NMDA was combined with DNQX (500 microM). Finally, the effect of a preliminary administration of DNQX on NO production was also studied in 2 rats.

In a first group of 8 rats, NMDA increased significantly the level of NO in the nuclei. Levels of NO reached a mean level of 148.87 ± 13.76 % of basal values ($p < 0.001$). In the second group (3 rats), pre-treatment with levetiracetam (3.6 µg) induced a peak level of NO after 20 minutes of 214.33 ± 32.31 % (comparison with group 1: $p = 0.051$). In a third group (3 rats), pre-treatment with levetiracetam (36 µg) induced a peak level of NO of 321.33 ± 77.16 % (comparison with group 1: $p = 0.006$). DNQX in combination of NMDA ($n = 3$ rats) induced a major increase in the production of NO (peak level: 364.16 ± 46.43 %; comparison with group 1: $p < 0.001$). We observed a plateau phase in the 2 rats receiving DNQX as a pre-treatment.

Pre-administration of levetiracetam interferes strongly with the NMDA-mediated production of NO in cerebellar nuclei of the rat. The increase in NO concentrations appears dependent of the dose and is stronger when AMPA antagonist are combined with NMDA.

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Investigation of kynurenine aminotransferases in human cerebrospinal fluid from normal human subjects and multiple sclerosis patients

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Kynurenic acid (KYNA) is a well-known endogenous antagonist of the glutamate ionotropic EAA receptors. Neuroprotective and anticonvulsive activities of KYNA have been demonstrated in animal models of neurodegenerative diseases and KYNA's involvement has been speculatively linked to the pathogenesis of a number of neurological conditions. In the CNS and in the periphery KYNA is synthesised from L-kynurenine by action of kynurenine aminotransferases (KATs). In the brain two enzymes KAT I and KAT II with different enzymatic properties are able to convert L-kynurenine to KYNA. Recently, we demonstrated formation of KYNA from L-kynurenine in CSF of normal human subjects (Baran et al. 2003 J Neurology 250, Suppl). Using assay conditions for KAT I and II the synthesis of KYNA from L-kynurenine was 155.2 ± 20.3 fmol/µl/h and 19.2 ± 4.3 fmol/µl/h, respectively. The aim of present study was to see whether CSF KATs is able to influence the conversion of L-kynurenine to KYNA using rat liver homogenate.

Formation of KYNA using a mixture of rat brain and liver homogenates is additive. CSF from a group of 25 human normal subjects (42.4 ± 3.4 years) and a group of 21 MS patients (37.4 ± 2.5 years) were analysed. Lumbar puncture was carried out to obtain CSF. CSF was coded in accordance with the Austrian Medical Research Council guidelines. Using radioenzymatical assay the activities of KAT I and KAT II in the rat liver homogenate (KAT I is ca. 280; KAT II is ca. 1,500 pmol/mg/h) in the presence of non-boiled CSF or boiled CSF samples were investigated. In the presence of non-boiled CSF samples of normal human subjects the formation of KYNA from rat liver homogenate using KAT I reaction conditions was significantly lowered (by 80 %; $p = 0.001$). Using boiled CSF samples the KAT T I activity was reduced by 52 %; $p = 0.001$, respectively.

Using CSF samples of MS patients KAT I activity of rat liver was reduced only by 30 % and with boiled CSF by 24 %. KAT II activity in liver homogenate was moderately influenced by human CSF. Using anti-rat and anti-human KAT I antibodies the CSF KYNA formation was further analysed.

Obtained data suggest that in human CSF the formation of KYNA due to KAT I is a reversible reaction and that human CSF contains compound(s) which significantly block(s) the KAT I activities. In MS patients the inhibition of KYNA formation was lowered and the importance of this finding needs to be clarified. Supported in part by FWF Austria, Project P15371 to H. Baran.

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Peptide nucleic acid as the backbone for the development of antisense-based compounds for CNS disorders

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Antisense drugs molecules are small complementary strands of DNA (oligonucleotides; ODNs) designed to bind to a specific sequence of nucleotides in the mRNA target, thus inhibiting production of the encoded protein. Polyamide nucleic acid (PNA) is the third generation of antisense chemistry. These molecules represent a novel concept in the nucleic acid therapeutics as they have improved nucleic acid properties and peptide-like chemistry.

Tyler et al. (PNAS, 1999), and Aldrian – Herrada et al. (Nucleic Acids Res., 1998), suggested that PNAs are internalized into neuronal cells and in high concentration can cross the blood brain barrier. To learn more about these special properties, PNAs uptake properties were studied in vitro and in vivo in endothelial, glial and neuronal models. In primary tissue culture models we could demonstrate selective PNAs uptake into subpopulation of glial, astroblasts, microglia and neuronal cells. FACS sorting analysis of fluorescence labeled PNA (NMB, C6, BEND3 cell lines neuronal, glial and endothelial cellular model, respectively) reveled that PNAs are taken-up by neuronal but not by glial or endothelial cells. Intracellular PNA uptake into NMB cells was found to be temperature sensitive. We also demonstrated that in low concentration there is a marked difference between PNA uptake into neuronal and endothelial cells, suggesting the existence of transport mechanism. In line with this assumption, PNA intracellular accumulation has a punctuated pattern, indicating endosomal/lysosomal trapping. Long term incubation of PC12, NMB or BEND3 cells with high concentration of PNA did not induce cellular toxicity. Following direct administration of PNAs into the brain selective uptake of PNAs into neuronal cells was demonstrated.

These results suggest that unlike ODNs (known to be neurotoxic in high concentrations), PNAs or modified PNAs could be the backbone for future nucleic-acid based therapies for CNS disorders.

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German Mouse Clinic – systematic, standardised and comprehensive neurological phenotyping of mutant mice

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Background: After complete sequencing of the human and murine genomes, it will be one of the prominent goals of the human genome project to understand the in vivo function of every single gene and the pathophysiological and clinical consequences of the respective mutations. This will be achieved by phenotyping of thousands of gene-mutant mouse models in a high-throughput approach.

Methods: The German Mouse Clinic (GMC) provides a systematic, non-invasive, phenotypic screen in order to characterize mutant phenotypes. The neurological screen within the GMC offers the neurological phenotyping of mutated mice to detect diseases of the mouse nervous system, understand the underlying mechanisms and develop reasonable therapeutic strategies. We perform a primary observational screen with a total of 33 measurements. Our secondary screen comprises grip strength and Rotarod testing, and the tertiary screen includes staircase test, electroencephalography and electromyography.

Results: Normal values for the used wildtype mouse strains have been compiled. Until now, nineteen mutant mouse lines have passed the primary neurological screen of the GMC and a new neurological phenotype could be assigned in ten.

Conclusion: High-throughput neurological investigation of mutant mice is feasible and yields hitherto unknown neurological phenotypes in a large proportion of tested mice.

P206

Protection of a Ginkgo Biloba extract against the effects of stannous chloride, a substance that may act promoting depression or stimulation of the cerebral nervous system

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Ginkgo biloba extract (EGb) is a phytoterapic used to increase peripheral and cerebral blood flow for treatment of ischaemic cerebral diseases and neurological disorders, such as, the Alzheimer's disease. This extract has several effects, including: increases the blood flow, acts as platelet activating factor antagonism and prevents the membrane against the damage caused by free radicals. It was demonstrated that tin, as stannous chloride (SnCl2), when injected into laboratory animals, it can produce stimulation or central nervous system depression. Since calcium (Ca) influx into the cytoplasm is indispensable to release the transmitter, it would be possible that SnCl2 increases the Ca2+ influx at the nerve terminals but not by blocking the K+ channels. There is no general agreement regarding its genotoxicity and it was discussed that the effects of this salt might depend on the physicochemical conditions and the route of its administration. SnCl2 has been used in many sectors of human interest, such as the food industry and nuclear medicine. This salt is directly administered to human beings endovenously when it is used as a reducing agent to prepare 99mTc-radiopharmaceuticals which are also used in cerebral studies. SnCl2 is capable to promote the generation of reactive oxygen species (ROS), that are responsible for the oxidative stress. Oxidative stress has been related with the aging and other neurological diseases. We decided to study the influence of the medicinal plant, the EGb, metal chelating and reactive oxygen species scavengers against the SnCl2 deleterious effects evaluating the supercoiled plasmid DNA. results show that SnCl2 produces lesions in vitro on supercoiled plasmid DNA. The literature has showed that these inactivation may be due to the production of ROS. We observed that the genotoxic effect of SnCl2 was partly inhibited or disappeared when the treatment were in presence of the Ginkgo biloba extract. Action similar to the metal chelating and ROS scavengers described in literature. In conclusion, it is possible to suggest that the SnCl2 biological effects associated with the generation of ROS can be inhibited by substance presents on the Ginkgo biloba extract.

P207

Direct isolation of a pure population of AC133+ dermal stem cells for use in brain repair

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Recent studies report evidence for the existence of a mammalian skin-derived multipotent progenitor population that could differentiate into neurons. To better characterize the neuronal potential of this tissue, we isolated AC133 positive cells from the fetal and adult human skin by flow-cytometry. Analysis of the markers harbored by these cells, CD34+, c-Kitlow-positive, Thy1low, and CD45, indicates the presence of a subset of immature hematopoietic/endothelial cell population. These cells cultured in a growth medium containing epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF) proliferate forming spheres and differentiate in vitro into neurons, astrocytes, and rarely into oligodendrocytes. Single cells from sphere cultures initiated from human AC133+ cells were replated as single cells and were able to generate new spheres, demonstrating the self-renewing ability of these stem cell populations. These spheres in different medium conditions can also differentiate into mesodermal lineages (endothelial, myoblasts) as well as smooth muscle and adipocytes cells. Brain engraftment of cells obtained from human AC133+-derived spheres generated different neuronal phenotypes: immature neurons and a most abundant population of well differentiated astrocytes. The AC133-derived astrocytes assumed perivascular locations into the frontal cortex. No donor-derived oligodendrocytes were found in the transplanted mouse brains. Several donor small rounded cells that expressed endothelial markers, were found close to the host vessel and near the SVZ. Thus, mammalian skin AC133-derived cells behave as a multipotent population with the capacity to differentiate into neuronal lineages in vitro and prevalently endothelium and astrocytes in vivo demonstrating the great plasticity of these cells and suggesting a potential clinical application.

P208

High-affinity binding at alpha2-delta protein of voltage-gated calcium channels and the analgesic and anxiolytic action of pregabalin in animal models

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Background and aims: Pregabalin is a potent ligand for the alpha2-delta protein, a subunit of voltage-gated calcium channels. These experiments test whether high-affinity binding of pregabalin to alpha2-delta protein is required for its analgesic and anxiolytic-like effects.

Methods: An amino acid mutation was incorporated into alpha2-delta type 1 protein to convert arginine at position 217 to alanine. Two stable fibroblast cell lines – expressing recombinant wildtype and mutant R217A proteins – were produced. Fresh frozen brain sections were obtained from wildtype and R217A mutant mice for (3H)pregabalin autoradiography. In vitro neurotransmitter release experiments using (3H)noradrenaline with neocortex slices were conducted with pregabalin, comparing tissues from wildtype and R217A mutant mice. Activity of pregabalin in a dorsal root ligation model of neuropathic pain and in the Vogel conflict test was compared in wildtype and R217A mice.

Results: Autoradiography confirmed that mutant mice had greatly reduced binding of radioligand in forebrain structures but only modest decreases in cerebellum. Noradrenaline-release studies of wildtype and R217A cortex show reduced effect of pregabalin in mutant tissues. Results with mutant mice in the dorsal root ligation model and in the Vogel conflict test indicate that high-affinity binding of pregabalin to alpha2-delta type 1 protein contributes to its pharmacologic actions.

Conclusions: These results suggest pregabalin has high-affinity for binding to the alpha2-delta protein, and they define a novel class of CNS-active drugs with efficacy in animal models of pain and anxiety.

P209

A strategy for drug discovery for cerebral oedema after stroke

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Despite advances in stroke management, mortality from progressive edema after MCA strokes approaches 80 % (Ayata and Ropper, 2002). Mice with genetic knockout of aquaporin-4 (AQP4) show reduced brain edema and better neurological outcomes after ischemia, implicating astrocyte AQP4 channels in the pathological process (Manley et al., 2000).

The goal of our work is to identify and characterize novel pharmacological blockers of AQP4 water permeability, and to determine if treatment with these potential blocking agents can significantly decrease the formation of cerebral edema after ischemic stroke in mice.

We have set up a strategy for screening known ion channel blockers as novel inhibitors for AQP4 permeability. Xenopus oocytes expressing AQP4 channels are analyzed by quantitative videomicroscopy to calculate osmotic water permeability values (Pf) using a swelling assay (50 % hypotonic saline) with and without treatment with candidate pharmacological agents. Preliminary data demonstrate untreated AQP4-expressing oocytes show a Pf value of 98*10^–4 ± 34*10^–4 cm/s that is significantly greater than the Pf value of –36*10^–4 ± 51*10^–4 cm/s in control oocytes, and we have identified several compounds that appear to block AQP4 water permeability. Ongoing experiments will confirm these findings and test for selectivity of block by evaluating effects on other aquaporin channels.

Novel AQP4 blockers are then tested in mice subjected to MCA. Anesthetized mice will be subjected to 1 hour of ischemia and 24 hours of reperfusion, and then evaluated for neurological function. The brain will be removed and stained with TTC for infarct size and evaluated for edema formation (Clark et al., 1997). Our preliminary results show an average of 46 % infarction and 3.4 % edema formation after ischemic stroke in the untreated group. Additional MCA groups will be treated with potential pharmaceutical blockers of AQP4. Our results thus far indicate that our novel combination experimental strategy is feasible and that this approach can be used successfully to discover a new class of agents for the treatment of stroke-related edema.

Multiple sclerosis

P210

A thorough investigation on cognitive, psychological and social aspects in benign multiple sclerosis

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Objective: A thorough investigation on cognitive, psychological and social aspects in benign multiple sclerosis (MS) patients.

Background: Benign MS is defined merely on the basis of EDSS score and disease duration, which fails to take into account other relevant dimensions of the disease.

Design/methods: Benign MS patients were identified from the databases of two Italian MS Centers. Inclusion criteria were definite diagnosis, disease duration ≥ 15 years and EDSS ≤ 3.0. Patients underwent an extensive revision of clinical and paraclinical information, neuropsychological testing through the Rao's Brief Repeatable Battery (BRB), evaluation of depression on the Montgomery and Asberg Depression Rating Scale (MADRS), of fatigue on the Fatigue Severity Scale (FSS), and of handicap on the Environmental Status Scale (ESS). Cognitive impairment was defined as the failure of at least 2 tests of the BRB (2 SDs below the mean normative values).

Results: One hundred and nine patients fulfilling the definition of benign MS were examined (86 women; mean age 44.7 ± 8.3 years; mean EDSS 1.7 ± 0.9; mean disease duration 21.6 ± 5.6 years; mean education 12.0 ± 3.8 years). Significant fatigue (FSS score > 4) was found in 52 patients (48 %), and significant depression (MADRS score > 8) in 66 patients (60 %); in particular, moderate to severe depression (MADRS score > 17) was observed in 21 patients (19 %). Cognitive assessment allowed us to identify 47 subjects (43 %) with cognitive impairment. Patients with cognitive impairment exihibited a significantly higher ESS score than cognitively preserved subjects (mean 2.2 + 3.4 vs 0.6 ± 1.6; $p < 0.01$); 29 patients (62 %) in this group had reduced or abandoned their work activity compared to 12 patients (19 %) in the cognitively preserved group (relative risk 3.2; 95 % CI 1.8–5.6).

Conclusions: Fatigue and depression are common problems even in benign MS patients. A sizable proportion of benign MS subjects shows cognitive impairment and experiences significant handicap in work and social life, despite minimal neurological impairment. Definition of benign MS solely on the basis of motor function fails to take into account relevant disease-related psychosocial problems.

P211

Cutaneous lymphocyte antigen epitope of PSGL-1 has a key role in brain-specific lymphocyte recruitment

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Background: Tethering and rolling are the first steps of the adhesion cascade leading to lymphocyte migration into the tissues. We have shown that alpha [1, 3] fucosyltrasferases and PSGL-1 (P-selectin glycoprotein ligand-1) have a critical role in the recruitment of lymphocytes in brain venules. Cutaneous lymphocyte antigen (CLA) represents a fucosyltransferaseVII-induced carbohydrate modification of PSGL-1 responsible for the interaction of PSGL-1 with E-selectin. CD4+ T helper cells are heterogeneous in terms of tissue-specific homing and cytokine synthesis phenotypes. Mechanisms for the acquisition of brain-specific recruitment phenotypes and their relationship with the attainment of polarized cytokine synthesis profiles of T cells are important but poorly understood.

Objective: The first goal of this study was to determine the role of CLA epitope of PSGL-1 in lymphocyte recruitment into the brain. The second goal was to further understand the molecular basis for the acquisition and integration of distinct brain-specific recruitment phenotypes and cytokine synthesis profiles in T cells.

Methods: Human Th1 and Th2 lymphocytes CLA + alpha4beta7– or CLA-alpha4beta7+ were generated using in vitro T cell culture systems. Intravital microscopy was performed directly through the skull in subacutely inflamed murine brain microcirculation.

Results: Human and murine Th1 cells efficiently tethered and rolled in brain venules, but very few Th2 lymphocytes were able to roll and firmly adhere to inflamed brain endothelium. Importantly, Th2 lymphocytes expressing CLA efficiently tether and roll along brain endothelium, while in contrast, Th2 cells CLA- displayed no adhesive interactions. Moreover, when we compared the adhesive interactions between Th1 cells CLA+ and CLA–, we observed that expression of CLA determined a significant increase of tethering and rolling in inflamed brain venules. Anti-PSGL-1 and anti-CLA antibodies almost completely abolished the recruitment of Th1 lymphocytes into the brain.

Conclusion: Our data show that CLA epitope of PSGL-1 is critical for tethering and rolling in brain venules and suggest CLA as an attractive pharmaceutical target in autoimmune diseases of the brain. Moreover, our data unveil that the capability to be recluted into the CNS is independent of the acquisition of Th1 versus Th2 cytokine synthesis profiles.

P212

Mitoxantrone improves cognitive dysfunction of patients in very active multiple sclerosis

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Background: Mitoxantrone was recently approved by the FDA and in most of European countries for the treatment of very active multiple sclerosis (MS). However, to our knowledge, the potential impact of this drug on cognitive dysfunction was not evaluated.

Aim: In the present study, we sought to evaluate changes in cognitive dysfunction in patients with very active MS treated with mitoxantrone.

Patients and methods: Fifteen consecutive MS patients with very active relapsing-remitting MS were included in this study. Very active MS was defined as a progression of at least one EDSS point or more than 3 relapses during the previous year and at least one enhanced lesion after gadolinium infusion on MRI. All patients were treated with a monthly intravenous pulse of mitoxantrone (20 g) for 6 months. Cognitive evaluation was performed before treatment (M0) and after 6 months (M6) of treatment. We also evaluated patients at 12 months(M12). To evaluate the learning effect, 15 healthy subjects were also tested. Global cognitive efficiency, memory and executive function tests were assessed. Depressive symptoms were evaluated with the Beck Depression Inventory. A non parametric Wilcoxon t test was used to investigate a group effect. The significance threshold was set at 0.01. A specific improvement in neuropsychological test was objective if no learning effect interfered.

Results: One patient did not complete the evaluation at M6, and another was excluded because of a too low score at the verbal intelligence scale. In the remaining 13 patients we found a significant and specific improvement at M6 in global cognitive efficiency ($p = 0.01$), executive functions through the Gonogo test ($p = 0.008$) and the Crossed taping ($p = 0.0008$). These results were sustained at M12 notably in global cognitive efficiency ($p < 0.01$), in the delayed recall of Grober and Buschke test ($p = 0.004$), phonemic fluency ($p = 0.002$) and executive functions in the Stroop test ($p = 0.01$). The improvement in global cognitive efficiency was not correlated with the clinical parameters.

Conclusion: Our study suggests that mitoxantrone has a positive effect on cognitive function especially on global efficiency, episodic memory and executive functions. Further studies will be needed to evaluate the long term impact of mitoxantrone on cognitive decline in MS.

P213

Subjective efficacy and side effects of alternative and complementary therapies used by multiple sclerosis patients

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Objective: To differentiate between alternative and complementary use of unconventional therapies by patients with multiple sclerosis (MS) and to evaluate subjective efficacy and side effects of complementary and alternative medicine (CAM).

Background: Utilization of CAM is very popular among MS patients. Different studies have disclosed a CAM use in up to 66 % of cases during the course of disease. Most studies did not differentiate between alternative and complementary use. There is insufficient knowledge how patients evaluate the efficacy of CAM and which experience with CAM they have made.

Design/methods: 154 patients with a clinically definite MS were investigated in a standardized interview. Patients were asked sociodemographic variables, aspects of their disease and if they are currently using CAM. All patients who reported a current use were investigated in detail which CAM they were using, alternative or complementary utilization, subjective efficacy and side effects.

Results: 75.3 % of the investigated MS patients in the study were woman which approximates the general MS population. The mean age was 42.5

years (SD = 12.0) and the mean duration of illness 6.8 years (SD = 6.4) with a mean EDSS of 3.3 (SD = 2.2). Most of the patients (68.8 %) had a relapsing remitting form of MS. At time of investigation 95 patients (61.7 %) reported that they were currently using CAM. On average they used 2.4 different therapies (SD = 1.6). 89.9 % of the overall utilized therapies (n = 227) were used complementary and 10.1 % were used alternatively to the conventional MS medication. MS patients reported improvement through CAM use in 65.8 %, no influence in 32.9 % and worsening in 1.3 %. For most of the CAM (95.5 %) no side effects were indicated, and the remaining 4.5 % were slight.

Conclusion: MS patients are using CAM primarily complementary to their conventional treatment. Therefore, neurologists should keep in mind that their patients are using CAM and should be aware of possible side effects and interactions between the two types of therapies. The fact that patients indicated a subjective improvement for two thirds of the reported CAM needs to be further investigated.

P214

Concentration effects of interferon-beta on the paracellular permeability of a brain endothelioma cell monolayer

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Background: Breakdown of the blood-brain barrier (BBB) is an early event in the pathogenesis of multiple sclerosis (MS). The reduction of Gadolinium-enhancing lesions in MS patients treated with interferon-beta (IFN-b) may be associated with a stabilization of the BBB, besides immunomodulatory effects. However, it remains to be established whether this effect is dose-dependent or not.

Objective: We examined, whether incubation of a monolayer of cultured brain endothelioma cells with different concentrations of IFN-b affects the paracellular permeability across these cells in vitro.

Methods: The immortalized endothelioma cell line bEnd5 from mouse brain capillaries was grown to confluence for ten days on semipermeable filters precoated with rat tail collagen. From the tenth day on, endothelioma cells were exposed to 100 and 1000 IU/ml IFN-b for another ten days. After a total of twenty days, culture media was replaced with Ringer-HEPES solution, and we determined the paracellular permeability of radioactive (14C)-sucrose and (3H)-inulin across the endothelioma monolayers during the assay period of 15 minutes as compared to untreated controls.

Results: After exposure to 100 IU/ml IFN-b for ten days, paracellular permeability of these monolayers was decreased as compared to untreated controls. However, exposure to 1000 IU/ml IFN-b even increased paracellular permeability as compared to controls.

Conclusion: The results show that incubation of a monolayer of brain endothelioma cells with IFN-b attenuates the permeability of brain endothelioma cells in vitro at a low IFN-b concentration, but increases paracellular permeability at a higher dose. However, it remains to be established whether the high-dose effect bears such deleterious consequences in vivo.

P215

Peroxiredoxin V changes in multiple sclerosis

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Multiple sclerosis (MS) is a central nervous system disease characterised by inflammation, demyelination, axonal loss and gliosis. Inflammation increases production of reactive oxygen species (ROS), which are highly chemically active and severely damage proteins, DNA, and cell membranes. Antioxidants are a natural source of defence against damage by ROS. Peroxiredoxin V is an intracellular protein with thioredoxin-dependent antioxidant activity in vitro. Peroxiredoxin V expression was investigated in cerebral sub-ventricular and spinal cord white matter by immunohistochemistry. Snap-frozen post-mortem tissue from normal controls (NC) (n = 5) and MS normal appearing white matter (NAWM) (n = 5), acute (n = 6), sub-acute (n = 6) and chronic (n = 7) lesions was examined. There was weak peroxiredoxin V staining in blood vessels in all tissues. In NC tissue, staining of axons, small cells and astrocyte cell bodies was weak. Similar staining was seen in MS NAWM although astrocytes processes were also evident. Strong reactive astrocyte staining was seen in acute lesions in addition to occasional macrophages. Axon staining increased in sub-acute lesions but astrocyte staining was reduced. In chronic plaques scar astrocytes showed a striking increase in peroxiredoxin V. These results indicate that peroxiredoxin V is not only increased in acute MS lesions where there is inflammation, but is also increased in chronic lesions, which suggests on-going ROS activity.

P216

Neurosurgical treatment of trigeminal neuralgia in patients with multiple sclerosis

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Background: Trigeminal neuralgia (TN) is a frequent pain syndrome in patients with multiple sclerosis. The neurophysiological explanation is not proven and an inflammatory process of the central or peripheral trigeminal nerve is considered. Treatment of choice is carbamazepine or gabapentine. If pharmatherapy fails or major side effects occur, neurosurgical treatment must be considered.

Methods: A prospective study of 20 patients with TN and associated multiple sclerosis (MS), operated during the last two years, is reported. All patients suffered from pharmacological intractable unilateral TN for more than 2 years. MS was diagnosed prior to the neuralgia with liquor examination and magnetic resonance imaging. An acute inflammatory process or demyelinisation in the trigeminal nerve or brainstem was excluded by MRI. In 17 patients a temperature controlled coagulation of the gasserian ganglion and in 3 patients a neurovascular decompression at the parapontine angle was performed.

Results: In all patients the puncture of the gasserian ganglion was successful. Sensory testing was performed using the unisolated tip of the puncture needle to evoke paraesthesias. Thermocoagulation with duration of 60–90 seconds and 70–74° Celsius was performed under sedation with iv. remifentanil and propofol. After this 13 of the 17 patients mentioned intraoperatively a slight hypaesthesia in the involved nerve branches. 15 of the 17 patients were immediately painfree, two patients had lower frequency and intensity of the neuralgia after the procedure. Three patients reported recurrent pain 2–4 months after thermocoagulation and the procedure was repeated successfully. In three cases of TN and MS a microvascular decompression was performed after demonstration of a neurovascular conflict in high-resolution MRI of the cerebellopontine angle. All patients were immediately pain free after the operation and also at one year follow-up examination.

Conclusion: Neurosurgical treatment like thermocoagulation in the gasserian ganglion and also microvascular decompression are safe and effective procedures. Concerning the cause of trigeminal neuralgia in MS a pathophysiological correlation must explain more than inflammation of the trigeminal pathway. If medicative treatment is insufficient neurosurgical consultation should be offered to patients with TN and MS.

P217

Comparison of clinical and paraclinical data between European and North African multiple sclerosis patients

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Background: North African patients presenting with multiple sclerosis (MS) seem to have different clinical and paraclinical data compared to Caucasian patients.

Objectives: The aim of this study was to determine whether there were differences in clinical and paraclinical data at baseline and during disease progression between European and North African patients presenting with MS.

Patients and methods: We retrospectively studied the clinical and paraclinical data of 50 consecutive North African patients presenting with clinically definite MS according to Poser et al.'s criteria (1983). Each patient was compared with 2 consecutive European patients matched for age and sex.

Results: The North African patients were significantly younger at onset ($p < 0.01$) and had a higher EDSS score after the first relapse than the European patients ($p < 0.001$). The relapse rate during the 3 years following the first clinical event was higher in the North African group ($p < 0.01$). The time to reach EDSS 3.0 was significantly longer in the European group ($p < 0.001$), but there was no difference in the time to reach EDSS 6.5. A cerebellar syndrome occurred earlier ($p < 0.001$) and was more severe in the North African group at the end point of the study ($p < 0.03$). Cognitive impairment was also more frequent in the North African group ($p < 0.001$). Paraclinical data were not significantly different in the two groups.

Conclusion: North African MS patients seem to have a more aggressive

form during the first years of the disease. These data should be taken into account in order to optimize treatment at the disease onset.

P218

Dopamine fails to regulate T-cell activation in multiple sclerosis. Effects of IFNb

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Background: Dopamine may modulate T cells activation in Multiple Sclerosis (MS). Immune cells may meet dopamine when it is released from nerves supplying lymphoid organs, from lymphocytes themselves or within the brain.

Dopamine can either inhibit the proliferation of lymphocytes when it acts on the D5R receptor subtype, or enhance the adhesion and activation of T cells through the D3R.

Objective: To assess whether the dopamine network of lymphocytes is involved in the pathophysiology of Multiple Sclerosis.

Methods: We investigated the immunomodulatory functions associated with dopamine and its D5R and D3R related receptors in peripheral blood mononuclear cells (PBMCs) from fourteen (14) stable Relapsing Remitting (RR) MS patients (MS), six (6) relapsing MS patients (MS relapsing), thirteen (13) MS patients undergoing to IFNb-1a (8) or IFNb-1b (5) treatment (MS IFN beta), six (6) patients affected from Other Inflammatory Neurological Diseases (OIND), and eleven (11) age and sex-matched healthy controls (HD). The dopamine levels were measured in plasma by HPLC. The expression of dopamine receptors (D3R, D4R, D5R) in PBMCs was assessed both at the mRNA and the protein level. PBMCs were also stimulated in vitro with anti-CD3+IL-2 and investigated for dopamine (0.001–1 microgram/ml) capability to regulate T cell proliferation, secretion of IFN gamma, expression of MMP-9 mRNA and of Th1/Th2 cytokines mRNA.

Results: We found increased dopamine levels in plasma from relapsing MS patients with respect to the other subgroups. The D5R receptor subtype was reduced in PBMCs from both stable and IFNb treated MS patients ($p < 0.0001$). The D3R receptor was expressed at normal levels in PBMCs from stable MS patients, but it was strongly reduced in PBMCs from MS patients undergoing to IFNb treatment ($p < 0.0001$). Dopamine inhibited T cell proliferation, MMP-9 expression, and enhanced T1/Th2 cytokines mRNA in PBMCs from HD but not from MS patients. Differently, dopamine renewed its regulatory effects on PBMCs from IFNb treated MS patients.

Conclusions: We demonstrate that differential expression of the dopamine receptors subtypes D5R and D3R underlies the loss of the inhibitory effects of dopamine on T cell proliferation, expression of MMP-9 mRNA and secretion of IFN gamma in MS. Availability of agonists/antagonists for dopamine receptors and effects of IFNb might open novel paths to therapeutic intervention.

P219

A follow-up of cerebrospinal fluid findings, especially oligoclonal IgG-bands, in multiple sclerosis patients treated with intrathecally applicated triamconolone acetate

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Background: An increased intrathecal synthesis of oligoclonal IgG is shown in approximately 95 % of MS patients.It is often assumed,that intrathecal IgG synthesis and oligoclonal banding patterns (OCB) are rigid intra- and interindividually and therefore not associated with disease activity,disease severity,clinical course and not qualified to predict anything about disease progression.In opposite to this assumption we observed intraindividuall changes in OCB.We evaluated the correlation between OCB and treatment with triamcinolone acetate (TCA),disease parameters,clinical course.

Methods: 37 MS-patients (McDonald-criteria applied) were treated with intathecal TCA 40 or 80 mg at 2 or 3 days intervals for different treatment periods and duration. CSF specimen were collected in average with 4 lumbar punctures per patient and analysed for IgG and OCB. We evaluated on these patients EDSS, 25 feet walking test, before and after treatment.We also noted age, sex, duration of disease, disease course, concomittant medication.We classified 2 groups according to the amount and appearance of OCB in time. According to the definition of at least 4 OCB as pathological we defined group I as stable before and after treatment. Group II was defined as changing from pathological to normal OCB-findings.

Results: The Age of both groups was equal, the age at start of the disease was lower in group I, meaning that group I had a shorter duration of disease. In both groups most patients had secondary progressive disease course only 2 patients in group II had relapsing-remitting MS and 3 patients had primary progressive MS, 2 in group II and 1 in group I. There were more female patients in group I, but more male patients in group II. Patients of group II received more TCA and were treated longer. Taking concomitant disease modyfying therapies into consideration there were more patients changing to Mitoxantrone in group I. The change of EDSS before and after treatment with TCA was equal in both groups. 16/37 patients had changing OCB in the observed period, 12/37 underwent a change from pathological to normal OCB, 10/37 lost OCB completely after TCA treatment and had pathological OCB before.

Discussion: Our results are in contradiction to the assumption that OCB are rigid parameters in the disease course of individual MS patients. It is discussed whether OCB might disappear as a natural phenomenon in the disease course or as an effect of TCA treatment.

P220

High-density single nucleotide polymorphism mapping of protein kinase C alpha gene in a UK population of multiple sclerosis patients

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Introduction: Whole genome scans in multiple sclerosis (MS) families have shown linkage to chromosome 17q22-24 and the homologous region in rats has been linked to experimental allergic encephalomyelitis (EAE). Using linkage analysis in Finnish extended multiplex pedigrees, the region of linkage in humans has been refined to a 2.5Mb region and 2 single nucleotide polymorphisms (SNPs) mapping to the middle of the shared haplotype region showed significant association with MS. Protein kinase C alpha (PRKCA) maps to this interval and spans approximately 0.5 Mb. PRKCA is involved in T cell regulation and proliferative responses. Furthermore, in EAE, PRKCA inhibitors ameliorate disease in susceptible animals. Hence it is a prime candidate MS susceptibility gene. We therefore investigated association of SNPs mapping to the PRKCA gene in a UK cohort of MS patients using high-density linkage disequilibrium mapping.

Methods: A case-control study was performed to investigate the association of 35 SNP markers spanning the PRKCA gene with a median marker interval of 7.8 Kb. 184 unrelated MS patients from the North West of England were recruited and 340 controls. All patients had clinically definite MS according to Poser criteria. DNA was extracted and genotyping was performed with Assays-on-Demand (ABI, UK) allelic discrimination assays on a Taqman™ platform. Haplotypes were assigned using SNPHAP software and additionally using a moving window analysis implemented in HelixTree sotware (Golden Helix Inc, USA). CLUMP software was used to compare distribution between cases and controls.

Results: Moving window analysis shows association to a haplotype of 2 SNPs (p value 2.4×10^{-5}) at the proximal portion of the gene. Using SNPHAP software to assign haplotype, and CLUMP software to analyse distribution, a haplotype of the same 2 SNPs mapping to the proximal region of the gene showed evidence for association (p value 4.0×10^{-8}, bonferroni corrected $p = 2.0 \times 10^{-7}$). The odds ratio for the susceptibility haplotype was 1.4 (95 % C. I. 1.1–1.9).

Conclusion: Our results provide further support for association of the 17q22-24 region with MS and implicate PRKCA as a possible MS disease gene. The region of the gene highlighted by this study should be prioritized when screening for disease associated functional mutations.

P221

Efficacy and safety of repeated intrathecal triamcinolone acetonide application in acute painful dysaesthesia due to inflammatory spinal cord lesions in patients with relapsing-remitting multiple sclerosis

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Circular thoracal painful dysaesthesia caused by acute inflammatory lesions of the spinal cord can be a symptom of exacebation in patients with relapsing remitting multiple sclerosis (RRMS). These dysaesthesia are often torturous for the patients and unsatisfactory to treat for the physician. In the present study, we describe four RRMS patients with acute painful dysaesthesia caused by spinal cord inflammation which received repeated intrathekal triamcinolone acetonide application (TCA) (steroid preparation with sustained release compound) injections after unsuccessful treatment with intravenous steroids.

The objective of this open, prospective study was to show the efficacy

and tolerability of repeated intrathecal TCA treatment. Each of the four patients was admitted to our hospital with acute painful dys- and paraesthesia caused by acute relapse in MS. All these patients had been treated first line with high dose intravenous steroids (1000 mg Methylprednisolone over 3 days/500 mg over 5days) without satisfactory regredience of the symptoms. As Gadolinium enhancing lesions in the spinal cord were prooved by MRI, we treated these patients with the sustained release steroid TCA intrathecally (3 to 6 times). We used an atraumatic needle for the puncture to reduce the risk of side effects. The treatment was well tolerated, no serious side effects occurred.The pain rated with the eleven point box scale decreased in every patient (mean point scale before treatment: 7, mean point scale after treatment: 2), in two patients the symptoms disappeared completely,.

We conclude that repeated intrathecal TCA injection provides substantial benefit as a second line treatment for RRMS patients with acute painful dysaesthesia due to spinal cord lesion.

P222

Long-term experiences after mitoxantrone therapy in multiple sclerosis

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Background: Mitoxantrone (Mtx) has been approved to treat secondary-progressive and progressive-relapsing multiple sclerosis (MS). The aim of this study was to evaluate the long-term outcome of patients treated with Mtx between 1994 and 1998 with particular interest of diagnosed malignant diseases during the follow up period.

Method: We evaluated 52 (35 female, 17 male) out of 87 MS patients treated with Mtx between 1994–1998 by patients data and telephone interview. The mean-time since finishing Mtx was 7 years. The parameters "discontinuation of Mtx", "personal long-term efficacy", "treatment procedure after end of Mtx", and "malignant diseases diagnosed after Mtx" were evaluated.

Results: Mtx was stopped in 31 (60 %) patients before reaching the maximum dose, in most of them (n = 20) within the first 3 applications. Therapy was stopped due to nausea/vomiting (n = 12), recurrent infections (n = 4), loss of hair (n = 2), aversion against Mtx (n = 3), changes of left ventricular ejection fraction (n = 2), depression (n = 2), raise of liver enzymes (n = 1). As to personal long-term efficacy, for 7 patients Mtx was discontinued because of treatment failure. A stabilising effect was reported by 13 patients and a clear improvement of disability by 8 patients, who reached the maximum dose of Mtx. The treatment time varied between 6 months (n = 18), 1 year (n = 8), 2 years (n = 14), 3 years (n = 8), 4 years (n = 4). Of all patients 36 (69 %) received immuno-suppressive therapy, like azathioprine, methotrexate or cyclophosphamide (n = 16) or immuno-modulating therapy, like interferon beta, glatirameracetate or immunglobuline (n = 20) after Mtx. In 7 patients treated with Mtx up to the maximum dose no other long-term treatment was needed. Malignant diseases in this group of patients were diagnosed in 3 out of 52 (6 %). One patient suffered from colon-carcinoma, one patient from chronic lymphatic leukaemia, and one died because of a acute myelogenous leukaemia.

Conclusions: The high frequency of discontinuation due to side effects reflects the low level of tolerability of this type of treatment. However, if treatment initiation was well tolerated most patients reached the maximum dose confirming the efficacy of Mtx in MS. Concerning the therapy regime following Mtx, our data reflect the need of studies resolving this question. Furthermore, in each patient the possible risk of malignant diseases following immuno-suppressive treatment should be seriously taken into account.

P223

Polymorphism of tumour necrosis factor-alpha promoter region (–308) and the first intron of lymphotoxin-alpha gene (+252) in Iranian patients with multiple sclerosis

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Background: Tumor necrotic factor-alpha (TNF-alpha) and lympotoxin-alpha (LT- alpha) are detectable in lesions of multiple sclerosis (MS) and have been implicated as major mediators of tissue injury in MS. The host ability in production of these cytokines is determined partially by the G-to-A transition at position –308 of the TNF-alpha promoter region and the +252 in the first intron of the LT-alpha genes.

Objective: To investigate the prevalence of –308 and +252 polymorphism in TNF-alpha and LT-alpha genes, respectively, in MS patients and their correlation to disease type and activity.

Methods: 70 MS patients and 64 age-matched normal controls were included in this study. 27.27 %, 59.1 % and 13.63 % of patients had chronic relapsing (CR), remitting relapsing (RR) and benign type of disease, respectively. The polymorphism at position –308 relative to transcription initiation site of TNF-alpha and the +252 polymorphism in the first intron of LT -alpha were determined by allele specific PCR and PCR-RFLP methods, respectively.

Results: No difference in the distribution of the TNF1 and TNF2 or LT1 and LT2 alleles were observed in patients as compared to controls. Furthermore, there was no significant association between alleles and disease activity and phenotype.

Discussion: We suggest that inherited alleles of these genes are not critical to disease formation. However, the frequency of TNF2 allele (associated with higher production of TNF-alpha) was higher in patients with low disease activity (1.5 folds) and benign type of disease (2 folds). Therefore, we suggest that TNF2 allele may be associated in someway to benign type or less aggressive form of disease.

P224

Low-dose oral methotrexate in chronic progressive multiple sclerosis: a 5-year prospective study

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Low dose oral methotrexate (LDOM, 7.5 mg/week) has been proposed as a therapy (tx) for chronic progressive multiple sclerosis (CPMS). We report here data on 43 consecutive patients (pts) aged 48 ± 9.9 years (yrs), 14 females, 30 secondary progressive (SP) treated since 1998. All pts had deteriorated in the yr before tx. Disease duration ranged 5–30 yrs, disease onset was at 19–60 yrs; tx was started at 44.6 ± 9.9 yrs. Mean tx duration is 34.5 ± 20.2 yrs. Six pts interrupted tx after less than 1 yr (2 toxicity, 1 inefficacy). Of the 37 pts completing at least 1 yr of tx (27 SP) 6 interrupted tx (2 inefficacy, 2 toxicity). Of the 27 pts completing at least 2 years of therapy (21 SP) only 2 interrupted tx for inefficacy. Of the 21 pts completing 3 yrs of tx (17 SP) 1 interrupted tx for bad compliance. Of the 15 pts treated for at least 4 yrs (12 SP) none interrupted tx and 6 (1 SP) have completed at least 5 yrs of tx. Further data are on the 37 pts with at least 1 yr of follow-up. EDSS increased from 5.3 ± 0.2 1 yr pre-tx to 6.1 ± 0.2 at T0 and stabilized at 6.2 ± 0.2 at yr 1 ($p < 0.001$); 78 % of pts were stable or improved (60 % of PP, 85 % of SP). Analysing the 10 primary progressive (PP) pts, EDSS increased from 4.2 ± 0.5 1 yr pre-tx, to 5.3 ± 0.5 at T0, then stabilized to 5.4 ± 0.5 at 1 yr ($p < 0.005$). In the 27 SP pts EDSS increased from 5.8 ± 0.2 1 yr pre-tx to 6.5 ± 0.2 at T0 and remained the same at yr 1 ($p < 0.001$). This effect was partly obtained associating 1 or more methylprednisolone (MP) courses to LDOM tx in 23 pts who were stable (18) or better (4) according to the EDSS score after 1 yr of tx. Among the 15 pts not receiving MP courses only 1 improved, 7 were stable. Gadolinium-enhanced MRI scans have been performed at baseline (stable in 8 % of patients, active in 25 %) and yearly thereafter. Among pts having an active scan at baseline only 3 % were still active at yr 1; of the 75 % not active at baseline 8 % were active at yr 1. Tolerability has been good in most: liver echography at yr 1 shows mild steatosis in 40 % and is normal in 60 %; blood chemistry has shown transient increases in liver enzymes (grade 2) in 40 %, none developed cirrhosis; blood cell counts have been transiently abnormal (grade 2) in 2. The most common clinical side effect is nausea, well controlled with domperidone pre-medication and dose fractionation. Other reported side effects are headache and fever. LDOM appears to be safe up to 5 years, with no serious toxicity after yr 1.

P225

Disease-modifying treatments in children and adolescents with multiple sclerosis

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With the development of newer disease-modifying agents (DMAs) and antimetabolic chemotherapeutic drugs, it is possible to modify the disease course of multiple sclerosis (MS) before reccurrent relapses become associated with the development of axonal injury. If such agents are indeed effective, they should be considered early course of MS in children and adolescents to delay the onset of clinically definite MS (CDMS).

This study was designed to reveal the effects of DMAs in patients with MS before 16 years of age, between 17 and 20 years, and after 20 years of age with childhood-onset MS(COMS). These patients have been followed by us in Child Neurology and MS units at least for 2 years. All the patients

had developed MS under 16 years of age; and have CDMS with relapsing-remitting course (RRMS)at the initiation of the treatments. The patients received DMAs at least one year.

In this series, 42 out of 105 patients with COMS have been receiving these agents. In 16 patients(pts), these treatments were initiated under 16 years of age (group 1). In the rest of the patients, DMAs were initiated between 17 and 20 years in 11 pts and after 20 years of age in 14 pts (group 3). In the first group, 16 patients (11F/5M)have been using DMAs: IFNB-1a (30mcg)(n = 8), IFNB-1a (44 mcg)(n = 3), IFNB-1b(8MIU)(n = 3), glatiramer acetate(n = 2). Mean age at onset of disease was 11.2 yrs, duration of disease ranged 2 to 9 yrs, duration of treatments ranged 1 to 4 yrs. Relapse rate 2 years before treatments ranged 1 to 3, EDSS at the initiation of treatments ranged 0.0–5.0, relapse rate 1 year after treatments ranged 0 to 1. EDSS 1 year after treatments ranged 0.0 to 5.0. Two patients developed secondary progressive course 1 year after treatments. The above-mentioned parameters were studied and were compared in group 1, 2 and 3.

In conclusion, this study revealed that disease- modifying agents were reduced the relapse rates in all groups in the first year of treatments and are safe and tolerated in children and adolescents with MS. Although early treatments seem to be effective, further prospective studies with prolonged follow-up will require to clarify whether therapeutic benefit is long-lasting.

P226
Long and short term prognostic factors in multiple sclerosis
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Background: We observed elsewhere that patients with more than 2 attacks in the first 2 years show significantly higher EDSS after 10 years; in this paper we evaluate prognostic factors so to find other indicators for early therapy.

Patients and methods: 95 patients, 23 m, 72 f, age at onset 29.16 yrs (11–50), with complete history of attacks, were included; follow up duration mean 8 yrs (2–31). Variables were: N. of systems at onset: 1 = 59; 2 = 27; 3 = 3; 4 = 4, optical neuritis: 22 pts; first inter-attack interval: 25.53 months (1–204); Attacks in the first 2 years: mean 1.90 (1–6); EDSS at 0–2yrs: N = 93; median = 1 (0–4.0), at 4–6 yrs: N = 66; median = 1.5 (0–5.0); at 8–10 yrs: N = 46; median = 2 (0–6.5); at 13–15 yrs: N = 22; median = 2 (0–4, 5); Shift to secondary progressive(SP); Years before starting DM therapy:4 (0–23); Therapy; Diagnosis made at onset. Statistics were made by Multiple Regression, Kruskal-Wallis, Mantell-Hanszel chi square and Kaplan-Meier curves.

Results: Outcome long time variables: EDSS at 10 yrs is in correlation with EDSS at 0–1 yr ($p = 0.001$) and N. of systems at onset ($p = 0.0043$). EDSS at 15 years is correlated with N. of attacks in the first 2 years ($p = 0.037$), the first EDSSs (at 0–1 yrs $p = 0.026$; at 4–6 yrs $p = 0.037$), and the therapy ($p = 0.040$). Shift to SP is less common in females (OR 0.33; CI 0.09–1.22, $p = 0.046$). Short time outcome variables: The first inter attack interval correlates only with EDSS at 10 yrs ($p = 0.027$). The EDSS at 0–1 yr (N = 46) correlates with the N. of systems at onset ($p = 0.001$), with the EDSS at 4–6 yrs ($p = 0.04$) and at 10 yrs ($p = 0.001$). The N.of systems interested at onset (N = 46) correlate either with EDSS at 0–1 yr ($p = 0.002$) and EDSS at 10yrs($p = 0.007$); Kaplan-Meier curves for first inter-attack interval show a suggestive but not significant trend for the N. of systems at onset, and a longer interval for optical neuritis (log-rank $p = 0.039$).

Discussion: Our data agree with most literature. In short time, optical neuritis shows longer intervals to a new attack; more systems interested at onset correlate with EDSS. In long time, EDSS at 10yrs is correlated with the N. of systems at onset, the first inter-attack interval, and the basal EDSS. Secondary progression is more common in males. We believe it could be useful evaluating, for early treatment, patients with more systems interested at onset, and incomplete recovery, in particular if males. In clinically isolated syndromes, particularly optical neuritis, waiting for a relapse could help for both diagnosis and prognosis.

P227
Cognition in the early stage of multiple sclerosis
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Background: Multiple Sclerosis (MS) is one of the most frequent inflammatory diseases of the central nervous system. It is well known, that cognitive functions are often impaired in the later stage of the disease. 45–50 % of all MS patients suffer from cognitive dysfunctions. 22–31 % of the patients show memory and learning deficits, 22–25 % deficits in attention and 12–19 % executive dysfunctions. Frequently quality of life is affected.

Objective: There is only little knowledge about cognitive dysfunctions in the early stage of MS and its treatment. The aim of our study was to find out specific patterns of cognitive dysfunctions in the early stage of the disease.

Methods: We included 21 MS-patients (7 male, 14 female, relapsing remitting MS, primary progressive MS) with an onset of first neurological symptoms within two years (mean 15 months) preceding the study compared to 22 healthy controls. The neuropsychological assessment consisted of five tests for memory and learning deficits, four tests recording attention deficits, two tests for executive functions and one test for spatial functions, completed by a depression scale and a test for assessing intellectuell capabilities. Patients and healthy controls underwent randomized examinations.

Results: We can demonstrate few cognitive dysfunctions in the MS-patients. As a main result decreased reaction time ($p = 0.005$), nonverbal memory deficit ($p = 0.001$) and planning deficit ($p < 0.001$) was found in most of the patients compared with healthy controls. High depression scores didn't show any influence on the test results of the experimental group.

Conclusions: Our findings suggest, that even in the early stage of MS cognitive dysfunctions are evident. In an ongoing study we correlate cognitive functions at the time of first symptoms consistent with the diagnosis of MS with the extent of lesion load in magnetic resonance imaging, magnetic transfer imaging and magnetic resonance spectroscopy.

P228
Long-term outcome in patients with chronic progressive multiple sclerosis
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Background: This is the first report in the medical literature documenting the therapeutic effect of combining mitoxantrone and intravenous immunoglobulins (IVIGY/ln treating chronic progressive multiple sclerosis (MS).

Method: Participating in this preliminary study were 36 MS patients, including 12 controls in group A on corticosteroids (primarily methylprednisolone), 12 patients receiving mitoxantrone and methylprednisolone in group B, and 12 patients receiving mitoxantrone, methylprednisolone, and IV1G in group C.

Results: After one year of treatment, the Kurtze Expanded Disability Status Scale (EDSS) scores showed a significant improvement ($p < 0.05$) when comparing group A to groups B and C. According to this scale group A patients deteriorated slightly, whereas group B patients improved 44 % and group C, 52 %.

Conclusion: Though our study was small and preliminary, the results are promising and reflect the potential benefit of combining low-dose mitoxantrone with high-dose 1VIG. Future directions to retest my hypothesis should take a double-blind, randomized approach involving more patients with chronic, progressive MS.

P229
How much do the first relapses influence outcome in multiple sclerosis?
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Background: Assessing prognosis of patients with different attacks in the first 2years, can help to evaluate costs and benefits of early treatment.

Patients and methods: 95 patients, 23 m, 72 f, age at onset 29.16 yrs (11–50), with complete history of attacks, were included; follow up duration mean 8 yrs (2–31). Variables were: N. of systems at onset: 1 = 59; 2 = 27; 3 = 3; 4 = 4, optical neuritis: 22 pts; first inter-attack interval: 25.53 months (1–204); Attacks in the first 2 years: mean 1.90 (1–6); EDSS at 0–2yrs: N = 93; median = 1 (0–4.0), at 4–6 yrs: N = 66; median = 1.5 (0–5.0); at 8–10 yrs: N = 46; median = 2 (0–6.5); at 13–15 yrs: N = 22; median = 2 (0–4, 5); Shift to secondary progressive(SP); Years before starting DM therapy: 4 (0–23); Therapy. Statistics were made by Multiple Regression, Kruskal-Wallis and Yates corrected chi square.

Results: EDSS at 10 years is correlated with EDSSs at 0–1 yrs ($p = 0.001$) and 4–6 yrs ($p = 0.011$), N. of systems ($p = 0.0043$), and, inversely, first inter-attack interval ($p = 0.0021$). At 15 years become significant attacks in the first 2 years ($p = 0.037$), therapy ($p = 0.040$), year of its starting ($p = 0.033$), and first EDSSs (0–1 yrs $p = 0.026$; 4–6 yrs $p = 0.037$). First inter-attack interval correlate only with EDSS at 10 yrs ($p = 0.027$). As to attacks in the first 2 years, there is significancy for EDSS at 10 yrs ($p = 0.032$), restricted only to patients with more than 2 attacks (stratificating, pts with 1 or 2 attacks: not significant; pts with 1, 2 and 3 attacks: $p = 0.047$; pts with 1 and

3 attacks: p = 0.028). Shift to SP is not different. Median EDSS at 10 yrs is 1.5 in pts with 1attack, and 2.250 in those with 2 or 3; the first inter attack interval is 50.94 months in the 37 pts with 1attack, 11.37 in the 32 pts with 2; 6.71 in the 21 pts with 3.

Discussion: The N. of attacks, when not high, modify only slightly and not significantly the prognosis of MS. Increasing observation at 15 years should enhance reliability. As to treatment, waiting for a relapse could be quite harmful, and could help in diagnosis and prognosis. Treating early 65 patients for 32 months, knowing EDSS unchanged at 10 yrs, is certainly more expensive than treating, on the second attack, 32 pts after 11 months, and other 33 after 51 (and also in these last the prognosis is not significantly worse): 2035 months of therapy would be saved without changing results. It could help evaluating for early treatment pts with more systems interested at onset, rather than clinically isolated syndromes; we treat this subject in a different paper.

P230

Direct comparison study of the effect of beta-interferons in Iranian patients with multiple sclerosis (results of a 6-year therapy)

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According to our data, the prevalence of MS in IRAN is about 40,000. So it seems Iran is a country with high prevalence of MS. During 6 years (from 1997 to 2002), we have studied the effects of beta-interferon (a and b group) on 214 patients with CDMS. This is a single blind study, physician was blind and the patients were divided into three groups. All patients of three groups were matched according to age (X = 28.7 ± 6 Y), sex ratio (3.35), age at diagnosis (25.8 ± 5.4 Y), EDSS (2.1 ± 1.5). Group A (72) received AVONEX 30 mg/IM, once a week, Group B (83) who received REBIF 22 MG/SC 3 times in week and group C (59) who received BETACERON 8MIU/SC every other day. The most important factors were the rate of patient without relapsing, progression of disease, mean number of T2 active lesions, mean number of T1 lesions and drug side effects. At the end of the 1st year in group A 55 patients (76.3 %) and in group B and group C 61 (73.5 %), 42 (71.2 %) were free from relapsing.According to the EDSS, in the end of the first year the progression of the disease were 0.6, 0.5 and 0.6 and in the end of the second year were 1.3, 1.2 and 1.2 and in the end of 5th year were 2.2, 2.0 and 2.35 respectively. According to appearance of new lesions in T2 MRI, in end the first year 79 %, 91.5 % and 88.3 % of the patients were free from lesions and in end of 5th year 45.3 %, 40.2 %, 41.4 % of the patients were free from new lesions respectively. The most unwanted side effects was skin rash in 56.2 % of the patient who received BETACERON, 45.4 % of the patient who received REBIF and 21.1 % with AVONEX. As a whole there is not any significant differences in therapeutic advantages of these interferons.

P231

The evaluation of the clinical course of patients with progressive multiple sclerosis treated with Novantrone

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Objective: To evaluate clinical course of patients with progressive MS treated with novantrone.

Methods: This was a one year interventional study of 35 patients with secondary progressive, worsening relapsing-remitting or progressive relapsing MS.

Inclusion criterias were age < 45 years, duration of the disease < 15 years, Kurtzke expanded disability scale(EDSS) < 7, active course of the disease, no administration of any other immunomodulator agents. The patients were treated with 12 mg/m^2 of the cytotoxic agent Novantrone, administered every 3 months for 12 months. Clinical assessments were performed every 3 months. Disabilities at the entry and every 3 months were evaluated based on the EDSS.The number of exacerbations over the 12 months were recorded.

Results: A statistically significant decrease in the mean number of exacerbations in worsening relapsing-remitting group was observed (P value = 0.0001)The mean percentage of decreased attack was 82 % (St. error = 4.84).

Significant improvement on EDSS was seen during treatment compared with the time before treatment (P value = 0.0001).Mean decrease in EDSS was 0.1743 (St. d = 0.3230). EDSS change in progressive relapsing group was not significant (P value = 0.406).The change in EDSS was not influenced by the duration of the disease or age.

Conclusion: Our study suggests that Novantrone might be effective in reducing disease activity, both by decreasing the mean number of exacerbations and by slowing the clinical progression.

P232

Side effects of interferon-beta 1a in relapsing-remitting multiple sclerosis

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Background: Over the past few years, interferon-beta has been widely used as a modifying treatment for multiple sclerosis and there are conflicting data about its adverse effects 'some of which such as major depression could be serious.

Methods: Study was made on 60 Iranian patients (19 male and 41 female) with relapsing-remitting multiple sclerosis diagnosed by Mc Donald's criteria, for 15 months from the first injection of interferon beta 1-a. All patients were seen 4 times during this 15 months study (0, 3, 9, 15 months after the first injection) and in each visit the following evaluations were performed: 1. Patients were asked carefully about their feelings and symptoms after every injection 2. The results of laboratory tests (CBC and LFT) were assessed. 3. Four psychological tests include: Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Hamilton Rating Scale for Anxiety (HRSA), Hamilton Rating Scale for depression (HRSD) were made.

Results: Among 60 studied patients at the first visit (after first injection) we had 41 patients with flu like syndrome (36 in the 2nd visit, 28 in the 3rd and 17 in the last one), 26 with headache (21, 17, 11), 10 with sleep disturbances (7, 4, 4), 22with muscle ache (17, 12, 8), 11 with MS motor symptoms exacerbation (9, 9, 7), 15 with urinary frequency (11, 10, 7), 5 with nausea and vomiting (3, 1, 0) and no patient (0, 0, 0) had injection site reaction. One 20-year-old woman had acute reaction (severe seizure, vomiting, headache, fatigue) after first injection, which leads to discontinuation of her treatment. Elevation in liver enzymes was found in 3 cases. Mild anemia developed in 2 cases. There was a significant relationship between urinary frequency and male gender (P < 0.001).

Conclusion: The adverse effects show significant improvement during the course of treatment and there were no serious complications related to treatment with interferon beta 1-a in multiple sclerosis patients. There is not significant relationship between use of interferon beta 1-a and development of depression.

P233

The measurement of antibodies binding to interferon-beta in Iranian multiple sclerosis patients treated with interferon-beta

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Background: Interferon beta (IFN-beta) is the most commonly used treatment in relapsing-remitting multiple sclerosis (MS). The immunogenicity of beta IFNs among Iranian patients under treatment has not yet been determined. In this study, for the first time in Iran, the level of binding anti IFN-beta was compared in patients receiving IFN-beta 1a (Avonex, Biogen) with patients treated with IFN-beta 1b (Betaferon, Berlex).

Methods: Blood sera was obtained from 60 patients treated with Avonex and 18 patients treated with Betaferon. Antibodies binding to IFN-beta were measured using ELISA.

Results: Binding antibodies (Babs) developed in 22 of 60 patients (36 %) receiving Avonex, whereas of 18 patients treated with Betaferon 12 (67 %) became Bab positive. No correlation was found between relapse rates and positive Bab.

Conclusion: This is a preliminary report of an ongoing study. Our results show that Betaferon is more immunogenic that Avonex among Iranian MS patients and this is compatible with prior studies in other countries. Since the effects of IFN-beta on MS disease activity and progression are partial, large sample sizes are required to demonstrate clinical correlates of binding antibodies. Also further study is needed to detect Neutralizing antibodies (Nabs) in Bab positive patients.

Extrapyramidal disorders

P234

Can static posturography help to identify fallers between Parkinson patients? A pilot study

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Introduction: Postural instability and falls reduce quality of life and increase morbidity and mortality of the patients with Parkinson's disease (PD). Recognition of the patients in the higher risk of falling has individual, social and economic consequences. This study is aimed to the specification of postural sway in the progression of PD and to define optimized posturographic measures which could predict future falls in PD.

Subjects and methods: Twelve early stage PD subjects without postural problems, 15 advanced PD patients with the history of falls and 13 age-matched controls participated in the study. Changes in the center of foot pressure (COP) in the anteroposterior (AP) and mediolateral (ML) directions during upright stance while eyes open and closed were measured by means of static posturography. The root mean square (RMS) and the sway path (SP) values from the displacement of the COP were calculated.

Results: Advanced PD patients were significantly more unstable in both directions than patients in early stages and elderly controls, which did not differ. RMS proved to be more pathognomonic than SP in that it is less affected by parkinsonian tremor. Ratios of ML and AP sway showed that patients in advanced stages of PD use distinct strategy of postural stabilisation predilecting for ML instability versus AP postural activity.

Conclusion: General increase of the sway and ML instability in advanced PD patients with the history of falls seem to be special variables, which could contribute to the identification of the the patients with the risk of falling. The ML sway is controlled by hip abductors and adductors, thus physiotherapy should be oriented to improve the strength and elasticity of these muscles. Future research with the prospective design and larger subject numbers is needed to confirm results of our study. Supported by Marie Curie Training Site QLK5-CT-2000-60087.

P235

Parkinsonism and exposure to neuroleptic drugs in residents of an Italian nursing home

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Objective: To estimate the prevalence of parkinsonism both idiopathic or due to exposure to neuroleptics in the residents of an Italian nursing home.

Background: Older people frequently show signs of parkinsonism but information about its prevalence in nursing homes is limited. Despite growing evidence about an increased incidence of parkinsonism due to neuroleptic drugs in the elderly, recent studies have shown that up to half of residents of nursing homes receive them.

Methods: We studied 339 residents of a nursing home located in Northern Italy. The demographic data and the medical history of each patient were recorded. A complete structured neurological examination was performed including the assessment of parkinsonism, depression, cognitive decline and disability. Parkinsonian signs were sorted into four categories of motor signs of parkinsonism: bradykinesia, gait disturbances, rigidity and tremor. Parkinsonism was defined as the presence of two or more parkinsonian-sign categories.

Results: The residents studied, composed of 261 women (77.6 %) and 78 men (22.4 %), had an age between 55 and 107 with an average of 83 (SD 11) years. Seventy-one subjects composed of 47 women (66.2 %) and 24 men (33.8 %) had parkinsonism. The mean age was 80.3 (SD 9.4) years, ranging from 64 to 98 years. In 37 subjects (52.2 %) parkinsonism was diagnosed through this study. The residents affected by parkinsonism were significantly younger than not affected ones ($p < 0.05$). Forty-five among the subjects with parkinsonism (63.4 %) had a cognitive decline, 44 (62 %) psychosis and 44 (62 %) depression. These conditions appeared significantly correlated to parkinsonism ($p < 0.005$). Subjects with parkinsonism appear to have a significantly higher rate of falls with bone fracture ($p < 0.05$). Neuroleptics were used by 36 (50.7 %) people with parkinsonism and 67 (25 %) without parkinsonism. Parkinsonism was found significantly correlated with the use of neuroleptics ($p < 0.005$).

Conclusions: Our results clearly show a high rate of parkinsonism in nursing homes greatly undiagnosed (52.2 %), in agreement with literature. Neuroleptic drugs used in institutionalised elderly are often associated with parkinsonism. Optimising medical and neurological services could help in choosing the suitable treatments for motor and behavioral disturbances, and also in improving the quality of life of many elderly living in institutions.

P236

Improvement of motor function in early Parkinson's disease by safinamide, a new neuroprotectant anticonvulsant

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Safinamide is a new anticonvulsant neuroprotectant that also modulates dopamine metabolism. As a first step in the development of safinamide as an anti-parkinson agent a study was designed to ascertain improvement of motor function in early Parkinson disease. The primary efficacy hypothesis was a significant increase of the number of responders (i. e. patients showing a > 30 % improvement in the UPDRS-III scores) compared to placebo.

In a double blind placebo controlled study 168 patients with early idiopathic Parkinson, were randomly allocated to 3 groups: 2 treatment arms (safinamide 0.5 and 1.0 mg/kg/day) or one placebo. Treatment lasted for 12 weeks. Motor function was evaluated with UPDRS-III and AEs were reported by the patients and monitored by laboratory tests.

The higher tested dose of safinamide (median 70 mg/day, range 40–90) significantly increased the percentage of responders from 21.4 (placebo) to 37.5 % ($P < 0.05$, calculated by logistic regression analysis). Correspondingly the UPDRS-III scores improved at treatment end versus baseline of an average 3.4 % in the placebo group, and 20 % in the higher safinamide. The lower safinamide (median 40 mg/day, range 20–40) group improved by 15.8 % their UPDRS-III scores without reaching significance, with a responders rate of 30.9 %. Incidence of AEs was lower in the safinamide groups compared to placebo. In the subgroup of 101 patients under stable treatment with a single dopamine agonist the degree of improvement was greater (47.5 % of responders, average 30.5 % UPDRS improvement) with safinamide 1.0 mg/kg/day.

In this first clinical study safinamide at the median dose of 70 mg/day (range 40–90) induced a significant improvement in motor performance in early Parkinson. This study suggests also that the beneficial effect is magnified when associated to a dopamine agonist. Based on tolerability equal to placebo, further studies shall explore efficacy at higher doses.

P237

Respiratory function in patients with Parkinson's disease

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Objectives: Respiratory dysfunction in patients with Parkinson's disease (PD) is a complex problem. A number of factors including disease cardinal symptoms, abnormalities of ventilatory control and treatment side effects may be responsible.The purpose of this study was to assess pulmonary function and respiratory muscle force in PD patients in relation to clinical parameters of the disease.

Methods: Fifty seven PD patients were studied. Their mean age was 58.1 ± 11.0 yrs. The cardinal symptoms of the disease and overall disability were evaluated by means of the Unified Parkinson's Disease Rating Scale (UPDRS). Pulmonary function was assessed by flow volume curve spirometry. Respiratory muscle force was measured by the maximal inspiratory (MIP) and expiratory pressure (MEP). Arterial blood gases were also measured

Results: Mean PO_2 and CO_2 levels were normal. Mean percentage predicted vital capacity (FVC) and forced expiratory volume in one second (FEV1) were within normal range (FVC = 82.2 ± 18.7; FEV1 = 89.9 ± 20.1). However abnormal FCV and FEV1 values were observed in 42.1 % and 36 % of PD patients respectively. Mean MIP was below normal levels (41.58 ± 25). Mean MEP was within normal range (58.04 ± 27.43), but in 43.5 % of PD patients it was below normal. PIM and PEM values correlated negatively with bradykinesia and UPDRS scores.

Conclusion: Our findings indicate that although subclinical pulmonary dysfunction is present in a considerable percentage of PD patients, their main respiratory problem arises from disturbances in respiratory muscle force. This should be taken into consideration in the rehabilitation management of PD patients

P238
Postural reactions to neck proprioceptive stimuli are increased in advanced Parkinson's disease
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Introduction: Sensory disturbances are a frequently overlooked symptom of Parkinson's disease (PD). In tasks requiring the judgement of limb position, these patients regularly underestimate the amplitudes of active or passive movements. We studied whether proprioceptive stimuli are also underestimated in situations in which they are essential for fast unconscious postural reactions during stance. This may be an explanation for frequent equilibrium disturbances in the PD population.

Subjects and methods: Bilateral vibration (1 mm, 80 Hz) was applied to the posterior neck muscles of 11 early stage PD subjects, 13 advanced PD patients and 13 healthy control subjects while recording the center of foot pressure displacements in the anteroposterior direction by means of static posturography. The averaged postural responses following the onset of the vibration pulse (duration 3000 ms) were analyzed.

Results: All three groups demonstrated similar pattern of the averaged postural reactions to the onset of vibration. Likewise, there were no intergroup differencies in the latencies of these reactions. However, advanced PD patients' reactions to neck vibration onset were significantly increased in comparison with the other two groups, which did not differ.

Conclusion: Contrary to the characteristically reduced velocity and size of voluntary limb movements in PD, velocity and amplitude of postural reactions as well as the gain of proprioceptive input signals seem to be increased in advanced PD. Supported by Marie Curie Training Site QLK5-CT-2000-60087.

P239
Apomorphine infusion in advanced Parkinson's disease: lessons to be learnt when treatment fails
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Continuous apomorphine infusion has been used for the last 15 years for controlling motor fluctuations in advanced Parkinson's disease. We report a cohort of 17 patients, treated with apomorphine pump over the last 2 years and focus on the 4 patients who subsequently proved completely unsuited to the treatment, despite good motor response and minimal short term side effects. 2 patients had to stop because of lack, or loss, of a supportive partner, and 2 patients with an undisclosed past history of excessive alcohol consumption used escalating doses of apomorphine. Psychological and social factors are important to consider before embarking on apomorphine as a mode of treatment.

P240
Myoclonus-dystonia syndrome associated with psychiatric disorders and findings in the brain perfusion SPECT
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Aim: We present the first Greek family with typical Myoclonus-dystonia syndrome (MDS) including the SPECT findings in one of the two patients examined.

Methods: Five living and two deceased individuals with clinical MDS were identified. Two brothers clinically affected provided a detailed family history, medical history, underwent a neurologic examination, psychiatric evaluation, neurophysiological testing, neuroimaging and SPECT examination.

Results: Brother I: Onset occurred at age 3, with jerky movements of the right lower limb, followed by upper limb involvement. By age 10 the jerky movements had worsened and progressed to the head. Left foot dystonia occurred at age 17. The symptoms were alcohol dependent and improved after the intake of 2–3 units. Stress caused transient worsening of myoclonus. Motor examination revealed myoclonus of the head, left arm, and left leg, left shoulder elevation, and left foot dystonia. The patient was rated as "definite" for both myoclonus and dystonia. Psychiatric history and psychiatric profile were remarkable for major depression and generalized anxiety disorder. Neuropsychological testing found moderate intelligence and cognitive deficits. Electrophysiological tests, EEG and MRI findings were unremarkable. Brain perfusion SPECT revealed bilateral temporal lobe hypoperfusion (more prominent in the left hemisphere).

Brother II: Onset occurred at age 10, with jerky movements of both upper limbs, followed by mild bilateral upper limb dystonia and dystonic tremor. The symptoms were mild until the age of 18 when head and upper limb myoclonus became very prominent. At the same time the patient started suffering panic attacks. The symptoms were alcohol dependent and improved after the intake of 2–3 units. The patient suffered from alcohol abuse.

Motor examination revealed myoclonus of the head, arms, shoulder elevation, and upper limb dystonia. The patient was rated as "definite" for both myoclonus and dystonia. Psychiatric history and psychiatric profile were remarkable for obsessive-compulsive disorder, major depressive disorder, alcohol dependence and panic disorder. Neuropsychological testing found moderate intelligence and cognitive deficits. Electrophysiologic test, EEG and MRI findings were unremarkable. Brain perfusion SPECT was refused.

Conclusion: Cognitive deficits, psychiatric abnormalities and pathological findings in the brain perfusion SPECT occurred in the first Greek family with typical MDS.

P241
Deep brain stimulation in Parkinson's disease: controversies between present electrodes activation theories and historical stimulation approaches (SAFN-SPC theories)
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Introduction: First electric stimulations of the brain with therapeutic aims were performed in the fiftees (septal area). In the decade of '70, some theoric and empiric premises were established. In that epoch, parameters of applied current were such ones that usual principles of electric action could not be considered as principles of brain electric stimulation. Nowadays, high frequency stimulation of the subthalamic nucleus or globus pallidus has proven to be a highly effective treatment for motor fluctuations and dyskinesias in advanced Parkinson's disease. The exact mechanisms of deep brain stimulation will remain a matter of debate. Different studies consider that it is worthwhile considering the position of active contacts with respect to structures located at the interface between the subthalamic nucleus and the subthalamic area (in the case of STN stimulation). So other structures located in the subthalamic area (not only nucleus) have to be considered for the therapeutic effect of DBS, for example the pallidothalamic fiber tracks, fields of Forel and the zona incerta.

Methods: It is assessed the variability of prior studies and experimental trials in pre-evidence levels of historical electric stimulation in the decades of seventies and eighties, by citation tracking. There were encoded methodological variables, publication variables and data concerning summary odds ratios, that depend on inclusion criteria and investigator variables, such evidence of experimental models and confluence of methodological issues.

Results/conclusions: 'Stable pathological condition' (SPC) theory served as a basis for therapeutic electric stimulation in different prototypical studies in such periods: its resolution deserved a necessity of unstability, disorganization of the long-term memory matrix that supported the condition and the activation of a compensatory mechanism. These first potential models were performed with electric stimulations of ventrolateral nucleus, medium center and pulvinar nucleus in thalamus and the diffuse upper brainstem regions and pallidal structures (Obrador, Smirnov). Concepts as stable artificial functional nets (SAFN)have a real similarity with actual theories about boundaries in a wide topographical stimulation in subthalamic area. SAFN is a theoric concept that, by means of simultaneous stimulation with electrodes generates a cybernetic network in brain systems, similar to recent developments in DBS

P242
An unusual presentation of ataxia-telangiectasia
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Ataxia-Telangiectasia (A-T) is an autosomal recessive disease with neurological and immunological manifestations, associated with an increased risk of malignancy. Usually, this condition is diagnosed in childhood with progressive cerebellar atrophy, oculomotor apraxia, choreoathetosis, immunodeficiency and telangiectasias of the conjunctivae starting before the age of 6 years. The gene frequency is between 1 in 100,000 and 1 in 300,000. The condition is fifteen times more common in females than males.

We want to report a 30 year old Algerian gentleman from a non-consanguinous family presented with a 27 year history of a movement disorder. He first developed motor problems after a childhood illness at the age

of 3, these have progressed slowly over the years. There is a strong family history of breast cancer, 2 sisters have breast adenocarcinoma. One affected sister who died at the age of 35 from breast cancer, had also a movement disorder which was more severe than in our patient. His father developed cancer of the prostate in his sixties. On examination he has a mild gait ataxia, normal tonicity and areflexia of the legs. He has mild dystonic and choreiform movements of his head and limbs, but normal oculomotricity and no conjunctival telangiectasia. Diagnosis of A-T type syndrome is aided by the discovery of a raised serum alpha-fetoprotein, abnormal radiation sensitivity of lymphoblasts, immunodeficiency with reduced immunoglobulins or T-cell deficiency and low or absent intra-nuclear serine-protein kinase ATM levels. We will discuss the use of these tests, coupled with karyotyping and ultimately molecular genetic testing which we have used to establish the diagnosis.

In conclusion we would like to present, using videotape footage, a case of 30 year old gentleman with a non specific disorder in whom a family history of breast cancer alerted us to the likely diagnosis.

P243

Persistent Parkinsonism developed during interferon-alpha therapy for chronic hepatitis

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Objective: To analyse a case of persistent parkinsonism developed during interferon-alpha (IFN-alpha) treatment for chronic hepatitis C.

Background: The IFN-alpha has antiviral and antiproliferative properties but its use is limited by frequent neuropsychiatric side effects. Recently chorea with frontal subcortical dementia and parkinsonism were reported even if IFN-alpha is not considered a drug inducing parkinsonism.

Case report: In 1996 a 60-year-old man without family history of brain disorders, was treated for 6 months with IFN-alpha for chronic hepatitis C and, two weeks later, developed mildly slowness, rigidity, rest tremor and clumsy gait that did not resolve after IFN-alpha discontinuation. Two years later rigidity and bradykinesia became severe and the diagnosis of Parkinson's disease was made. TC imaging, thyroid tests, serum tests, EEG and neuropsychological tests were all normal. The patient started levodopa at the daily dose of 300 mg with moderate response. In the following years the parkinsonism worsened and the patient developed motor fluctuations; the daily dose of levodopa was increased to 500 mg and a dopamine agonist was added. Actually he has a severe parkinsonism with moderate response to antiparkinsonian drugs. The brain MRI study, performed in November 2003, shows no abnormalities related to hepatitis C encephalopathy and no signs of idiopathic Parkinson's disease. T2 weighted and FLAIR sequences show sub cortical white matter and deep bilateral multiple hyper intensities probably due to repeated acute interferon-related episodes.

Conclusions: Parkinsonism developed during IFN-alpha therapy might be drug-induced, as IFN-alpha inhibits dopaminergic neuronal activity and reduces striatal dopaminergic levels, with mechanisms not yet clarified. In our case the drug did possibly speed up the clinical manifestation of a degenerative dopaminergic defect. To test this hypothesis other tests have been planned.

P244

Parkinsonian syndrome as a side effect of oral methotraxate intake: case report

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Aim: We describe a 70-year-old woman who developed severe parkinsonism after treatment with oral methotrexate.

Case report: A 70-year-old female with a 10-year history of polyarticular form of chronic tophaceus gout received methotrexate on base of strong clinical evidence of rheumatoid arthritis co-existence. The patient received a total of 25 mg of methotrexate for short term before being admitted to the University Hospital of Patras due to severe methotrexate side effects. Methotrexate treatment was immediately discontinued. 3 weeks later she became less communicative and increasingly passive and disinterested. She complained of slowness, softness of speech and inability to walk or stand unassisted. Neurological examination revealed masked facies, hypophonia, severe lower limb predominant rigidity cogwheel rigidity, and marked bradykinesia with left lateralization. There was no tremor. She had no exposure to neuroleptics or any other dopamine-receptor-blocking agents. There was no history of exposure to heavy metals or toxins. General biochemistry, parathyroid hormone, proteins, tumor markers, were either normal or negative. A head CT scan revealed mild atrophy. CSF assay showed no cells. The treatment with carbidopa-levodopa, with dose increases up to 750 mg of levodopa/day was initiated, resulting the improvement of parkinsonism within 10 days. 2 months later she was re-admitted for further investigation. Neurological examination revealed that she was fully oriented and demonstrated no evidence of cognitive dysfunction. However, she had an expressionless facies and was still slightly hypophonic. Mild bradykinesia and rigidity with left side predominance were also evident. She also had mild axial rigidity, a festinating gait with little arm swing, turn and start hesitation, and severe postural instability. Both resting and action tremor was absent. Levodopa was then discontinued without worsening of parkinsonism. A brain MRI revealed ischemic periventricular lesions. EEG revealed non-specific intermittent abnormalities scattered over the frontal parasagital areas. [123I]-B-CIT SPET was normal.

Results: Parkinsonism improved with levodopa and signs improved over months despite stable dosing of levodopa and eventual withdrawal of the methotrexate.

Conclusion: We report the only patient with chemotherapy induced parkinsonism not suffering from neoplastic disease and the second patient in the literature with methotrexate induced parkinsonism.

Epilepsy

P245

Care for women with epilepsy: documentation in case notes and patient perspective

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Treatment with antiepileptic drugs (AED) has special implications for women's health. Several international guidelines for management of women with epilepsy (WWE) have been developed since 1989. The first review of the subject in Norwegian was published in 1999. When we evaluated case notes on management of 141 WWE of childbearing age in our department in 2002, we found that published guidelines had had disappointingly little effect on clinical practice.

Approximately 180 WWE aged 16 to 42 years were treated with AED in our department between November 1st, 1999 and February 29th, 2004. Documentation reflecting adherence to guidelines was abstracted retrospectively from electronic medical records. A 28-month period with "passive dissemination" of guidelines was compared with two consecutive 12-month periods during which active strategies for implementation were applied. Data include documentation in case notes of information given about contraception, pregnancy-related issues, need for folic acid supplementation, and bone-health. Detailed data was collected on follow-up during pregnancy. Serum folic acid measurements were recorded if available. A questionnaire was mailed to 157 patients in February 2003, asking about the information they had received on the above-mentioned issues.

Judged by documentation in case notes, recommendations according to published guidelines were only given to a minority of patients. There was no marked improvement in the first 12-month period after focusing on care for WWE, though notes on pregnant WWE had become more detailed. Data from the second 12-month period will be available after March 1st, 2004. Patients who responded to the questionnaire (n = 112, 71 %) had received information on interaction between AED and oral contraceptives (41 %), the need to plan pregnancy (66 %) and to supplement folic acid (52 %) more often than was documented in case notes. Information on bone health had been given to only 5 % of patients.Folic acid values below the normal range (< 5 nmol/l) were measured in 11 of 61 of patients (18 %) using an AED known to interact with folic acid metabolism.

Conclusion: Implementation of guidelines is a demanding process. Efforts to change practice patterns will have to continue.

P246

Influence of LY 300164 (Talampanel) – a novel antiepileptic drug, on the anticonvulsant activity of conventional antiepileptics: an isobolographic analysis

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LY 300164 (Talampanel) is a newer antiepileptic drug which acts through the inhibition of AMPA/kainite receptors. In initial clinical studies, it demonstrates broad spectrum of anticonvulsant action.

The objective of this study was to isobolographically evaluate the in-

teractions between Talampanel and a number of antiepileptic drugs against maximal electroshock (MES)-induced convulsions in mice. Electroconvulsions were produced by means of an alternating current (ear-clip electrodes, 0.2-s stimulus duration, tonic hindlimb extension taken as the endpoint). The isobolographic analysis distinguishes 3 most important types of interactions, among them the most accepted are: pure additivity, supra-additivity and sub-additivity. The protective activity of two-drug mixture, applied in 3 fixed dose ratio combinations, was estimated and expressed as the ED50 values (dose of antiepileptic drug protecting 50 % of animals) of these drugs against MES-induced seizures in mice. Moreover, the adverse effects were determined in the chimney test and passive avoidance task in mice. Interactions between LY 300164 and carbamazepine, valproate, diphenylhydantoin or phenobarbital caused pure additivity, in both MES and chimney tests. All combinations of LY 300164 with studied antiepileptics induced no adverse effects, evaluated in the passive avoidance task. Also, pharmacokinetic interactions could be excluded, because there were no changes in plasma concentrations of these antiepileptics. Finally, the isobolographic analysis revealed that LY 300164 combined with conventional antiepileptics might result in positive (additive) interactions, in clinical practice.

P247
The efficacy and side effects of Topiramate on refractory epilepsy in infants and young children, a multicentre clinical trial
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Objectives: This study was conducted to assess the efficacy and safety of topiramate (TPM) in refractory epilepsies in infants and young children.

Methods: A prospective clinical trial was performed in three tertiary care hospitals on 47 children aged 6–60 months with a diagnosis of refractory epilepsy. Topiramate was added to at least two or more other baseline antiepileptic drugs. The efficacy was rated according to seizure type, frequency and duration.

Results: Children with refractory epilepsy were classified according to their clinical and neurophysiological profile into infantile spasm 9 (19 %), lennox-gastaut syndrome 25 (53 %) and other epilepsies 13 (28 %). Topiramate was initiated as an add on therapy at a daily dose of 1 mg/kg/day for two weeks, followed by a 2-week titration at increments of 1–3 mg/kg/day, up to a maximum of 10 mg/kg/day. After 6 months of treatment, 9 of the children (19 %) had 100 % fewer seizures, 19 (40 %) had a more than 50 % seizure reduction and 5 (11 %) achieved 25 % reduction in their seizure frequency. Of the remaining 14 children (30 %), in 9 children (19 %) the seizure frequency remains unchanged and in the last 5 patients (11 %), there is worsening in the seizure frequency. Topiramate appeared to be equally effective in infantile spasm, lennox-gastaut syndrome and children with other types of epileptic syndrome as the percentage of those achieved reduction in seizure frequency were nearly similar. Mild to moderate adverse effects were present in 25 (53 %) of children and mostly represent somnolence, anorexia and nervousness. One of the children develops hypothyroidism.

Conclusion: Topiramate was effective and relatively safe as add on therapy in infants and young children with refractory epilepsy including infantile spasm, lennox-gastaut syndrome and other epilepsies. The adverse side effect was generally mild or moderate.

P248
Psychosis associated with topiramate
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Purpose: To investigate the frequency and risk factors of psychosis related to topiramate use and its risk factors.

Methods: We reviewed the files of all 95 epileptic patients who used topiramate as add on or monotherapy.

Results: Three patients developed psychosis during topiramte treatment, which subsided after its discontinuation. The following feature noticed: 1). All were young females aged 18–25 with childhood onset epilepsy. 2). All had intractable temporal lobe complex partial seizures. 3). All had topiramate as add on therapy. 4). Duration of topiramate therapy ranged from 2–4 months with medium dose of 150 mg/day. 5). Mental subnormality noticed in 2 patients, one mild another moderate with history of abnormal behavior. 6). Agitation, restlessness, pacing, physical and verbal aggressiveness, spitting, delusional ideas were common features for all. 7). All needed antipsychotic drugs for few weeks.

Conclusion: Psychosis associated with topiramate is rare, but real risk in young females with childhood onset of intractable temporal lobe epilepsy within 4 months of its use. The risk is higher on those with mental subnormality.

P249
Was epilepsy already known in the Old Kingdom?
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The Edwin Smith Papyrus deals with neurotraumatology of brain and spine and is believed to be written about 1700 BC. It is likely to be only a copy of a much older work dating back about 2500 BC, thus the period the great pyramid was built at Gizeh.

Case 20 is most intriguing as it describes trauma of the temporal region.

Case Twenty: "Title: Instructions concerning a wound in his temple, penetrating to the bone, (and) perforating his temporal bone.

Examination: If thou examinest a man having a wound in his temple, penetrating to the bone, (and) perforating his temporal bone, while his two eyes are blood shot, he discharges blood from both his nostrils, and a little drops; if thou puttest thy fingers on the mouth of that wound (and) he shudder exceedingly; if thou ask of him concerning his malady and he speak not to thee; while copious tears fall from both his eyes, so that he thrusts his hand often to his face that he may wipe both his eyes with the back of his hand as a child does, and knows not that he does so …"

Intriguing is the presence of copious tears. In no other case this phenomenon is mentioned. This case is strikingly similar to the clinical presentation of dacrystic epilepsy. Moreover, it gives a sound explanation for the unexpected presence of weeping in this case. Other signs consist of trunk antepulsion, focal motor convulsions, head deviation, confusion and retrograde amnesia. In this ancient case the unvoluntary and uncontrolled (the patient doesn't know he is moving his hand repeatedly tot his face) movements of one hand with the back of his hand are clearly a dynamic sign and might represent focal motoric convulsions. It also resembles with the nose-wiping automatism, seen in the post-ictal phase of temporal lobe epilepsy. Longterm post-ictal aphasia originates in the language-dominant hemisphere and the nose-wiping is nearly always seen in the ipsilateral hand, so this neurotrauma did apparently affect the Broca area.

On the coincidence of all clinical features, revealed by an on-the-field specialist of the Old Kingdom, we can conclude that this case probably gives the first clinical description of a patient suffering from a post-ictal phase with aphasia and motor automatisms due to a traumatic lesion of the speech-dominant temporal lobe.

P250
Clinical experience with diazepam rectal gel in adult patient with mental retardation and intractable epilepsy
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Introduction: Safety and efficacy of diazepam rectal gel (DRG) has been established in clinical practice especially in children. This study examine its role among adult patients with mental retardation and intractable epilepsy.

Methods: Retrospective study, charts of adult patients who used DRG was reviewed. Data collected about patient diagnosis, efficacy and side effect with DRG use among these patients.

Results: 12 patients were found, 5 male and 7 females, age ranged from 16–30 years (mean: 19 years). All were mentally retarded with intractable seizures since childhood. Seven had generalized seizures while the other four had complex partial seizures with secondary generalization. All patients used to come frequently to emergency department (ED) (mean 0.5/month). DRG in doses of 5–20 mg (mean 10 mg) was effective in stopping prolonged seizure or repeated seizures in 90 % of the occasion of its use within 10 minutes. ED visiting reduced to 0.1/month. No side effects reported apart from somnolence in 50 % of patients.

Conclusion: DRG is effective and well tolerated in this group of adult patients. It can be given by non-medical care giver and it leads to fewer ED visiting, improve control and quality of life for patient and their caregivers.

P251
Epileptic seizures and visual hallucinations caused by levofloxacin: a case report
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We report the induction of neurological symptoms in a female treated with levofloxacin because of an urosepsis.

Case report: A 63 year old female is treated with claritromycin, because of fever and chills due to an urosepsis. Since she does not recover, levofloxacin is started on admission to our regional general hospital.

On the fourth day of antibiotic therapy, the patient develops dysphasia and visual hallucinations. She collapses on the toilet: after a hypertonic phase, she develops clonic jerks, witnessed by her husband.

Fenytoin is started and patient is transferred to the intensive care unit. Soon after admission here, she develops a second generalized tonic-clonic seizure, which can be resolved by administration of diazepam intravenously.

Laboratory work up: Spinal fluid examination, a broad serological investigation and brain Computed Tomography are normal.

Magnetic resonance imaging of the brain shows only some aspecific punctiform lesions with enhanced signal on FLAIR, there are no arguments for an encephalitis nor septic emboli nor tumour.

Outcome: Levofloxacin is withdrawn and replaced by amoxicillineclavulinic acid.

As patient showed ion disturbances (hyponatremia) (allthough already recovered at the day the seizures occurred) the antihypertensive medication was changed.

Patient recovers well and develops no seizures in the follow up period of six months. Fenytoine-therapy can succesfully be withdrawn.

Discussion: We report a case of induction of visual hallucinations and tonic-clonic epilepsy four days after starting levofloxacin-treatment for an urosepsis. In the sparse literature high risk factors include old age and renal failure with concomittant ion disturbances. Of all fluoroquinolones, levofloxacin is supposed to be the least at risk, although since then another two elderly patients developed hallucinations and/or seizures after levofloxacin administration at our regional hospital.

P252
Epilepsy and cerebrovascular diseases
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Objective: To evaluate the incidence in cerebrovascular disease (CVD) of the epilepsy (E.), the crisis type, the EEG alterations, the CT brain and NMR cerebral lesions and the risk factors (R. F.) for CVD and for E. and their correlations.

Methods: We evaluated 1360 pz (756 males -M- and 604 females -F-) patients (pz) age range 28 to 86 years (mean age 64.2 anni) admitted in our Neurologic Department in the last 5 years for cerebrovascular disease (CVD) and divided them in two groups: 1) RIA/minor strokes and strokes: 890 pz (522 M 368 F) age range 28 to 70 years (mean age 58.8). 2) Chronic cerebrovascular disease (CCVD): 470 pz (234 M and 236 F) age range 58 to 86 years (mean age 69.6 years).

Results: We observe: 108 pz (8 %) with epileptic crisis (E. C.) (64 M, 59.25 % and 44 F, 40.75 %). In the 1° group we observed E in 88 pz (10 %). In 8 pz the E. C. preceded the ischemic event from 1 to 3 monthes ("premonitoring" crisis), in 65 pz E. C. were contemporary and in 15 pz were successive from 1 to 6 monthes ("tardive" crisis). In the CCVD group the E. C. appeared in 20 pz (4.2 %). In the 1° group the E. C. were with focal onset in 56 pz (72 %), focal onset with successive generalitation in 8 pz and generalizated in 24 pz. In the CCVD the E. C. were with focal onset in 4 pz, with successive generalization in 2 pz and the generalizated E. C. in 14 pz. (70 %). The intercritic EEG was normal in both groups in 33 pz (30.5 %) showing diffuse slow alterations in 50 pz (46.4 %) and slow focal alterations in 25 pz (23.1 %). The CT brain scan and NMR disclosed cerebral focal lesions according to clinical signs in 81/108 pz (75 %) with cortical localization in 75/81 pz (92.6 %) and with prevalent involvement of the cerebral territory of the middle cerebral artery in 50/81 pz (61.7 %). The R. F. were: in the 1° group familiarity, hypertension, systemic atherosclerosis; in the CCVD group also atrial fibrillation and smoke, in both groups head injuries and the alcoholic abuse.

Conclusions: The incidence of E. C. in our pz, according with literature data, is 8 %. E. C. may precede the stroke with a clinical meaning as a TIA. E. C. are more frequent in the 1° group; instead in 2° group E. C. are mostly generalizated. The E. C. are mostly with a parzial onset. The cerebral lesions are focal and mostly cortical. Last we didn't observe significant differences between R. F. factors for CVD with E. C. compared with the pz without E. C.

Dementia/Higher function disorders

P253
Quantitative EEG recording Lewy body dementia, Parkinson's disease with dementia and Alzheimer's disease
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Objective: Quantitative EEG(QEEG) recordings with abnormal dominant frequency variability, mean frequency, low frequency activities have been described in Lewy Body Disease (LBD), separating LBD from Alzheimer's Disease (AD) patients. The main hypothesis is that QEEG findings in Parkinson's Disease with dementia (PdD) might help to differentiate LBD phenotypes, thus allowing a classification of PDD akin to LBD or to AD

Background: 10–25 % patients with dementia are affected by LBD and 25–40 % of patients with Parkinson's Disease are affected also by dementia (PPD). Consensus criteria have been developed for LBD, while there is not yet a consensus on the hypothesis that PDD is akin to LBD.

Methods: QEEG was recorded with 32 channel Neuroscan Synamps system measuring mean dominant frequency, dominant frequency variability, power spectra frequency amplitudes, longitudinal and traversal coherence. 20 patients affected by PPD, 20 patients affected by LBD, 20 patients affected by Ad were selected according to consensus criteria, groups were matched by age, sex, and education. MMSE, Mattis Dementia Rating scale (CDR), Neuropsychiatric Inventory (NPI), ADAS-cog. and QEEG recordings (performed on 90 epochs of 2 seconds) were obtained in all patients.

Results: MMSE and DRS sores were similar in the three groups of patients. UPDRS were significantly higher in PDD patients NPI scores showed significant predominance of hallucinations, apathy and sleep disturbances in LBD. QEEG showed that the comparison between LBD and PDD was not significant, the comparison AD-PDD was significant for dominant frequency variability ($p < 0.001$). The pattern of QEEG abnormality consisting of dominant frequency variability (> 2.2 Hz) reduced coherence and low frequency activity was observed in 90 % (18) of LBD, 45 % (9) of PDD, 15 % (3) of AD patients. The QEEG pattern in PDD patients was correlated to the presence of hallucinations an sleep disturbances but no with CDR, MMSE, ADAS-cog.

Conclusion: In PDD a QEEG pattern of abnormality similar to the pattern observed in LBD is found in 50 % of patients. The finding suggests that two different phenotypes of dementia can be distinguished in PDD.

P254
Dementia with Lewy bodies: a Voxel based morphometry and diffusion tensor imaging study in vivo
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Demetia with Lewy bodies (DLB) is the second most diffuse form of dementia after Alzheimer's disease. Conventional magnetic resonance (MR) imaging studies reported conflicting results assessing neuro-radiological features of DLB. Aim of the present study was to assess the macro- and microscopic tissue damage in DLB using voxel based morphometry (VBM) and Diffusion Tensor Imaging (DTI).

Eleven patients with DLB and 9 sex- and age-matched healthy subjects were studied using MR, obtaining dual-echo, magnetization-prepared 3D-T1 weighted (MPrage) and DTI scans. Subjects with more than 4 T2 hyperintense MR lesions were excluded. All processing was done in SPM2 (www.fil.ion.ucl.ac.uk/spm). MPrage images underwent VBM. The mean diffusivity (MD) and fractional anisotropy (FA) maps were derived from the diffusion tensor, normalized to a template, and compared using SPM. Comparing patients with DLB to controls, VBM analysis on MPrage images showed regional grey matter (GM) volume loss in the insula, in the frontal and temporal lobe bilaterally, and in the left parietal lobe. Statistically significant increases of MD in the patients were found in the same anatomical regions of GM volume loss and additionally in the bilateral orbitofrontal areas and in the right uncus. Decreased values of FA were found bilaterally in the pre-central and post-central gyrus and in the left superior frontal gyrus of the patients compared to controls.

Although most of the areas with altered MD or FA were also associated to GM volume loss, some additional regions only characterized by DTI abnormalities were detected, suggesting the potential of DTI to assess tissue damage in its early stages. Although little is known about the neuro-physiological functions of the insula, its bilateral involvement might contribute to determine the cognitive impairment in DLB. Medial temporal lobes resulted relatively preserved in the VBM analysis, consistently with the observation that memory is typically mildly impaired in DLB at the early stages. Interestingly, areas of increased MD were detected in the right uncus, whose involvement might account for the typical visual hallucinations in DLB. Finally, the microscopic involvement of sensory and motor areas might reveal a high sensitivity of FA measures detecting sub-clinical abnormalities in the early stages of the disease.

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Memory improvement after repetitive transcranial magnetic stimulation (rTMS) in elders with cognitive impairment

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Introduction: Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that modulates cortical excitability. Though the mechanisms are not yet well understood, a few studies are now emerging indicating that rTMS might transiently improve cognitive functions such as short-term memory (1), reasoning (2) and picture naming (3).

Objective: To investigate the putative positive effects of a single session of high frequency rTMS on memory performance in subjects with cognitive impairment.

Subjects: Twenty-nine subjects with memory impairment and a score of 0.5 in the Clinical Dementia Rating Scale (CDR) (4). Methods: Subjects were administered an encoding memory task before and after rTMS consisting on learning 10 face-name pairs. Free recall of names and recognition were assessed once the subjects had completed the learning task. Subjects were given two equivalent counter-balanced memory tasks before and after rTMS to avoid learning effects. Individuals were randomly separated into two groups: an active rTMS ($N = 19$) and a sham rTMS ($N = 10$). After the first memory assessment (base-line), all subjects received either sham or active rTMS (MAGSTIM SUPER®) using a double-cone coil. The intensity of TMS pulses was set at 80 % of motor threshold and the frequency at 5 Hz. Ten rTMS trains lasting 10 s each were delivered during a 5-minute period. Inter-train interval was 20 s. TMS coil was positioned over the vertex in all patients, but in the sham stimulation group the coil was positioned tangentially over the scalp. Statistical analysis: Memory performance before and after TMS was compared using two-way repeated measures ANOVA, being the intra-factor 'memory performance (free recall and recognition)' and the inter-factor 'real vs. sham TMS'.

Results: Main effects of 'memory' ($F = 0.11$; $p < 0.75$) and 'real vs. sham' ($F = 0.05$, $p < 0.83$) factors were not significant. However, there was an interaction between the two factors ($F = 5.307$, $p = 0.029$). Post-hoc analyses revealed that only patients receiving real rTMS improved in recognition memory after the stimulation ($t = 2.334$, $p < 0.031$).

Conclusions: Present results suggest a potential role of rTMS in facilitating declarative memory among individuals with memory impairment.

P256

Expression of metabotropic glutamate receptors (mGluR) and functional consequences of their activation in T-lymphocytes from Alzheimer patients

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The progressive cognitive deterioration in Alzheimer disease (AD) has been associated to a hypoactivity of glutamatergic pathways in the hippocampus and the neocortex. This hypothesis is mainly based on the involvement of glutamate in long-term potentiation and thus learning and memory, through the activation of its ionotropic receptors. Recently however, metabotropic glutamate receptors (mGluR) have been recognized as important modulators of glutamatergic neurotransmission. Based on the finding that these receptors are expressed on human T-lymphocytes we investigated their expression and function in AD patients.

Fifteen patients with probable AD, and an equal number of age-matched, non-demented individuals were included in the study. T-lymphocytes were separated from peripheral blood through ficoll gradient centrifugation and total RNA was isolated. Specific primers for mGluR1, mGluR2, mGluR3 and mGluR8 were used for semi-quantitative PCR, with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as reference. Whole-cell patch-clamp recordings were performed on single T-lymphocytes to assess modulation of Kv1.3 channels by extracellular glutamate.

Reverse transcription PCR on peripheral T-lymphocytes demonstrated that these cells express mRNA for mGluR receptor subtypes 1, 2, 3 and 8. There was no significant difference in the expression levels of these receptors between AD patients and age-matched controls. Activation and inactivation gating of Kv1.3 channels in T-lymphocytes from control individuals is shifted to more negative potentials by –15 mV and –10 mV respectively, in the presence of glutamate concentrations similar to physiological plasma levels (10 μM). This effect is mediated through cognate metabotropic receptor activation. Interestingly, when T-cells from AD patients were used under the same experimental conditions, the inactivation gating properties of the channel were only slightly affected (–4 mV). This indicates that although mGluRs are normally expressed on cells of AD patients, the intracellular signaling pathways triggered by their activation are probably impaired.

Our results demonstrate that AD is associated with important abnormalities in mGluR-mediated signaling. This impairment does not seem to result from a decrease in the expression levels of the receptors but rather suggests a dysfunction in one or more components of the intracellular pathways that are linked to their activation.

P257

Alcohol intake affects cognitive decline

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Background: In one hand, mild to moderate alcohol intake, defined as one to three glasses per days, is associated with lower mortality, reduced risk of coronary heart disease and possible protection against age-related cognitive decline and neurodegenerative disease, as found by several large-scale population based studies. In the other hand, alcohol intake is a risk factor for cerebral haemorrhage and vascular dementia. In our knowledge, there is no data on the effect of alcohol intake on the evolution of cognitive decline.

Aim: To study the influence of alcohol intake on Mini Mental State (MMS) decline in Alzheimer's disease (AD), mixed dementia (MD) and vascular dementia (VaD).

Method: The cohort was composed of 434 AD, 104 MD and 80 VaD. Patients came for a first consultation at the Lille Memory Clinic between 1998 and 2001. They received at least two MMS examinations at 12 months or more interval. The subjects were classified as no drinkers, moderate drinkers (1 to 3 glasses per days) and heavy drinkers (more than 3 glasses per days).

Results: We have information about alcohol intake for 228 AD, 95 MD and 51 VaD. 62 % of patients of the whole population was no drinkers, 26 % moderate drinkers and 12 % heavy drinkers and there was no significantly difference between the different dementias. Women were significantly more represented in each group of drinkers. Age at onset was 74 years (±8.1). MMS at first visit was 20.8 points (±5.3). The mean follow-up was 2.9 years (±1.9). MMS annual decline adjusted for age, sex, education and MMS at first visit was 1.34 points (±3). Alcohol intake significantly accelerated cognitive decline in VaD (OR = 4.43 (1, 05–18, 8)), whereas it did not influence significantly the progression of cognitive decline in AD and MD.

Conclusion: Alcohol intake seems to be harmful on the cognitive decline in VaD.

P258

The pattern of cognitive performance in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

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Background and Purpose: Subcortical ischemic vascular lesions which are intimately related to small vessel disease (SVD) are a major cause of dementia. CADASIL is a monogenic form of SVD due to mutations in the Notch3 gene. In the course of the disease, patients almost invariably develop cognitive deficits eventually leading to vascular dementia.

Methods: To analyze the characteristics of cognitive impairment in CADASIL, we conducted a prospective study in 65 mutation carriers (mean age 47.3 + 10.5 years) and 30 controls, matched with respect to educational level and age (47.2 + 14 years). All subjects underwent a series of neuropsychological tests, including global cognitive scores (Mattis Dementia Rating Scale [MDRS], Mini-Mental State Examination), the VaDAS-cog battery as well as specific tests on executive function and attention with

measures of processing speed and error monitoring. Subgroups were defined according to age and MDRS scores.

Results: We found that CADASIL patients had pronounced deficits in attention and executive performance with particular impairments of timed measures (Stroop II and III, Trail Making) and the number of correct responses (symbol digit and digit cancellation tasks) (all $p < 0.002$). Measures of error monitoring (Stroop III, Trail Making, Symbol digit, Maze) were also affected but to a lesser extent (all $p < 0.05$). Prominent deficits were further present on verbal fluency and ideational praxis. Recall, orientation, and receptive language skills were largely unaffected. Subgroup analysis revealed a similar profile in subjects aged below 45 years. Subgroup analysis further revealed a similar profile in individuals with early impairment of global cognitive performance (MDRS score > 123) and in those with marked cognitive deficits (MDRS score < 122).

Conclusions: Our findings highlight processing speed as the most substantial area of cognitive impairment in CADASIL, with less pronounced yet significant deficits of other aspects of executive performance and attention. This profile of cognitive impairment enables the construction of targeted test batteries for clinical trials. We hypothesize, that the profile of dysfunction in CADASIL described here represents the core of the cognitive syndrome associated with SVD and subcortical ischemic vascular lesions.

P259

Modulation of interleukin 18 by treatment with acetylcholinesterase inhibitors in Alzheimer patients

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There is strong evidence that inflammatory mechanisms are involved in the pathogenesis of Alzheimer's disease (AD), contributing to neurodegeneration. Increased levels of circulating proinflammatory cytokines have been reported in AD patients. In addition epidemiologic studies suggest that anti-inflammatory treatment provides some protection from AD. Interleukin(IL) 18 is now recognized as an important regulator of innate and acquired immune responses. Apart from the known synergy of IL18 with IL12 to drive T helper (Th) 1 responses, recent reports show that IL18 can also induce IL4 production and thus facilitate the differentiation of Th2 cells. To our knowledge IL18 has never been studied in AD.

Aim of our study was to investigate the effect of therapy on IL18 release. Twenty-one AD patients were studied (9 M, 12 F, mean age 74.5 ± 7) before (T0 AD) and during treatment (T1 AD) with an acetylcholinesterase inhibitor (AChEI) to assess IL 18 production by peripheral blood mononuclear cells (PBMC) cultures in AD patients. Ten healthy controls (HC), sex and age matched, served as a control group. Cytokine concentration in culture supernatants was assessed using commercially available ELISA kits. Statistical analysis was performed using two-sample paired Student's t-test. Before therapy we found similar levels of IL18 between T0 AD and HC, both in basal conditions (T0 AD 24.99 ± 5.33 pg/ml vs HC 23.32 ± 8.27 pg/ml; n. s.) and after PHA stimulation (T0 AD 49.29 ± 6.99 pg/ml vs HC 26.7 ± 7.06 pg/ml; n. s.). T1 AD showed significantly higher levels of IL18 than pre-therapy, both in basal conditions (T1 AD 63.32 ± 5.33 pg/ml vs T0 AD; $p = 0.02$) and after PHA (T1 AD 175.41 ± 16.42 pg/ml vs T0 AD; $p = 0.01$). Interestingly our data show that AChEI treatment significantly increases IL18 production in AD patients in basal conditions and after PHA stimulation. IL18 is involved in cytokine regulation and is able to polarize the immune response. Furthermore IL18 appears to play a direct immunomodulatory role in synaptic plasticity. Numerous studies have suggested that AChEI, the most successful treatment for AD, given orally to AD patients act as disease-modifying agents, may facilitate the memory processes and exert neuroprotective effects.

Our results suggest that AchEI might exert part of their beneficial effects through the modulation of the cytokine network.

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Cathepsin D expression and processing in fibroblasts from Alzheimer's disease patients

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Previous studies established that the population of neurons that frequently degenerate in Alzheimer's Disease (AD) exhibit robust up-regulation of the lysosomal system. Cathepsin D is the main lysosomal aspartic protease and has previously been suggested to play a role in AD. We investigated the expression of cathepsin D at peripheral level, using as cell model skin fibroblasts from AD patients affected either by sporadic or familial forms of the disease, including pre-symptomatic individuals. By enzymatic assays, we observed a down-regulation of cathepsin D in 50 % of AD patients examined. These decreased levels were consequent to regulation at transcriptional level, as we observed by RT-PCR. Moreover, we observed by Western Blotting (WB) that treatment with amyloid beta1-42 peptide at nanomolar concentrations induced an alteration of cathepsin D maturation, increasing the amount of unprocessed forms. It is worth mentioning that this alteration can also be induced either by oxidative stress (e. g. by H_2O_2 treatment), thus indicating that high levels of amyloid beta1-42 peptide could induce oxidative stress in primary fibroblasts.

Trasformation by oncogenic ras alters the processing and subcellular localization of cathepsin D. We revealed a parallel increase of ras transcript and ras protein in AD fibroblasts by WB. To investigate the role of ras in the expression of cathepsin D, we over-expressed in primary fibroblasts a ras mutant (rasV12) known to induce premature senescence. Primary fibroblasts infection with a retrovirus encoding a costitutively active ras decreased levels of the protease cathepsin D, without affecting its processing. In addition, we observed that expression of a different aspartic protease, presenilin 1 (PS1), whose proteolytic cut is widely recognised as responsible of the gamma-secretase cleavage of APP, is up-regulated following ras expression, thus indicating that APP processing is modulated by ras activation.

These results provide evidence that lysosomal dysfunction is not confined to CNS. In addition, enzyme changes, both in terms of activity and of processing, might be related to the pathogenesis of the disease and also be considered a potential peripheral diagnostic marker.

Cathepsin D promoter elements responsive to ras activation, the effect of different ras mutants and MAPKs inhibitors on APP processing and on cathepsin D expression are currently under investigation.

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Do white matter hyperintensities and lacunes of basal ganglia affect progression of cognitve decline in Alzheimer's disease?

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Background: Cerebral white matter lesions (WML) and lacunes seen on MRI scans are associated with age, vascular risk factors and cognitive decline in the elderly. WLM prevalence is increased in Alzheimer's disease (AD). Cerebro-vascular disease may play an important role in determining the presence and severity of the clinical symptoms of AD but the relationship between WML, lacunes and cognitive decline in AD remains unclear.

Aim: To study the impact of WML and lacunes on Mini Mental State (MMS) decline in AD.

Methods: 248 consecutive AD patients with or without MRI cerebrovascular lesions were included after their first consultation at the Lille Memory Clinic from 1998 to 2000. They received at least two MMS examinations at 12 months or more interval. Hypersignals on proton density and T2-weighted MRI scans were assessed using the Scheltens' half-quantitative rating scale (1993).

Results: 195 patients were diagnosed with AD and 53 with AD and severe cerebro-vascular lesions, i. e. mixed dementia (MD). More women were found in the AD group ($p = 0.038$). Educational level was significantly higher in MD group ($p = 0.0008$) as were vascular risk factors. Age at onset was 69.6 years (±9.2), without significant difference between the two groups. There was no difference for the delay at inclusion. MMS at first visit was 20.8 points (±4.94). The mean follow-up was 2.9 years (±1.3). MMS annual decline adjusted for age, sex, education and MMS at first visit did not differ significantly between AD or MD patients and was 1.6 points (±3). A higher MMS annual decline was associated with alcohol intake, while smoking had protecting effects. No significant relationship was found between MMS annual decline and sub-cortical hypersignals on MRI in the AD group. In the MD group, only hypersignals in basal ganglia were significantly associated with a higher cognitive decline.

Conclusion: Sub-cortical cerebro-vascular lesions do not seem to affect cognitive decline in AD patients, while basal ganglia lacunes increase MMS decline in MD.

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Diagnosis and management of behavioural disorders in an acute memory unit
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Behavioural disorders are frequent during the course of dementia. They may be consecutive to the pathological process of dementia or to an additional somatic pathology. When the occurrence is acute, behavioural disorders are often related to delirium, the cause of which must be found, instead of the systematic prescription of psychotropic drugs.

The aim of the study was to review the causes of acute behavioural disorders found in consecutive demented patients, who entered an acute care memory unit (ACMU).

Method: the ACMU is a closed and secured unit of two beds located in one of the neurological wards. It is dedicated to demented patients with agitation. At entry, a complete somatic examination, a Mini-Mental Status Examination (MMSE) and a standardised work-up including blood and urine biology, brain imaging, ECG and abdominal X ray are performed.

Results: 64 consecutive patients hospitalised between 2000 and 2002 in the ACMU were included. The mean MMSE at entry was 7.7 points. The mean duration of hospitalisation was 13.3 days. At least one organic coexisting pathology was found in 100% of the patients. Urinary infection (25%), neuroleptic prescription (15.6%), pneumonia (14%), dishydratation (11%) and seizures (8%) were the most frequent pathologies. Fractures, subdural haematoma, pulmonary embolism, and cancers were diagnosed also. Behaviour usually improved with the management of the co-occurring disease.

In conclusion, various somatic and iatrogenic disorders may be the cause of behavioural disorders. A standardised work-up is useful in the management of acute behavioural disorders in demented patients.

P263
Brain tissue damage in dementia with Lewy bodies: a diffusion tensor MRI study in vivo
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Demetia with Lewy bodies (DLB) represents the second most diffuse form of dementia after Alzheimer's disease. However, a relevant percentage of misdiagnoses is still reported. Conventional magnetic resonance (MR) imaging studies reported conflicting results assessing neuro-radiological features of DLB. SPECT studies reported diffuse cortical hypoperfusion particularly involving the occipital lobe. Aim of the present study was to assess in vivo the presence and the distribution of microscopic brain tissue damage from patients with DLB using Diffusion Tensor Imaging (DTI) assessed by Region of Interest (ROI) analysis. Eleven patients with DLB and 9 sex- and age-matched healthy subjects were studied using MR, obtaining dual-echo and DTI scans. After estimation of the diffusion tensor, mean diffusivity (MD) and fractional anysotropy (FA) maps were derived for every voxel. Subjects with more than 4 T2 hyperintense MR lesions were excluded. Several anatomical white matter (WM) ROIs were selected, and the corrispondent MD and FA regional quantities were measured from every subject.

Patients with DLB showed statistically significant, after Bonferroni's correction ($p < 0.005$) higher MD values in the parietal lobes, in the caudate nucleus, in the corpus callosum and pericallosal areas. FA was significantly decreased ($p < 0.005$) in the parietal and occipital lobes, in the pericallosal areas and in the caudate nucleus when compared to controls. In other areas, MD increases (frontal and occipital lobes, putamen) and FA decreases (frontal and temporal lobes and corpus callosum) were close to significance (p ranging from 0.008 to 0.05). The location of WM microstructural abnormalities in regions (corpus callosum and pericallosal areas) with a high prevalence of fibre tracts connecting cortical associative areas, suggests the presence of Wallerian degeneration secondary to neuronal loss in the associative cortex. Conversely, the less prominent involvement of temporal and frontal lobe WM is consistent with a relative preservation in global neuro-psychological and memory functions in the early stage of DLB. The selective involvement of the occipital lobe suggests a possible distinctive marker for DLB and a putative explanation for visual hallucinations. The abnormalities found in the caudate nucleus suggest DLB and Parkinson's disease might share a similar nigro-striatal involvement which might be caused by common patho-physiological mechanisms.

P264
The mossy fibres of the cerebellar cortex in Alzheimer's disease
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Alzheimer's disease is a heterogeneic neurodegenerative disorder of presenium and senium, affecting mainly the higher mental faculties. The neuropathological hallmarks of the disease, namely the neurofibrillary tangles, the amyloid deposits and the synaptic alterations are mostly prominent in the hippocampus and the cortex of the brain hemispheres.The cerebellar cortex is better perserved in comparison with other cortical areas and subcortical neuronal structures. In ten early cases of Alzheimer's disease we attempted to describe the morphological alterations of the mossy fibers, which represent the main afferent system of the cerebellar cortex.Specimens from the vermis and the cerebellar hemispheres were studied, using silver impregnation techniques and electron microscopy. The morphometric estimation of the cerebellar cortex revealed that the number of mossy fibers were significantly decreased in comperson to normal controls. In addition, the number of the mitochondria was dramatically decreased in the majority of the mossy fibers, which normaly demonstrated an excessive number of those organelles. A substantial number of mitochondria demonstrated fragmentation of cristae and abnormal accumulation of lipid material. The synaptic vesicles,which are numerous in normal mossy fibers, were also decreased and demonstrated an impressive polymorphism. The surface area of the mossy fibers and the ratio between mossy fibers and granule cells was decreased in the cerebellar hemispheres, in comparison with normal controls. The post synaptic terminals, namely the granule cell dendritic spines, showed a marked alteration of the spinal apparatus. In conclusion, the cerebellar cortex, although demonstrates minimal typical Alzheimer's pathology, is characterized by an impressive poverty of the afferent fibers, which moreover showes a substantial alteration of the mitochondria and the synaptic vesicles.

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Biopsy as a diagnostic tool in Creutzfeldt-Jakob disease
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The differential diagnosis of Creutzfeldt-Jakob-Disease (CJD) encompasses a broad range of neurological and psychiatric disorders. This includes inflammatory CNS-diseases, many neurodegenerative disorders and paraneoplastic syndromes. They may have very similar clinical aspects. At the time technical methods like csf, eeg or mri give only clues for diagnosis. For this reason brain samples are gained to exclude treatable differential diagnosis and to define the diagnosis CJD. This survey discusses whether brain biopsy in cases of suspicious CJD is a helpful diagnostic tool and the operative risk is justified. Within the scope of the German CJD Surveillance Unit since 1992 over 1600 patients with suspected CJD were examined. Thereof in 26 cases a diagnostic brain biopsy was performed. These biopsies were made stereotactic or with open technics. In 10 of 26 patients by biopsy the diagnosis of CJD could be defined. The results of the remaining 16 patients contain exclusion of CJD by special staining, describing morphological changes and sometimes diagnosing a special entity, for example a tumouros process. In 12 of the 16 patients without defined CJD the pathologists only described the existing variances without defining a diagnosis. In 10 of the 26 patients during the course an autopsy was performed. In 5 cases the biopsy diagnosis CJD could be confirmed. In the remaining 5 cases with defined CJD no autopsy was performed. In 4 patients there were evaluated a post-mortem diagnosis, which could not be described by brain biopsy. In 9 of 10 confirmed CJD patients diagnosis were clinically classified as probable or possible CJD. At the time a defined diagnosis of CJD is possible only by histological examination. Because until now there is no treatment of this disorder known, the aim of brain biopsy is to identify treatable differential diagnosis. In our 26 cases only in a few patients a define diagnosis after brain biopsy could be established. Frequently only describing informations like atrophy or gliosis were gained. Due to the fact that no clear diagnosis was revealed, no treatment could be initiated. The define diagnosis of CJD is relevant for hygienic questions. In most of the examined cases of CJD, the clinical classification following the established criteria would be sufficient to establish a diagnosis. Overall a brain biopsy does not seem to be so helpful, that the operative and hygienic risk is justified.

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Effects of some flavonoid compounds on the neuronal death induced by beta amyloid peptide in cultured cerebral neurons

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It has been well known that an excessive accumulation of beta amyloid peptide (A beta) is one of the major mechanisms responsible for neuronal death in Alzheimer's disease(AD). Flavonoids, primarily antioxidants, are a group of polyphenolic compounds synthesized in plant cells. To find out some flavonoids compounds which could inhibit A beta induced neuronal death, the effects of some drugs and flavonoids on the neuronal death induced by A beta fragment 25–35 (A beta 25–35), were examined in mouse cortical cultures.

A beta 25–35 induced a concentration- and exposure-time- dependent neuronal death. The 20 μM A beta 25–35-induced neuronal death was significantly inhibited by either treatment with Trolox or ascorbic acid. Ca2+ channel blockers and NMDA receptor antagonist (MK-801) also inhibited the neuronal death. Cycloheximide, a protein synthesis inhibitor, and ZVAD-FMK, a pan-caspase inhibitor, significantly inhibited the neuronal death. Chromatin condensation and TUNEL staining positive neurons, hallmarks of apoptosis, were observed in cultures treated with A beta 25–35. Ten flavonoid compounds [apigenin, baicalein, catechin, epicatechin, epigallocatechin gallate (EGCG), kaempferol, luteolin, myricetin, quercetin, rutin] except apigenin showed strong 1.1-diphenyl-2-pycrylhydrazyl (DPPH) scavenging activity under cell-free conditions. The 10 flavonoid compounds except apigenin at concentration of 30 μM also significantly inhibited the neuronal death induced by 20 μM A beta 25–35 at the end of 24 hr exposure. Epicatechin, EGCG, luteolin and myricetin showed more potent and persistent neuroprotective action than other compounds.

These results demonstrated that oxidative stress, Ca2+ influx via membrane calcium channels, activation of NMDA receptor and apoptotic neuronal death process were involved in the A beta induced neuronal death, and anti-oxidative flavonoid compounds, especially epicatechin, EGCG, luteolin and myricetin, inhibited the neuronal death. These findings suggest that these 4 compounds may be developed as neuroprotective agents against AD.

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Does a correlation exist between the Clinical Dementia Rating and Global Deterioration Scale in the quantification of the Alzheimer's disease severity?

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Background: There are several methods to evaluate the severity of dementia, some of them are the "Clinical Dementia Rating" (CDR Hughes, 1982) and "Global Deterioration Scale" (GDS Reisberg, 1982). The GDS is a global rating scale is rating according seven point scales: a scored of four or higher is usually considered to be indicative of dementia; and a scored of three is consistent to mild cognitive impairment. The CDR is a global scale too that takes into both results of clinical testing of cognitive performance and a rating cognitive behaviour in everyday activities. The CDR performance in six categories from 0 to 3 and sum of boxes.

These methods have a clinical relevance because they indicate the most adequate treatment to Alzheimer's disease patients. There are few studies that compare these scales in order to know if they are comparable.

Objectives: To establish the correlation interscales we used them in old people who lived in a nursing home and met the criteria for dementia.

Methods:

Subjects: Elderly people between 70–94 years who met the NINCDS ADRDA and DSM IV criteria for dementia.

Two independent raters (neurologist and geriatrics) established the global and individual punctuation of the CDR and GDS using a semi-structurated interview to evaluate the severity. In order to get the best classification an analysis of independent categories was conducted (memory, orientation, judgment, care, community and hobbies)

Results: Twenty patients mean (age 85 ± 6; 85 % women; primary level schooling) participated. The correlation between CDR and GDS was 0.78 at a level of $p < 0.001$. The same stage of severity in both scales showed variability in the total sum of boxes.

Conclusions: Both scales are adequate. The CDR give us more information than GDS of the evolution of Alzheimer's disease because is more objective (sum of boxes) to define the cognitive impairment. But the results suggest an interchange between scales. Further studies are needed to establish reliable results.

P268

The effect of psycho-affective and personality characteristics on memory performance

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Introduction: Subjective memory complaints are a frequent and growing reason for consultation in the elderly. They represent a common major symptom for psychiatric disorders, such as depression and anxiety, as well as for early Alzheimer disease. The clinical differentiation of these situations assumes great importance since we are dealing with highly prevalent conditions with different treatment strategies and prognosis.

Purpose: To evaluate the relationship between subjective memory complaints and objective measures of: memory functions; personality characteristics and affective states.

Participants and Methods: the individuals evaluated in this study were identified through a population based survey (pilot study; N = 111) of mild cognitive impairment and dementia in a Portuguese community of 25,000 inhabitants (people aged 55–79 years). All participants, which scored positive for subjective memory complaints, and had either objective memory impairment or abnormal score on the geriatric depression scale (N = 73) were recalled for further evaluation.

Measurements: (1) Attention: digit span forward and backward; (2) Memory Functions: sub-test of logical memory, verbal memory with interference, paired-associated learning and visual memory from Bateria de Lisboa de Avaliação de Demências; (3) Memory Complaints: Subjective Memory Complaint; (4) Personality traits and affective state: Geriatric Depression Scale, Hospital Anxiety and Depression Scale, Brief Symptom Inventory; (5) Activities of Daily Living: Blessed Dementia Scale.

Results: Completed evaluation 47 participants (64 %); 13 M:34 F, mean age 66.32 yrs±7.1; educational level 3.83 yrs±3.4. Subjective memory complaints were present in 89.4 % and from those 52.4 % had objective impairment in at least one memory measure. Depressive symptoms and abnormal anxiety levels were present respectively in 17–47 % and 23–45 % according to the measure used. We found signs of psychopathological disturbance in 27.7 % of participants. From 22 participants with memory complaints and objective memory defects, 23 % had important depressive symptoms and 64 % had anxiety. From the 20 participants without objective memory impairment, 65 % showed no anxiety and 80 % were free of depressive symptoms.

Conclusions: Anxiety and depression do not seem to influence the presence of subjective memory complaints. Nonetheless anxiety has a negative impact in memory performance in our sample.

P269

The effect of depression on the performance of cognitive tasks in patients with dementia

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Background: In the evaluation of elderly individuals with dementia, the presence of depression is occasionally a feature that the clinician should be aware of. In patients with dementia the presence of depressive symptomatology may complicate the clinical picture or change the expression of various cognitive functions.

Method: The study group consisted of two groups of patients: The first group, (n = 16) followed-up with a diagnosis of dementia as shown with clinical, neuropsychological and behavioural evaluations and scoring lower than 12 in Geriatric Depression Scale (GDS) were accepted as the group free from depression. The second group (n = 16) had GDS scores higher than 12 (highest: 24). The age, gender distribution, education level and follow-up period were similar in the two groups. The following tests were used to evaluate cognitive performance: Clock Drawing test, Boston naming test, Verbal memory processes (VMP) test-short term memory, VMP-recall, VMP- recognition, Stroop test, Story Recall. The results obtained from the two groups were compared and evaluated.

Results: The mean GDS was 8.1 (+ 2.4) and 16.0 (+ 2.8) respectively. A positive correlation was found between GDS and Stroop ($r = 0.51, p < 0.01$). In order to compare the means of the two groups, t-test for independent samples was used. The only statistically significant ($t = -1.9, p < 0.05$) difference was found between the means of the two groups for Stroop test.

Conclusion: Depressive symptoms appear to complicate the clinical picture in some dementia patients and alter the performance in some neurocognitive tests, e. g., the Stroop test.

P270
Dementia in patients with neurocysticercosis
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Objective: To determine the prevalence, associated factors, and clinical outcome of dementia syndrome in patientes with no treated neurocysticercosis (NCC).

Methods: 90 consceutive patients with NCC, range age 18–70 years. We assesed with cogniteve tests (neurobrhavioral cognitive examination, informant questionarie for cognitive dementia) and classified as having dementia or not, according to DSM-IV criteria. Data from CT and MRI and CSF were also registered. This was done in all cases before and after (6 months) treatment with albendazole.

Results: 15 % (14) of the patients were classified as demented. The neuropychiatric disorder was found to be associated withh older age, lower scholar level, and increased number of parasitic lesions in the frontal, temporal and parietal cortex. After 6 months, 78.5 % (11) of the patientes initially classified as demented, did not fulfill any longer the DSM-IV criteria, and all cognitive functions showed significant improvement

Conclusions: Considering the age range, the prevalence of dementia in subjects with NCC seems to be high. The assiciation with a higher number of lesions supports a relationship between NCC and dementia, and most of the patients showed an improvement after the sdtandar pharmacological treatment.

Clinical neurophysiology

P271
Influence of transcutaneous electrical nerve stimulation on exteroceptive EMG suppression
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Noxious digital nerve stimulation during isometric contraction of hand muscles leads to transient suppression of the electromyographic activity which is known as the "cutaneous silent period" (CSP). Most of the CSP is due to a protective spinal reflex mediated by A-delta fibers. Pharmacological interventions including fentanyl failed to influence CSPs. The aim of this study was to investigate whether high-frequency, low-intensity transcutaneous electrical nerve stimulation (TENS), a neurophysiological antinociceptive strategy, would affect opiate-insensitive CSPs. Ten healthy subjects underwent assessment of the effect TENS on the CSP. Surface electromyographic (EMG) recordings were obtained from thenar muscles following recurrent nociceptive digit II stimulation. Group average CSP duration was shortened relative to baseline recordings following 15 minutes of TENS. The amount of exteroceptive EMG inhibition was slightly increased due to a concomitant suppression of transcortical long-loop reflexes, which may be present within the CSP. Thus TENS exerts an influence on both inhibitory and excitatory circuits involved in protective reflexes. These effects are likely mediated at the spinal segmental level through TENS-associated presynaptic inhibition of nociceptive A-delta fibers. The findings are in agreement with known opiate-insensitive mechanism of TENS at the spinal level, and a previously reported insensitivity to fentanyl of CSPs.

P272
Electroneuromyography study before and after liver transplantation in Brazilian familial amyloidotic polyneuropathy type 1 patients
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36 patients with FAP type I were followed by ENMG in subsequent evaluations before and after liver transplantation.

The objective was to correlate clinical findings, sensory action potentials (SAP), and sympathetic skin response of the hand (SSR) during the course of the disease and try to establish if LT changed it.

In 25 patients the second evaluation was done at a mean time of 14.8 months, in 17 the third at 15.8 months, in 5 a fourth at 9.6 months, in 2 a fifth at 6 months and 1 year, and in 1 patient a sixth one was done in a 6 months interval. The time of disease at the evaluations varied from 6 months to 16 years. At their first evaluation 38.8 % of the patients had SAP not obtained in the nerves of the arms and 75 % in the nerves of the legs. At their second evaluation 56 % had SAP not obtained at nerves of the upper extremities and 92 % at the lower extremities. At their third ENMG 64.7 % of them had SAP no obtained in the arms and 76.4 % in the legs. 12 patients were evaluated in intervals of 6 to 12 months after LT. At the evaluation before LT 41.6 % has SAP not obtained in the nerves of the arms and 91.6 % at the legs. Those numbers turned to 75 % and 100 % (n = 12) at their first evaluation after LT (mean time of 1 year), then to 40 % and 100 % (n = 5) at a second ENMG, and to 100 % and 100 % in subsequent evaluations in one patient. SSR was absent in the hand in 77.7 % of the cases and this number increased to 100 % in the following ENMG. For those who underwent LT SSR were not obtained since after LT. Changes of the SAP correlate with the presence of sensory symptoms in the legs in 98.6 % of the cases and of the arms in 80.8 %. SSR abnormality correlates with the presence of autonomic disturbance in 85, 52 % of the patients. In 17 patients (26 %) SAP was normal at the nerves of the hands and SSR was not obtained indicating that the afferent fibers of the SSR reflex were spared. Of these patients 94.1 % had sensory complaints and 88.2 % had autonomic.

In this group of patients LT did not affect ENMG results concerning SAP and SSR.

There was a strong correlation between the presence of sensory symptoms and SAP and SSR and autonomic disturbances. The results were the same for that group who had only the efferent fibers of the SSR compromised. The presence of sensory symptoms in those patients indicates that small nerve fibers were mostly affected at the time of the evaluation.

P273
EEG-EEG connectivity changes after chronic stroke are correlated with functional recovery
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Introduction: It remains unclear why some patients who have a motor stroke make a good functional recovery. Functional imaging studies in stroke patients have shown increased task-related brain activation in several motor areas during contraction of the affected hand when compared to healthy subjects. However, relatively few studies have attempted to correlate this with stroke outcome. Moreover, these studies have focussed on how motor areas may individually contribute to compensation. In this study, we investigate whether different cortical areas interact to form dynamic assemblies that may then compensate for disability. Interaction patterns between different cortical areas may be investigated using coherence between scalp electroencephalographic (EEG) signals. Coherence was thus evaluated in healthy controls and in patients with chronic stroke before and during performance of a handgrip task.

Methods: 16 healthy subjects (mean [SD] age 51.3 (11.4) years) and 25 patients with chronic unilateral stroke and having varying degrees of motor recovery (54.0 (13.1) years) were included. All subjects were right-handed. The degree of functional recovery following stroke was assessed using a range of outcome measures. Principal components analysis was performed on the behavioural data set to obtain overall outcome scores. Scalp EEG was recorded at rest and while subjects performed a unimanual grip task. Task-related changes in power and coherence in the 9–25 Hz frequency band were calculated for each hand tested, followed by a 'hand difference' index of the asymmetry in these measures. Correlations were sought between any abnormal task-related changes and the degree of functional recovery.

Results: Compared to healthy subjects, hand-related asymmetries in task-related EEG-EEG coherence were increased between mesio-lateral frontal areas of the affected hemisphere ($p = 0.031$), over mesial frontal areas ($p = 0.010$) and over lateral frontal areas of the unaffected hemisphere ($p = 0.018$) when stroke patients gripped with their affected hand. Mesial hand-related asymmetries in task-related power and coherence were negatively correlated with recovery ($p = 0.017$ and 0.018, respectively).

Conclusion: Increases in task-related coupling between cortical areas may dynamically compensate for brain damage following stroke. Some of this coupling, particularly that over mesial frontal areas, diminishes as patients make a functional recovery.

P274
Thermal thresholds predict painfulness of diabetic neuropathies
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Introduction: Pathophysiology leading to painful diabetic neuropathy is still unknown.

Method: Thirty patients with peripheral diabetic neuropathy without any biographic differences (17 men, 13 women, mean age 52.4 ± 2.52 years) were investigated. 15 patients had spontaneous neuropathic pain and 15 patients were pain free. Patients were followed over 2 years and examined

at the beginning and thereafter every 6 months. Clinical severity and painfulness of the DN was assessed by the neuropathy impairment score (NIS) and visual analogue scales (VAS). For evaluation of thinly myelinated Adelta- and C-fibers cold and warm thresholds were obtained. For analysis of thickly myelinated fibers nerve conduction velocities (NCV), compound muscle action potentials (CMAP) and vibratory thresholds (VT) were recorded. Moreover, heart rate variability (HRV) was evaluated in order to assess cardiac vagal function. In order to reduce day to day variability of pain and nerve function, mean values of the 6 time points over 2 years were calculated and used for further analysis. All data were compared to an age- and sex-matched control group.

Results: There were significant differences between patients and controls ($p < 0.001$), but in general, patients with neuropathic pain were indistinguishable from pain free patients. In the pain group, however, VAS pain ratings were linearly correlated to the impairment of small fibers (cold perception thresholds ($p < 0.03$), warm perception thresholds ($p = 0.058$)).

Conclusion: Pain in diabetic neuropathy seems to be predicted by damage of small nerve fibers and subsequent deafferentation.

P275

Identification of motion-sensitive visual areas and their transcallosal connectivity in unilateral cortical dysplasia by fMRI

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Malformations of cortical development such as focal cortical dysplasia cause about 10 % of intractable epilepsies in children. Cortical motor and cognitive functions were found in brain activation studies abnormally localized and connected atypically. We describe a patient with focal cortical dysplasia of the temporo-parieto-occipital cortex of the right hemisphere which was associated with a significant impairment of visual motion perception within the contralateral visual hemifield. Functional magnetic resonance imaging (fMRI) focused on the following questions: Is it possible to localise primary visual and visual motion sensitive areas in the dysplastic right-hemispheric temporo-parieto-occipital cortex and are transcallosal visuo-visual interactions and visual-vestibular cortical interactions – as described in normal subjects – preserved?

Imaging was done using a Siemens MRI 1.5 Tesla scanner and echo-planar imaging sequences during visual motion stimulation. A total number of 28 slices covered the whole brain. Data processing was done using SPM99 and MATLAP scripts.

During hemifield motion stimulation primary visual cortex areas were activated contralaterally and deactivated ipsilaterally to the stimulated hemifield. Transcallosal excitatory visuo-visual interaction was evident as bilateral activation in temporo-occipital areas that correspond best to motion-sensitive area MT/V5 during left and right hemifield motion stimulation. Within the dysplastic hemisphere MT/V5 was found displaced anteriorly, superiorly and medially and separated into 2 separate activation clusters. The total number of activated voxels was about half as compared to the unaffected hemisphere in MT/V5 which corresponded to the significant impairment of visual motion perception mediated by the dysplastic hemisphere. During visual motion stimulation not only visual and ocular motor areas were activated, but the parieto-insular vestibular cortex showed signal decreases according to the concept of an inhibitory visuo-vestibular interaction for motion perception.

Thus, fMRI was suitable to analyse abnormally localised visual areas in focal cortical dysplasia and to prove preserved excitatory and inhibitory transcallosal visuo-visual and visuo-vestibular connectivity.

P276

Electrodermal activity during different phases of a golf-swing

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Objective: The golf-swing requires high demands on the athlete's physical and psychological condition. To investigate the influence of these parameters measurements of electrodermal activity (EDA) are introduced for the first time in golf. Hypothesis: Electrodermal responses to sport-specific stimuli allow the definition of standardized indices. Objective evaluation of a golf-swing by means of these indices becomes operational.

Methods: After a golf-specific warm-up 29 low handicappers had to reach a defined goal on the driving range. Each swing was preceded by the individual pre-swing-routine of each player. EDA was monitored continuously with external definition of key-points of the swing. A score-system was administered to assess the objective outcome of each swing.

Results: Repetitive golf-swings lead to increased EDA. During each phase of a golf swing specific EDA-Indices can be defined. Score of each stroke decreased significantly with longer pre-start duration ($p < 0.05$). The better the objective outcome of a swing, the less is the EDA-amplitude of the phasic reaction directly after swing ($p = 0.000$) and the better is the golfer's handicap ($p = 0.001$). The phase of regeneration can be subdivided into 3 sub-phases by EDA-measurements, of which the very first period after swing is of big importance concerning the outcome of the next stroke. Significant differences between players of different age and sex could be demonstrated.

Conclusion: Electrodermal indices appear to be a useful means to analyse single phases of a golf-swing. States of physically and psychologically mediated autonomic arousal in golf can be assessed by neurophysiologic methods such as EDA and will be used for control of practise and competition to enhance the performance of the golfer.

P277

Early neurophysiological diagnosis of true neurogenic "thoracic outlet syndrome" (TOS)

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Patients and methods: Twenty-seven patients, diagnosed as having a TOS, were studied. The diagnosis was previously made by clinicians unrelated to our electrophysiological laboratory.

Each patient was called back. History taking, physical examination and neurography evaluation were systematically performed. All had a cervical spine radiograph and a vascular-doppler flow study, otherwise the request was made.

According to their history, clinical features and vascular-doppler, 3 groups were established: UNLIKELY TOS (n = 7, 4 women and 3 men, mean age = 48.7), VASCULAR TOS (n = 10, 8 women and 2 men, mean age = 41.6) and NEUROGENIC TOS with or without a vascular component (n = 10, 10 women, mean age = 44.8).

We studied the medial antebrachial cutaneous nerve amplitude (MACN SNAP amplitude), radial SNAP amplitude/MACN SNAP amplitude ratio and the difference between minimal F-M latenties of median and ulnar nerves (F ulnar – F median) in these 3 groups (in bilateral TOS, only the worst side was considered) and in a group of 52 healthy subjects.

Results: Control subjects: mean MACN amplitude was 18 ± 5 µV, lower limit of normal (LN) was 7.7 µV; mean amplitude ratio was 2 ± 1, upper LN was 3.8; mean F ulnar – F median was 1.1 ± 0.8 ms, lower LN was –0.4 ms.

Pathologic features were distributed as follows: 1) C7 transverse process or cervical rib: 0/7 case in UNLIKELY TOS, 2/10 cases in VASCULAR TOS and 4/10 cases in NEUROGENIC TOS; 2) MACN amplitude < 7.7 µV: 1/7 case in UNLIKELY TOS, 2/10 cases in VASCULAR TOS and 3/10 cases in NEUROGENIC TOS; 3) amplitude ratio > 3.8: 1/7 case in UNLIKELY TOS, 2/10 cases in VASCULAR TOS and 7/10 cases in NEUROGENIC TOS; 4) F ulnar – F median < –0.4 ms: 1/7 case in UNLIKELY TOS, 1/10 cases in VASCULAR TOS and 5/10 cases in NEUROGENIC TOS.

Conclusion: Our results suggest that the amplitude ratio (radial SNAP amplitude/MACN SNAP amplitude) is more sensitive than the MACN amplitude for the diagnosis of TOS. The difference between F-wave latenties of median and ulnar nerves (F median 0.4 ms longer than F ulnar) can strengthen the presumption of TOS, as far as there is no associated carpal tunnel syndrome.

P278

Analysis of sharp and spikes wave transients in neonatal polysomnography

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Introduction: The clinical significance of Sharp and spikes wave transients (ST) for both preterm and fullterm infants needs more investigation. Sporadic sharp wave may be either normal or anormal, depeding on clinical context, the EEG background activity, location, morphology and age postconceptional.

Objective: To identify and quantify sharp and spikes wave transients found in neonatal polysomnography of healthy term newborn babies throughout different sleep-stages.

Design/Methods: Thirty-two neonatal polysomnographic studies of term babies from the Hospital de Cl nicas da Universidade Federal do Paraná (UFPR) were reviewed. The babies were term, healthy, legal age of two days and with adequate monitoring during pregnancy. Polygraphic studies were performed in a 21 channels EEG machine, with montages internationally accepted standards for the neonatal period and without se-

dation. Quantify sharp and spikes wave transients and analyzed in each sleep-stages.

Results: The mean duration of the polygraphic studies was of 57 minutes. The total number of sharp and spikes wave transients was 206 (6.4 per exam), of which 106 were in quiet sleep, 55 in active-sleep and 41 in transitional sleep. Showed a total of 0.1 sharp and spikes wave transients per minute. In quite sleep were 0.17 sharp and spikes wave transients per minute, in active-sleep 0.07 per minute and in transients sleep 0.19 per minute. The Kruskal-Wallis test shows that sharp and spikes wave transients are more frequently in sleep-quiet.

Conclusions: In the normal term babys sharp and spikes wave transients mostly during quiet-sleep. Even thus, sharp and spikes wave transients per minute were more frequentlly in sleep transients. In newborn healthy we found the number of sharp and spikes wave transients during one minute in each sleep-stages.

P279

Electroencephalographic evaluation of lead-intoxicated children

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Objective: The aim of our study was to establish the eletrencephalographic changes/patterns found in children from Adrianópolis (Paraná, Brazil) with abnormally high blood levels of lead, as a result of environment contamination from a local factory. We also tried to correlate eletrencephalographic (EEG) changes with factors related to variation of lead blood levels.

Population and Methods: Twenty children, range 2 to 14 years of age (mean 9.6 y/a), who suffered from chronic lead intoxication were studied. Blood lead levels were measured by atomic absorption spectroscopy and ranged from 20.1 to 35.8 mg/dL (mean 25.42 mg/dL). All subjects had an EEG recording and underwent either intelligence measurement or a more complete neuropsychological evaluation, depending on their age. Brain CAT scans and whole blood count (WBC) were also performed. EEG recording was standardized, with recordings samples of wakefulness, sleep (spontaneous or induced by chloral hydrate), photic stimulation and voluntary hyperventilation, if the subject was cooperative.

Results: All of the children had normal physical and neurological examinations and none of them had a history of seizures. Of the thirteen children who underwent neuropsychological testing, 6 had low range normal IQ and 7 had borderline for mental retardation results. Brain CAT scans were abnormal in only two subjects, both of which had parenquimal calcifications suggestive of neurocysticercosis. WBC disclosed anemia in 9 children. EEG evaluation failed to disclosed a specific pattern. However, 5 EEG recordings showed an irregular slow activity and in one of those epileptiform changes were also found. Statistical analysis (student's t test) showed no correlation between blood lead levels and abnormal EEG findings in either the normal or abnormal EEG groups

Conclusion: There's no specific EEG pattern in those children who suffered chronic lead intoxication. Higher blood lead levels do not predispose to EEG abnormalities, even though such abnormalities were found in a proportion higher than that expected for age-matched controls.

P280

Impaired grip force and load force coupling during cyclic movements in cerebellar patients

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Several studies suggested that the cerebellum plays a crucial role in the grip and load force coupling in holding and lifting of objects. In general healthy subjects can precisely anticipate grip force to movement induced loads probably by using an internal forward model which is assumed to be located within the cerebellum.

We tested eight subjects with unilateral or bilateral cerebellar pathologies and eight healthy controls. We investigated the grip force adjustments to the load fluctuations when performing cyclic movements with a hand held instrumented object at three different frequencies. Both groups produced similar maximum accelerations of the object and therefore similar maximum loads at all movement frequencies showing that patients as well as control subjects were able to produce similar arm movement kinematics. Compared to the control group patients established highly increased grip force levels. Nevertheless the minimum force ratio across all movement frequencies was remarkably consistent indicating the anticipation between grip force level and load force level was stable across different speeds throughout the movement. Looking at the temporalspatial relationship between grip and load profiles patients showed significantly decreased coefficients of cross correlation implicating impaired prediction of the inertial load fluctuations. Clinically, the upper limb ataxie score of these patients did not correlate with either the increased grip force level nor the inaccurate temporal coupling between grip and load force profiles. Thus, a more general motor dysfunction cannot account for the obvious deficit in grip force regulation of movement induced loads.

Compared to earlier studies our results underline the fact that cerebellar patients tend to establish elevated grip force levels, which may reflect a more general control strategy. In addition, cerebellar patients reveal deficits of the temporo-spatial coupling between grip and load forces in object manipulation. We can therefore conclude that cerebellar lesions do interfere in the process of grip force scaling of environmental loads.

P281

The prognostic value of follow-up computerised tomography of brain in adult patients with moderate and severe head injury following motor vehicle accident

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Objective and Methods: The aim of this study is to predict the outcome of the adult patients with moderate and severe head injury in motor vehicle accident by using clinical parameters (age, Glasgow Coma Scale), initial CT scan of brain parameter (intracranial haemorrhage, volume and site of intracranial haemorrhage, midline shift and hydrocephalus) and follow-up CT scan of brain parameter (residual intracranial bleed, post-traumatic hydrocephalus, midline shift and gliosis). The patient is assessed clinically on admission for GCS. Those categorised into moderate and severe head injury with initial CT scan and follow-up CT scan of brain 6 weeks later will be selected for the study. The parameters were analyzed statistically using univarite analysis, chi square test and logistic regression. The p value of < 0.05 is taken as significant level.

Results: A total of 31 patients were selected, 67.7 % were males and 32.3 % were females. The GCS of the patients were statistically significant as outcome predictors. Other significant predictors analyzed from the study are midline shift and volume of subdural haemorrhage in the initial CT scan and post-traumatic hydrocephalus and gliosis in the follow-up CT scan.

Conclusion: The study showed that the above-mentioned parameters are significant predictors of outcome. The author also have suggested a new outcome predictors by using the parameters from follow-up CT scan i. e. presence of gliosis, site of gliosis and post-traumatic hydrocephalus.

P282

Report of a patient with multifocal motor neuropathy with conduction block presenting with hemiparesis

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Multifocal motor neuropathy with conduction block (MMNCB) is an important and treatable form of autoimmune neuropathy associated with anti GM1 antibody.

It usually presents with slowly progressive asymmetric weakness and later atrophy of distal extremities and occasional cramps and fasiculations mimicking motor neuron disease.

Electrodiagnostic studies including multifocal conduction block of motor nerves in affected limbs with normal sensory studies and high titer of anti GM1 antibody confirms the diagnosis in the setting of appropriate clinical picture.

Intavenous immuneglobulin (IVIG) is the treatment of choice. in some resistant cases cyclophosphamide is a good alternative.

we present a 37 yrs old man presenting with multifocal weakness of limbs, beginning 6 months before with selective weakness of left extensor indicis and later extending to handgrip and left leg. At first the pattem of left hemiparesis caused confusion with upper motor neuron lesion by a local neurologist but later the progression of weakness to RT hand and areflexia in affected limbs explained the nature of disease.

Electrodiagnostic studies in our center confirmed the presence of multifocal conduction block in many motor nerves of affected limbs in the presence of normal sensory studies.

IVIG was started with a dramatic response.

We conclude that MMNCB should be considered in every patient with motor neuron disease like syndrome with benign course and lack of cranial involvement.clinical suspicion and accurate electrodiagnostic evaluation is the key of diagnosis.

P283
Transcranial magnetic stimulation in anxiety disorders
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rTMS is a recently introduced method capable of altering cortical excitability beyond the time of stimulation. It has been employed in several psychiatric disorders with variable degrees of efficacy. In this study 28 patients with anxiety disorders, with inadequate response to oral medications, and 12 normal controls were included. Among the patient group, twenty two continued the study. So we ended up by 34 subjects divided into three groups:

The first group was subjected to rTMS and consisted of 12 patients (8 females and 4 males, age range 22–35yrs) with anxiety disorder: 8 with generalized anxiety disorder, 3 with panic disorder and 1 with generalized anxiety disorder and panic attacks. A second group of 10 patients: 7 with generalized anxiety disorder and 3 with panic disorder was sham- treated. All patients fulfilled the ICD –10 symptom check list criteria. Hamilton anxiety rating scale HARS was applied to all patients before starting and after finishing the rTMS sessions.

A third group of normal 12 age-matched controls was studied for determination of cortical motor threshold and MEP amplitude.

TMS procedure: Determination of the cortical motor threshold (CMT) to all three groups. rTMS technique was applied for patient group 1 only. Sham stimulation was done to patient group 2. Results: The treatment was generally tolerated with no serious side effects. Cortical motor threshold and amplitude: (CMT & CMA) CMT was lower in the patient groups ranging from 25–55 % of the output stimulus intensity (mean 46.15 %) as compared to the control group ranging from 50–85 % (mean 68.3 %), which showed statistical significance (p: 0.00004). The mean amplitude of the motor evoked response was higher in the patient group (1507.1 uv) than the control group (1179.5 uv), however not reaching statistical significance. Hamilton Anxiety Rating Scale (HARS) was applied to all participants prior to treatment sessions and after the last session.

First group (real treated): showed statistically significant improvement on the HARS, while the sham-treated group showed non significant improvement. Mean duration of improvement lasted for 3 weeks ± 6 days. Conclusion: patients with generalized anxiety disorder and panic disorder showed an increased cortical excitability than normal controls. Patients receiving real rTMS showed significant and lasting improvement than those who were sham-treated.

Child neurology

P284
Knowledge of the brain in children grades 2–4
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Children have a rapid knowledge acquisition in domains of psychology, biology, physics and an intuitive understanding of the world, based on their everyday experience. But when and how do they acquire knowledge about the brain? They cannot see it, they know it is somewhere beneath the hair and between the ears. We asked 77 children from 2–4 grade elementary school with a brain questionnaire. Results were discussed in the context of different mental models and facts of the brain.

Methods: Our study included 77 pupils (41 m, 36 f), mean age 8 yrs (SD = 0.98) in 2nd, 9 yrs (SD = 0.37) in 3rd, and 10 yrs (SD = 0.50) in 4th grade. To screen out children with abnormally poor cognitive functioning the Kaufmann-ABC-Test was used. The children were interviewed individually 45–60 minutes. Children's responses were noted and tape recorded, interviews included a questionnaire and a drawing task. The brain questionnaire was developed on the basis of extensive pilot work. Its final version consists of 77 questions on 16 domains about the brain. The domains were split in questions about the structure of the brain (e. g. size and colour of an adult braint, consistence, connections to other organs), brain functions (learning, memory, emotions, etc.) and what happens when the brain is destroyed. The children were also asked to draw a brain with free colour choice. To control drawing capabilities the children had to draw a tree.

Results: The brain questionnaire showed that pupils of 2nd grade know the brain is necessary for thinking and some of the senses are connected with the brain, also that seeing, hearing, but not tasting and touching are functions of the brain. The 3rd grade group chose more realistic views of the brain and functions of the brain were extended. For 4th grade the brain was the centre of human beings which controls everything in man. Independent from the grade most pupils drew a lateral view of the brain with outlines of a gyral and sulcus pattern. The 2nd grade but not 4th grade children often drew the brain together with the head. Also, 4th grade children did not use as many colours as 2nd and 3rd grade children, the brains often looked like clouds and was not so much round shaped.

Conclusion: In the span of 2 yrs from 2nd to 4th grade mental models of the brain are rapidly modified and the brain is increasingly conceptualized as the centre of a person. Also, brains are regarded as universal, and knowledge exists that every animal has it.

P285
Site-directed mutagenesis of brain microvascular LAT1 large neutral amino acid transporter at residues 88, 98, 183 and 331
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The brain is selectively vulnerable to the pathologic effects of hyperaminoacidemia, such as occurs in phenylketonuria (PKU). The hyperphenylalaninemia of PKU causes an inhibition of cerebral protein synthesis, which arises from altered amino acid availability in the brain linked to the hyperphenylalaninemia. The availability of amino acids in the brain is regulated by the blood-brain barrier large neutral amino acid transporter type 1 (LAT1) isoform, which is characterized by a high affinity (low Km) for substrate large neutral amino acids. However, some patients with phenylketonuria have normal brain development despite the high blood phenylalanine (Phe) suggesting that these patients may have a polymorphism within the LAT1 coding region that leads to a high Km LAT1. Recent studies support this hypothesis and show that marked changes in the affinity and capacity of the LAT1 are caused by single nucleotide polymorphisms (SNP, J. Neurochem. 84:1322, 2003). Therefore, the aim of the present investigation was to evaluate the effect of other amino acid residues of the LAT1 coding region that may be involved in the affinity and/or capacity of this transporter. Site-directed mutagenesis (SDM) was performed to convert cysteine (C) residues located at positions 88, 98, 183 and 331 of rabbit LAT1 to serine (S) residues. The transport activity and Km of mutated LAT1 molecules were investigated with 3H-Phe in frog oocytes injected with cRNA and compared with rabbit wild-type LAT1. No significant changes were seen in the Km and Vmax of the following mutants: C98S, C183S, C331S, and the double mutants C88S+ C183S and C98S+ C183S. On the contrary, there was a significant reduction in the Vmax for the C88S mutant compared to wild-type LAT1 (3.31 ± 0.33 vs 6.59 ± 0.84 pmol/oocyte/min, respectively, mean ± SE, determined by non-linear regression analysis, $p < 0.005$). Data are consistent with the following conclusions, 1) C98S, C183S and C331S single point mutations have no effect on Km and Vmax of rabbit LAT1; 2) the C88S mutant markedly reduced the Vmax of the LAT1; and 3) the LAT1 transport of Phe was nearly normalized when the double mutation C88S+ C183S was produced. These studies provide further evidence that marked changes in the capacity of the LAT1 are caused by single nucleotide polymorphisms and that the phenotype can be restored with a double mutation.

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P286
Pilot study of salbutamol in congenital myopathies
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Several studies have documented positive effects of beta adrenergic agonists on human skeletal muscle with regard to muscle mass and strength. The aim of this pilot study was to evaluate the effect of the beta agonists in children with Central Core Disease (CCD) and Multi-minicore disease (MmD).

Thirteen patients, 8 with CCD (mean age 17.5 years) and 5 with MmD (mean age 13.6 years) received oral Salbutamol 2 mg qid,. Measures of efficacy were the change from baseline at 3 and 6 months in muscle strength, assessed by MRC score, myometry, functional measures and in forced vital capacity. Statistical analysis was performed using repeated measures ANOVA (significance level < 0.05).

Two patients stopped the medication after one month because they did not notice any improvement and another one after 4 months because of increased tremors and palpitations. The remaining ten (6 with CCD and 4 with MmD) completed the course of Salbutamol without any significant adverse effects.

There was a significant increase in myometry, MRC scores and forced vital capacity between baseline and the six- month assessments. For both myometry and MRC the difference was already significant at 3 months and

associated with a significant increase in functional abilities assessed with a structured functional scale. Our results suggest that Salbutamol was overall well tolerated and might be beneficial in CCD and MmD patients. Larger prospective randomised, double-blind, placebo controlled trials with Salbutamol will be needed to confirm these preliminary findings.

P287
Hippocampal reductions in adolescents with antecedents of prematurity: a VBM and stereological MRI studies
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Preterm subjects have been reported to have grey matter decreases on different brain structures. Advances in magnetic resonance analysis allowed to identify subttle structural cerebral damage in subjects without aparent neurological sequelaes. Memory impairment is one of the cognitive deficits associated with prematurity. The purpose of this study was to compare the optimized Voxel Based Morphometry (VBM) and Magnetic Resonance Imaging (MRI) Stereology techniques for identify possible hippocampal reductions in 22 adolescents (8 girls/14 boys) with antecedents of prematurity (age 13.45 + 2.13). All 22 subjects had perinatal complications (anoxia, periventricular hemorrhage or fetal suffering). No one had focal brain lesions. The sample was matched to 22 controls by age and handedness (age 14.14 + 2.55; 11 girls/11 boys). Five subjects were left-handed. For memory examination we used the Rey Auditory Verbal Learning Test (RAVLT) and the Rey Complex Figure Retention. All MRI acquisition was performed on a GE Signa 1.5 Tesla scanner (General Electric, Milwaukee). For the VBM we used the SPM2 (Statistical Parametric Mapping, University College London) running in the Matlab 6.5. Stereological measured were performed by using the ANALYZE 5.0. Patients had significant impairment in both verbal and visual memory measurements. We found that both techniques of neuroimaging analysis showed a decrease in left hippocampal volume in premature group compared to controls (VBM: $p < 0.0001$; stereology: $p = 0.001$). In addition, stereological measures detected a volume reduction in the right hippocampus in prematures ($p = 0.002$). We obtained significant correlations between verbal learning and hippocampal reductions, with both techniques (VBM: $p = 0.001$; stereology: $p = 0.027$) in patients. VBM also showed a positive correlation between verbal long term retention and hippocampal reductions ($p = 0.033$). Visual memory did not correlated with right hippocampal volume in any case. The inter-correlation analysis between techniques showed that grey matter volume reductions by VBM strongly correlated with left hippocampal volume reductions measured by stereology ($p = 0.008$). Our results demonstrate that both techniques are able to detect hippocampal damage in adolescents with antecedents of prematurity, but with different sensitivity. Stereological techniques detected right hemisphere damage, not observed by VBM. In contrast, the VBM achieved stronger correlations with neuropsychological sequelae.

P288
Locus heterogeneity of infantile neuroaxonal dystrophy and pantothenate kinase-associated neurodegeneration
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Background: Infantile neuroaxonal dystrophy (INAD) and pantothenate kinase-associated neurodegeneration (PKAN) have several features in common. In particular, pathological examination shows widespread axonal swelling and spheroid bodies in the central nervous system in both diseases. Accordingly, there has been a long-lasting discussion, as to whether these syndromes are distinct entities or manifestations of a continuum. The recent discovery of mutations in the gene for pantothenate kinase 2 as the genetic cause of PKAN offers now the opportunity to determine if INAD and PKAN share a common genetic etiology.

Methods: We performed haplotype analysis in three and mutation screening in seven INAD families.

Results: In one consanguineous family, haplotyping showed no common allele in the parents as well as discordance between two affected siblings. Sequence analysis did not show mutations in the pantothenate kinase 2 gene in eight patients.

Conclusion: These data provide strong evidence that INAD is not allelic to PKAN.

P289
Effect of treatment with PDTC and IRFI 042 on strength and fatigue in MDX mice
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Previous studies provided evidences that generation of reactive oxygen species and activation of transcription factor NF-kB may play important roles in the pathogenesis of Duchenne muscular dystrophy. We tested whether IRFI 042, a vitamin E-like antioxidant, and PDTC, a NF-kB inhibitor, could have an effect on muscle weakness in mdx mice.

We treated 48 5/6-week old mdx and wild type mice with intraperitoneal injections of PDTC (50 mg/kg), IRFI 042 (20 mg/kg), or vehicle, three times a week for five weeks. Data regarding weight, survival and forelimb strength and fatigue were collected. Motor performance measurements were carried out using a grip meter attached to a force transducer which measures peak force generated.

Mdx mice treated with IRFI 042 or PDTC showed at the end of treatment a significantly higher forelimb strength than vehicle controls (IRFI 042: 53.6 %, $p < 0.001$; PDTC: 53.1 %, $p < 0.05$) as well as higher strength normalised to weight (IRFI 042: 57.8 %, $p < 0.001$; PDTC: 54 %, $p < 0.05$). Furthermore PDTC-treated mdx mice had significantly less fatigue than vehicle animals (–120 %, $p < 0.004$).

Our results suggest that PDTC and IRFI 042 might have a beneficial effect on weakness and fatigue in mdx mice. Further studies are needed to investigate the morphological and biochemical substrates of such encouraging preliminary results.

P290
Intensivity of neurochemical processes correlate with the alectrophysiological changes in children with epilepsy
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Epilepsy (E) has been defined as recurrent convulsive or nonconvulsive seizures caused by partial or generalized epileptogenic discharges in the cerebrum. One of the mechanisms of E is mediator imbalance in brain. Glutamate (Glu) release in high concentration activates several postsynaptic glu receptor (GluRs)/ion channel complexes, leads to Ca2+ entry into neurons, membrane depolarization and activates several Ca dependent cytodestructive enzymes. This process may be responsible for the initiation of neuronal damage, which may cause of the appearance of autoantibodies (aAB) to fragments of GluRs in blood. The determination of GluRsaAB, ionized calcium (Ca2+) in blood and the quantitative measurements of electroencephalogram (EEG) were performed in children with E and in control group (CG). GluRs aAB were estimated using the ELISA, synthetic peptides (analogues of GluR1 and NR2) were used as antigens. The level of NR2aAB and GluR1aAB simultaneously was measured in 25 children with E. The individual evaluation of spectral power (SP) and spectral rate (SR) of EEG were performed for 30 E patients. In 101 patients with different Es the significant increase more than by 1.5–2 times of GluR1aAB serum level was revealed vs CG ($p < 0.05$). The high level of aAB to GluR1 and NR2 was determined in 92 % and 80 % of cases, respectively. The indirect correlation between GluR1aAB level and Ca2+ and the direct correlation with frequency and type of seizures (S) and the SP increase was revealed. The highest level of SP and aAB was measured in children with generalized S (tonic-clonic and absences). The level of full SP was increased in 50–60 times vs basic one in these cases. In focal epileptiform activity in children with partial Es the SP increases was lower. In children with normal aAB level the SP was near to normal. The a-rhythm was increasing in the frontal lobe simultaneously with the aAB level increasing. The increasing of the aAB from basic to high level correlated with the increasing of the level of SP of basic rhythms. In the highest aAB level (more than 1.5 times vs basic) the increasing of delta-, teta-activity in whole brain more expressed and the decreasing of SR were revealed. These results show the unity of neurophysiological and neurochemical processes in brain.

P291
Pathophysiology studies improve the effectiveness of a therapeutic approach to Tay-Sachs disease
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Tay-Sachs (TS) disease is a GM2 gangliosidosis due to the deficiency of the Hexosaminidase A (Hex A, E. C. 3.2.1.52) which is a heterodimer of alpha- and beta-subunit, encoded by two different genes (HEXA and HEXB) located respectively on the chromosome 15 and 5. Inherited defects in the alpha-subunit gene leads to the absence of the Hex A and a massive accumulation of the GM2 ganglioside and related lipids mainly in neuronal lysosomes. Consequences are a severe cellular dysfunction and a rapid progressive neurodegeneration. Currently, TS treatment is restricted to supportive care and appropriate management of intervening problems. Therapy for TS disease, requires an active Hex A production in the central nervous system and a therapeutic approach whose effect velocity could be faster than human disease progression. To this end we are developing a gene/cell approach based-therapy for TS disease. We are combining the efficacy of the gene therapy strategy by using a viral vector encoding for the Hex A alpha-subunit to restore the Hex A activity and the therapeutic potential of stem cells to repair the neurodegenerated brain. To improve the effectiveness of our strategy we first studied the patophysiology of TS disease. We analysed the levels of Hexosaminidase isoenzymes (A and B) in C57/BL6 (wild-type) mice and TS mice brain at different age (embryonic vs. adult). Our results indicated an increase of Hexosaminidase activity in adult and postnatal wild-type mice with respect to the same activity measured in the mice at embryonic stage. In addition we observed a specific correlation between the expression of the alpha and beta subunits forming the Hex isoenzymes with the mouse age as showed by ionic-exchange chromatography. These data were confirmed in similar experiments performed in embryonic, postnatal and adult TS mice and supported the suggestion that elucidation of molecular mechanisms leading the patophysiology of this metabolic disorders is critical for definition of therapeutic parameters.

P292
Clinically identifiable congenital neurologic malformations in the labour wards of Hamadan, West Iran
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Introduction: Congenital anomalies remain a leading cause of death among infants in both the neonatal and post neonatal periods in developed countries.

Objective: In order to determine the pattern of anatomically obvious congenital malformations seen in labor wards in Hamadan city, 12,804 cases were evaluated.

Patients and Methods: This prospective study involves all neonates (group I), stillbirth and intra uterine fetal death (group II), with gestational age more than 3 months, in labor wards of 3 hospitals with a confirmed clinical diagnosis of congenital malformation during a one year period (September 2000 to August 2001).

Results: Among 12,804 cases [12, 460 in group I and 344 in group II], clinically identifiable congenital malformations were seen in 97 (0.76%) cases [47 (0.38%) in group I and 50 (14.53%) in group II]. The most commonly affected anatomical organ were central nervous system, which was detected in 48 (49.48%) patients [12 (25.5%) in group I and 36 (72%) in group II]. Among the central nervous system anomalies hydrocephaly, spina bifida, and meningocele were found in 4, 3, and 5 cases of group I, respectively. These anomalies were seen in 11, 4, and 2 cases of group II, respectively. Anencephaly was detected in 19 subjects of group II. Craniofacial anomalies were detected in 12 (12.37%) cases [7 in group I and 5 in group II], including: microfacial (4 cases), microcephaly (2 cases), and cleft-lip and cleft-palate (6 cases). Otic involvements were seen in 11 (11.34%) subjects [4 in group I and 7 in group II], including: ear lobe crease (8 cases), ear agenesis (2 cases), and skin-tag (1 case). Ophtalmic anomalies consist of hypertelorism (3 cases), eyelid disorder (1 case), and cyclopia (1 case). Also, 2 cases with anophtalmy were detected in group II.

Conclusions: These findings may be useful in aiding clinicians, patients, and policymakers of our region in reducing the risk of neurologic congenital malformations, a source of high perinatal mortality and morbidity rates.

P293
Neurophysiological diagnostic procedures as a predictor of outcome in viral encephalitis in a paediatric population
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Viral infections of the central nervous system (CNS) pose a threat to the health of people throughout the world. However, effective treatment of CNS viral disease remains difficult because only a few pathogens can be treated with specific antiviral agents. Beside treatment it remains unknown why some of the patients have good therapeutic answer while some of them don't.

During two year period (2002–03) at the University Children's Hospital of Belgrade 18 patients were hospitalized and treated because of viral encephalitis. Age range was between 8 months and 11.5 years.

First EEG pattern were encephalopatic in 17/18 patients. Second EEG showed specific slow, low amplitude activity in 18/18 patients. Third EEG recording showed some signs of recovery in 7/18. We have found that those results correlated with neurolological finding during illness and were in some way solid predictor of future outcome.

When performing Somatosensitive Evoked Potentials (SSEP) in 10/18 we have found low amplitude of cortical answers but terminal latencies within normal ranges. Those findings correlate with final outcome: 3/18 no sequels, mild psychomotor delay in 6/18 and 1/18 moderate psychomotor delay. In 8/18 patients SSEP findings were pathological or could not be found. This was in close relation with final outcome (severe psychomotor retardation in 6/18 and 2/18 died).

In our two year survey we have found that neurophysiological investigations were very reliable prognostic parameter in treatment of viral encephalitis.

P294
Agyria-pachygyria complex and epilepsy
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Introduction: Agyria-pachygyria complex or lissencephaly is a severe neuronal migration disorder characterized by absence of gyri and sulci (agyria) or by their reduction to broad, flat gyri an shallow sulci (pachygyria). By magnetic resonance imaging criteria lissencephaly can be divided into five types.Type I (classic lissencephaly) and type II (cobblestone lissencephaly) are the most commonly encountered and well established forms.

Patients and methods: We studied 15 patients diagnosed with agyria-pachygyria complex based on brain computed tomography or magnetic resonance imaging.Fourteen patients were classified as isolated lissencephaly and one had Miller-Dieker syndrome.

Results and discussion: Ten patients experienced epileptic seizures with onset during first year of life. All patients had early severe hipotonia followed by progressive hypertonia with developmental delay.

The aim of this study is to underlie the importance of neuroimaging techniques in recognition of this entity.

Cerebrovascular disorders

P295
The effect of chronic cerebral hypoperfusion on middle cerebral artery occlusion-induced cellular damage in spontaneous hypertensive rats
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An ischemic stroke can result from various mechanisms such as atherothrombosis, caridoembolism or hemodynamic compromise. It has been reported that patients with atherothrombotic stroke have less severe neurological deficits and smaller cerebral infarction than those with cardioembolic stroke. When exposed to a sufficient but sublethal alteration of their environment, most living organisms acquire transient tolerance to subsequent and otherwise lethal environmental changes. To test the hypothesis that chronic cerebral hypoperfusion induces tolerance to the subsequent severe ischemia, we examined the effect of chronic cerebral hypoperfusion on brains subjected to acute focal ischemia by means of two well- known animal models, namely middle cerebral artery occlusion/reperfusion(MCAO/R) and bilateral common carotid arteries ligation

(BCAL). Chronic cerebral hypoperfusion was successfully induced in the male spontaneous hypertensive rat(SHR) by BCAL. Rats that were bred for 4 weeks after BCAL or sham operation were subjected to MCAO/R using a nylon suture model. The animals' brains were then prepared for paraffin blocks or frozen blocks. Subsequently an in situ nick translation study, immunohistochemical staining for apurinic/apyrimidinic endonuclease/redox factor-1 (APE/Ref-1) and matrix metalloproteinase(MMP)-9 and zymography were performed. Thirteen of the 45 rats that underwent BCAL died while all 27 rats that underwent the sham operation survived. The number of positive cells in the in situ nick translation study, which was taken as an indication of cellular injury, was significantly reduced in those rats that were subjected to chronic cerebral hypoperfusion. Immunoreactivity for APE/Ref-1, which plays a role in DNA repair, was markedly increased in the brain tissues of those rats subjected to chronic cerebral hypoperfusion. Indirect evidence of extracellular matrix remodeling, which might be associated with adaptive arteriogenesis or angiogenesis, was obtained in the form of increased MMP-2 activity in the hypoperfused brain. The findings of this study provide experimental evidence for the hypothesis that chronic sublethal cerebral hypoperfusion is protective for subsequent severe ischemic insults, which was in part supported by increased DNA repair activity and evidence of extracellular matrix remodeling in tissue with chronic cerebral hypoperfusion.

P296

Strong association of ischaemic stroke in type 2 diabetes patients with decreased insulin sensitivity and increased plasminogen activator inhibitor-1 levels

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Background and Aims: Decreased insulin sensitivity (IS) plays a crucial role in the pathogenesis of atherosclerosis, but their role in ischemic stroke has not yet been elucidate.Therefore, this study was aimed:(a)-to analyze insulin sensitivity and plasma insulin (PI) levels in 30 patients with Type 2 diabetes and ischemic stroke (group A), 30 patients with Type 2 diabetes without ischemic stroke (group B), 30 nondiabetics with ischemic stroke (group C), and 30 healthy controls (group D; (b)-to compare in these patients the changes in IS and PI levels with those in plasminogen activator inhibitor (PAI)-1 levels, being important factor contributing to the pathogenesis of atherosclerosis.

Materials and Methods: Ischemic stroke was defined as atherothrombotic infarction confirmed on cranial computerized scan or magnetic resonance imaging.The patients with ischemic stroke were included in the study providing that did not show signs of lacunar and cardioembolic stroke or coronary heart disease.Insulin sensitivity levels were determined by frequently sampled intravenous glucose tolerance (FSIGT) test with minimal model analysis (Si index). PI levels were determined by RIA, and PAI-1 levels by plasminogen chromogenic plasmin substrate assay.

Results: We found that Si levels were significantly lower in group A compared to group B (1.14 ± 0.31 vs 2.41 ± 0.89, $p < 0.05$), and in group C compared to group D (3.72 ± 0.66 vs 6.82 ± 0.92 $min^{-1}/mU/l \times 104$, $p < 0.001$). PI levels were significantly higher in group A compared to group B (21.2 ± 2.8 vs 15.9 ± 1.6, $p < 0.05$), and in group C in comparison to group D (16.2 ± 2.1 vs 9.1 ± 1.4 mU/l, $p < 0.05$). Simultaneously, we found that PAI-1 levels were significantly higher in group A compared to group B (6.1 ± 0.2 vs 4.5 ± 0.4 mU/l, $p < 0.05$), and in group C in comparison to group D (5.0 ± 0.3 vs 2.6 ± 0.1, $p < 0.01$). Moreover, we found that Si and PI levels significantly correlated with PAI-1 levels both in Type 2 diabetes ($r = 0.441$, $r = 0.388$; respectively, $p < 0.05$) and nondiabetic subjects ($r = 0.512$, $r = 0.436$, respectively, $p < 0.05$).

Conclusion: Our results signify that appearance of ischemic stroke in Type 2 diabetes patients was strongly associated with decreased insulin sensitivity and increased PI levels.The results imply that insulin resistance in association with compensatory hyperinsulinemia underlying the development of the stroke, might exert their atherogenic influence through the impairment in fibrinolysis.

P297

Effects of dexamethasone in primary intracerebral haemorrhage

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Background: Previous study revealed the value of dexamethasone in the treatment of vasogenic edema associated with brain tumor and abscess. However there is poor documented studies show its use in primary intracerebral hemorrhage.

Objective: Evaluation of dexamethasone effects in primary intracerebral hemorrhage.

Metods & materials: Overall 255 patients 40 to 80 years old, were studied by using a double-blind randomized block design. Subjects were randomly assigned to144 patients in dexamethasone and 81 patients in placebo group. Then mortality, GI bleeding, fever, electrolytes disturbances, hypertension and hyperglycemic status analyzed in two groups. Ethical considerations was employed and subjects were followed by appropriate statistical methods for 21 days to assess the major outcomes.

Results: The death rate and fever at the 21st day was much higher in the dexamethasone group (dexamethasone vs. placebo, 49.3 % vs. 23.45 % $p = 0.021$). and (40.2 % vs. 24.7 % $p = 0/018$) but there was no statistical association between two groups about other complications such as GI bleeding, hyponatremia, hypokalemia, hyperkalemia, hypertension and hyperglycemic state in patients with and without past medical history of diabetes mellitus.

Conclusion: Using dexamethasone for treatment of primary intracerebral hemorrhage should be reconsidered.

P298

HAMLET hemicraniectomy after MCA infarction with life-threatening oedema trial

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Background: Patients with massive space-occupying hemispheric infarction have a poor prognosis. Non-randomized studies suggest that decompressive surgery reduces mortality and improves functional outcome of survivors. HAMLET is a randomized controlled trial to study the efficacy of decompressive surgery to reduce mortality and to improve functional outcome in patients with supratentorial infarction and space-occupying edema.

Methods: The study design is that of a multi-center, randomized clinical trial, which will include 112 patients aged up to 60 years with a space-occupying infarct in the territory of the middle cerebral artery leading to a decrease in consciousness. Patients will be randomized to either decompressive surgery, consisting of a large hemicraniectomy and a duraplasty, followed by intensive care treatment, or conservative treatment, consisting of intensive care treatment or 'standard' therapy on a stroke unit. Randomization will be stratified according to the intended mode of conservative treatment. The primary outcome measure is functional outcome assessed by the modified Rankin Scale at one year. Other outcome measures include the Barthel Index, the NIH Stroke Scale, the Montgomery and Asberg Depression Rating Scale, and quality of life as determined by the SF36 as well as a visual analogue scale.

Trial status: HAMLET has started in September 2002 in seven Dutch centers. Other centers are invited to participate.

P299

Efficacy of fasudil hydrochloride for cerebral vasospasm following early clipping surgery in subarachnoid haemorrhage patients

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We retrospectively evaluated the efficacy of fasudil hydrochloride in prevention of symptomatic cerebral vasospasm (SVS) after subarachnoid hemorrhage (SAH). Since 1992 to 2001, we have performed early clipping surgery within 72 hours after onset in 499 SAH patients. One hundred and eighty four patients (Group A) were treated with modified triple H therapy and postoperative cerebro-spinal fluid drainage were used as controls. The other 315 patients (Group B) were treated with the above treatment and intravenous administration of fasudil hydrochloride (90 mg/day for 14 days). Clinical grades were assessed using Hunt and Kosnik grading scale and CT grades were assessed using Fisher's classification. Clinical outcome was assessed at 6 months after onset of SAH using Glasgow Outcome Scale. Statistical analyses were performed by chi-square statistics. Odds ratios (ORs) and their 95 % CIs were calculated by logistic regression analysis.

There were no significant differences in age, gender ratio, clinical and CT grades and location of aneurysms between both groups. As compared with Group A, Group B had significantly lower incidence of SVS (37.0 vs. 16.8 %, $p < 0.0001$; OR, 0.38; 95 % CI, 0.25 to 0.59), SVS-related brain infarction (35.9 vs. 7.3 %, $p < 0.0001$; OR, 0.14; 95 % CI, 0.08 to 0.24), death (14.7 vs. 5.1 %, $p = 0.0003$; OR, 0.28; 95 % CI, 0.14 to 0.56) and higher rate of good recovery (44.6 vs. 65.7 %, $p < 0.0001$; OR, 2.42; 95 % CI, 1.66 to 3.55).

Although definitive conclusion on the efficacy of fasudil hydrochloride

cannot be drawn because of an open trial, these results suggest that our postorerative combined therapy with fasudil hydrochloride after early clipping surgery may reduce the incidence of SVS, SVS-related brain infarction and mortality rate in SAH patients, resulting in better clinical outcome.

P300
Oral contraceptive pills misuse and cerebral vein sinus thrombosis: a growing health problem in Isfahani women
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Background: In recent years, consumption of oral contraceptive pills (OCPs) has been significantly increased in Iran for contraception purposes. Simultaneously, an increasing rate of OCPs misuse and resultant side effects including cerebral vein sinus thrombosis (CVST) has been reported. In this study, the reasons and the ways of OCPs consumption have been investigated in Isfahani women with CVST considering the cultural and religious factors.

Methods: During a 4-year period (1998 to 2001), patients admitted to Al-Zahra Medical center with suspicion of CVST received an MRI and MRV to get the definite diagnosis. For all cases with CVST an investigation was performed to find out the possible etiologies. Among those who were taking OCPs an extra investigation was conducted to evaluate the reason and the way of OCPs use.

Results: Fifty Out of 65 patients with CVST were females, among them 31 patients (60.8 %) were taking OCP and 20 out of these 31 patients (64.5 %) had a history of OCPs misuse (improper indication or self treatment for fasting in Ramadan or for traveling to religious cities). In six OCPs users who were affected by CVST in a shorter period after starting OCP (less than 3 months), congenital or acquired coagulopathic disorders (antiphospholipid antibody or protein S deficiency) were detected.

Discussion: It seems that one possible cause for higher prevalence of CVST observed in recent years is increased OCPs use and resultant coagulopathy. With respect to the considerable proportion of OCPs misuse among women with CVST, a proper educational program should be designed to aware Isfahani women about possible serious complications resulting from OCPs misuse. The possible role of the other hereditary coagolopathic disorders must be considered in patients that are affected by CVST in a shorter period after starting OCPs (less than 3 months).

P301
Brain white matter lesions and blood pressure
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Objective: To investigate the relationship between office and 24 h blood pressure (BP) values and severity of brain damage in middle age pts with untreated essential hypertension (EH) stage II.

Design and Methods: Magnetic resonance imaging (MRI) and 24 h BP monitoring were performed in 55 untreated pts (51.6 ± 1.5 years; 37 males) with EH stage II. Office BP (average of 3 measures), 24 h, daytime (D) and nighttime (N) BP were obtained separately for systolic (SBP) and diastolic (DBP) values. All patients were divided into 3 groups depending on the severity of brain damage: gr.I (n = 18) without brain white matter lesions (WML), gr.II (n = 19) with single WML and gr.III (n = 18) with multiple WML. Office BP and 24 h BP values were related to WML by bivariate correlation analysis and multivariate regression analysis.

Results: Office, 24 h, D and N SBP were significantly ($p < 0.01$) higher in gr.III pts than in gr.I and II pts. The corresponding 24 h, D and N DBP were significantly ($p < 0.01$) higher in gr.III pts than in gr.I and II pts. Gr.III pts had higher variability of 24 h, N SBP and 24 h, D, N DBP than gr.I and gr.II pts. The night-time fall in SBP and DBP was in normal limits (dipper) in gr.I and gr.II pts, but in gr.III pts it was less than 10 % (non-dippers). Bivariate correlation analysis have shown that WML were related with average office and 24 h SBP values (Office: $r = 0.71$; $p < 0.001$; 24 h: $r = 0.57$, $p < 0.001$, D: $r = 0.51$, $p < 0.001$; N: $r = 0.59$; $p < 0.001$); only average 24 h DBP values (24 h: $r = 0.52$, $p < 0.001$, D: $r = 0.45$, $p < 0.01$; N: $r = 0.58$; $p < 0.001$); as well with night-time fall in SBP and DBP (SBP: $r = -0.50$, $p < 0.001$, DBP: $r = -0.41$, $p < 0.05$); and variability of N SBP ($r = 0.50$; $p < 0.01$) and N DBP ($r = 0.49$, $p < 0.01$). Multiple regression analysis have shown that only N SBP and variability of N SBP are independent predictors of WML in pts with EH.

Conclusion: Our data suggest that severity of brain damage in pts with EH depends on the BP rhythm and variability of N SBP and N DBP, average 24 h SBP and DBP values and as to office BP it depends on only SBP.

P302
Intracranial arteriosclerosis: a transcranial Doppler study
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Introduction: TCD is a non-invasive pulsed ultrasonic tool that is used in the investigation of cerebrovascular disease. The TCD gives reliable results in the study of the extra and intracranial circulation with high index of sensitivity and specifity.

Aim: Intracranial arteriosclerosis has been poorly described in the literature, particularly in relation to different risk factors. We used pulsatility index (PI) of the middle cerebral artery (MCA) as a tool to assess the degree of intracranial arteriosclerosis in relation to age, sex, hypertension, diabetes, hyperlipidemia and smoking.

Methodology: Patients referred to TCD, from January 2001 to January 2002, were included. Patients with diseases that would expect to affect the PI calculations apart from arteriosclerosis were excluded. Intracranial arteriosclerosis was identified when the right middle cerebral artery PI is more than 1.12.

Results: 309 patients were included, 204 men and 105 women, with a mean age of 51.8 ± 17.8. Intracranial arteriosclerosis was present in 142 patients (46 %). 51 % of men were having intracranial arteriosclerosis, while it was present only in 36 % of women. Intracranial arteriosclerosis was clearly associated with advanced age (67 % in more than 60 years of age). Hypertension and diabetes were the most common risk factors seen with intracranial arteriosclerosis, particularly if they coexist together (15 %, 8 % and 21 % respectively). There were fewer patients with intracranial atherosclerosis who had only hyperlipidemia (1.4 %) or only smokers (4.2 %).

Conclusion: Advanced age is the most important factor that is associated with intracranial arteriosclerosis. Hypertension and diabetes are the most important modifiable risk factors that are associated with intracranial arteriosclerosis, particularly if coexist.

P303
Intracranial carotid atherosclerosis in Egyptian patients with ischaemic stroke
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Stroke is a significant cause of morbidity and mortality. Only 43 % to 80 % of survivors are able to return to their previous lifestyle, and long-term care for those who are disabled is expensive. The aim of this work is to study the prevalence of intracranial atherosclerosis in Egyptian patients presenting with acute ischemic stroke.

All patients had thorough neurological examination, study of blood sugar, lipid profile, and uric acid analysis. MRI and MRA were performed within 7 days of the onset of stroke, Sixty one patients had Carotid Duplex examination as well.

One hundred and five consecutive patients admitted to the Stroke Unit of Ain Shams University Specialized Hospital, with the diagnosis of acute ischemic stroke were analyzed, eighty two patients (76 %) had intracranial vascular abnormalities in the MRA. Patients with intracranial vascular abnormalities ranged in age from 55–88 years with a mean age of 64.8 years. Twenty four were females and fifty eight were males. Sixty four lesions (68 %) involved the anterior circulation and thirty (32 %) involved the posterior circulation. Only 15 (12.3 %) patients had evidence of carotid stenosis and 5 patients (8 %) had stenosis greater than 70 %. Carotid plaques were present in forty four patients (72.1 %).The most common artery affected was ACA (anterior cerebral artery)(34 %) followed by intracranial ICA (internal carotid artery) (19 %). Embolic lesions presented as complete occlusion of the artery accounted for 14.8 %, while atherosclerosis accounted for 85.2 % of lesions. This study revealed that intracranial atherosclerotic disease is independent of the extracranial stenotic atherosclerotic carotid artery disease, and is not just an extension of the extracranial disease as reported in western population.

P304
Centrum ovale infarctions: a clinico-radiologic correlation
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Centrum ovale infarcts account for only 2 % of all strokes but they are underestimated because small infarcts can be silent, or misclassified as deep

perforator infarcts. We Studied thirty patients with acute infarction in the centrum ovale as proved by diffusion MRI. All patients had detailed clinical examination, laboratory work up, MRI study with diffusion sequence and limited magnetic resonsnace angiography TOF. Most of the cases presented with lacunar syndrome picture: 16 cases (53 %) had sensorimotor stroke, 8 cases (27 %) had pure more stroke, and 4 (13 %) cases presented with ataxic hemiparesis. But the clinical picture is different from the classic lacunar syndromes as will be discussed. Also, one patient presented with dysarthria (3 %), and another one presented with monoparesis of the right upper limb. Hypertension is the single most important risk factor in these patient occurring in 23 patients (77 %), followed by diabetes in 11 patients (37 %), hyperlipidemia in 10 patients (33 %), smoking in 9 patients (30 %) and ischemic heart disease in 8 patients (27 %).

Poster session 2

Neurobiology

P305

Direct comparison of microvascular endothelial function and carotid intima-media thickness in patients with large vessel and small vessel ischaemic strokes

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Objectives: To determine the role of endothelial dysfunction in small vessel stroke (SVS) versus large vessel stroke (LVS) using the novel paradigm of digital retinal imaging (DRI) in patients hospitalised with acute ischaemic stroke (AIS). Endothelial assessment may aid early definition of stroke subtype and allow for selection of therapies tailored towards endothelial dysfunction.

Background: The relationship among atherosclerosis, endothelial dysfunction and SVS versus LVS is not well understood. The retinal microvasculature is derived embryologically from the cerebral circulation and DRI may permit non-invasive assessment of endothelial function in AIS.

Design/Methods: Our sample consisted of ten patients consecutively hospitalised with AIS matched for age and risk factors and categorised into SVS or LVS by a stroke neurologist using TOAST criteria. Endothelium-dependent retinal microvascular responses and endothelium-independent retinal vasodilatation in response to sub-lingual glyceryl trinitrate were assessed with inhalation of three gaseous mixtures (100 %O_2, 10 % O_2+90 % N_2, 10 % O_2+10 % CO_2+80 % N_2). Retinal photographs were taken at defined intervals prior to and following gas inhalation. Operator-directed image analysis was used to measure arteriolar diameters from digital images and carotid intima-media-thickness (IMT) measurements were obtained using a standard technique and blinded to stroke subtype.

Results: Endothelial-dependent responses to hypoxia were significantly impaired in SVS versus LVS subtype (t-test, $p = 0.013$), while no significant between group difference was found for endothelial-independent response to GTN (see table). Additionally carotid IMT measurements were significantly higher in LVS (0.796 ± 0.212) versus SVS (0.704 ± 0.123 mm, t-test $p = 0.02$).

Discussion: We found significantly impaired retinal arteriolar responses in SVS subtype compared with LVS suggesting that lacunar stroke is associated with impaired endothelial function of the microvasculature. SVS was also associated with significantly lower carotid IMT values. Our findings support meaningful pathophysiological differences between SVS and LVS and the validity of pursuing stroke subtyping. Arteriolar dynamics may prove a valid biological marker underpinning specific stroke subtypes. Further study using DRI may enable therapeutic measures to be targeted towards specific stroke subtype.

P306

Histamine decreases transendothelial permeability of brain endothelioma cells in vitro in the absence of ICAM-1

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Background: Breakdown of the blood-brain barrier (BBB) is an essential part of the pathogenesis of multiple sclerosis (MS). ICAM-1 is hypothesized to play a crucial role in transendothelial migration of T-cells across the BBB in MS. Histamine increases BBB permeability through H_2-receptor mediated mechanisms in vivo and in vitro.

Objective: We examined the paracellular permeability of brain endothelioma cell monolayers in vitro after histamine challenge in the presence or absence of ICAM-1.

Methods: Three different immortalized cell lines from mouse brain capillaries were used: the wild type bEnd5 line, the bEndalfI1.1 line derived from ICAM-1 knockout mice which lacked ICAM-1 expression, and the bEndalfI1.1 + wt reconstituent of the same cell line that had been successfully retransduced with a plasmid containing wild type ICAM-1. The cells were grown to confluence for two weeks on semipermeable filters precoated with rat tail collagen. The paracellular permeability of radioactive [14C]-sucrose and [3H]-inulin across the endothelial monolyers was determined after challenge by exposure to 6 µg/ml histamine during thae assay period. For all three cell lines, permeability was compared to unchallenged controls.

Results: Exposure of the wild type endothelioma cell line bEnd5 to histamine increased paracellular permeability as compared to unchallenged controls. In contrast, the bEndalfI1.1 cells, which lacked ICAM-1 expression, exhibited a decrease in permeability upon histamine challenge. However, when the experiment was performed with the wild type reconstituent bEndalfI1.1 + wt, histamine neither increased nor decreased paracellular permeability.

Conclusion: These results indicate that in the absence of ICAM-1 challenge of brain endothelial cell lines with histamine decreases paracellular BBB permeability in vitro. Therefore, ICAM-1 may be involved in histamine mediated BBB permeability.

P307

Isolated intracranial fibromuscular dysplasia resulting in large hemispheric infarct

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Background: Pathology proven fibromuscular dysplasia (FMD) involving the intracranial vessels in the absence of extracranial vessel involvement has not been previously reported.

Case History: A 36-year-old right handed female was transferred from an outside hospital where she had presented 1 day earlier with headache and a mild left hemiparesis. She had a history of a prior right hemisphere stroke aged 27 years. Our admission examination found a left homonymous hemianopia, visuospatial neglect, sensory inattention and mild left facial and arm weakness. Admission CT brain showed subacute infarction in the right posterior cerebral (PCA) territory and a more recent infarct involving the posterior division of the right middle cerebral artery (MCA). The patient's neurological status deteriorated within 8 hours and repeat CT brain showed the original infarcts with evolution of the more recent right middle cerebral artery (MCA) infarct, intraventricular haemorrhage, oedema and midline shift. The patient did not respond to medical intervention for raised intracranial pressure and neurosurgical intervention to decompress the right hemisphere was considered, but not pursued. The criteria for brainstem death were fulfilled within 32 hours of presentation to our hospital.

Results: Neuropathologic examination demonstrated an older right PCA infarct and a more recent right MCA infarct resulting in midline shift, diencephalic herniation and secondary brainstem haemorrhages. The anterior and posterior circulation vessels on both sides showed marked FMD with complete thrombotic occlusion of the right PCA, dissection with variable non-thrombotic occlusion of the right MCA and a 70 % occlusion of the left MCA. The extracranial circulation and renal arteries appeared normal.

Conclusions: Isolated intracranial-FMD resulted in a fatal large hemispheric stroke in our patient and was likely the pathogenic mechanism underlying her prior stroke. Of note, she was not on any form of antithrombotic therapy since her first stroke event. Isolated intracranial-FMD is exceptionally rare, but its associated vascular thrombotic complications may be prevented with anticoagulation. Restricted access to intracranial imaging modalities, however, particularly in the Irish healthcare system may result in underdiagnosis of this stroke mechanism, with consequent increased neurologic morbidity and mortality.

P308

Anterior circulation infarction associated with diffuse cerebral vasospasm after uncomplicated resection of an acoustic neuroma

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Background: Delayed ischaemic neurological deficit secondary to cerebral vasospasm is a well recognised sequel to subarachnoid haemorrhage. The degree of vasospasm is variable it is usually asymptomatic or associated with transient neurological dysfunction.

Methods: A 30-year-old man presented with a progressive three-month history of headache and ataxia. CT brain revealed a cerebellopontine angle (CPA) tumour, which was subsequently resected without apparent complication. Postoperatively the patient had a left lower motor neurone facial weakness, but was otherwise neurologically intact. He was discharged on the sixth postoperative day. Pathological examination demonstrated a cystic acoustic neuroma. He represented with a major non-dominant hemispheral stroke syndrome encompassing visuospatial neglect and a dense left hemiparesis twelve days post-operatively. Admission CT brain revealed a small extra-axial haematoma at the site of the craniotomy, but no other pathology. Repeat CT brain confirmed the interval evolution of a right middle cerebral artery territory infarct with involvement of the subcortical structures and mild mass effect. He had no obvious stroke risk factors. Stroke work-up including thrombophilia and autoimmune screen, ECG, carotid duplex scan and echocardiography revealed no obvious stroke mechanism. A formal cerebral angiogram showed diffuse vasospasm in the carotid and basilar circulations with severe MCA involvement bilaterally.

Results: Antiplatelet, statin and nimodipine therapy were commenced and his BP was maintained with intravenous fluids. Angioplasty and stenting of the symptomatic right MCA vasospasm were considered but not pursued, as his clinical neurological course was stable. A repeat cerebral angiogram performed three weeks later showed resolution of the diffuse vasospasm.

Conclusions: Symptomatic diffuse cerebral vasospasm (CV) is a rare complication of microneurosurgical procedures such as treatment of intracranial aneurysms or of skull base tumours. Delayed CV has been reported previously in association with uncomplicated CPA tumour resection in only 3 patients but the diffuse involvement, shown by angiography, makes this case unique. We discuss possible patho-physiological mechanisms underlying the diffuse cerebral vasospasm affecting the anterior circulation and highlight possible intra-operative risk factors and treatment approaches.

Muscle disorders

P309

Spontaneous recovery of a childhood-onset mitochondrial myopathy caused by a stop mutation in the mitochondrial cytochrome C oxidase III gene

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Recently, we reported on a patient suffering from mitochondrial myopathy with ragged red fibers (RRF), lactic acidosis, exercise intolerance and delayed growth with a heteroplasmic G9379A nonsense mutation (W58X) in the mtDNA encoded COIII subunit gene. An actual follow up examination of the patient showed remarkable clinical and electrophysiological improvement. On a repeated muscle biopsy signs of histological and immunohistological improvement of the mitochondrial myopathy were found, which was associated with a significant decrease (from 93 % to 50 %) of the mutational load of G9379A in skeletal muscle confirming a spontaneous regression of the disease. Myoblasts of the patient did not carry the mutation, therefore we suggest that the fusion of wild-type mtDNA containing myoblasts into existing muscle fibers might positively influence the mutational rate in our patient's muscle.

Our results demonstrate the variable course of diseases caused by mtDNA mutations. We suggest that this possible positive outcome should be considered in counseling patients with mtDNA mediated disorders.

P310

Clinical and genetic study in a patient with muscle phosphofructokinase deficiency

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Muscle phosphofructokinase deficiency is a metabolic myopathy characterized by early muscle fatigue, proximal weakness, compensated hemolytic anemia and hyperuricemia.

We report on a 45 year-old man who, since he was 25, complained of diffuse myalgias, vomiting and myoglobinuria after physical exercise. Often hospitalized because of high serum CK levels (160,000 IU/l). He also had a mild cardiopathy with hypertrophic ventriculi. Neurological examination was unremarkable. Family history was negative for neuromuscular disorders but his 15 year-old son had slightly elevated serum CK (600 IU/l). Laboratory tests revealed mild reticulocytosis 2 % (v. n. 0–1.5 %), increased serum bilirubin 1.8 mg/dl, (n. v. 0.4–1) and hyperuricemia 8.5 mg/dl (n. v. 5–7). Ischemic forearm test showed a normal lactate rise. Muscle biopsy failed to show glycogen storage and biochemical studies revealed a 4 % PFK residual activity. Direct sequencing of PFK entire coding region evidenced two mutations in heterozygosity, one point mutation A to C determining an aminoacid change D591A, located in a quite conserved protein region, the second one (reported in an Italian patient) was a IVS6–2A/C. His three brothers and one son were heterozygous for the point mutation D591A whereas the son with hyperCKemia arbored only the IVS6–2A/C in heterozygosity. Absence of chronic muscle weakness and muscle glycogen storage as well as normal lactate rise are quite unusual features of a long-standing PFK deficiency, but biochemical deficiency was confirmed by presence of two mutations in heterozygosity.

P311

Idiopathic hyperckemia: follow-up of a large population of asymptomatic/oligosymptomatic patients

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Six years ago we performed a retrospective study of 114 patients presenting asymptomatic/oligosymptomatic hyperckemia, a diagnosis being made in 21 of them (Prelle et al. 2002). We now present the results of a long-term follow-up in 49 (52.7 %) of the still undiagnosed 93 patients.

Nobody has developed any specific neuromuscular disorder, but a diagnosis of dystrophinopathy carrier has been indirectly made in a female patient, and, in another case, a condition of type I SMA carrier is under investigation.

Almost all subjects still have hyperckemia,though the mean CK value is lower than before. CK levels have become normal in 6 subjects without any modification of their working/physical activity.

Over half of the subjects have remained asymptomatic, 5 previously oligosymptomatic patients now referring partial or complete improvement.

One patient has died of a throat carcinoma, and three have developed non-neuromuscular disorders (monoclonal gammopathy, nephropathy, non-alcoholic steatosis). Though the association between hyperckemia and cancer is known, no correlation has been thus far reported with the other diseases.

Also, we noted no follow-up differences between patients with pathologic EMG and/or muscle biopsy and those with normal results at first examination, which seems to be against the hypothesis that only subjects with normal exams are indeed affected with idiopathic hyperckemia.

P312

Concurrent presentation of ocular myasthenia and euthyroid Graves ophthalmopathy

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Myasthenia gravis may coexist with other autoimmune disorders. Prevalence of Graves disease in patients with myasthenia Gravis is 3 to 8 %. Conversely, the frequency of myasthenia gravis in patients with hyperthyroidism is 20 to 30 times that in the general population. Ocular muscles represent a common target of these disorders. About 90 % of patients with thyroid-associated ophthalmopathy have hyperthyroidism. The remainder have autoimmune hypothyroidism or are euthyroid at presentation. When

myasthenia with ocular manifestations and euthyroid ophthalmopathy coexist diagnostic errors may occur.

We report the case of a 34-year old man with a short history of vertical and horizontal diplopia with diurnal variation. There was bilateral exophthalmus and ptosis of the left lid. Because of the combination of the above symptoms and signs, coexistence of thyroid-associated ophthalmopathy and ocular myasthenia was suspected. Magnetic resonance imaging of the orbits revealed thickening and high signal intensity on T2 (due to the edema) of the right superior rectus and bilateral inferior recti, as well as mild thickening of the right lateral rectus without high signal intensity, findings consistent with thyroid ophthalmopathy. Laboratory investigation revealed subclinical hyperthyroidism with marginally positive antibodies to thyroglobulin. Diagnosis of ocular myasthenia was based on positive Tensilon test, single-fiber electromyography of the orbicularis oculi and clinical response to pyridostigmine. Therapy with methylprednisolone, methimazole and pyridostigmine was set, with excellent clinical response.

Concurrent presentation of ocular myasthenia and euthyroid Graves ophthalmopathy is rare and may be easily overlooked due to overlapping clinical features of the two disorders and the absence of symptoms of hyperthyroidism and generalized myasthenia. However, prompt diagnosis and institution of immunosuppressive therapy in patients with thyroid ophthalmopathy in the early-dynamic phase of the disease will prevent irreversible damage of the extraocular muscle and optic nerve function.

P313

A retrospective long-term follow-up study of 26 patients with pure inflammatory myopathy. Contribution to the prognosis of polymyositis

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Background: A refinement of diagnostic criteria for inflammatory myopathies (IM) allows to distinguish between polymyositis (PM), dermatomyositis (DM) and sporadic inclusion body myositis (sIBM). The diagnostic of PM is based on clinical and histopathological evidences, treatment remains empirical and prognosis is variable.

Objective: To improve the understanding of clinical course and prognosis of PM.

Patients/Methods: Adult patients diagnosed from 1992 to 2003 followed for at least 2 years with pure autoimmune "polymyositis", according to the registration systems for clinical and muscle biopsy diagnoses. Patients with "possible myositis", DM, sIBM, PM associated with connective tissue disease, sarcoidosis or malignancies, have been excluded. Inclusion criteria for eligibility were subacute onset, symmetric proximal weakness, muscle biopsy confirmative of endomysial and extend mononuclear cell infiltrates, and CK more than two times elevated. Patients had been treated with either corticosteroids, immunosupressive agents or intravenous immunoglobulines. We re-examined periodically 22 of the 26 included patients (80 %).

Results: Seven patients were male and 19 female, the age of onset of the disease was during the second (4 cases), third (3 cases), fourth (7 cases), five (6 cases), sixth (3 cases), seventh (2 cases) or eighth (1 case) decades. Four patients presented as a juvenile form (< 18 years), three as a "dropped head", three with a predominant dysphagia, four with a severe and rapid muscular atrophy, the rest with classical proximal weakness. Four patients had died (19 %), – two during the first weeks after onset and two, a few years later, all of them with generalised weakness. Three patients (15 %) with the juvenile form remain disabled due to muscle calcinosis. Six patients (30 %) remain stationary under steroid therapy. Five patients (22 %) remain asymptomatic and without treatment. Three patients (15 %) with persistent chronic weakness have been diagnosed with dysferlinopathy after re-evaluation.

Conclusions: Prognosis in PM is highly variable and appears to be independent of the treatment applied and the degree of initial muscular atrophy but related with the age at onset. Juvenile forms tend to be more disabling at long term due the calcinosis. Exitus in more frequent among older patients. In patients with chronic PM, the diagnosis of dysferlinopathy should be ruled out.

P314

Erectile dysfunction in myotonic dystrophy type 1

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Myotonic dystrophy (DM1) is an autosomal dominant disorder caused by an unstable (CTG)n repeat expansion in the DM1 protein kinase (DMPK) gene. The DMPK gene expression is pleiotropic and includes the premature expression of several age-related signs, symptoms and metabolic disturbances including hormonal dysfunctions, progressive decrease in muscular mass, presenile cataracts, alopecia, reduced alertness, insulin resistance, dyslipidemia, erectile dysfunction and hypogonadism.

The aim of this study was to evaluate the frequency and characteristics of erectile dysfunction in a series of DM1 patients.

Twenty-eight consecutive men with DM1, aged between 18 and 62 years (median 37 years), and 28 normal age-matched controls, accepted to participate in the study. The subjects' sexual function was assessed using the International Index of Erectile Function (IIEF), an internationally validated 15-item questionnaire. The IIEF addresses the relevant domains of male sexual function, i. e. erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction.

Twenty-one patients and 6 controls had an erectile dysfunction ($p < 0.001$). The dysfunction in DM1 group was severe in 8 subjects, moderate in 4 and slight in 9. Patients showed a significant lower scores in erectile function ($p < 0.001$), orgasmic function ($p = 0.005$), intercourse satisfaction ($p = 0.005$) and overall satisfaction ($p = 0.002$), compared to controls. On the contrary the scores in sexual desire in patients and controls were not different. Age and CTG expansion showed no correlation with the different scores.

Three/four of patients in our DM1 series showed symptoms of erectile dysfunction, without changes of sexual desire. Medical treatments of erectile dysfunction could find an interesting field of application in DM1.

P315

Conus medullaris lesion causing bilateral lower limb myokymia

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Background: Myokymia describes involuntary, undulating contractions of muscle fibres caused by bursts of single motor unit potentials firing at rates of 5–150 Hz. It can be associated with various central and peripheral nervous system disorders (e. g. multiple sclerosis, Guillain-Barre syndrome) and may be focal or generalised.

Case: We describe the case of a 69 year old man who presented 24 years ago with involuntary twitching in both legs. Examination revealed myokymia in both quadriceps muscles without hypertrophy (video to be shown). The rest of the neurological examination was entirely normal. Electromyography (EMG) revealed spontaneous, repetitive motor unit activity limited to the quadriceps femoris muscles. There was no evidence of myokymia else where. Extensive investigation at the time revealed no cause of the myokymia. In 1989 when MRI imaging became available further investigation of his spine was carried out. This showed a lesion in the posterior aspect of the conus involving the origin of the filum terminale consistent with a lipoma or hamartoma.

Discussion: This case demonstrates that focal myokymia may be related to an underlying structural lesion. We suggest that in bilateral lower limb myokymia without evidence of an underlying neuropathy that a conus medullaris lesion is sought. In addition, it is clear that muscle hypertrophy is not universal in the presence of prolonged myokymia.

P316

Chronic fatigue syndrome and mitochondrial myopathy: a diagnostic approach with the bicycle ergometer graded exercise test

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Objective: To analyze the clinical features of patients with chronic fatigue syndrome (CFS) diagnosed in our hospital, to determine the aerobic work capacity of them and compare it with that of two groups: one with mitochondrial myopathy (MM) and another healthy control group.

Methods: We studied consecutive patients meeting the Oxford criteria for diagnosis of the CFS and MM patients between 1998 and 2003. Clinical features, electromyography results, neuropathological findings (muscle biopsy) and response to a bicycle ergometer incremental exercise test were analyzed. Statistical analysis: Mann-Whitney U test

Results: 43 subjects: 12 with CFS, 21 with MM and 16 healthy. All of them had similar age range. CFS patients: mean age 44 years (range: 29–61), 9 female and 3 male. Fatigue (100 %), muscle pain (90 %), sleep disruption (90 %), exercise intolerance (80 %), mild myophatic changes in electromyography (95 %) and mild histological findings in striate muscle biopsy (58 %) were the more important characteristics. Graded exercise test: CFS patients had a lower peak work rate ($p < 0.001$), peak oxygen uptake ($p < 0.001$), anaerobic threshold (52.1 ± 10.7 vs 63.3 ± 14 $p < 0.005$) and

efficiency of muscular work than healthy subjects, and also CFS patients had greater cardiovascular response to exercise ($p < 0.005$) than patients with MM.

Conclusions: CFS is a clinical diagnosis of exclusion. They are more frequently female, and the most have mild changes in electromyography and muscle biopsy.The bicycle ergometer graded exercise test showed statistically significant differences between patients with CFS and MM, and healthy controls.

P317
Exacerbation of myasthenia gravis during interferon alpha and interleukin-2 therapy
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Interferon alfa (IFN-a) and interleukin-2 (IL-2) are used now for the treatment of chronic viral hepatic and some malignant diseases. We describe a case of one patient who developed exacerbation of myasthenia gravis (MG) during IFN-a and IL-2 therapy. He was suffering from MG since July 2002 (MG was diagnosed on the base of clinical picture, decrement of repetitive nerve stimulation and positive anti-ACHR antibody titer). Before it had been discovered renal cell carcinoma in this patient in 1997.

The occurrence of auto-immune diseases or deterioration of pre-existing disorders has recently been described after cytokine treatment. The present report gives evidence to the exacerbation of MG by externally administered IFN-a and IL-2 in a patient with metastasized renal cell carcinoma. A 55-years-old man received IFN-a;–2b (Intron A) and interleukin-2 (Proleukin) in July 2003. 4th day after administration of IFN-a and Il-2 he developed intermittent diplopia. 7th day after beginning of treatment he had mild weakness of limb and neck muscles and 3 days later he suffered from generalized weakness. The treatment with IFN-a and IL-2 was discontinued 14 days after the first administration. We have started with PE (5 times), but patient's condition was still worsening and later he developed myasthenic crisis (MC). Patient was admitted to ICU. MC was very serious and continued 1 month. At his most recent visit, in January 2004, the patient was stable.

P318
The effect of pain on the quality of life in neuromuscular disorders
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The aim of the study is to compare the quality of life in neuromuscular patients with and without pain. Thirty nine different kind of neuromuscular patients are included to the study. Twenty two of these patients (Age: 40.22 ± 17.35) complaint with musculoskeletal pain, 17 of these patients (Age: 31.76 ± 13.64) haven't got any pain. The quality of life of these patients is evaluated with Nottingham Health Profile. Pain complaint is evaluated Visual Analaog Scale (0–10). The patients are divided into two grups according to their pain complaint. Disease duration of the patients in the grup included pain complaint is 8.63 ± 6.91 year, pain severity is 5.02 ± 2.64 and the localization of the pain is on lumbosacral region. Disease duration in the other grup is 5.93 ± 5.94 year. When the total points of quality of life index is compared, the quality of life of the patietns without pain is more significant than the other grup ($p < 0.05$). When the subparameters of Nottingham Health Profile is compared there is only a significant difference in pain and functional ability is found ($p < 0.05$). As a result as pain isn't a primer semptom in neuromuscular patients because of the muscle weakness, muscle shortness and postural adaptations it could be seemed as a secondary problem and could effect the quality of life.

Multiple sclerosis

P319
Novel macrophage-specific imaging in inflammatory lesions of the CNS by superparamagnetic iron particle based ultrasound
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Background: The non-invasive and dynamic detection of inflammatory cell infiltration is critical for the diagnosis and monitoring of inflammatory CNS disorders. The recent development of superparamagnetic iron particles (SPIO) as sensitive contrast agents for macrophage neuroimaging with MRI (Bendszus M., Stoll G., J Neurosci. 2003; 23:10892–6) allows the specific detection of macrophages.

Objective: To test the value of ultrasonographic techniques with SPIO as a contrast enhancing macrophage marker.

Methods: In a prototypic model of autoimmune CNS inflammation, experimental autoimmune encephalomyelitis (EAE) in congenic Lewis rats ($n = 10$), we evaluated site and extent of hematogenous macrophage infiltration, using SPIO enhanced US imaging of rat brains during a relapse of EAE.

Results: We show marked focal echogenicity in EAE-typical areas of the brain including the periventricular region, the cerebellum and the brain stem. The US imaging results closely correlated with the results from SPIO enhanced MR-imaging, with histologic studies showing iron-laden macrophages in demyelinated lesions, and with the course of EAE.

Conclusion: These results suggest that SPIO enhanced US may become a valuable non-invasive tool for monitoring of macrophage infiltration in the CNS, but also for other inflammatory organ diseases.

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P320
Increased risk of autoimmune thyroiditis in multiple sclerosis in Sardinian patients carried by CTLA-4 gene
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Background: Cytotoxic lymphocyte antigen 4 (CTLA-4) molecule plays a key role in immunological tolerance by T cells downregulation. CTLA-4 polymorphisms have been reported associated and linked to organ specific autoimmune diseases, such as autoimmune thyroid diseases (ATDs) and multiple sclerosis (MS). In order to verify the role of CTLA-4 in MS and in the co-occurrence of ATDs in MS patients, we analyzed two CTLA-4 polymorphisms in Sardinian MS patients with (ATD+) and without (ATD–) ATD. Presence/absence of ATDs in patients was defined according to the "Thyroid American Association" criteria.

Subjects and Methods: In total, 637 MS patients (440 women and 197 men) were included in the study. Thyroid function was analyzed in 449 patients: 76 patients were ATD+, while 373 were ATD–. In 188 patients both parents were also typed.

CTLA-4-318 C/T and exon 1 +49 A/G polymorphisms and HLA-DRB1-DQB1 analysis were performed using high molecular typing with ASO probes and dot-blot hybridization.

Haplotypes resulting from combination of –318 C/T and +49 A/G polymorphisms were analyzed. Association of CTLA-4 polymorphisms with MS was studied by the transmission disequilibrium test (TDT), with or without conditioning families to the carriage of HLA-DRB1-DQB1 predisposing (DR+) or not predisposing (DR–) haplotypes. A case-control design was used to analyze association of CTLA-4 polymorphisms in patients with ATDs, comparing patients ATD–, ATD + and controls (C), with or without conditioning patients according to DR+/DR–.

Results: No evidence of association of the –318 C/+49 A/G haplotype was found in families, either considering families with or without conditioning for the DR+/DR– haplotype in probands. Combination of CTLA-4 haplotypes did not differ in patients ATD– compared to C, either in the whole population or conditioning for DR+/DR–. An increased risk ($OR = 1.8$, $P = 0.01$) was found in patients ATD + carrying the –318 C/+49 G haplotype and, conversely, a decreased risk ($OR = 0.5$, $P = 0.006$) was found in patients ATD+ carrying the –318C/+49A haplotype compared to C. The risk was independent from the HLA haplotype, thus supporting an independent role of CTLA-4 in favouring ATDs.

Conclusion: Our results do not support a role of CTLA-4 polymorphisms in susceptibility to MS in Sardinian patients, but showed an effect on ATDs risk. These findings might partially explain conflicting results regarding role of CTLA-4 gene in MS reported in other populations.

P321
APOE e4 frequency in African-American MS patients and association with disease severity
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Objective: To determine the frequency of APOE e4 in African-Americans with MS and correlation with disease severity.

Background: The APOE gene is a polymorphic gene located on chro-

mosome 19, with e2, e3, and e4 being the most common allele types. In Caucasians, the frequency of APOE e4 has been estimated at 10 to 20 %. There is growing interest in how APOE e4 expression may influence outcome in chronic neurological disease. Several investigators have studied the association between APOE e4 and the severity of disease in MS. Most data suggest that APOE e4 predisposes to greater disability and more aggressive disease course although some investigators have found to the contrary. We have previously reported that MS appears to be clinically more aggressive in AA with MS compared to Caucasian MS patients. However, no study has examined the frequency of APOE e4 in AA MS patients or its association with disease severity.

Methods: 96 well-characterized AA MS patients at our MS Clinic were enrolled. Time to EDSS 6.0 and 6.5 were available when applicable. MRI and CSF data were also available. Blood for APOE e4 was processed by laboratory technician blinded to clinical features. Presence of APOE e4 was determined after establishing demographic features, minimizing bias from the retrospective collection of clinical data and its potential association with APOE e4 allele.

Results: Mean age, EDSS and disease duration (DD) were 42.8 years, 4.8 and 9.6 years, respectively, for the entire cohort (n = 96). 40 of 96 (41.7 %) patients were heterozygous carriers for APOE e4. Mean age, EDSS, and DD were 41.1 years, 5.0, and 8.7 years, respectively. In the APOE e4 positive group, time to EDSS of 6.0 (n = 21) and 6.5 (n = 12) were 4.8 and 6.6 years, respectively. In the APOE e4 negative group, time to EDSS 6.0 and 6.5 were 6.3 and 10.4 years, respectively. Preliminary analysis showed that APOE e4 positive AA MS had greater involvement of spinal cord MRI abnormalities than APOE e4 negative patients. Results on additional patients and detailed statistical analyses will be presented.

Conclusions: Our study showed a much higher frequency of APOE e4 allele in AA MS patients compared to Caucasians. Furthermore, it appears that the presence of APOE e4 allele predisposes to a more aggressive disease course and greater disability in a shorter period of time. Further, large prospective studies are warranted to study the association of APOE e4 to disease severity in AA MS patients.

P322

Increasing incidence of multiple sclerosis in the province of Sassari, Sardinia

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Previous population-based prevalence studies demonstrated that Sardinia, is a high-risk area for multiple sclerosis (MS), with prevalence rates of 150 per 100.000, i. e., 2- to 3-fold higher than in other Italian or Caucasian populations, and in contrast with the 'latitude gradient theory'. An increasing prevalence trend was also reported for the past 3 decades. The aim of the present study was to analyse MS incidence trend over time by time periods, sex, disease course, age of onset and province sub-areas of residence as identified in linguistic studies.

A total of 690 (F:M ratio of 2.57) MS patients (Poser criteria) identified using the patient registry at the Inst. of Neurology, University Hospital of Sassari, with disease onset between 1965 and 1999 within the province of Sassari, Sardinia, were included in the analyses. The study area lies between latitude 40°30'N and 41°N and encompasses 90 administrative communities, mostly populated by Sardinian natives. The total population increased from 397,891 (1971 census) to 453,628 (2001 census).

The incidence showed a marked and significant increase in the beginning of the study period with 1.2 per 100,000 in the period 1965–69 and 2.3 in the period 1970–75 to a rather stable rate above 6.0 for all the last three five-year periods of 1985–89, 1990–94 and 1995–1999. A similar distribution over time was found for all of the six linguistic sub-areas. There were only 194 (28 %) male patients, but no significant difference in trend was found between the sexes during the study period. A steady and significant increase in the mean age at onset was found from 26.3 years in 1965–69 to 30.6 years in 1995–99.

Sardinia is a high risk area for MS and the disease appears to significantly having increased over time. As from comparisons with other surveys, improved diagnostic accuracy and epidemiological methodology, and genetic make-up cannot per se fully explain such observations. The increasing susceptibility to MS and the shift in age at clinical onset suggest a change in exposure to an exogenous etiological factor in this area.

P323

Short-term clinical validation for the immunomodulatory drug-matching method in multiple sclerosis patients

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Currently, the clinical decision related to which immunomodulatory treatment will be initiated in multiple sclerosis (MS) patients is arbitrary. In the present study we correlated between the laboratory method for drug selection and short-term clinical outcome in relapsing-remitting (RRMS) patients. The immunomodulatory drug matching method is based on inhibition of cytokine secretion after peripheral blood mononuclear cells were stimulated in short-term culture (48 h) by synthetic myelin oligodendrocyte glycoprotein (MOG) immunodominant peptide in the presence of either interferon beta-1a, interferon beta-1b, Copaxone or IVIg. TNF-alpha level was measured by ELISA in the supernatants. We hypothesized that an immunomodulatory drug with higher in-vitro TNF-alpha inhibition activity will induce a better suppression of disease activity.

The in-vitro immunomodulatory drug matching method was applied for 54 RRMS patients. Following the laboratory test, 40 patients received an immunomodulatory drug according with the in-vitro drug matching results (matched group), while 14 patients received treatment different from the laboratory test results (non-matched group). The number of relapses was compared between groups after short-term follow up of 16 weeks. In the matched group, 2.5 % of patients (1/40) had an acute relapse, while in the non-matched group 28.6 % of patients (4/14) developed a clinically defined relapse ($p < 0.01$).

Our results suggest a good clinical correlation between short-term clinical outcome and in-vitro inhibition of cytokine secretion. Accordingly, we propose the use of the immunomodulatory drug matching method to assist neurologists in the clinical decision as to which immunomodulatory drug the patient will receive.

P324

Influence of first year interferon-beta treatment on quality of life in multiple sclerosis patients

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Objective: To evaluate the impact of interferon (IFN)-beta on quality of life (QoL) in multiple sclerosis (MS) patients during the first year of treatment.

Background: IFN-beta has been shown to have beneficial effects on the course of MS, but the influence of route and frequency of administration and side effects on QoL are often underestimated.

Design/Methods: One hundred twenty seven MS patients, 101 relapsing remitting and 26 progressive course, were analysed. Forty-one patients received IFN-beta and 86 patients were disease modifying treatment free. The treatment duration was 3.62 + 1.92 months (range1–9). No patient was under steroid from at least three months before study entry. QoL was assessed using MSQoL54 inventory scale and related to clinical, demographic and MRI parameters. A complete clinical assessment included clinical disability (EDSS), cognitive function (Mini mental state examination MMSE), fatigue (fatigue severity scale-FSS) and depression (Beck depression inventory-BDI). Brain MRI was performed on a 1.0 Tesla. T2 and T1 lesion loads were evaluated by a semiautomated segmentation technique based on local thresholding.

Results: Treated and untreated MS groups did not differ in MSQoL-54 physical and mental health scores, EDSS, FSS and BDI. Untreated patients had higher age at observation ($p = 0.03$) and disease duration ($p = 0.016$) in comparison to treated group, whereas treated patients showed higher T2 lesion load ($p = 0.03$). By multivariate analysis (Backward), FSS ($p = 0.0001$), BDI ($p = 0.0001$), EDSS ($p = 0.0001$) and age at observation ($p = 0.002$) were the main factors inversely related to physical health QoL, contributing to 80 % of variance. BDI ($p = 0.0001$) and age at observation ($p = 0.004$) were the variables included in the model that explained 50 % of variance of mental health QoL. IFN-beta treatment did not influence the QoL, neither relationship was found with disease course and MRI lesion load. IFN-related side effects were found in 49 % of patients and fatigue was more frequent (19 %). The QoL was not influenced by side effects, however in treated group FSS was significantly associated with a poor physical health QoL.

Conclusions: The QoL in MS was negatively associated with fatigue, depression, EDSS and age at observation. First year IFN-beta treatment did not influence the QoL, nevertheless the fatigue was the best predictor of a poor physical health score in treated patients.

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P325

Relationship of cognitive performance with illness variables in patients with multiple sclerosis

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Background: The presence of cognitive impairment in patients with multiple sclerosis (MS) has been known since Charcot. Although a series of studies investigating the cognitive impairment in MS patients exist, they concern group of patients differing in the disease type, disease duration, age of disease onset and the physical disability. This may explain the contradictory findings that have been reported regarding the factors (illness variables) relating with the cognitive performance in the specific group of patients.

Goal: Purpose of the present study is to investigate the relationship between cognitive impairment and disease duration, age of disease onset, physical disability, as well as to examine whether patients with relapsing-remitting (RR) and secondary-progressive (SP) MS present distinct neuropsychological profiles.

Method: The present study was conducted in the University Neurology Clinic of the General Hospital AHEPA in Thessaloniki. Participants were 25 patients suffering from relapsing-remitting MS, 15 from secondary-progressive MS and 15 healthy controls. Neuropsychological evaluation was performed using the WAIS-R. Physical disability was measured using the Expanded Disability Status Scale (EDSS).

Results: Our results reveal no correlation between variables of cognitive performance and either disease duration (Pearson values ranging from $r = -0.118$ to $r = 0.304$, $p > 0.05$) or age of disease onset (Pearson values ranging from $r = 0.015$ to $r = 0.322$, $p > 0.05$). Moreover, no correlation was observed between variables of cognitive performance and physical disability (Pearson values ranging from $r = -0.099$ to $r = -0.352$, $p > 0.05$). Finally, the comparisons of the RR with the SP patients indicate that SP patients perform slightly worse only on tasks requiring motor speed such as Block Design ($p = 0.031$), Object Assembly ($p = 0.045$) and Digit Symbol ($p = 0.040$).

Conclusions: Our findings demonstrate that illness variables such as disease type, disease duration, age of disease onset and physical disability are not significantly related with variables of cognitive performance in patients with MS. Finally, they indicate that RR and SP patients present in general similar cognitive patterns.

P326

Bcl-2, Bax, Cytocrome-c mitochondria mediated apoptosis proteins during glatiramer acetate treatment in multiple sclerosis patients

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There is emerging evidence that apoptotic deletion of autoreactive lymphocytes is defective in patients with Multiple Sclerosis (MS), thereby permitting these cells to perpetuate a continuous cycle of inflammation within the Central Nervous System (CNS). The cause of this lymphocyte resistance to cell death in MS is not fully understood, but appears to involve apoptotic defects at multiple cellular levels. Recombinant interferon-beta (rIFN-beta) is reported to enhance lymphocyte apoptosis but also Glatiramer Acetate (GA)-mediated immunomodulation might involve the apoptotic elimination of T helper cells.

Aim of this study was to analyze pro (Bax, Cyt-c, APAF-1) and anti-(Bcl-2) apoptotic proteins in peripheral lymphocytes cytosol and membranes fractions during GA treatment in relapsing-remitting (RR) MS patients.

Blood samples from 10 RR MS patients were longitudinally collected before and every three months during GA treatment. Ten healthy individuals blood samples were also analyzed.

Cell membranes and cytosols from Peripheral Blood Mononuclear Cell (PBMNC) were obtained and membrane Bcl-2, Bax, Cyt-c and cytosolic Cyt-c and APAF-1 were quantified by western blot analysis followed by densitometric scanning.

Our results showed significant decrease in mitochondrial associate Bcl-2 anti-apoptotic protein and increase in Bax pro-apoptotic protein during GA treatment. Interestingly release of cytochrome-c from mitochondria in the cytosolic fraction was increased more than two-fold during the follow-up study, whilst APAF-1 did not change.

These data show that apoptosis induction could represent a possible mechanism explaining the beneficial effect of GA on MS disease process.

P327

Normal and abnormal brain tissue volumes and neuropsychological status in relapsing-remitting multiple sclerosis

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Introduction: Cognitive dysfunctions occur in up to 60 % of patients with multiple sclerosis (MS), are already present in the initial stages of the disease, and have been found to correlate with total lesion load (LL) at conventional MRI, although this correlation was not evident at the disease onset.

Aim of this study was to assess the relationship between brain tissue volumes, as measured by segmentation of conventional brain MRI studies, and neuropsychological (NP) status in relapsing remitting (RR) MS patients with short disease duration.

Material and methods: 87 RR-MS patients (52 females) were enrolled. Mean age ± SD was 34.2 ± 8.5 years, Expanded Disability Status Scale was 2.3 ± 0.7, and disease duration 1.7 ± 3.3 years.

MRI protocol included conventional spin-echo sequences providing T1w (500/10) and PD/T2w (2400/10–80) 3 mm-thick axial images, sampling the entire brain at 48 levels.

MRI triplets were segmented into grey matter (GM), white matter (WM), abnormal WM (aWM), and CSF with a fully automated procedure. Tissue volumes were normalized by intracranial volume. All patients underwent 1) the Brief, Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis (Rao); 2) the Stroop color/Word interference test; 3) the National Adult Reading Test; 4) the Hamilton test. Stepwise multiple regression analysis was performed separately for each NP score.

Results: Among the brain tissue volumes, GM loss correlated to the 'Word List Generation' perseverations ($p < 0.001$), while CSF inversely correlated to both number and speed of correct answers under interfered conditions at Stroop test ($p < 0.01$); no relationship emerged with Stroop interference. PASAT ('hard' condition) correlated to normal-appearing WM volume ($p < 0.01$). No correlation was observed between LL and any of the NP tests.

Conclusions: Our results show a correlation between GM loss and selected NP tests in RR-MS patients, suggesting a different mechanism for cognitive impairment beyond simple disconnection due to the presence of demyelination plaques. Differences between our results and previous studies focusing mainly on LL or global atrophy suggest different mechanisms possibly involved in the pathogenesis of cognitive impairment in early stages of the RR-type disease.

P328

Multiple sclerosis in a genetic isolate from the Netherlands

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Background: Identification of genes involved in the etiology of multiple sclerosis (MS) has proven difficult. This has at least partly been hampered by the heterogeneity of the populations studied thus far. The study of genetically isolated populations to identify genetic factors involved in this complex disease has gained interest. Few pedigrees of MS families are known. In some studies MS has been shown to be associated with type I diabetes mellitus (DM) or autoimmune thyroid disease.

Objectives: Purpose of this study was to identify MS cases within a Dutch genetically isolated population and attempt to link them to a common ancestor. A second purpose was to assess the familial association of type I DM, autoimmune thyroid disease and MS and the association with HLA class II alleles. Finally, a genome screen will be performed.

Methods: This study is part of a larger research programme named Genetic Research In Isolated Populations (GRIP) in the Southwest Netherlands. All MS patients were traced and an extensive family history was taken. Special emphasis was paid to the co-occurrence of autoimmune disease. Genealogical data extended up until 14 generations, with support of an experienced genealogist. DNA was isolated from all patients, relatives, and if possible spouses.

Results: Thirty-five female and 13 male MS patients were identified. Mean age at onset of symptoms was 32 years and at diagnosis 38 years. Forty patients had a relapsing remitting course and 8 a primary progressive course. Twenty of the 48 patients could be linked to a common ancestor. Clinical characteristics of these 20 patients were not different from those of the patients who could not be linked to the pedigree. Familial co-occurrence of MS was observed in 21 % of the 48 patients. Seventeen percent of the cases had a relative with thyroid disease and 10 % had a relative with type I diabetes mellitus. Families with no co-occurrence of autoimmune diseases did not have different clinical characteristics as families

with co-occurrence of such ailments. HLA-DR2 positivity was equal amongst MS patients and controls (25 %).

Conclusions: Familial aggregation of MS is high in this Dutch genetic isolate, with a substantial co-occurrence of other autoimmune diseases. HLA-DR2 is not specifically linked to the MS cases. Other genes that contribute to MS, and perhaps also to thyroid disease and type 1 DM could be involved. A genome screen is currently being performed.

P329

Switching disease modifying therapies in multiple sclerosis patients: a study on 110 patients

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Introduction: Three interferons (IFN) and Copaxone have been licensed as disease modifying therapies (DMT) for relapsing multiple sclerosis (MS) patients. In clinical practice, some patients switch from one DMT to another. This is due not only to poor perceived effect of the drug, but also to side effects and voluntary decision. We studied, from a large cohort of MS patients treated with DMT, the outcome of a group switching from one drug to another for disease activity and decreased compliance.

Patients and methods: We enrolled 540 patients from 1997 to 2003, in a main tertiary MS centre in southern Italy, treated with one among the available DMT. All patients underwent to regular clinical and laboratory examinations. Disease activity was defined as perceived lack of efficacy (relapses and disability progression). Decreased compliance was due to side effects and voluntary decision. Avonex and Rebif 22 were defined as lower-dose IFN; Betaferon and Rebif 44 as higher-dose IFN.

Results: 110 patients (20.4 %) switched DMT, after a mean ± SD (range) time of 24 ± 17 months (1–109). Patients were treated with Avonex (29 %), Betaferon (38 %), Copaxone (7 %), Rebif 22 (21 %), and Rebif 44 (5 %). Fifty-nine (53.6 %) patients changed DMT (usually shifting to a lower-dose IFN or Copaxone) after a mean therapy time of 22.7 ± 16.1 (1–62) months, due to decreased compliance. Fifty-one (46.4 %) patients switched to other DMT (usually a higher-dose IFN) after a mean therapy time of 25.6 ± 18.6 (2–109) months, due to disease activity. After switching therapy, 70 % of the patients (67 % in the disease activity group, and 73 % in the decreased compliance group) did not stop the new therapy, after a mean follow-up of 18.1 ± 13.7 (1–60) months, whereas 30 % interrupted the therapy, or switched again DMT, after 15.8 ± 11 (2–48) months.

Conclusions: In a large cohort of MS patients treated with DMT, 20.4 % switched drug after an about a 2-year therapy, due to perceived lack of efficacy or decreased compliance. In this series, 70 % of these patients remained on therapy to the new DMT, after a 18-month follow-up.

These results suggest that switching DMT may be considered a therapeutic opportunity (1) in patients with disease activity and perceived lack of DMT efficacy, in which a period with higher-dose IFN therapy may be useful; and (2) in patients with decreasing compliance or remarkable side effects, in which a period with lower-dose IFN therapy may be useful.

P330

Assessment of multiple sclerosis fatigue by use of a fatigue diary

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Objective: To assess level of fatigue in Multiple Sclerosis (MS) patients by means of a daily diary and to compare this assessment with existing measures.

Rationale: Fatigue is a common but complex symptom in MS. To obtain a more accurate picture of variation over time it is proposed that a frequently repeated measure is needed. A daily diary is a simple and familiar way of administering a repeated measure.

Method: A daily diary was kept for 56 days by 78 patients with clinically definite MS, chosen randomly from an outpatient population, irrespective of whether they felt they suffered with fatigue. The diary allowed estimation of fatigue severity on a modified visual analogue scale (VAS) at three times during the day. A brief description of any activity at the time was also noted and subsequently categorised into 5 levels of energy expenditure by the investigators. At five equitemporal time points throughout the study, the Fatigue Severity Scale (FSS) was administered. At three equitemporal time points the Guy's Neurological Disability Scale (GNDS) was administered.

Results: The results were analysed for Pearson correlation between FSS, the fatigue domain of GNDS and VAS scores at coincident time points (or the same day regarding the three VAS scores). There was moderate correlation between FSS and GNDS fatigue ($r = 0.65$, $p < 0.01$). However, there was only poor correlation between FSS and the VAS scores (Morning VAS $r = 0.20$, $p < 0.05$; Afternoon VAS $r = 0.30$, $p < 0.01$; Evening VAS $r = 0.23$, $p < 0.01$). Likewise, correlation between GNDS fatigue and VAS scores was weak but slightly higher than the FSS and VAS scores (Morning VAS $r = 0.29$, $p < 0.01$; Afternoon VAS $r = 0.38$, $p < 0.01$; Evening VAS $r = 0.34$, $p < 0.01$).

Conclusion: The poor to moderate correlations between both the FSS and GNDS fatigue domain with the VAS scores indicate that the measures are capturing different aspects of fatigue. This may be due to both the fact that fatigue varies with time and to problems with the very definition of fatigue. The GNDS fatigue domain defines fatigue as 'tiredness' and refers the subject to the past month. The diaries defined the limits of the VAS as being 'lively and alert' and 'completely washed out'; the temporal context was the preceding part of the day. The FSS makes no allusion to either the meaning of the word fatigue or the temporal context to which the scale is related. A more sophisticated method of assessing this complex symptom is necessary.

P331

Effect of MRI co-registration on serial brain atrophy measurement in multiple sclerosis

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Background: Serial magnetic resonance (MR) coregistration is an important component of medical image analysis. The effect of coregistration on the measurement of whole brain atrophy from serial scans in the short-term, in patients with multiple sclerosis (MS) has not been tested.

Objective: To test the effect of serial MR coregistration on brain atrophy measurement using different semiautomated and automated brain atrophy techniques in patients with relapsing-remitting (RR) MS.

Methods: Twenty eight patients with RR MS (mean disease duration 4.9 years, mean age 34.4 years and mean EDSS 1.4) were scanned at baseline and monthly for a period of three months with 2D spin-echo T1-weighted sequences obtained with non-gapped 3 mm axial slices. The percent change in brain volume (PCBV) was calculated by two semiautomated (Buffalo and Trieste) and also separately by two automated (Buffalo automated and SIENA) brain atrophy techniques. For coregistration of serial images we used a robust, fully automated linear image registration tool (FLIRT). PCBV was calculated before and after coregistration comparing scans from the following time periods: 1) baseline to month 3, 2) baseline to month 1, 3) month 1 to month 2, and 4) month 2 to month 3.

Results: The highest mean PCBV measured on non-coregistered images was detected for the baseline to month 3 time period, and ranged from –0.02 % for Buffalo semiautomated to –0.07 % for Trieste (p = NS). The highest mean PCBV measured on coregistered images was detected for the baseline to month 3 time period, and ranged from –0.07 % for SIENA to –0.09 % for Buffalo semiautomated (p = NS). At all time points of the study, there was no significant difference of mean PCBV measured on coregistered and non-coregistered images when comparing the results among the three brain atrophy segmentation algorithms.

Conclusions: This study did not demonstrate short-term changes in normalized brain volume during a three month period in patients with RR MS. Such changes could not be detected whether or not serial MR scans were coregistered. The type of segmentation algorithm used to measure whole brain atrophy did not affect the sensitivity of detecting any changes. A longer observation period is needed to assess whether the coregistration can affect brain atrophy measurement.

P332

Fatigue in multiple sclerosis: a clinical and quality of life assessment

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Background: Fatigue is among the most common symptoms of multiple sclerosis (MS) occurring in up to 80 % of patients. Often, patients define fatigue as one of their most disabling symptom, as it profoundly disrupts their occupation and social functions.

Objective: In the present study we aimed to survey the frequency and severity of fatigue and evaluate its impact on disability and quality of life in MS patients within the first decade from disease onset.

Methods: Fatigue was measured by the self-reported fatigue severity scale (FSS) in MS patients randomly selected from our computerized database according to the following criteria: definite diagnosis, disease duration of at least one year and expanded disability status scale (EDSS)

score < 5.5. Patients that responded as suffering from fatigue that impaired at least 25 % of their daily life activities were further assessed by the fatigue impact scale (FIS) and RAYS quality of life questionnaire. Demographic and clinical variables were evaluated for statistical correlations.

Results: Of 259 elligable patients that reported to suffer from fatigue, 122 patients (47.1 %, 91 females, mean age 41.8 years, mean disease duration 6.8 years) satisfied the additional criterion (fatigue impaired by at least 25 % their daily life activities). These patients were defined as suffering from significant fatigue, and had a mean FIS score of 74.7. Most (91.7 %) had a relapsing-remitting disease course, and the mean EDSS score was 2.9. Fatigue was reported to persist in 69 % of patients for more than one year, occurred most of the day in 30.9 %, and in 59.8 % was not associated with effort. The FIS score correlated with the three functional subcategories of the RAYS quality of life questionnaire assessing physical, psychological and social aspects ($p < 0.001$). No correlations were found between FIS score and disease duration or neurological disability.

Conclusions: Significant fatigue was found to occur in a nearly half of MS patients within the first decade from disease onset. Fatigue affected quality of life but was not associated with degree of neurological disability.

P333

Expression of type I interferon receptor in multiple sclerosis patients treated with different interferon-beta molecules

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Background: Multiple sclerosis (MS) is an inflammatory-demyelinating disease. IFN-beta has been shown to be effective in relapsing-remitting and secondary progresive multiple sclerosis with exacerbations. However, some MS patients fail to respond to IFN-beta therapy fully. The biological activity of IFN-beta is exerted through the IFN type I receptor, composed of two subunits, IFNAR1 and IFNAR2. Deficiency of one or both of these subunits may lead to a loss of interferon activity. We quantified the expression IFNAR1 and IFNAR2 in peripheral blood mononuclear cells (PBMC) from MS patients treated with different IFN-beta molecules.

Methods: mRNA expression of IFNAR1 and IFNAR2 was assessed by real-time RT-PCR quantification in PBMC. Results was expressed as a ratio of each gene with a house keeping mRNA expression as reference to normalise mRNA levels. Clinical disease activity was registered in a protocol during treatment. Patients were classified as responders or non-responders according to the annual relapse rate and EDSS.

Results: A total of 241 MS patients, according to the treatment, were classified in three groups: 53 treated with IFN-beta1b (Betaferon), 50 with IFN-beta1a (Avonex), 79 with IFN-beta1a (Rebif) and 59 without treatment. The results were statistically analysed by comparisons with a healthy control group. A non parametric test showed significant decrease in IFNAR2 expression in patients treated with IFN-beta compared to patients without treatment and healthy controls ($p = 0.001$). There was no differences in the IFNAR1 or IFNAR2 expression between patients with any of the treatment used.

Conclusions: Although we found a decrease in both IFNAR1 and IFNAR2 expression in MS patients respect to healthy controls, these were statistically significant in those MS patients treated with IFN-beta overall in IFNAR2 subunit.

P334

Self efficacy in multiple sclerosis: analysis of two UK scales using the Rasch measurement model

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Objective: To analyse and, if necessary, modify two existing scales measuring self efficacy in Multiple Sclerosis (MS) using the Rasch measurement model.

Rationale: Self Efficacy is the individual's belief that they have the ability to overcome challenges presented to them. It has been shown to predict psychological well being in chronic diseases such as arthritis, cancer, epilepsy & MS. In order for any scale to be used as a meaningful outcome measure it must posses both unidimensionality & items which operate at an interval scale. Both these constructs can be determined by using the Rasch model.

Method: Data from two scales, developed in Liverpool, UK (Rigby & Arlie), measuring self efficacy in MS, were obtained from a postal survey of MS patients from two centres in the UK. The data were analysed using the RUMM2020 Rasch analysis computer software.

Results: 294/600 questionnaires were returned (response rate of 49 %). Initial analysis, of 153 respondents, showed significant misfit to the model. Since both scales intended to measure self efficacy & were developed from a similar patient population, the items from both were pooled. It was necessary to collapse the 6 responses to items in the Rigby scale to 4, in order to achieve ordered probability thresholds. 12 non-functioning or redundant items were deleted. The resultant scale had 13 items, each with scores of 0 to 3. Rasch parameters: item fit residual range –0.602 to 1.446 (ideally $< \pm 2.0$), mean 0.235, SD 0.590 (ideally 0 & 1 respectively). Chi squared probability 0.529 i. e. no significant deviation between observed data & that expected from model. Person fit residual mean –0.336, SD 1.394 (ideally 0 & 1 respectively). Person Separation index 0.856 (ideally > 0.8).

Conclusion: The unified Liverpool scale fits the Rasch model & can be considered as measuring a unidimensional construct of self efficacy & that the item scores operate at the interval level.

P335

Measurement of cerebral grey and white matter atrophy from various MRI pulse sequences using different segmentation algorithms

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Background: Using magnetic resonance imaging (MRI) analysis methods, the brain can be divided into cerebral grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) compartments, providing information on the topography of atrophy. The segmentation of GM and WM volumes is usually performed by fully automated algorithms. Recent case-control studies have demonstrated that atrophy affects both GM and WM compartments from earliest stages of MS. It is not clear to what extent segmentation algorithms and pulse sequences affect the measurement of GM vs. WM atrophy in MS.

Objective: To determine whether the measurement of whole brain GM and WM fractional volume (FV) is influenced by MRI pulse sequence and segmentation algorithm in patients with relapsing-remitting (RR) multiple sclerosis (MS) and in normal controls (NC).

Methods. GM- and WM-FVs were obtained in 25 patients with RR MS (mean disease duration 8.1 years, mean age 42.5 years and mean EDSS 3) and in 17 age- and sex-matched NC. Brain MRI segmentation was performed from 3D SPGR T1-weighted images (WI), 2D-T1-WI, fluid attenuated inversion recovery (FLAIR) images and T2-WI using three different segmentation algorithms: SPM2, SIENAX and Hybrid SIENAX.

Results: The GMFV was significantly lower in the MS group vs. NC when measured from 3D SPGR T1-WI with Hybrid SIENAX ($p = 0.013$). On the same pulse sequence, the SIENAX algorithm revealed a trend ($p = 0.068$), whereas SPM2 did not find a statistically significant difference between the two groups ($p = 0.147$). There was no statistically significant difference between MS and NC for the WMFV, measured from all four pulse sequences with all three segmentation algorithms. When the GM- and WM-FVs were compared on the same pulse sequences using the various segmentation algorithms, we found a significant difference for all four sequences ($p < 0.002$ after Bonferroni correction for multiple comparisons). When the GM- and WM-FVs were compared on different pulse sequences using the same segmentation algorithm, we found a significant difference for all three algorithms ($p < 0.01$ after Bonferroni correction for multiple comparisons).

Conclusions: MRI estimates of GM- and WM-FVs are dependent on both the type of pulse sequence and the segmentation algorithm. The most optimal pulse sequence in this study for measuring atrophy of GM and WM associated with MS was the 3D SPGR T1-WI.

P336

Caregivers burden in multiple sclerosis

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Providing care for a person with Multiple Sclerosis (MS) has a major impact on all areas of the caregiver's life. MS caregivers have been in fact reported to have deficits in their physical, mental and social well-being, also for the predominantly young age of MS patients, the unpredictable course of the disease, the absence of a cure, the potentially disabling symptoms. The purpose of this study was to describe the profile of MS patient caregivers, assess their burden and its relationship to patients characteristics. 12 patients with definite MS, 4 males and 8 females aged 23–60 (mean age 40.25 years), and their corresponding caregivers (aged 31–62, mean age 45 years) were studied. The Caregiver Burden Inventory (CBI), which evalu-

ate the domains of objective, evolutionary, physic, social and emotional burden, the Beck Depression Inventory (DBI) and the Endler Multidimensional anxiety scales-state (EMAS-S) were submitted to MS caregivers and to age-matched control caregivers of patients affected by serious chronic cardiopathies. Moreover, also MS patients depression and clinical status with the Expanded Disability Status Scale (EDSS) were assessed. The primary caregiver was generally the spouse (75 %, 2 wives and 7 husbands), beyond to 2 mothers and 1 brother. CBI mean score was 22.5 (max value 60), with pathological scores in 4 cases (33 %, against 12 % of controls), significantly related to BDI and EMAS-S in 2 of them and to MS patients BDI. The highest scores were observed in evolutionary, physical and social burden domains of the scale, in husbands rather than in wives and other relatives, and mainly related to the EDSS value rather than the disease duration. In conclusion, differently from other chronic serious illness, our finding indicate that MS caregivers are more frequently distressed and in need of assistance. The burden appears to be strictly related to their depressive feeling and to the actual patients impairment. Since patients' quality of life is strictly related to the quality of the support they receive from their primary caregivers, a greater attention toward caregivers needs, including psychosocial and pharmacological interventions, of utmost importance for the well-being of the patient-caregiver dyad.

P337
Evaluating the linguistic validity of the Functional Assessment of Multiple Sclerosis (FAMS) questionnaires: 10 additional languages. Status report
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To evaluate the performance of newly-translated Portuguese, Japanese, Hebrew, Russian, Ukrainian, Hungarian, Czech, Arabic, Korean, and Traditional Chinese FAMS questionnaires, preliminary psychometric properties of the translations were assessed using both qualitative and quantitative data. The translation methodology included two forward translations by native speakers in each language, a reconciled version of the two forwards by a third translator, back-translation of the reconciled version by a native English speaker fluent in the target language, and three independent reviews by native speaking experts. 222 MS patients (Portugal: 20, Japan: 20, Brazil: 19, Israel: 34, Ukraine: 20, Hungary: 20, Czech Republic: 19, Kuwait: 10, Korea: 20, Taiwan: 20, Egypt: 10 and United Arab Emirates: 10) read and answered the questionnaire in Portuguese, Japanese, Hebrew, Russian, Ukrainian, Hungarian, Czech, Arabic, Korean, or Trad. Chinese. Retrospective debriefing interviews were conducted to obtain patient feedback on the translations as well. Statistics comprised of analyses (descriptive statistics and reliability analyses) on the quantitative data, and qualitative analysis of participants' comments. As for results, the age range was 17 to 65 years. The group comprised of 154 women and 68 men; 93 % received treatment. Individual performance: 19 % had normal activity and no symptoms; 41 % had some symptoms due to MS with no bed rest; 28 % had symptoms due to MS and bed rest > 1/2 of waking day; 10 % had symptoms due to MS with bed rest > 1/2 of waking day; 2 % were obliged to stay in bed. The FAMS performed very well in all target languages. Cronbach's alpha coefficients for total FAMS were high (per language range = 0.93–0.96; entire group = 0.95), indicating overall scale homogeneity comparable to the original US English version. Based upon statistical analyses and comments from patients, revisions were made to the Hebrew, Trad. Chinese and Ukrainian versions only. Participants were comfortable with the questionnaire and felt that the questions addressed issues important to MS. The final versions of the Portuguese, Japanese, Hebrew, Russian, Ukrainian, Hungarian, Czech, Arabic, Korean, and Trad. Chinese FAMS are linguistically acceptable and show good psychometric performance, and are now ready for inclusion in clinical trials and other research studies to evaluate the quality of life of patients with MS.

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P338
Short-term rehabilitation in multiple sclerosis patients – significance and predictors of efficacy
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Background: Rehabilitation has significant effects in the treatment of patients with disabilities.

Objectives: To assess the effects of short-term rehabilitation on neurological disability in patients with multiple sclerosis (MS), and evaluate clinical predictors for better outcome.

Methods: Fifty consecutive MS patients (28 females, mean age 45.6 years, mean disease duration 12.7 years) underwent a comprehensive rehabilitation treatment program that included daily physiotherapy, occupational therapy and hydrotherapy for a period of 3 weeks. All patients underwent neurological examination and disability was scored using the Expanded Disability Status Scale (EDSS) at baseline and three months after completing the rehabilitation program. Rehabilitation was considered successful if associated with a decrease by at least 0.5 point in the EDSS score.

Results: Twenty-one (42 %) patients benefited from the rehabilitation program according to the pre-defined EDSS outcome measure. Mean EDSS at baseline decreased from 6.1 to 5.5 at three-months follow-up ($p = 0.027$). The major change occurred in the pyramidal functional system score that decreased from a mean of 3.3 to 2.8. Logistic regression analysis demonstrated that cognitive and cerebellar impairments (functional score > 3) were associated with a lesser chance to benefit from rehabilitation treatment.

Conclusions: Short-term rehabilitation can improve disability in significantly impaired MS patients. Cognitive and cerebellar impairments are associated with lesser efficacy.

Extrapyramidal disorders

P339
Safinamide add-on to L-dopa and dopamine agonist in Parkinson's disease. An oper escalating dose 6-week trial
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In a previous controlled study oral safinamide (SAF) improved motor performances in early Parkinson patients at a median dose of 40 and 70 mg/day. In that study tolerability was equal to placebo and the higher dose provided a significant increase in number of responders (i. e. patients with a UPDRS-III scores improvement > than 30 %). Thus, a pilot study to investigate safety and efficacy of higher doses was designed. In this single centre trial 14 patients treated with a single dopamine agonist and 11 treated with levodopa, with mean UPDRS-III of 17.1 + 4.9 received oral SAF once a day at 100, 150 and 200 mg with 2 week incremental steps. Tolerability was evaluated by report of AE and laboratory tests. Efficacy was measured by UPDRS II-IV at each visit. All subjects reached the highest dose. No serious AE occurred during the study. Only 9 patients experienced a total of 19 AEs 7 of which were deemed to be possibly drug related. One patient withdrew for a non serious AEs and one was lost to follow up. Levodopa treated patients at week 6 had a mean UPDRS-III decrease of 1.5 points (9.3 %), dopamine agonist treated patients showed a mean decrease of 4.1 points (22.70.4 %, $P < 0.001$). An improvement was seen at each dose escalation. Platelets MAO B activity was equally inhibited at > 96 % at all doses. The results of this study suggest that SAF provides incremental motor improvement in the tested dose range, at which MAO B inhibition was maximal, confirming the hypothesis that other mechanisms such as glutamate release inhibition come into play. This hypothesis must be confirmed in controlled studies.

P340
Effect of selegiline on c-Jun N-terminal kinase activty in the substantia nigra of MPTP treated mice
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MPTP selectively affects dopaminergic neurones of the substantia nigra (SN) via monoamine oxidase-B (MAO-B) conversion to its toxic metabolite MPP+. The current study investigated MPTP-induced activation of the JNK signalling pathway (Saporito et al. (2000) J Neurochem 75, 1200) and the effect of the MAO-B inhibitor selegiline. Male C57Bl6 mice received two injections of saline or MPTP (30 mg/kg; s. c.) 24 h apart. Selegiline (seleg, 10 mg/kg; s. c.) or saline, was given 30 min prior to MPTP on each occasion. Mice were killed at 3 and 6 h after the second MPTP injection. MPP+ levels were assessed in striatal extracts using a novel mass spectrometry assay. Tyrosine hydroxylase (TH), phospho-c-Jun and phospho-JNK expression in the SN were examined by immunohistochemistry (IHC) on paraffin sections. In MPTP/saline treated mice, MPP + levels were significantly elevated at 3 and 6 h to 58.7|*plusmn*|12.5 and 44.2|*plusmn*|3.9 ng/ml respectively, while in MPTP/seleg treated mice this was reduced to 7.2|*plusmn*|0.9 and 2.7|*plusmn*|0.3 ng/ml respec-

tively. TH-positive cell number in the SN of MPTP/saline treated mice were not significantly reduced at 3 and 6 h timepoints, though pyknosis was evident. Double staining IHC revealed a significant increase in both TH/p-c-Jun and TH/p-JNK labelling index (number of TH/p-c-Jun or TH/p-JNK positive SN neurones normalised to total number of TH-positive SN neurones) in MPTP/saline treated mice at 3 h (8.8|*plusmn*|1.9 and 0.4|*plusmn*|0.6 respectively) and 6 h (18.9|*plusmn*|1.8 and 4.0|*plusmn*|1.3 respectively) which was reduced to zero in MPTP/seleg treatment groups. These data confirm that MPP+ activates JNK signalling in vivo, and that selegiline prevents MPP+ formation and thus JNK pathway activation. This together with early signs of cellular distress indicate that JNK pathway activation may be an early marker for cell death in this model.

P341
Rapid-onset dystonia-parkinsonism: a clinical, biochemical, genetic and imaging study of one French family
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We report an unusual rapid evolution of craniocervical predominant dystonia and parkinsonism affecting a french family. A review of literature is given.

Three members of studied family are affected. The propositus is a 48-years-old man who developed after exercise, at age of 35, abrupt postural instability, dysarthria, dysphagia, bulbar symptoms, segmental limb dystonia especially of hands, and parkinsonism. A stabilization of symptoms will be noticed in few months. His sister presented at age of 45, semiology more "frustre" following an episode of emotional stress. Symptoms improved and stabilized within few weeks. The son of propositus developed at age of 16 in one week clinical signs similar to his father, after falls.

Neuroimaging was normal for all patients. DAT-Scan of propositus and his son showed a normal fixation and a preservation of nigro-striatal dopaminergic pathway. Biochemical studies of cerebrospinal fluid (CSF) of father and son showed low level of dopamine metabolite homovanillic acid (HVA) and 5-hydroxy-indoleacetic acid (HIAA), especially in case of the son.

Clinical, biochemical and imaging features of this family corresponding of Rapid-onset dystonia parkinsonism (RPD) described at first by Dobyns et al. (1993). Genetic studies of father and son showed a linkage with chromosome 19q13, proved by Kramer (1999) as responsible for RPD.

RPD is a distinct autosomal dominant movement disorder with variable expressivity and reduced penetrance. RPD is characterized by sudden onset over hours to days of combination of dystonic and parkinsonian symptoms. Most affected individuals have limb and cranial dystonia with dysarthria and dysphagia accompanied by bradykinesia, slow gait, and postural instability. Sudden onset, or worsening of symptoms, occurs after stresses, prolonged exercise or emotional stress. The progression over years is minimal or absent. Some patients have reduced levels of HVA in the CSF yet little or no response to L-dopa. PET studies revealed no loss of the dopamine transporter. Diagnostic criteria were made by Brashear (1997).

Clinical, biochemical, imaging and pathological features are suggesting more a dysfunction in dopaminergic neuro-transmission, rather than a degenerative disease, resulting in permanent neurologic disability.

P342
Repetitive transcranial magnetic stimulation in Wilson's disease
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Introduction: In treatment of motoric disturbances repetitive transcranial magnetic stimulation is used. However, in movement disorders occuring as essential symptoms of neurological form in Wilson's disease this therapy has not been evaluated yet.

Methods: Therapeutic effectiveness of repetitive transcranial magnetic stimulation (rTMS) was examined in eight patients suffering from Wilson's disease with movement disorders. A single subtreshold rTMS was carried out above the motor hand area of the primary motor cortex on both sides. The fine motor skills of the hand were tested by means of the V-scope system, the UPDRS (motorial section), a writing test and a writing movement recorder (CS-System), each before and after treatment.

Results: The rTMS resulted in slight improvement of writing test and fine motor skills of the hand in V-scope system in two patients. However, there was no statistical significance. The UPDRS showed positive therapeutic effects in four patients in the hand area with best improvement of 5 points decrease and average of 2.6 points.

Discussion: In view of the small group of eight examined patients, the positive clinical effects let us presume that positive therapeutic effects are possible. Despite the long history of the disease in every patient repetitive transcranial magnetic stimulation is able to influence movement disorders in a positive way.

P343
Meige's syndrome associated with thalamopedoncular infarct: a case report
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Introduction: Meige's syndrome was first described in 1901 as the association of blepharospasm (BS) and oromandibular dystonia. Its occurrence in thalamo-pedoncular stroke has rarely been reported and illustrates the implication of rostral brainstem-diencephalic structures in the pathogenesis of this focal dystonia.

Case report: A 59-years-old right-handed man, without medical past history, was admitted in emergency for the sudden onset of a transient blindness, followed by diplopia and decreased consciousness. Neurological examination showed left hemiparesis and vertical ocular palsy. Magnetic resonance imaging revealed bilateral thalamic paramedian infarct with right mesencephalic involvement. Aetiological assessment revealed a patent foramen ovale associated with atrial septal aneurysm. He was treated by aspirin. His neurological symptoms rapidly improved except a mild oculomotor trouble and instability. About seven months later, he suffered from a bilateral blepharospasm with an oro-facial component (Meige's syndrome) predominating on the right side. The use of botulinum toxin injections into the affected muscles provides symptomatic relief for a few months.

Discussion: Meige's syndrome is usually idiopathic with insidious onset. Jankovic and al. (1983) first described symptomatic forms, generally several months after focal ischaemic or demyelinating lesion of the rostral brainstem or diencephalon. They suggested the possibility of a denervation hypersensitivity of the facial motor neurons or their release from supra- nuclear inhibition. Indeed they studied the blink reflex and showed an enlargement and prolongation of the R2 component, suggering that interneurons conveying the late R2 component were hyperexcitable.

More recently, there have been a few descriptions of BS secondary to cortical lesions, providing the basis for the concept that lesions in any specific part of the motor loop (cortex-basal ganglia-thalamus-cortex) may produce this focal dystonia by disarraying motor subroutines, as suggested in writer's cramp.

Botulinum toxin is actually considered as the "drug of choice" in the management of idiopathic as well as symptomatic Meige's syndrome

P344
The effect of pergolide and piribedil on parkinsonian tremor in patients with early Parkinson's disease
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Background: Although all the dopaminergic drugs are effective to some extent in parkinsonian tremor, it is not possible to remark a single drug as an effective therapy for this type of tremor. Levodopa makes a reduction about 30–50 % in UPDRS tremor subtest.But dopamin agonists produce a more prominent reduction in tremor. They usually are very efficient in newly diagnosed, tremor predominant patients without cognitive dysfunction.They are also used in late satges of PD refractory to anticholinergics and levodopa. The response of tremor to farmaco therapy is dubiqious and all the drugs must be used before referring the patient to surgery.

Objective: The aim of the study is to compare the effectiveness of piribedil (trivastal) and pergolide in patients with early stages of PD with predominant tremor and mild or absent bradikynesia in a controlled randomised open group.

Method: It is an open, randomized, controlled study consisting of 30 PD patients in Hoehn & Yahr stage I–II, with low scores in UPDRS. Each group consisted of 10 patients. Piribedil (150 mg) amd pergolide (0.75 mg) are randomised to patients in the two treatment gropus consisting of 10 patients each. The doses are titrated in each treatment group according to the standart protocol. All the patients are evaluated neurologically and UPDRS scores are obtained and tremors are recorded before starting the treatment. The tremor records and UPDRS scores of the patients are reevaluated 3 months apart in the two treatment groups(0, 3, 6, 9, 12 th months) and their response to treatment are recorded during the12 month follow up period. The 3rd group of age and UPDRS matched PD patients are used

as controls without any treatment. There was no change in both follow up parameters in the control group who are not receiving any treatnment.

Results: The group receiving piribedil showed a reduction of 20 % in parkinsonian tremors' frequency, and 12 % reduction in UPDRS motor scores ($p > 0.05$), whereas the group receiving pergolide showed a reduction about 75 % both in tremor frequency and UPDRS motor scores ($p < 0.005$).

Conclusion: The results of this open labeled, randomised, controlled study comparing the effectiveness of piribedil and pergolide revealed that pergolide has an statistically significant and clinically prominant effect in reducing and/or abolishing tremor in patients with early, tremor predominant PD during the 12 month follow up period.

P345

Cognitive impairment and dementia in patients with extrapyramidal disorders

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Background: Complementary neuropsychological investigations in patients with extrapyramidal disorders were used to assess the frequency and the type of cognitive impairment and dementia.

Material and methods: 145 consecutive patients admitted to Clinic of Neurology in Skopje: 128 with different forms of Parkinsonism, 11 with Wilson disease and 6 with Huntington disease. Complementary neurophysiological and morphological assessment (CT, MRI, EEG) of the initial dementia and the other changes were also used in all patients. All patients were evaluated 1 year with a neuropsychological battery that included a screening battery (the Mini Mental State Examination, tests for the assessment of memory, the Hamilton Depression Scale and the Hachinski Ischemic Score) and a apprehensive battery administrated to those who had a low score in the MMSE or in the memory screening test. Dementia was defined according to the DSM IV criteria.

Results: 145 patients were evaluated. All patients with Wilson and Huntington disease (n = 17) had deficits in cognitive domains, but only 3 had cognitive deficits compatible with dementia. From total 128 patients with Parkinsonism, 53 % of the patients have positive CT findings, and in 47 % have negative. Findings of the MRI are almost the same as those of the CT, except in the vascular Parkinsonism, in which 2 patients had infarct in the thalamus and basal ganglia.

From patients with different forms of Parkinsonism (n = 128) 42 % had no cognitive impairment.

7 % had cognitive deficits compatible with dementia. Another patients (51 %) had memory deficits and impairment in one other cognitive domain. Patients with memory deficits were also older than patients without memory dysfunction, very often associated to alcohol consumption.

Conclusion: Our data suggests that impairment in cognitive domains are the most frequent deficit found in patients with extrapyramidal disorders. Neuropsychological examination showed a high frequency of cognitive memory decline. Subcortical forms of dementia had also an increased frequency (7 %) in patients with parkisonism.

P346

A case of postencephalitic parkinsonism

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Background: Acute encephalitides due to several viruses may be associated with transient or self limited parkinsonism. We report a case of postencephalitic parkinsonism in a man who developed extrapyramidal symptoms during the course of encephalitis of unknown etiology but presumed viral.

Case Description: A 29 year old man was transferred from a referring hospital because of headache, chills, fatigue and fever with suspect of encephalitis. On CSF examination lymphocytosis and high level of protein was detected. The patient was diagnosed as encephalitis. Although virus spesific antibodies for HSV, Rubella and Measles have been negative both in serum and CSF, he was treated ampirically with 14 days of antiviral agent Acyclovir. While recieving antiviral regimen, rigidity of all four limbs, bradymimi and dysarthia were noticed. On follow up clinical signs (video recorded) were recovered spontaneously and on repeated lumbar puncture, cell reaction and protein level decreased. Magnetic resonance imaging (MRI) showed focal hyperintense lesions at pons- midbrain level. Repeated MRI revealed regression on observed lesions and Proton magnetic resonance spectroscopy (P-MRS) showed minimal decrease on N-acetyl acetate (NAA) level and this was reported as minimal nonspecific neuronal loss. SPECT showed diffuse hypoperfusion predominantly on posteriotemporal part of left hemisfere.

Conclusion: Postencephalitic parkinsonism is a diagnostic rarity. The diagnosis should be suspected in any parkinsonian patient, particularly with a young and acute onset.

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Pergolide monotherapy in the treatment of early Parkinson's disease: results of a 3-year follow-up of a randomised controlled study

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Objective: The aim of the study is to determine the effectiveness of pergolide monotherapy in providing symptomatic relief in patients with eraly PD.

Background: The most frequent complication of levod [i]pa therapy is the occrence of motor fluctuations and early treatment with dopamine agonists may reduce the risk of motor complications.Pergolide which is a D1-D2 agonist has been studied as "add-on" therapy, but there are few controlled clinical studies evaluating the efficacay of pergolide monotherapy, and even fewer clinical trials using pergolide as a monotherapy for a long period.

Method: The efficacy and tolerability of pergolide is evaluated in a double blind, randomized, 3 year trial versus placebo. Patients with a diagnosis of idiopathic PD, with a modified Hoehn & Yahr score I–III, and a score more than 14 points in UPDRS part III at baseline were enrolled to the study. There were 20 patients in the treatment arm(mean age 61.7) and 20 age matched patients in the placebo group.

Results: Patient characteristics were similar in the two groups at the beginning of the study. The pergolide group showed a significantly important percent of responders (defined as a –40 % decrease in UPDRS part III score at end point) compared to placebo(65 % versus 11 %; $p < 0.005$). Pergolide treated group have a significantly greater improvement than placebo treated patients ($p < 0.001$) in UPDRS and Global Clinical Impression Scale (GCIS). At the end of 3 years the mean pergolide dose was 3.06 mg/day.12 patients in the placebo group were significantly disabled at the end of 2.8 years and were started either an agonist or levodopa at the end of the trial period (3 years). 19 patients in the pergolide group are still taking pergolide monotheraphy, although some required dose adjustments. One patient in the pergolide group required Levodopa at the end of the trial. Side effects were mild, becouse all the patients used domperidon started at the beginning of the trial. There were no drop outs due to the side effects of the treatment.

Conclusion: The results of this study reveals that pergolide monotherapy can be considered as an efficiaous and well tolerated first line treatment in patients with early PD.

Epilepsy

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Australian Pregnancy Registry of Women on Antiepileptic Drugs (AEDs)

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Aim: To determine the relative risks of foetal malformations associated with AEDs in pregnancy. Background: The Australian Registry is a centralised, voluntary, prospective project, which collaborates closely with European Registry (EURAP). The Australian health system is advanced, with universal health cover, centralized, accessible populations, a single language, and well organized lay and professional bodies. The Registry is nationwide, recruiting i. women with epilepsy taking AEDs; ii. untreated women with epilepsy and iii.those taking AEDs for other indications.

Results: Earlier, at 40 months status, we had observed a dose-effect relationship between valproate (VPA) use in the first trimester and an increased of birth risk defects (BD). Folate supplementation failed to prevent VPA related defects, including neural tube defects. Our current material comprises results of 48 months data collection. Of 726 potential participants 568 have enrolled, with 492 birth outcomes, which include 432 live normal births, 26 defects(6 detected only within first year after birth), 6 induced abortions with defects, 16 spontaneous abortions, 7 stillbirths and 4 lost to follow up, and 1 abortion for maternal indications. Of the AEDs, VPA was associated with defects in 16.5 % of women (102 on monotherapy (M) and 46 on polytherapy (P)), numbering 19 and 6 defects respectively. Phenytoin taken by 16 patients on M. and 19 on P each group showing a

single defect (8 %). Carbamazepine (CBZ) taken by144 cases on M, and 56 on P, resulting in 4 defects (M) and 2 defects (P) respectively 0.6 %. Lamotrigine (LTG) taken by 49 patients on M. and 58 on P., with no defects on M. and 4 defects on P. (3.7.%). The only other agent associated with a defect was topiramate in polytherapy, 7 patients received P., 2 on M. (11 %). Polytherapy with LTG comprised 89 patients, monotherapy 49 patients. Medications used in polytherapy with LTG, associated with defects, comprised VPA in 3 cases, phenytoin in one case. Statistical evaluation of these figures, relationships to epilepsy syndromes, and relative efficacy of drugs employed for control of epilepsy, are currently in progress.

Conclusions: The Registry is an acceptable model for the study of AEDs in pregnancy. To date VPA appears to be related to an increase in FMs, particularly at high dose, whilst LTG monotherapy appears free of related malformations after 48 months.

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Epilepsy in Sturge-Weber syndrome

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Introduction: Sturge-Weber syndrome (SWS) is a neurocutaneous syndrome associating congenital cutaneous and leptomeningial angioma. Epilepsy occurs in 70–90 % of cases. The most important studies describing epilepsy in SWS were performed at a time where new antiepileptic drugs (AED) were emerging. Our purpose is to analyze semiology and evolution of epilepsy as well as response to AED and surgical treatment.

Patients and methods: We performed a retrospective among paediatricians and neurologists from West of France. 14 cases were studied aged 8 to 12 years at inclusion.

Results: The age at onset of epilepsy could be from birth till the age of ten, with an average at the age of two. 73 % of patients were boys and 27 % girls. The length of follow-up varied from one to thirteen years except for one patient (only one hospitalisation). 60 % of patients had hemiplegia which appeared in 40 % of cases after a seizure. Eleven had a mental retardation which did not exist before onset of epilepsy and seemed stabilized with decreasing of seizures. The most common presentation of epilepsy was partial seizures. In most cases, electroencephalographic abnormalities were depression of activity over the hemisphere of the leptomeningial angioma. The first treatment was antiepileptic drugs and in this study carbamazepine and vigabatrin seemed to be the most effective treatments, topiramate did not suit because of its secondary effects. Epilepsy was drug resistant in 10 cases, but in most patients more severe at the onset than later. Hemispherotomy was performed in one patient because of recurent partial motor status epilepticus; seizures disappeared after surgery with a follow-up of 7 years. There was an improvement of the cognitive performances with persisting severe hemiparesia.

Discussion: Seizures and mental retardation constituted the major handicap for these patients. Surgery seemed to improve the cognitive development but with a motor handicap so it is difficult to propose without a preexisting hemiparesia.

Conclusion: The evolution of epilepsy seemed to determinate the mental development. Earlier the epilepsy begins, higher is the mental retardation. The mechanism of this phenomenon is not perfectly clear.

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Electrencephalographic evaluation of patients with chronic hepatic disease submitted to liver transplantation

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Hepatic encephalopathy (HE) encompasses a wide spectrum of neuropsychiatric disturbances, usually reversible, observed in patients with significant liver dysfunction. In order to better asses the electroencephalographic changes found in patients with chronic hepatic failure submitted to liver transplantation (LT) at the Serviço de Transplante Hepático do Hospital de Clinicals da UFPR, Curitiba, the authors prospectively followed 20 patients, the youngest one being 15 years old, who had all underwent LT. The variables included physical examination, classification of HE and liver disease, electroencephalogram and assessment of cognitive functions with the following neuropsychological tests Mini-Mental State, Trail Making Test Part B, Digit Span subtest used in the Wechsler Adult Intelligence Scale – Revised (WAIS-R), Word Fluency (FAR) and Category Fluency and the Clock Drawing Test. The severity of HE was graded according to the findings of the physical examination, neuropsychological testing and EEG. Subclinical HE was diagnosed when the EEG disclosed a diffuse slowing of background activity or at least two neuropsychological tests were abnormal in the absence of clinical findings. EEG was prospectively evaluated, with a baseline recording in the pre-transplantation period (pre-LT) and 30 and 90 days after the transplant (post-LT). Mean posterior baseline rhythm frequency (PBRF) was of 8.8 ± 1.9 Hz in the pre-LT period, 9.8 ± 1.7 Hz at 30 days post-LT and 9.9 ± 1.7 at 90 days post-LT and this increase in the PBRF was considered significant ($p < 0.0001$). Fifteen patients were evaluated 30 days after LT, and 3 of them (20 %) had a slow EEG: 1 with a IIA slowing, 1 with a IIIA and one with a IIIB. EEG recording of 14 patients 90 days after LT disclosed a IIIA slowing in just one patient. Three patients also had triphasic waves in their EEGs. The diagnosis accuracy of PBRF, background slowing and the occurrence of triphasic waves were evaluated in comparison with NPTS as the gold standard for the diagnosis of HE. As a result, EEG parameters had a good specificity and positive predictive values (PPV), with low sensitivity and negative predictive values (NPV). Final assessment of improved HE in the post-LT period considered NPTS as the gold standard, but also demonstrated that EEG abnormalities have high specificity and PPV, but low sensibility and NPV.

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Value of 1H MR spectroscopic imaging in diagnostics of MRI-negative extratemporal focal epilepsy

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Objective. It has been demonstrated that 1H magnetic resonance spectroscopic imaging (1H CSI) has a significant value in lateralization of temporal lobe epilepsy. Studies focused on the use of 1H CSI in extratemporal and especially MRI-negative patients are however scarce. We report four "nonlesional" cases where 1H CSI considerably helped in the localisation of epileptic focus.

Methods. Two girls (14 and 11-year-old) and two boys (8 and 9-year-old) with pharmacoresistant focal epilepsy were studied on a 1.5-T Siemens Vision MR system. 1H CSI examination was directed to the epileptic focus localised by the scalp EEG and ictal SPECT and/or FDG-PET. 1H CSI spectra measured with TE = 135 ms in transversal orientation were evaluated using the program CULICH which is based on the LCModel technique.

Results. Repeated MRI studies with a protocol for patients with epilepsy were normal in all the children. Based on the seizure semiology, scalp EEG and functional imaging (ictal SPECT and/or FDG-PET), the epileptic focus was in individual patients localised to the left frontal, fronto-parietal, parietal and parietooccipital regions. In the suspected regions, 1H CSI detected localised decrease in N-acetyl aspartate (NAA) in three children and localised increase in choline (Cho) and decrease in total creatine (Cr) in one boy. Subsequently, subdural electrodes mapping and focal cortical resections were performed in two of the patients. The former confirmed that the seizure onset zone collocalised with 1H CSI abnormality in both the patients. Histopathological analysis of the resected brain tissue revealed MRI-undetected severe cortical dysplasia of the Taylor type in both cases.

Conclusions. 1H CSI can be more sensitive to some discrete malformations of cortical development than conventional MRI. The study proved the importance of 1H CSI for the localisation of an epileptogenic zone in "nonlesional" focal epilepsy cases.

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Aetiological spectrum of symptomatic seizures in adults: a retrospective study of 105 consecutives cases

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The purpose of this study was to evaluate the frequency and aetiology of symptomatic epileptic seizures in adult patients. We retrospectively studied 105 patients over 20 years old of age admitted to our Unit with epileptic seizures (2.82 % of all admissions) in 1994–2003, 69 males and 36 females, aged 23–85 (mean age 56.9 years). We evaluated routine blood laboratory tests, EEG, cerebral CT scan and in some selected cases carotid Duplex ultrasound and MRI. The aetiology of seizures was based on history, neurological findings and diagnostic investigations. Cerebrovascular disease (CVD) was the most frequent cause of seizures (42 cases, 40 %, 26 males and 16 females, mean age 68.7 years), while the remaining aetiologies were: traumatic brain injury in 12 (11.4 %), chronic alcohol abuse in 18 (17.1 %), brain tumour in 16 (15.2 %), in 4 of them metastatic, arteriovenous angioma in 5 (4.8 %), toxic causes in 4 (3.8 %: drug abuse in 3 and

acute suspension of Lorazepam in 1), metabolic disorders in 3 (2.9 %), ipoxic causes in 2 (1.9 %: Sleep Apnoea Syndrome in 1 and Motor Neuron Disease in 1), central nervous system infection in 1 (0.9 % %), Multiple Sclerosis in 1 (0.9 % %), unknown aetiology in1. In the group with CVD, 7 had acute symptomatic seizures, while the others had late-onset seizures, in 3 after antiepileptic drugs were discontinued. Ct scan showed a single ischemic lesion in 21 patients, in 7 with associated diffuse cerebral atrophy, cerebral haemorrhage in 9, multiple ischemic lesions in 8 and cerebral atrophy with chronic white matter lesions in 4. The predominant type of seizures were generalized tonic-clonic, 66.7 %, particularly in all patients with chronic alcoholism, in 92.3 % of patients with brain injury and in 52 % of stroke patients. Simple focal seizures occurred in 17 cases (16.2 %) with secondary generalisation in 18 (17.1 %), mainly in those with brain tumour and stroke. EEG was normal in 25 cases (23.8 %), showed focal abnormalities in 24 (22.9 %), with associated diffuse slowing in 25 (23.8 %), especially in those with CVD (13 and 11) and brain tumour (8 and 6); diffuse theta and delta activity in 14 (13.3 %, in greater percentage in toxic and metabolic disorders); it was not performed in 17 cases (16.2 %). In conclusion, in our study symptomatic seizures are frequent enough in adults (2.82 % of all admissions), with prevalence of CVD in those over 40 years; EEG and type of seizures show a good correlation with focal or non focal aetiology

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The intractable epilepsy problem in developing countries: is there a way out?

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Introduction: Epidemiological studies estimate one million people in India with intractable epilepsy. However, like all developing countries, epilepsy surgery is underutilised in India, only 650 cases having been operated. The non-availability of intra-operative electrocorticography (ECoG) and SPECT/video-EEG(VEEG) has restricted this programme to big centres.

AIMS:We wished to see how many of our operated cases could have been operated without VEEG, SPECT and ECoG at slightly smaller centers with only EEG, MRI and facilities for a standard anteromedial temporal lobectomy (AMTL).

Results: All 155 cases of intractable epilepsy operated at our centre have been included.-this included 7 corpus callosotomies, 3 hemispherotomies and 46 lesionectomies under ECoG guidance. Ninety-nine patients underwent standard AMTL without ECoG guidance for Mesial Temporal Sclerosis (MTS)/lesional temporal lobe epilepsy.

Among these 99, MRI identified the side of MTS/temporal focus correctly in 90. Three had features of bilateral MTS, 2 had bilateral foci of gliosis and 4 had normal MRI, all these patients evidently requiring detailed evaluation. Among the 90, VEEG revealed discordant foci (to the MRI identified focus) in 13 and was non-contributory in 8. Ultimately, even the 13 patients with discordant VEEG underwent AMTL on the MRI identified side and all 13 had good seizure outcome. SPECT was non-contributory in 9 of these 90 patients and revealed discordant foci in 4. All the 4 with discordant SPECT localisation ultimately underwent AMTL on the MRI identified side with good outcome.

SPECT/VEEG was therefore useful in only 9 patients with equivocal MRI findings. All 90 patients with clear-cut MRI localization had nothing added by VEEG/SPECT. Therefore 90 of our 155 patients (58 %) could have undergone surgery at a centre equipped with only EEG, MRI and AMTL facilities.

Our Class I seizure outcome rates are comparable to international standards.

Conclusion: The need of the hour for developing countries is to create awareness regarding epilepsy surgery and creation of a 2 tiered epilepsy surgery programme. The first tier equipped with EEG, MRI and trained neurologists, neurosurgeons and neuroradiologists can undertake AMTL which is a large proportion of the epilepsy surgery burden. More complicated cases can be referred to bigger centres. This strategy is likely to popularise epilepsy surgery but would definitely require strict surveillance.

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Episkop®: A new brief screening instrument for detecting cognitive impairment in patients with epilepsy

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It is well known that patients suffering from epilepsia may have cognitive impairments which significantly affect activities of daily living. These deficits are frequently not assessed in routine examinations, and economical screening instruments used for epilepsia patients are not available yet. For this purpose the "Episkop®" was developed.

The test: The Episkop® consists of six subtests that assess different aspects of memory, executive function, speed of processing and visuoconstructive abilities: (1) Word list, free recall (2),Word interconnecting test, (3) Spot position test 4) Drawing executive test (5), Free delayed recall of the word list, (6) Cued recall of the word list.

Patients and controls: 102 subjects (57 female, 45 male, mean age 47 yrs [SD = 12, 29]) were tested. The group was split in 41 healthy controls (CG), 20 patients with epilepsia (EP), and 41 patients suffering from various neurological diseases without dementia (ND).

Results: Time duration of the test was about 10 min. Word list (max. 24): CG: 15.26 (SD = 3.04); EP: 12.42 (SD = 2.73); ND: 11.98 (SD = 3.78). Word interconnecting test: CG: 40.23 sec (SD = 8.43); EP: 129.21 sec (112.46); ND: 81.61 SD = 58.26).Spot position test (max. 44): CG: 36.52 (SD = 4.15); EP: 34.08 (SD = 5.18); ND: 32.0 (SD = 6.95). Drawing executive test (max. 22): CG: 19.26 (SD = 1.32); EP: 17.78 (SD = 2.25); ND: 18 (SD = 2.65). Free delayed recall (max. 12): CG: 8.63 (SD = 2.08); EP: 3.92 (SD = 13.17); ND: 5.18 (SD = 3.29). Cued recall: CG: 1.37 (SD = 1.25); EP: 1.57 (SD = 1.34); ND: 1.61 (SD = 1.51). In nearly all subtests the CG was superior in test performance. Patients with epilepsia showed inferior test behaviour especially in the word interconnecting test and delayed recall condition.

Discussion: The screening instrument Episkop® is easily to perform and to evaluate and well accepted by the patients. In a short time a broad range of cognitive functions can be assessed and classified as normal or impaired.

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Women with epilepsy who have only ever taken valproate are significantly more likely to have the hormonal characteristics of polycystic ovary syndrome

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A group of 155 women (105 with epilepsy of whom 54 had only ever taken sodium valproate and 51 had only ever taken lamotrigine or carbamazepine) and 50 women of comparable age who did not have epilepsy had follicle stimulating hormone, luteinising hormone and testosterone measured between day 2–6 of their menstrual cycle and an MRI of their ovaries. Women with epilepsy, irrespective of what drug they were taking, were more likely to have polycystic ovaries on scanning: but only women taking valproate, particulary if from an early age, when unprotected by an oral contraceptive, were significantly more likely to have hormonal evidence of the polycystic ovary syndrome. This may be an important observation.

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Ventricular extrasystoles and bigeminus as an ictal feature in symptomatic epilepsy

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A variety of changes in cardiac rhythm during seizures has been described, predominantly tachycardia, but also bradycardia. Increase in heart rate even has been proposed to differentiate epileptic from non epileptic seizures. It has been associated more frequently with mesial temporal lobe epilepsy and generalized seizures. Whereas sinus tachycardia is very common, other ECG abnormalities have been described in about 20 % of seizures. Ventricular extrasytoles have rarely been described as an ictal feature.

We present the case of a 22-year-old male with a history of tuberous sclerosis, who suffered from refractory seizures. His seizures were very brief, lasting from a few seconds to approximately half a minute and consisted of visual hallucinations described as flashes and psychomotor alterations with agitation and incoherent utterances. Neurologic examination was normal. A CT scan revealed round calcifications without surrounding edema localized in the left parietal, right occipital and right frontal lobe. Previous EEGs including 24 hrs registration had detected paroxisitc slow acitvity and repetetive sharp waves in the right temporo-occipital region, but no seizures. During Video-EEG monitoring he presented three seizures. Clinically they consisted of blinking and psychomotor agitation, the patient referred visual hallucinations and palpitations. On EEG, two seizures showed only movement artefacts, in the third there were right parieto-occipital spikes and the end of the seizure. During each of the three seizures there were premature ventricular depolarizations on ECG, devel-

oping to form a bigeminus rhythm along the seizure. Tachycardia and/or bigemini were not observed out of the context of seizures. A 24 hrs-ECG performed later showed frequent supraventricular extrasytoles, but no ventricular. The patient was asymptomatic throughout the recording. Ecocardiografia showed no sign of intracardiac morphologic changes (e. g. rhabdomyoma).

We present this case firsly for its rarety – ventricular premature depolarization is a rare ictal feature, bigemini have not been described in this context, yet, to our knowledge. Secondly it illustrates well the importance of ECG recordings simultaneously with EEG monitoring, as some seizures, especially with foci not easil detectable by surface electrodes may have electrocardiografic alteration as the sole electrophysiological substrate of an ictal event, that in some cases may be otherwise missed or misinterpreted.

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Investigation of oxidant/antioxidant parameters in penthylenetetrazol-induced seizures in mice and the protective effect of erdosteine treatment

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Oxidative injury in the brain is increasingly recognized as a common pathway of cellular injury in many acute neurologic insults. There is little known about the relationship of oxidative injury in brain and human epilepsy, however. In rodent epilepsy models, it has been shown that oxidative stress may have a contributory role in neuronal and glial cell death. Pentylenetetrazol (PTZ) is an agent widely used in the assessment of putative anticonvulsant drugs and is suggested to induce repetitive firing of nerve fibers and shorten the refractory period. PTZ may trigger a variety of biochemical processes including the activation of membrane phospholipases, proteases, and nucleases. Marked alterations in membrane phospholipid metabolism result in the liberation of free fatty acids, diacylglycerols, eicosanoids, lipid peroxides and free radicals. This suggests that the administration of central nervous system-selective antioxidants may have protective role in seizures occurring through this mechanism, and suggests its potential use in seizures. Thus, the aim of the present work was to study the effects of erdosteine, as an antioxidant drug, on the free radical generation and processes of lipid peroxidation formation during model epileptiform seizures in mice. Erdosteine has been shown to have a potent free radical scavenging activity in various in vivo studies. It was demonstrated that 10 mg kg-1 day-1 erdosteine treatment for 5 days prevented oxidant injury induced by cisplatin in rat kidney. It has also shown a cardioprotective action against doxorubicin-induced cardiotoxicity in rats and this activity was proposed to be due to its antioxidant property. The present study was therefore designed to evaluate the effects of erdosteine against oxidative stress in PTZ-induced seizures in mice.

Oxidative damage was evident by the: increase in malondialdehyde and nitric oxide levels in brain tissue, decrease in brain superoxide dismutase and glutathione peroxidase activities, and increase in brain xanthine oxidase and adenosine deaminase activities. These alterations were partially prevented by erdosteine treatment. Furthermore, administration of erdosteine did not inhibit the seizures; however, it significantly increased the latency of convulsions. In conclusion, we consider that erdosteine prevents the PTZ-induced oxidative stress in mice seizure model to preserve antioxidant enzymes activity in brain tissue.

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A pilot study of safinamide in medically intractable epilepsy. Tolerability, drug-drug interaction and preliminary efficacy data

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Safinamide is an alpha-aminoamide endowed with sodium channel blocking activity and MAO B inhibitory activity, currently being developed for the treatment of epilepsy and Parkinson's disease. The purpose of this pilot study was to evaluate its tolerability and interaction potential when given as adjunctive therapy in 43 adults with epilepsy experiencing at least 2 seizures/mo (mostly partial-onset seizures) despite treatment with up to 3 antiepileptic drugs (AEDs).

After a prospective 2-week baseline, safinamide was added at a dose of 50 mg and increased every two weeks to 100, 200 and 300 mg, given orally once daily. Total duration of safinamide treatment was 12 weeks. The protocol allowed dose reductions if tolerability problems occurred. Serum concentrations of safinamide and associated AEDs were determined at regular intervals during the study.

No serious adverse events (AEs) were observed. Five patients withdrew due to non-serious AEs or withdrawal of consent, while 38 completed the study and 37 reached the 300 mg dose. Eighteen patients reported one or more AEs, the most frequent being dizziness, headache, vertigo and visual disturbances.

Addition of safinamide did not significantly change the serum concentration of concurrently administered carbamazepine, phenobarbital and valproic acid. Serum safinamide concentrations were linearly related to dose and tended to be lower in patients comedicated with enzyme inducing AEDs compared with patients not receiving enzyme inducers. At study end, 16 of 39 evaluable patients (41 %) had a > 50 % reduction in seizure frequency compared to the 2-week prospective baseline.

The study indicates that safinamide is well tolerated within the dose range tested and does not affect the kinetics of some commonly co-administered AEDs. Further studies are required to evaluate its potential efficacy in patients with refractory epilepsy.

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Supratentorial cavernous hemangiomas and epilepsy: surgical outcome in a 5-year retrospective study

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Objective: Epilepsy represents the most frequent symptom of cavernous hemangiomas. Characterization of the epileptic seizures in relation to the site of the lesion before surgery, the use of antiepileptic drugs (AEDs) and the surgical outcome in these patients are reported.

Materials and Methods: We present here our case series who underwent surgical removal of cavernomas from 1998 till 2003. 29 patients with supratentorial cavernomas were operated of which 27 could be included in this report.

Results: Cavernomas were more frequent in frontal and temporal lobes and rare in occipital lobes. At least one epileptic seizure was the presenting symptom in 11 patients and 3 presented with seizures after other symptoms at onset. The average time elapsed between the first symptoms and surgery was 22.9 months (1–192 months). Seizures before surgery, originated more often in frontal (70 %) and parietal (57 %) than in temporal (25 %) lobe. After surgery, 12 of the 14 patients (85.7 %) became seizure-free. The rest improved markedly.

The two patients who continued to present seizures after surgery referred a dramatic decrease in frequency of seizures. Only one patient had neurologic sequelae post-operatively (worsening of pre-existing motor deficit).

All patients who presented seizures and most others were started on AEDs before surgery. The majority of patients were put on AEDs after surgery. At three months, in those patients with no recurrence of seizures after surgery, AEDs were discontinued in 54.5 % of patients who were already seizure-free before surgery and in 42.8 % of those who had seizures before surgery.

Discussion: Our series confirm that epileptic seizures are a frequent symptom of supratentorial cavernomas (specially frontal lobe cavernomas)and are the presenting symptom in about 50 %. The majority of the patients became seizure-free after surgery, with acceptable risks of neurologic sequelae (< 4 %), considering the cumulative risk of hemorrhage in untreated patients.

Conclusions: No conclusion on the usefulness of pre operative AED prophylaxis or treatment, at least in patients undergoing surgery after a short interval from seizure onset. However, it is not possible to rule out a learning phenomenon in patients who continue to experience seizures during a long time interval before surgical removal of cavernoma. The rationale for AED use both pre and post operatively requires further randomized prospective trials.

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Risk factors of epilepsy first developed in adults in Tatarstan

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The aim of the investigation is to establish the risk factors of epilepsy first developed in adults.

203 patients with different types of epileptic seizures have been integratedly investigated (96 male, 107 female). Simple partial seizures have been diagnosed in 36 patients, complex partial seizures – in 22 patients, 69 patients suffering from primary generalized seizures, 38 – from partial secondary-generalized seizures and 38 patients have polymorphic ones.

The patients' age varied from 18 to 81 years old. The examination has been carried out in Interregional Clinical-Diagnostic Center in Kazan. The diagnostic complex comprised clinical analysis and instrumental diagnostics methods: magnetic resonance imaging (MRI), electroencephalography (EEG), auditory brainstem evoked potentials (ABEPs) and transcranial Doppler sonography (TCD).

In 89.2 % of patients the focal neurological syndrome has been revealed. However, it is impossible to judge confidently the epilepsy form and its risk factors only taking into account clinical aspect.

EEG has revealed epileptiform discharges in 36.9 % of patients (focal – in 31.5 %, generalized – in 5.4 %), focal slow-wave discharges – in 17.2 % and in 96 % of patients the diffuse disturbances the brain bioelectrical activity have been registered.

MRI has revealed brain structural lesions in 79.3 % of patients. MRI organic lesions have been found in 76.7 % of negative EEGs patients and in 79.1 % of patients – with positive epileptiform discharges. Foci of epileptiform and pathological slow-wave activity coincided with the morphological substrate localization in 32.3 % of patients.

As the result of complex examination various the risk factors of epilepsy have been established: 12.3 % of patients suffered from chronic brain ischaemia, 13.8 % of patients – from tumours, 4.4 % of patients are in the state "after tumour removal", 7.4 % of patients are in the state "after the stroke", the arterial aneurysms have been revealed in 1 % of patients, arteriovenous malformations – in 2.5 %, cerebral cavernous angiomas – in 3.9 %, nonspecific vascularitis – in 1 %, traumatic disease of brain – in 6.4 %, the aftereffects of neuroinfections – in 1 %, encephalopathy of complex genesis – in 7.9 % of patients, residual encephalopathy – in 11.8 % of patients. We have failed to reveal actual cerebral pathology in 32 % of patients.

Thus, it is possible to determine wide spectrum of factors of risk of development of epilepsy only by means of complex diagnostics.

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Serum hormone concentrations before and after first electroconvulsive therapy in men

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Introduction: Electroconvulsive therapy (ECT) is an effective treatment of severe depression but its mechanism of action is still unknown.

Purpose: The aim of the study was to investigate the effect of first ECT on serum hormone concentrations in patients with severe depression.

Material and method: Serum concentrations of prolactin (PRL), adrenocorticotropin (ACTH), thyrotrophin (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), cortisol (F), triiodothyronine (T3), thyroxine (T4), estradiol (E2), progesterone (P) and testosterone (T) were estimated by RIA or IRMA in 5 men (mean age 34.20 ± 8.70 years) with severe depression. Before ECT all men were receiving psychotropic medication. None of the patients had clinical symptoms of endocrine disorders. Blood samples for hormonal investigations were taken before and 15 min., 2 hours, 6 h, 12 h, 24 h after first electroconvulsive shock.

The men without endocrine dysfunction in the same range of age who underwent identical intravenous anaesthesia for minor maxillofacial surgery were studied as controls.

Results: Before and after first ECT mean serum LH, T and T3 concentrations were significantly decreased and PRL, F and E mean levels were significantly elevated in men with depression as compared with control group. No significant changes in mean serum hormones concentrations after ECT as compared to levels before ECT was observed.

Conclusion: Complicated hormonal changes find before electroconvulsive therapy in patients with severe depression suggest the influence of psychotropic treatment as well as the illness on endocrine system.

P362

Role of basal ganglia in temporal lobe epilepsy

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Ictal symptoms occurring during partial seizure are supposely secondary to cortical dysfunction. However, it has been suggested that basal ganglia might be involved in partial seizures with specific symptoms such as ictal dystonia or rotary seizures. The aim of this study was to determine whether cerebellum and basal ganglia play a role in ictal dysfunction by using …

Methods: Twenty patients with temporal epilepsy underwent successful surgery (Engel class 1a: seizure free for at least 2 years). Pre-surgical data were analysed. Ictal-interictal SPECT difference imaging coregistered with high resolution MRI scans were used to localize cerebral blood flow changes in the cerebellum, the caudate and lenticular nuclei and the thalamus. Ictal symptoms during the same seizure were retrospectively analysed from the video recordings. They were divided in 3 categories (motor, awareness, tonus) with 4 stages(0 = no symptom; 4 = strong symptoms). Differences of blood flow in regions of interest were correlated with the clinical stages.

Results: Data were available from 17 patients. Five had tonus abnormality (hypertonia 2, dystonia 3) but no significant change between ictal and interictal SPECT was found.

Most of ours patients had a simple motor activity (n = 13), their blood flow changes reached > 8 % in the lenticular nucleus and > 5.5 % in the thalamus. In one patient who had clonies, blood flow changes was almost 23 % in the caudate nucleus and 14 % in the lenticular nucleus. No significant modification was found in the cerebellum area.

Five patients have normal awareness, low impairment of consciousness was found in 5 patients, mild in 5 patients, and deeper in one. Patients with low consciousness seemed to have significant blood flow increase (+ 12.8 % in the lenticular nucleus and + 7.6 % in the thalamus).

Discussion/Conclusion: Consciousness impairment and simple motor automatism during temporal lobe seizures are linked to hyperactivity in the basal ganglia and the thalamus. These results can help to understand the complex role of subcortical structures in epilepsy. A better knowledge of their function can be useful for development of new treatment, and particularly be helpful to find the optimal target for therapeutic deep brain stimulation. However, further study is necessary to confirm and clarify the role of this structures in epilepsy.

P363

Topiramate add-on therapy in patients with intractable epilepsy

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We investigated the efficacy and tolerability of Topiramate as add-on therapy to Cypriot patients with intractable, treatment- resistant partial-onset and generalized seizures.

Forty-four intractable patients, ages 9–65,were studied retrospectively for a 12 month period. Patients received TPM as add-on therapy to 1–5 (mean 2.4) anticonvulsants. We compared mean seizure frequency for a 3-month period prior to and 12 months after introduction of TPM. Maximum doses ranged from 100 to 900 mg daily. All subjects had physical and neurological examinations, routine baseline hematological, biochemical, and urinary investigations at entry.

4 patients (9.1 %) became seizure free. 7 patients (15.9 %) had seizure reduction of ≥ 75 %. 8 patients (18.2 %) had seizure reduction of ≥ 50 %. 1 patient (2.3 %) had seizure reduction of ≥ 25 %. 12 patients (27.3 %) had no significant change from baseline and 4 patients (9.1 %) worsened. Topiramate was discontinued in 7 patients representing a withdrawal range of 15.9 %.

Reasons for discontinuation of TPM were either lack of efficacy (2 patients, 4.5 %), adverse events (1 patient, 2.3 %) or both (3 patients, 6.8 %). 1 patient (2.3 %) was lost to follow up and another patient (2.3 %) underwent epilepsy surgery 6 months after initiation of treatment with TPM.

Behavioral/psychiatric side effects (20.5 %), weight loss (18.2 %), dizziness and/or nausea (13.6 %), drowsiness (13.6 %) and somatic pain (13.6 %) were the most frequently reported side effects. TPM worsened 4 out of 8 patients with pre-existing psychiatric illness.

A reduction of 20.4 % on the number of concomitant antiepileptics was achieved. 3 patients (7 %) were on TPM monotherapy at the end of the study period; 2 patients achieved seizure freedom whereas the third had a seizure reduction of more than 75 %.

Our results show that TPM is an effective drug with a substantial rate of seizure-free patients even in this population of highly pharmacoresistant cases.

41% of our patients with refractory epilepsy experienced a reduction of 50 % or more on their seizure frequency with the addition of TPM in their antiepileptic drug regimen during the twelve months of their evaluation.

However, the adverse drug reaction profile of the drug indicates that a risk-benefit assessment should be carried out before TPM is prescribed to patients with psychiatric illness. Weight loss seems to be a frequent problem as well as CNS related adverse events and somatic pain.

P364
Orgasm-induced epilepsy
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Neurologic conditions such as transient global amnesia, monocular blindness, syncope, subarachnoid hemorhage, intracranial hematoma, embolic strokes, and severe headaches precipitated by sexual activity (orgasm, intercourse, and masturbation).

We report a 30 year-old female patient who had generalize tonic clonic seizures without incontinence and aura, three times after orgasm during the last 2 months. She had postictal confusion for 15 minutes. Her first seizure was 4 month ago which was not related to epilepsy after orgasm. Her first seizure was spontaneous generalized tonic-clonic seizure in the morning when she was in bed. She felt that her organs were bigger, and than she had tonic-clonic seizure, lasted for about one minutes without incontinence. She had a one year history of migraine without aura. She had also experienced previous episodes of intercoital cephalgia. She was born at term without any complication. There was no history of febrile seizure. There was no seizure in the family history. Her psychomotor development and general examination was unremarkable. Her cardiovascular and neurologic examinations were normal. Laboratory findings revealed no abnormality. The interictal EEG showed discrete right centrotemporal region epileptic focus. No abnormalities were found on cranial magnetic resonance imaging. The attacks were completly controlled with carbamazepine.

The right hemisphere plays an important role in human sexual functions. The production of hormones controlling sexual functions shows a right-sided predominance. The recurrent epileptic attacs, together with the EEG abnormalities, raises the possibility of an epileptic aetiology in the temporal region. We suggested that this is only a particular form of temporal lobe epilepsy.

P365
Chronic encephalitis and epilepsy in an adult patient: a variant of Rasmussen's syndrome?
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Background and purpose: Rasmussen's encephalitis is a chronic progressive disease of unknown etiology consisting of focal seizures, hemiparesis and intellectual deterioration. Usually it begins in the childhood but exceptionally it can occur in the adult age. We report an adult patient with chronic asymmetrical encephalitis with histopathological confirmation but with an unusual clinical course.

Methods: A 51-year-old woman was admitted due to an episode of what was considered viral encephalitis. She recovered with no secuela. All through the next 2 years she suffered from episodes of fever and encephalopathy, sometimes accompanied by partial complex seizures that improved partially with high-dose steroids. At the age of 54 she developed a simple partial status accompanied with a mild right hemiparesis during some days. One year later she had again partial complex seizures and a severe right hemiparesis, right homonymous hemianopia and aphasia. She did not improve neither with high-dose steroids nor with immunoglobulins. The patient kept on worsening and she died at the age of 55 from aspirative bronchopneumonia.

Results: The magnetic resonance imaging showed no abnormalities all through 3 years subsequent from the onset. After that it showed an increased T2 and FLAIR signal in the left temporal-occipital areas. The cerebral SPECT at that moment indicated a hypoperfusion in the left parietal-temporal region. The electroencephalograms revealed diffuse slow waves and periodic lateralized epileptiform discharges in the left hemisphere. The brain biopsy had the typical changes of chronic encephalitis.

Conclusion: In adult patients the Rasmussen's syndrome can show clinical differences from the disease in the childhood, so that should make us wonder whether they are different entities or the same.

Dementia/Higher function disorders

P366
Gene-gene interaction between interleukin-1A and interleukin-8 increases the risk of Alzheimer's disease
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Background: Microglial activation by beta-amyloid in Alzheimer's disease (AD) brain induces upregulation of proinflammatory cytokines, especially interleukin (IL)-1A, as well as certain chemokines, namely IL-8. A polymorphism in the promoter region (–889) of the IL-1A has been shown to confer increased risk for AD, but other studies failed to replicate such an association, perhaps due to the interaction of genetic modifiers in individual patients.

Objective: The postulated common pathway of IL-1A and IL-8 in the cerebral inflammatory response, prompted to examine the combined contribution of both IL-1A (–889) and IL-8 (–251) gene polymorphisms, to the susceptibility for AD.

Methods: The study included 276 AD patients (69 % women; mean age 75.6 years; SD 8.9; range 50–98 years) who met NINCDS/ADRDA criteria for probable AD. Control subjects were 237 unrelated individuals (71 % women; mean age 79.9 years; SD 7.9; range 63–98 years) with Mini Mental State Examination scores of 28 or more, which were verified by at least one subsequent annual follow-up assessment.

Results: The presence of the IL-1A (–889) allele 2 conferred a marginally significant increase in the risk for the disease (odds ratio 1.4, 95 % confidence interval 1.0–2.0, $p = 0.053$), and the presence of the IL-8 T/T genotype was not associate with AD (OR 1.3, 95 % CI 0.9–1.9, $p = 0.135$). However, the subjects carrying both polymorphisms had about two times higher risk of developing AD than subjects without these risk genotypes (OR 2.1, 95 % CI 1.2–3.7, $p = 0.007$).

Conclusions: Our findings indicate that the risk effect of the allele 2 of the IL-1A (–889) gene is only apparent in the presence of the T/T genotype of the IL-8 (–251) polymorphism, suggesting a synergistic effect of these two loci on the risk of AD.

P367
Combined deviation in the two dimensions of the subjective vertical in patients with spatial neglect
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Background: In the frontal plane, patients with right cerebral lesion usually present an anticlockwise deviation of the subjective visual vertical, which is associated with a disorder of body posture. But the occurrence of a similar disorder in the sagittal plane has never been assessed.

Objective: To investigate the accuracy of the SVV in the frontal and sagittal planes in those patients.

Method: Eight patients presenting with a right hemispheric stroke were evaluated. Four were regarded as neglect (N+) in the classical tests of line bisection, scene drawing and bell cancellation. They were compared to four non-neglect (N–) and four healthy subjects (C). They sat in the dark, facing a luminous bar adjustable in rotation, either in the frontal plane, or in the sagittal plane, and had to place it verticaly. Statistics were performed using repeated measures ANOVAs.

Results: In the frontal plane, N+ patients showed a significant anticlockwise deviation of the SVV (–8.8°), in comparison with the N– (–1.9°) and C (0.4°) groups. In the sagittal plane, N+ patients showed a significant posterior inclination (–4.5°), in comparison with the N– (0.04°) and C (1.1°) groups. In addition the Spearman test showed a significant correlation between both deviations in the patients population.

Discussion: This study, while confirming the anticlockwise deviation already reported in the frontal plane, showed for the first time that this phenomenon is associated with a posterior deviation of the SVV.

P368
New mutation in first Belgian cases of Nasu-Hakola disease
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Introduction: Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL) or Nasu-Hakola disease is a recessively inherited disease with genetic heterogeneity presenting as a presenile de-

mentia with frontal lobe syndrome, basal ganglia involvement and bone cysts. The latent period extends to early adulthood. The first symptom is skeletal pain followed by spontaneous bone fractures. The frontal lobe syndrome and extrapyramidal symptoms develop around age 30, culminating in severe dementia and death in the 4th and 5th decade. DAP12 and TREM2 are the two PLOSL genes. Approximately 25 % of PLOSL patients have a mutation in TREM2 and 75 % in DAP12.

Patients: A 39-year-old male presented with complex partial seizures and psychiatric disturbances. Past medical history revealed an accidental elbow fracture 4 years before. Neurological examination revealed a frontal lobe syndrome with loss of judgement and social inhibition, and impairment of memory and attention. Frontal release signs, cogwheel rigidity and upper motor neuron involvement with Babinski signs were present. One year later the frontal lobe syndrome and dementia worsened, leading to unemployment and growing inability to perform the activities of daily living.

His 41-year-old sister started to complain of pain in the lower limbs at age 29, followed by several pathological bone fractures. Neurological symptoms emerged at age 39 with dementia and frontal lobe syndrome, complex partial seizures and eventually a bedridden state with mutism and severe deficit of higher cortical functions, pseudobulbar and frontal release signs, cogwheel rigidity, pyramidal signs and severe dysphagia.

Neuroimaging in both patients showed symmetrical basal ganglia calcifications with cortico-subcortical atrophy. Total body X-ray showed multiple cystic bone lesions, mainly in ankle and wrist joints.

Methods and results: Molecular genetic analysis in both patients revealed a homozygous mutation in the TREM2 gene with a homozygous conversion of nucleotide C to T at position 97, resulting in a premature translation termination codon at position 33 in the amino acid chain (Gln33Stp). This is a new mutation in the TREM2 gene.

Conclusion: Patients presenting with presenile dementia and frontal lobe syndrome of unknown origin should be screened with X-ray to look for asymptomatic bone cysts. Genetic testing of TREM2 and DAP12 genes allows confirmation of the diagnosis of Nasu-Hakola disease.

P369

Implicit learning of a sequential motor task in patients with mild cognitive impairment: preliminary results

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Background and Objectives: While motor task performance is usually impaired in Alzheimer's disease, it has not been described in mild cognitive impairment (MCI). Our hypothesis is that a subclinical dysfunction may be evidenced in patients with MCI through a protocolized study of acquisition of motor skills.

Methods: The study was performed in 6 patients with MCI and their 6 spouses who served as age-matched healthy volunteers. Subjects were facing a computer screen in which there was an aerial view of a schematic football field, the goal-keeper in the centre of a 12 cm long goal-line, and the figure of a ball (target) 15.5 cm from the center of the goal-line. Subjects kept their right hand in contact with a linear potentiometer, which moved the goal-keeper along the goal-line. A key stroke started the movement of the figure of the ball in pre-determined directions. The only instruction given to the subjects was to try to intercept as many balls as possible. For each trial, we recorded reaction time in ms from onset of ball displacement to the first movement of the potentiometer and noted whether the direction of the movement was correct or incorrect, and whether the subject stopped or failed to stop the ball.

Results: Reaction time was variable in all subjects since the first trial. However, most control subjects had a significant reduction between the 11th and 12th trials, which was demonstrated in some by their movement starting even before the ball began to move. Mean reaction time values in the last half of the series of 20 trials (last 10 trials) showed a 22 % improvement respect the initial half of the series (first 10) in control subjects (paired t-test; $p < 0.001$) while it did not improve in patients (12 %, non-significant). The number of errors was significantly higher in patients than in control subjects while the number of successful ball stops was significantly higher in control subjects than in patients. Accurate description of the sequence (explicit learning) was made by only subjects from the control group.

Conclusions: Our preliminary results suggest that implicit learning of a motor task seems to be defective in patients with MCI. This may be due to an attentional deficit or to a limited fixation of the motor task trace in short term memory neuronal loops.

P370

Impaired hippocampal recruitment during an episodic memory task in patients with myotonic dystrophy

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Objective: To investigate if there is hippocampal damage in myotonic dystrophy type 1 and 2.

Background Impairment of cognitive function is frequent in patients with myotonic dystrophy (DM1) and proximal myotonic myopathy (DM2). It remained unresolved, however, whether memory impairment results from subcortical or cortical malfunction.

Design/Methods: Extensive cognitive performance was investigated in a group of patients ($n = 9$; age 16–60 y) with DM1 and DM2 and 8 age matched controls (age 20–61 y). In addition, episodic memory was assessed with 5 repetitive learning and recall trials of 10 abstract geometric patterns during fMRI. Data were acquired with a 1.5 Tesla whole-body MRI system. Statistical analysis was performed with SPM99.

Results: Behavioral data revealed differences between patients and controls in attentional tasks ($p < 0.04$), executive functioning ($p = 0.017$), general intelligence ($p = 0.012$) verbal (delayed recall: $p < 0.000$) and visual episodic memory (initial: $p = 0.011$, delayed recall: $p = 0.002$). In the fMRI task differences were only observed in trial 3–5 (controls: 4.4 ± 1.5, 6.3 ± 1.7, 7.2 ± 1.2, 8.2 ± 1.2, 8.9 ± 1.2 and DM: 5.0 ± 1.3 (n. s.), 5.2 ± 1.5 (n. s.), 5.6 ± 1.7 ($p = 0.031$), 6.7 ± 1.4 ($p = 0.034$), 6.8 ± 2.5 ($p = 0.025$)).

fMRI analysis revealed in single group analysis a failure of hippocampal activation in DM1 and DM2 patients on high familiarity recall. Group comparison between controls and patients revealed predominant bilateral hippocampal activity in controls. In contrast, patients showed enhanced activation in regions of supplemental motor areas and in the anterior cingulate.

Conclusion: It could be demonstrated that in DM1 and DM2 compared to controls there is an impairment of verbal and visual episodic memory supported by an fMRI finding of a reduced hippocampal activity in the patients group. We therefor conclude that malfunction of hippocampal recruitment underlies impairment of episodic memory in mildly affected patients with DM1 and DM2.

P371

No evidence for association of the monocyte chemoattractant protein-1 (–2518) gene poymorphism and Alzheimer's disease

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Background: Activation of microglia is a central part of the chronic inflammatory process in Alzheimer's disease (AD). The monocyte chemoattractant protein-1 (MCP-1) is a chemokine that plays a role in microglia migration and accumulation at sites of beta-amyloid deposition in the AD brain. A polymorphism (A/G) in the regulatory region (–2518) of the MCP-1 gene affects the level of MCP-1 expression, and individuals bearing the MCP-1 G allele have a stronger inflammatory response with higher peripheral tissue damage.

Objective: We investigated whether the MCP-1 (–2518) G variant (AG and GG genoypes) might be responsible for susceptibility to AD. Methods: The study included 328 AD patients (69 % women; mean age 75.8 years; SD 9.9; range 50–98 years) who met NINCDS/ADRDA criteria for probable AD. Control subjects were 315 unrelated individuals (71 % women; mean age 80.5 years; SD 7.5; range 63–100 years) with Mini Mental State Examination scores of 28 or more, which were verified by at least one subsequent annual follow-up assessment.

Results: There were no statistical differences in the distributions of MCP-1 genotypes in the AD group when compared to controls: when compared to AA genotype, the odds ratio for the AG genotype was 0.98 (95 % confidence interval 0.70–1.36), and 0.84 (95 % confidence interval 0.43–1.68) for the GG genotype.

Conclusions: Although supporting evidence for the biological role of MCP-1 in AD exists, the MCP-1 (–2518) polymorphism distribution does not differ between patients and controls, and therefore, this polymorphism is unlikely to confer genetic susceptibility to AD.

P372
Profile of declarative memory in ageing and mild cognitive impairment
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Background: Mild cognitive impairment (MCI) is recognized as a transitional state between the normal aging and Alzheimer's disease. Differential diagnosis between Mild Cognitive Impairment (MCI) and normal aging is not well established, but it is known that patients with Alzheimer's disease show a progressive declarative memory impairment.

Objective: To evaluate whether performance on declarative memory tasks can help to differentiate normal aging and patients with MCI.

Method: We compared performance on declarative memory tasks between thirty control subjects and fifty-three unselected patients diagnosed with MCI according to criteria by Petersen et al. (1999, 2001)(aged: > 50 to 80 years)(23M/30F), from a wider cohort of patients with subjective memory complaints referred to our Neurological Service. Declarative memory tasks included paradigms of picture recognition and prospective memory, semantic memory tasks (subtest Information-WAIS and Recognition of Famous people) and an autobiographical questionnaire.

Results: ANCOVA, using age and sex as covariates, showed that the MCI group performed significantly more poorly than the control group on Picture Recognition ($p < 0.028$) and Famous Face identification ($p < 0.01$). Both tasks showed the highest ability to differentiate between controls and MCI subjects: approximately 70 % were correctly classified.

Conclusions: A declarative memory profile can help to differentiate patients with MCI and normal aging. Specific tasks of picture recognition and of famous face identification could help to improve the differential diagnosis of MCI.

P373
A survey of voter participation by cognitively impaired elder persons in Belgium
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Introduction: This study had two goals: 1. to investigate which factors influence the voter participation of demented outpatients. 2. to investigate the knowledge on politics in demented outpatients.

Only two recent studies deal with this topic, both conducted after the presidential elections in the USA. Elections in Belgium are considerably more complicated as multiple political parties run for the elections and every party proposes several candidates. Furthermore, the elections were conducted using a computerized system (using a touch screen/electronic pen).

Because in Belgium in recent years many political parties changed name and many politicians finished their career, we studied if cognitively impaired persons were familiar with both old and new names of the political parties and if they recognized both 'ancient' and 'new' politicians.

Methods: 1) During the three months following the federal elections on may 18th 2003, n = 41 demented outpatients/care-givers were asked about voter participation.

The care-givers were asked if they considered the patient was able to vote. The data were compared to the Mini mental state examination (MMSE), Global deterioration Scale (GDS), Basic-ADL and Instrumental-ADL results.

2) N = 26 demented patients were tested using a powerpoint-presentation consisting of 24 slides. Three subsets of questions were asked: a. give or recognize the name of a political party; b. recognize photographs of politicians; c. recognize the names of politicians. N = 24 control subjects aged > 65 y underwent also the 24 slide test.

Results: 1) 28/41 patients partipated to the elections. Patients living at home with their spouse particpated more to the elections. Their was a highly significant correlation between partipation and GDS, Instrumental-ADL, care-giver evaluation. 2) Patients scored significantly worse than control persons ($p < 0.0001$) for all three subsets. There was a significant correlation between global testscore and Instrumental-ADL and GDS. Demented patients recognized 'ancient' politicians better than contemporary ones.

Discussion: 1) There is a correlation between voter particpation and the severity of dementia and decline of praxis, but not of pure cognitive decline (MMSE). Only one care-giver considered the computerized system to negatively influence participation. 2) Political knowledge is merely an ADL-function and declines as the dementia progresses. Demented patients recognize older politicians better than contemporary ones.

P374
Impaired recognition of face and Chinese character without object agnosia
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A leading account of high-level visual recognition proposes that the recognition of faces, objects, and words is mediated by two processing capacities (Farah MJ, Cognitive Neuropsychology, 1991). Faces are processed as non-decomposed perceptual wholes, whereas words require decomposing process to need the capacity to represent numerous parts. Object recognition appears to require both of these capacities. Thus, patients with alexia and prosopagnosia should be impaired in object recognition. We report a case of a 70 year-old right-handed man who suddenly developed left hemianopia with prosopagnosia. A marked impairment in the ability to recognize familiar faces and learn new face-name associations was evident. In contrast, identification of characteristics of faces (gender, age) and distinguishing different faces were relatively preserved. As an accurate error analysis, we adopted Korean Boston naming test (KBNT) as test for object recognition, and Korean word list and Chinese word list specially designed as that for word recognition. He showed no deficit in object recognition (6 % errors). The patient could not recognize some Chinese words apparently (48 % errors). However he could read Korean words relatively well (0 % in real words and 14 % in pseudowords errors). Brain magnetic resonance (MR) imaging revealed right posterior cerebral artery infarction. This pattern of performance coincides with the expectation of the two-capacity theory, in the point that he showed no deficit in the recognition of Korean word. The selective alexia to Chinese words suggests that recognition of Chinese words may be processed through the face recognition route. This explanation agrees with that of the selective alexia to one type of Japanese characters (Kanji).

P375
Glu298Asp polymorphism of the e-NOS and homocysteine levels in patients with Alzheimer's disease and vascular dementia
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Background: Elevated total plasma homocysteine (tHcy) levels have been demonstrated to be a risk factor for vascular dementia (VaD) and Alzheimer's disease (AD). Besides, several genetic polymorphisms have been proposed as susceptibility factors, including the genotype Glu/Glu of the polymorphism Glu298Asp in eNOS gene. Moreover, further studies suggest that this polymorphism seems to have no effect on plasma levels of homocysteine, folate and lipids, and on vascular endothelial function in healthy subjects.

Objective: 1) To determine the distribution of the Glu298Asp polymorphism and of the ApoE genotype in a population of Italian patients with AD compared with age-matched controls.

2) To detemine tHcy levels in AD and VaD patients and correlate them with e-NOS and ApoE genotype.

Methods: The distribution of the Glu298Asp polymorphism as well as ApoE genotype was determined in a population of 384 Italian patients with AD as well as in 244 age-matched controls. Genomic DNA was isolated from blood and polymorphisms were determined by PCR-RFLP assay. tHcy levels were evaluated in 84 out of 362 AD patients as well as in 24 VaD patients.

Results: The frequency of the Glu298Asp in both our AD and control populations was similar to the one reported for Caucasians. No differences in the distribution of the polymorphism between AD and controls were shown, even stratifying for the presence of e4 allele. tHcy levels in AD patients homozygous for the mutation were lower compared with wild type or heterozygous. The same trend was observed in VaD patients.

Conclusions: The Glu298Asp polymorphism seems not to be associated with AD, both by itself or in combination with the e4 allele. However, the presence of two mutated alleles may contribute to lower the levels of tHcy, thus decreasing the negative effects due to hyperhomocysteinaemia.

P376

n-NOS C276T polymorphism in patients with Alzheimer's disease

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Background: Different isoforms of nitric oxide synthases (NOS), including neuronal (n-NOS) are overexpressed in Alzheimer's disease (AD) brains, suggesting a critical role for nitric oxide (NO) during the pathogenesis of the disease. A novel polymorphism in human n-NOS gene was identified, consisting in a C/T transition located 276 base pairs downstream from the translation termination site (C276T).

Aim: To determine the distribution of C276T polymorphism in n-NOS gene and ApoE genotype in a population of Italian patients with AD compared with age-matched healthy subjects.

Methods: The distribution of C276T and ApoE were determined in a population of 384 patients with AD, diagnosed according to NINCDS-ADRDA criteria, and in 244 controls. Genomic DNA was isolated from blood and polymorphisms were determined by PCR-RFLP assay.

Results: The frequency of the C276T mutation in Italian control population was similar the one previously determined in Caucasians. No differences in the distribution of C276T between patients and controls were shown. Stratifying by gender or ApoE status, no differences in allele frequency were observed. On the contrary, the frequency of C276T polymorhism was significantly increased in patients with an early onset (EOAD; age at onset < 65 years) compared with late onset (LOAD; > 65 years).

Conclusions: The presence of the C276T polymorphism seems to be a risk factor for EOAD, and exerts its effect without any interaction with the ApoE e4 allele.

P377

Acetylcholinesterase inhibitor-treatment modulates CCR5 and RANTES expression in PBMCs: implication for the pathogenesis of Alzheimer's disease

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Background: Alzheimer's disease (AD) is characterized by loss of memory, associated functional decline and behavioural disturbances. The symptoms of AD have been shown to be associated with abnormalities in many neurotransmitter systems, the most common of which is a deficiency in cholinergic system within the central nervous system. In the pathogenesis of AD, immune and inflammatory-related proteins have been implicated as mediators in response to brain injury. Interaction between cytokines and chemokines may modify the "cytokine cycle" which is a proposed pathogenic mechanism for neuro-degeneration in AD. Therapeutic approaches have involved cholinesterase inhibitors (ChEI) that increase the concentration of acetylcholine.

Objective: To study the effect of treatment with ChEI on immune system function in AD patients and to analyze the expression of CCR5 and RANTES in PBMC of AD patients, before and during AchEI-treatment, compared with healthy controls. Material and Methods: 21 patients with clinical diagnosis of AD according to DMS IV-R and NINCDS-ADRDA were studied. All patients underwent blood withdrawal before and after 1 month of AchEI treatment (Donepezil, 10 mg/die). Reverse-Transcriptase-Polymerase Chain Reaction was used to determine mRNA of CCR5 and RANTES, released levels of RANTES were determined by ELISA assay.

Results: Both CCR5 and RANTES mRNA expression were analyzed, and bands from electrophoresis gel were quantitated with computational scanning software and relative expression ratios of CCR5/G3PDH and RANTES/G3PDH were calculated. A significant difference was found between AD patients and healthy controls ($p = 0.023$ and $p = 0.013$ respectively). Expression of CCR5 and RANTES were reduced in PBMC from treated AD patients when compared with PBMC from untreated AD patients ($p < 0.05$). Levels of RANTES were enhanced in AD patients compared to healthy controls, and were statistically reduced by treatment with AchEI ($p < 0.05$).

Conclusion: Our previous results suggest that PBMC may be an important source of inflammatory cytokines and chemokines involved in AD. This study suggest that CCR5 and its ligand, may both contribute to the pathogenesis of Alzheimer's disease. The correlation between CCR5 and RANTES suggests that their interaction play a role in the progression of the disease. The stabilizing effect of AchEI-treatment may be related to a reduction of CCR5 and RANTES expression and production.

P378

Measuring the attitude to know and the will to decide in cognitive impairment

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Introduction: autonomy is the ethical principle related with personal decision making and self determination. People with dementia can not accomplished their autonomy and will, because they loose competence.

Objective: the objective of this presentation is to introduce a new test, developed to measure the attitude, will to know and decision making, of competent individuals, in questions related with cognitive impairment and dementia; and the preliminary results of its validation.

Methods: a self-administrable 11 item questionnaire was created following standardized guidelines (peer-reviewed designed, weighted answers, revised by field-expert). The 11 questions measured the information which a person would like to receive in the potential situation of cognitive impairment and what decisions to make. Each question has three possible "weighted" answers. 107 healthy people (mean age 44.3, 20–80 years) without history of neurological disorder nor major psychiatric alterations were tested and retested after one week. Data was analysed using SPSS for Windows version 9.0. Factor analysis was executed by an exploratory principal – components analysis on the correlation matrix of the 11 items with orthogonal rotation using the Varimax procedure and Kaiser method. The internal consistency was assessed by the Cronbach's alpha and the external validity with Pearson's correlation coefficient.

Results: internal consistency as assessed by the Cronbach's alpha was 0.74; $p < 0.01$. The test-re-test analysis for the whole test showed a correlation of 0.82; $p < 0.01$ and all single items also had a significant positive correlation. The factorial analysis disclosed the presence of two factors, one was related with getting information and the other with decision making.

Conclusion: we have developed a test which measures the will to receive information and to participate in future decisions related with dementia. The preliminary results show that the test has good internal consistency and correlation through time. This test will allow to fulfil the principle of autonomy, since it will allow healthy individuals to make their own decisions on dementia related issues while still competent.

P379

Two-year follow-up of the effect of treatment with cholinesterase inhibitor on cognitive functions and cerebral blood flow in Alzheimer's disease and vascular dementia

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Background: Cholinesterase inhibitors (ChE-I) are widely approved for the treatment of patients with Alzheimer's disease (AD). The cholinergic hypothesis of AD, as well as the therapeutic action of ChE-I in the disease, were confirmed in many studies. There is increasing evidence that patients with vascular dementia (VaD) also exhibit cholinergic deficit and could benefit from ChE-I. Cholinesterase inhibition leads to an increase of regional cerebral blood flow (rCBF) and prevents deterioration of the cognitive functions in these illnesses. However, less is known about the long-term efficacy of the ChE-I.

The aim of the present study was to investigate the effects of treatment with rivastigmine, one of the inhibitors of acetylocholinesterase (AChE-I), on the rCBF and the cognitive functions in patients with AD and VaD, during a period of 24 months.

Material and method: The clinical assessment, neuropsychological examination, CT (or MRI) and SPECT with 550 MBq of Tc-99m HMPAO, were conducted at the onset of the study, after 12 months and after 24 months. In SPECT, semiquantitative analysis was performed over the cerebrum and the cerebellum, using circuit regions of interests (ROIs).

At the first examination AD was diagnosed in 25 patients and VaD in 8 patients. All patients were treated with rivastigmine during the time of observation. After 24-months the number of patients decreased, from different reasons, to 17 with AD and 4 with VaD.

Results: In patients with AD treated with rivastigmine during the first 12 months, the rCBF increased by 5–7 % in the temporal areas and 3–5 % in the frontal areas. After the next 12 months rCBF returned to the initial level, with the exception of the motor cortex, where it remained increased by 5–6 %. However, the cognitive functions were constant only during the first 12 months of treatment and decreased significantly during the next 12 months.

In patients with VaD the rCBF increased in all the regions of the brain, except for the temporal anterior regions, and remained at an elevated level

for the next 12 months. The cognitive functions deteriorated slowly, but not as fast as in the case of AD.

Conclusions:

(i)Treatment with cholinesterase inhibitor during the 24 months prevents a decrease of rCBF in patients with AD,

(ii)The cognitive functions after 24 months undergo deterioration.

(iii)The effect of ChE-I treatment on patients with VaD is similar to that in patients with AD.

P380

Presentation and management of memory complaints in 726 general physicians: results of a questionnaire

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Objective: To examine the perception and the practices of general physicians (GP) with regard to memory complaint (MC).

Background: MC is a frequently reported symptom in general medical practice. It requires a rigorous diagnostic approach based on interrogation and clinical examination. Faced to the increase of MC, what are now the attitudes of GP?

Methods: Data from 726 French GP were obtained from a 13-item questionnaire evaluating epidemiological aspects and practical details of MC management.

Results: The mean age of the GP was 47.6 ± 7.6 years, 84 % were men, 59 % worked in rural areas. The average number of consultations for MC per week was 12.1 ± 12.8. For 80 % of the GP, a MC significantly increases their consultation time. GP estimated that 55 % of their patients with a MC had between 60 and 80 years. Over 61 % of the GP evaluated Instrumental Activities of Daily Living, 46 % used the MMSE, 43 % the 5-word memory test, 24 % the clock drawing task, and 6 % used other tests whereas 12 % performed no cognitive test. GP prescribed haematological tests (59 %), CT scanning (22 %), EEG (4 %), MRI scanning (3 %). A normal CT scanning excluded a memory consultation for 32 % of the GP. GP referred to memory specialists between 39 % (60–70 year-old) to 16 % (> 90 year-old) of their patients. A young patient (82 %) with a recent (64 %) and severe (95 %) MC was the best profile to be sent to a memory specialist whereas an older patient (76 %) with an ancient (73 %) and mild (93 %) MC was the best profile to not be sent to a memory specialist. Patients were preferentially sent to neurologists (85 %), then memory clinics (32 %), geriatrists (22 %), psychiatrists (9 %). The mean delay for a memory consultation was 5 weeks and 63 % of the patients were referred in the first month. The proposed therapies were medications (91 %), books or CD-ROMs (27 %), cognitive stimulation (22 %), memory rehabilitation (15 %). Before 60 years, MC were estimated to be due to anxiety, depression or psychiatric treatment. From 60 to 70 years, estimations were: anxiety or depression (35 %), psychiatric treatment (28 %), stroke (30 %), normal aging (43 %) and Alzheimer's disease (AD) (49 %). After 70 years, normal aging and AD were the predominant explanations. Postgraduate teaching has a significant impact upon management of MC.

Conclusions: This questionnaire confirmed the frequency of MP in general medical practice and showed that the GP successfully adapted their attitudes to the emergence of MP.

P381

A randomised, open study of the use of rivastigmine as an adjunct therapy to piracetam in the treatment of aphasia – a preliminary report

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Background and purpose: Aphasia is common after left middle central artery territory strokes and is perceived as a major disability by the patients and their relatives. Although the spontaneous recovery within first weeks after stroke is usual, the degree is very variable. Actually there is only a weak evidence suggesting GABA-ergic drug piracetam may be effective in the treatment of aphasia after stroke in humans. However, animal studies have demonstrated decreased levels of brain neurotransmitters including acetylocholine(ACh) after cortical stroke and more rapid recovery with therapy aimed at increasing Ach. The aim of present study was to determine the effect of acetylcholinesterase and butyrylocholinesterase inhibitor rivastigmine as an adjunct therapy to piracetam in the treatment of aphasia.

Methods: In a prospective, open study, 30 aphasic patients with an acute nonhemorrhagic infarction are randomly assigned to receive either 3 mg rivastigmine and 4.8 g piracetam or piracetam only. All patients undergone the same scheme of 1-hour session of speech/language therapy. The neuropsychological evaluation is performed at baseline, at day 14th and at 3 month. The test battery includes the following tests: the Boston Aphatic Test, Lodzki Clinical Tests of Aphasia.

Results: 11 patients have been enrolled so far, and it's expected to finish the study before April 2004. Although there were no differences between the two groups before study entry, by 2 weeks of treatment we noticed a slight difference in gain scores between the groups, with the greater gain in the rivastigmine group ($P < 0.05$).

Conclusion: Administration of rivastigmine as an adjunct therapy may enhance the level of improvement from aphasia comparing with only piracetam and speech therapy. However this effect must be confirmed basing on larger group of patients. The analysis of 30 patients consisitng of neuropsychological evaluation at 2 weeks and 3 month visits will be presented during the ENS Meeting in Barcelona.

P382

No association of cystatin c polymorphism in Italian subjects with Alzheimer's disease

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Background: Cystatin C is an amyloidogenetic protein that colocalizes with beta-amyloid within the arteriolar walls of subjects with Alzheimer's disease (AD) and congophilic amyloid angiopathy. Recent data have suggested that a coding polymorphism in the cystatin C gene (CST3) may influence the risk of sporadic AD (sAD). However, as far as we know, no systematic data on Italian population have been reported.

Objective: To investigate whether the CST3 is genetically linked to sAD.

Study design: A case-control genetic association study of an Italian dataset of 180 sAD cases (63 % women, mean age ± SD of 73.6 ± 8.0) and 180 age-and sex-matched, cognitively normal controls. All subjects were genotyped for CST3 and apolipoprotein E (APOE).

Results: There were no significant differences in CST3 G/G, G/A, and A/A genotype or G and A allele frequencies between cases and controls. As suspected, the presence of at least one APOE4 allele was significantly associated with AD (odds ratio = 3.5, 95 % confidence intervals = 2.0–6.0, $p < 0.0001$). When cases and controls were stratified according to APOE4 carrier status, no significant difference was found. Similar results appear after stratification for age at onset of AD (early onset AD = < 65 vs late onset AD = ≥ 65).

Conclusions: The present study suggests that the CST3 is not a susceptibility gene in Italian AD subjects.

P383

Cognitive impairment in Wilson's disease

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Objective: In addition to hepatic and extrapyramidal motor clinical symptoms, Wilson's disease patients also exhibit subclinical disorders of other central nervous pathways. Cognitive dysfunction is often complained and patients suffer from additional psychiatric symptoms.

Methods: In this study, an cognitive impairment profile was performed with SISCO (SIDAM) including mini mental state in 21 patients with Wilson's disease (16 patients with the neurological form, 5 patients with the non-neurological form) undergoing long-term medicamentous therapy. Results of cognitive testing were correlated to the neurological score on initial and follow up presentation.

Results: Results of cognitive screening show slight cognitive impairment in the investigated patients with Wilson's disease being on long-term treatment. Median result of SISCO was 52.5 (35–55) in the neurological form and 53 (49–55) points in the non-neurological form. However, there is no statistical significance in correlation to the severity of neurological score.

Conclusions: Psychopathologic symptoms and cognitive impairment in Wilson's disease is frequently reported by patients beeing on long-term treatment. Since movement disorders often have improved with therapy additional observing of cognitive function seems to be useful. However, cognitive impairment occurs independently of the severity of neurological symptoms.

P384
Psychological impact of Alzheimer's disease diagnosis disclosure: preliminary results
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Introduction: Alzheimer's disease (AD) diagnosis may represent an important emotional distress both for the patient and the caregiver.

Objective: our objective is to investigate if there are any emotional and psychological changes in both the patient and the caregiver after diagnosis disclosure.

Methods: consecutive AD patients (NINDS-ADRDA criteria) and their caregivers were evaluated before and after diagnosis disclosure. Patients were evaluated with the neuropsychiatric-inventory and the geriatric depression scale, and caregivers with the Beck's depression inventory (BDI), STAI and COPE questionnaire. The scores before and after diagnosis were analysed, using SPSS for windows version 10, through a paired T-test.

Results: this preliminary results are based on our initial 7 patients and 7 caregivers. Diagnosis disclosure did not produce neither clinical nor significant change in the outcome measures of the patient. By contrast, caregivers were severely affected, which was reflected on the outcome measures: BDI, from 7.6 to 14.7, $p = 0.0001$, STAI from 20.4 to 31.4, $p = 0.01$).

Conclusion: our preliminary results suggest that diagnosis disclosure mainly affects the caregiver, therefore psychological support and treatment should be directed towards them.

P385
Posterior cortical atrophy or focal-onset Alzheimer's disease? A clinical, neuropsychological and neuroimaging study
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Objective/Methods: To report longitudinal clinical, neuropsychological and neuroimaging findings in a patient presenting with isolated progressive visual agnosia, illustrating the difficulty of differentiating posterior cortical atrophy (PCA) from Alzheimer's disease (AD) with prominent visual deficits.

Results: A 64-year old lady presented with a progressive two-year history of difficulty locating objects visually. She was anxious that this might be due to AD because her mother had died in her eighties, reportedly from typical (amnesic) AD. Examination showed left visual extinction, left neglect alexia, and optic ataxia. Neuropsychology showed impaired visuospatial and constructional functions, but verbal reasoning, verbal memory and language were preserved, confirming the clinical suspicion of focal right hemisphere pathology. Magnetic resonance (MR) imaging showed diffuse brain atrophy but MR spectroscopy (temporal and occipital voxels) was normal. SPECT imaging showed focal right temporoparietal perfusion deficit. A diagnosis of PCA was suspected. Despite apparent clinical stability on follow-up, repeat neuropsychology fourteen months later showed deterioration in verbal memory and verbal reasoning, establishing a diagnosis of AD.

Discussion: Initially PCA was suspected because of the focal neuropsychological and SPECT perfusion deficits and the normal MR spectroscopy. Only with the emergence of additional neuropsychological deficits over time was the diagnosis revised to AD.

Conclusion: Cases fulfilling suggested diagnostic criteria for PCA may best be regarded as examples of single non-memory domain mild cognitive impairment (MCI) which may or may not evolve to AD.

P386
The use of an Italian version of the Informant Questionnaire on Cognitive Decline in the Elderly (It-IQCODE) in a consecutive cohort of a memory clinic outpatient service
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Introduction: The availability of questionnaire which a subject's relative informs of the decline suffered by this in his cognitive capacity is a useful tool in the clinical practice. Most of the present screening tests for the detection of dementia fail with mild dementia. Jorm et al. presented the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), a simple instrument that uses a close relative to obtain information on the cognitive decline of a patient.

Methods: we performed a study of an Italian version of IQCODE, in order to determine the effectiveness to detect dementia over 120 consecutive memory clinic outpatients.

Results and conclusion: The It-IQCODE showed a diagnostic sensitivity of 83 %, specificity of 90 %, positive predictive value of 78.6 % and negative predictive value of 92.5 %; Likelihood Ratio = Sensitivity/(100-Specificity) = 8.300; Prior Odds = Prevalence/(100 – Prevalence) = 0.429]. The values of sensitivity and specificity were similar to that of the Mini-Mental State Examination (MMSE). The results in this study showed the It-IQCODE as a good test for the detection of mild dementia, with greater diagnostic usefulness than MMSE, since provides informations even in subjects with language disturbances.

P387
Dementia and relapsing polychondritis
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Introduction: Relapsing polychondritis (RP) is a rare autoimmun connective tissue disorder characterized by episodic inflammation of cartilaginous structures. Neurologic manifestations occur in approximately 3 % of patients. The most common neurological deficit is extraocular muscle palsy. On rare occasions meningoencephalitis, dementia, cerebellar signs and cranial nerve involvement might be seen.

Case: A 61 years old male presented with subacute progressing dementia. The Mini Mental State (MMS) score was 10/30. He has a diagnosis of relapsing polychondritis for 1.5 years treated with immunosuppressor agents including methotrexate and corticosteroid prior 6 months. On neurological examination, no sign other than dementia was detected. Physical examination revealed a mild hyperemia and edema of the bilateral auricles. Initial cranial Magnetic Resonance Imaging (MRI) revealed hypointense lesions on T1 sequences and hyperintense lesions on T2 and Flair sequences located on bilateral periventricular regions, sentrum semiovale and corona radiata. The lesions showed punctated contrast enchancement. Cerebrospinal fluid (CSF) study showed pleocytosis and elevated protein level (95 mg/dl). CSF culture was found sterile. Stereotactic brain biopsy obtained from the lesion located on the sentrum semiovale of the parietal region. Biopsy showed focal perivascular lymphositic infiltration with edema, but no evidence of demyelination, neoplasia or infection. Clinical symptoms and signs were gradually improved in 5 months in associated regression of the lesions seen on the follow up cranial MRIs. Pleocytosis was dissappeared on the repeated CSF studies. The final MMS score was 29/30.

Clinical picture was reversible dementia associated with aseptic meningoencephalitis due to the relapsing polychondritis.

Conclusion: In the evaluation of the etiology of dementia autoimmun disease like relapsing polychondritis should also be considered as a rare cause. Awareness of neurologic complications of relapsing polychondritis may lead to early diagnosis and treatment.

Clinical neurophysiology

P388
Corticomotor threshold measurements in amyotrophic lateral sclerosis
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Background: Amongst various hypotheses put forward for the pathogenesis of amyotrophic lateral sclerosis (ALS), the excitotoxic hypothesis has had both neurochemical and neurophysiological support, the latter deriving mainly from transcranial magnetic stimulation studies. Regarding corticomotor threshold (Thr), however, contradictory results have been reported as some studies found reduced Thr in a subset of patients whereas other studies did not confirm this.

Objective: To perform Thr measurements in ALS patients categorized according to the physical signs in the hands.

Subjects and methods: 38 patients (11 of whom females) suffering from definitive ALS entered the study after giving informed consent for the procedures. A group of 78 neurologically normal subjects was also studied. The mean age at symptom onset in the patients' group was 60 years (range: 37–86) and the mean disease duration was 17 months (range: 3–71). Thr was defined at rest in 1 % steps using the method of Mills & Nithi. Briefly, lower Thr (LT) corresponds to the highest intensity which evokes motor evoked potentials (MEPs) with a probability of zero whereas upper Thr (UT) is the lowest intensity which evokes MEPs with a probability of one.

Mean Thr (MT) is the arithmetic mean of UT and LT. Regarding physical signs in the hands, 9 patients had no abnormal findings, 7 had upper motor neuron signs, 11 lower motor neuron signs and 11 mixed signs.

Results: In the control group, MT had a median value of 40.5 (range: 27.5–59).In the subgroup of ALS patients with no abnormal physical signs in the hands or only lower motor neuron signs median MT was 37.5 % (range: 23.5–47.5) and 31.5 % (range: 17.5–50), respectively. These differences, however, did not reach statistical significance (Kruskal-Wallis and Dunn's test, $p > 0.05$). In contrast, in patients with upper motor neuron signs and mixed signs, median MT was 53 % (range: 29–100) and 79.5 % (range: 27–100), respectively (Kruskal-Wallis and Dunn's test, $p < 0.05$).

Conclusion: ALS patients with upper motor neuron signs in the hands or mixed signs have increased corticomotor Thr. In contrast, patients with no abnormal signs or lower motor neuron signs only, tended to have lower Thr compared to controls. However, this tendency did not reach statistical significance and, therefore, these results do not provide clear evidence for increased corticomotor excitability in ALS

P389

Neuronal correlates of visual self-motion perception (FDG-PET study)

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Circularvection (CV) is induced by large-field visual motion stimulation during which the subject perceives the moving surroundings as being stable and himself as being moved. Earlier PET and fMRI studies of self-motion perception showed responses in the parieto-occipital and temporo-occipital cortex, as well as in the anterior insula [1, 2]. The aim of this fluorodeoxyglucose (FDG)-PET study was to define areas involved in the processing of self-motion induced by coherent clockwise visual motion stimulation. We, therefore did correlation analyses between the metabolic effects and perception of body tilt and degrees of lateral head tilt.

FDG-PET (Siemens, Germany) was performed in 14 healthy subjects (8 m, 7 f; mean age 29.5 years) during self-motion induced by a computer-animated coherent dot pattern moving clockwise and displayed on a large screen. Correlation analyses with the amount of lateral head tilt (degree) and the perceived intensity of body tilt (scale 0 to 10) were performed with the SPM99b software.

A total of 12 of 14 subjects perceived a body tilt during visual motion stimulation (7 ipsiversive, 5 contraversive to stimulation direction). Positive correlation was found between the intensity of perceived body tilt and the parieto-occipital cortex (occipital gyrus/cuneus BA 18/19 right; upper parts of the inferior parietal lobule bilaterally, BA 40), the right inferior frontal gyrus (BA 44), and the anterior cingulate gyrus (BA 6). Smaller areas were located in the medial frontal gyrus (BA 6/8) and the lingular (I) and central lobule (III) of the vermis. These clusters represent areas known to be involved in the processing of body orientation in space.

Positive correlation with the head tilt, all ipsiversive to the stimulus direction, was found bilaterally for the putamen, the lateral thalamus (Voe, Do), and in the substantia nigra/crus cerebri of the midbrain. These areas are responsible for the control of motor function of the head.

References

1. Brandt, et al. (1998) Brain 121:1749–1758
2. Kleinschmidt, et al. (2002) NeuroImage 16:873–882

P390

Brainstem and cerebellar activation during horizontal and vertical optokinetic stimulation in fMRI

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Earlier fMRI studies during horizontal optokinetic nystagmus (OKN) showed bilateral activations of a cortical network in the primary visual cortex, motion-sensitive areas in the temporo-occipital cortex as well as in cortical eye fields [1, 2]. Due to earlier technical limitations the studies were restricted to the cortex. From animal studies it is known that certain brainstem nuclei and cerebellar areas are involved in the processing of ocular motor answers. The aim of this study was to identify and differentiate brainstem and cerebellar areas involved in the generation of horizontal (hOKN) and vertical OKN (vOKN) in humans.

Nine healthy volunteers were examined using a clinical 1.5 T scanner. The protocol included 320 volumes each of 40 slices of a T2*-weighted EPI sequence in alternating blocks of ten images at rest (looking at stationary target) and ten during either small-field hOKN or vOKN (computer generated stripes, no self-motion perception). Subjects lay supine, their view was corrected by a mirror to a projection surface. Statistical analysis was done with SPM99b.

During hOKN and vOKN activations were found in the pretectum and posterior thalamus bilaterally. In addition, during hOKN activations were located in the dorsal medullary and pontine brainstem, whereas during vOKN they were found in the paramedian ponto-mesencephalic brainstem. Under both stimulation conditions cerebellar activations were located in the superior/inferior semilunar, simple, and quadrangular lobules, flocculus, as well as in the pyramis (VIIa), decline (VI), and folium (VII) of vermis.

This study shows activations in the brainstem identically located for both stimulation directions, which can be attributed to the nuclei of the optic tract (NOT) and accessory optic system (AOS) situated in the transition zone between the posterior thalamus and the midbrain. These neuronal substrates are known to be responsible for the execution of OKN.

For hOKN, additional areas can be attributed to the dorsal pontine nuclei, the PPRF, and probably perihypoglossal area responsible for the execution of slow phases and horizontal fast phases of nystagmus. For vOKN, additional areas could be attributed to ocular motor nuclei (III) and the rostral interstitial nucleus of MLF (riMLF). The latter might reflect the involvement of the saccadic system in fast phases.

References

1. Bucher, et al. (1997) Neurology
2. Dieterich, et al. (2003) Exp Brain Res

P391

Multi-modality neurophysiologic monitoring during cardiac surgery is associated with lower-than-expected incidence of brain injury

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Background: A large, multi-center trial has prospectively established a 6.1 % incidence of serious brain injury associated with coronary revascularization [1]. Since this trial used no neurophysiologic monitoring, we compared this expected incidence with that achieved through continuous assessment of 1) cerebrocortical synaptic activity (EEG), 2) cerebral blood flow and embolic activity (transcranial Doppler ultrasound or TCD), and 3) cerebrocortical oxygen balance (transcranial near-infrared spectroscopy or NIRS).

Methods: From 2000 through 2002, 496 revascularization and/or valve replacement procedures were performed with multimodality bi-hemispheric neuromonitoring. Four-channel EEG examined anterior and posterior watershed regions, while two-channel TCD measured middle cerebral artery flow velocity and two-channel NIRS monitored the prefrontal anterior watershed. Detected physiologic or anesthetic imbalances were corrected conservatively.

Results: Neurophysiologic imbalance requiring intervention was detected in 88 % of the surgeries (EEG 25 %, TCD 13 %, NIRS 50 %). All but 3 % were correctable. Seven patients (1.4 %, $P < 0.001$ vs. expected) awoke from surgery with a new serious brain injury. Only one such injury did not develop a noteworthy EEG change intraoperatively.

Discussion: The high rate of observed noteworthy physiologic imbalance is consistent with the large body of evidence indicating the potentially injurious effects of cardiopulmonary bypass on the brain. Fortunately, the much lower-than-expected incidence of serious brain injury suggests that injury may be avoided by multi-modality neurophysiologic monitoring and the judicious correction of detected physiologic and anesthetic imbalance.

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References

1. Roach GW, et al. (1996) New Engl J Med 335(25):1857–1863

P392
Assessment of the neurological examination by quantitative sensory testing in facial pain syndromes
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Background: In different facial pain syndromes the clinical examination can demonstrate different forms of sensory disturbances. In trigeminal neuralgia (TN) a sensory deficit is not found. However within the trigger zone slight deficits in sensory and temperature discrimination were described. In patients with trigeminal neuropathic pain (TNP) a hypaesthesia, hyperaesthesia or allodynia is usually present. A clinical test for an objective examination to assess neurological disturbances is given by quantitative sensory testing (QST). The aim of this prospective clinical study was to demonstrate the differences of QST in patients with TN and TNP.

Methods: A standard protocol for QST in the face was developed. Testing was performed with controlled, graded and physiological stimulations for thermal, tactile, mechanical, vibration and pain sensory in the distribution of the peripheral trigeminal branches. Muscle pain was evoked using a compression force gage pressed on the masseter muscle. An electrical thermodetector, von-Frey Filaments and pinpricks were used in 44 patients with TN and 18 patients with TNP. Current medication of the patients was noted at time of examination.

Results: In patients with TN and no prior surgery an elevation of the warm and cold sensory detection thresholds in the involved nerve branches was found compared with the non-pain side ($p < 0.05$). This could also be detected for non-involved nerve branches on the pain-side. No significant side differences could be found for cold and heat pain sensory limits. In patients with neuropathic pain significant differences were seen for warmth and heat pain sensory limits, which were lower at the pain side compared with the healthy side ($p < 0.05$). In both patient groups significant differences could be seen in the muscle pain test with a lower pain threshold on the involved side ($p < 0.05$).

Conclusion: Specific sensory differences could be found in patients with TN and TNP. In patients with TN cold and warm sensory limits are elevated at the pain side. This effect was not seen in TNP, but the sensory limits for warmth and heat pain were lowered on the pain side and better than on the contralateral side. QST is a safe method and can demonstrate sensory perception deficits in different facial pain syndromes.

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P393
The sudomotor skin response to controlled temperature and pain stimulation
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Background and Objectives: A controlled rise in temperature induces two types of sensations. Warmth is usually felt between 34 °C and 39 °C, while heat pain is experienced at a variable temperature above 41 °C. We considered that the subjective experience of these two different sensations could generate a change in electrodermal activity and give rise to a sympathetic sudomotor skin response (SSR) in the palm of the hand.

Subjects and Methods: Ten healthy volunteers participated in the study. They were sitting comfortably on a chair, with their forearms above a small table. Surface electrodes were attached to the palm and dorsum of their left hand. Thermal stimulation was delivered by the thermode from a thermotest placed in contact with the skin of the ventral aspect of their left forearm. Stimuli were presented in two conditions. In the first one, the temperature was made to rise from 31.5 to 47.5 °C, at a rate of 2.5 °C per second. In the second condition, with the thermode placed in contact to another skin site, we repeated the stimuli for 5 successive ramps separated by 10 seconds of rest. The temperature profile and the SSR recordings were entered into a BIOPAC recording system (Bionic España, S. A.) for off-line analysis.

Results: Subjects had a large number of oscillations in electrodermal activity before and during the thermal stimulation, while there was a significant decrease of electrodermal activity once the stimulus was over. With single stimuli, subjects exhibited a well defined SSR at a latency of 2.45 s ± 0.25 s after onset of the temperature rise (early SSR). This response showed a rapid decrease in amplitude in all subjects, and became absent in most of them after the second stimulus when we applied the train of 5 successive stimuli. A second SSR was also consistently seen coinciding with the peak of the heat sensation (late SSR). With repetitive stimulation, this response showed a variable amplitude, being persistently elicited by all stimuli of the series in most subjects.

Conclusions: The SSR can be elicited by thermal and heat pain stimulation in healthy subjects. Early SSRs may be the expression of activation of temperature receptors and had a fast habituation rate. Late SSRs could be the expression of activation of pain receptors and had significanlty slower habituation rate. The analysis of sympathetic mediated responses to temperature and pain stimuli might help in the functional assessment of small fiber afferent pathways.

P394
High frequency oscillations in the SSEPs of patients with cortical myoclonus: a heterogeneous spectrum
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Cortical myoclonus are characterized from a neurophysiological point of view by the presence of very high amplitude SSEPs ("giant SSEPs"). During the last decade, there has been a growing interest on the so called high frequency oscillations (HFOs) in the earlier part of the SSEPs (series of small amplitude waves that appear in the first 20 ms of the SSEPs, observable after applying filters in the 450–750 Hz band). The purpose of our work was to study the HFOs in a group of patients with cortical myoclonus and giant SSEPs of different origins and in a group of 10 controls, in order to establish or discard any relationship between the size of the SSEPs, the presence and type of myoclonus and the HFOs.

20 patients with cortical myoclonus and 11 healthy controls were studied. SSEPs were obtained by electrical stimulation of the right median nerve. All the recordings were performed using a 16-channel Bio-Logic amplifier system. HFOs were studied by means of time-frequency transforms (Gabor) in the 450–850 Hz range.

Two components were found in the SSEPs from normal subjects. The early component (13 ms) had a lower frequency (mean: 560 Hz) and a more diffuse topography, while the late component (18 ms) was fronto-rolandic and had higher frequency (mean: 695 Hz). Three different patterns were found in the cortical myoclonus group. Two patients had increased amplitude and delayed latency of these components. Nine patients had a complete suppression of the HFO. The rest of the patients had HFOs with lower amplitude and longer latency than the controls. There was no relationship between the maximal amplitude of the giant SSEPs and the HFOs. In conclusion, a marked heterogeneity in the HFOs from patients with cortical myoclonus was found. Patients with Ramsay-Hunt syndrome or storage diseases were more severely affected.

P395
Ballistic reactions under different motor sets
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The need for a fast reaction is often encountered in human occupation and physical activities of daily life. In preparation for performing task specific ballistic movements, subjects may choose among different possibilities for setting up their motor apparatus, ranging from quiet resting to different types of muscle activation. In the study presented here, we investigated whether differences in the motor set modify either the reaction time or the kinematic characteristics of the movement. Subjects wearing surface EMG recording electrodes in the wrist extensors (WE) and wrist flexors (WF) muscles were requested to react to the presentation of a visual stimulus by performing a ballistic wrist extension movement of an amplitude of about 50° in the following experimental conditions: resting quietly, which was considered as the control condition (CC); isometric contraction (IC), in which subjects were required to activate WE and WF muscles isometrically; rapid oscillations (RO), in which subjects were requested to make a fast oscillatory wrist movement, and slow oscillations (SO), in which subjects were maintaining a slow oscillatory motion of the wrist. To constrain the movement to the wrist joint and limit the action of postural muscles, subject's forearm and hand were attached to joined non-resistive metallic platforms, allowing for free non-frictional displacement. In the EMG recordings, we measured the size of the EMG bursts in agonist and antagonist muscles, and the inter-burst intervals. In movement recordings, we measured movement onset latency and the velocity profile. Movement onset was delayed in SO with respect to all other conditions. Conversely, peak velocity was larger in all test conditions in comparison to CC. There were no differences in the size of the first EMG burst of the agonist muscle, but significant changes occurred in the subsequent bursts recorded in the ag-

onist and antagonist muscles. Our study indicates that the motor program used to execute a ballistic voluntary movement is influenced by the conditions of the motor system. The configuration of the motor set should be specifically considered in the search for improving the speed of the reaction and the kinematics of ballistic movements.

P396
Facial reflex abnormalities in non-degenerative vertical gaze palsy
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Distinctive brainstem reflex abnormalities, characterized by loss of orbicularis oculi (OO) reflex with retained mentalis (M) response, have been described in patients with progressive supranuclear palsy (PSP). Aim of this study was to investigate whether the same abnormalities are present in patients with vertical gaze palsy due to midbrain lesions.

Six patients with complete vertical gaze palsy were examined. Four patients had a midbrain infarction, 1 patient had a bilateral thalamic infarction, and 1 patient had an anti-Ma2 paraneoplastic syndrome with both vertical and horizontal gaze palsy. Two patients with midbrain stroke were re-examined after recovery of downward gaze palsy. Six age-matched controls were also examined.

In all patients, EMG activity was recorded with pairs of surface electrodes. The active recording electrodes were placed on the lower eyelid for OO muscle and on the lateral aspect of the chin for M muscle. Electrical stimuli were delivered with surface electrodes to the median nerve at the wrist using an intensity able to induce a supramaximal compound action potential in the thenar muscle. Patients underwent also blink reflex examination, using standard methods, in order to verify the integrity of the trigemino-facial reflexes.

In 5 of 6 patients, OO response to median nerve stimulation was bilaterally absent, whereas M response was retained. In one patient with left midbrain stroke, low amplitude EMG activity was recorded only from the contralateral OO muscle. Patient with bilateral thalamic stroke showed normal OO and M reflexes. In 2 patients with midbrain stroke, OO responses could be recorded at 3-month follow-up, when downward, but not upward, gaze palsy had recovered. However, EMG activity was lower recording from the OO muscle ipsilateral to the stroke side. Blink reflex latencies were normal in all patients. In all controls, OO and M responses could be elicited. The dissociation between OO and M responses was present only when both up- and downward gaze palsy were present. Our results show that patients with symptomatic vertical gaze palsy had the same distinctive facial reflex abnormalities previously observed in PSP patients. The midbrain structures lesioned in these patients may be involved in both the control of vertical gaze and the generation of OO responses to peripheral nerve stimulation.

P397
The use of transcranial magnetic stimulation in the clinical evaluation of suspected myelopathy
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Background: Central motor conduction time (CMCT) and motor evoked potential (MEP) latency measured using transcranial magnetic stimulation (TMS) are parameters used to evaluate electrophysiologic function of the corticospinal tract. Prolongation of CMCT and MEP latency may indicate conduction dysfunction. Prolonged MEP latency in muscles innervated by a given spinal segment with normal values in a more rostral segment can be used to localize the conduction defect.

Aim: To investigate the utility of TMS in evaluating suspected myelopathy.

Method: Case records of patients with suspected myelopathy in which TMS studies contributed to clinical management were reviewed.

Results: 5 cases were found in which TMS studies contributed to clinical management. One patient had several medical conditions that could have caused his clinical manifestations. Another had multiple lesions seen on spinal imaging. A third patient had equivocal radiological evidence for cord compression while in the fourth, the clinical significance of radiological signs seen at the site of a previous spinal surgery site was uncertain. In the fifth patient, the relevance of a spinal lesion seen on neuroimaging to his clinical manifestations was uncertain. In all these patients, CMCT and MEP latency measurements helped in the localization of the level of conduction defect and in determining the significance of lesions seen on neuroimaging.

Conclusion: TMS study is helpful in localizing the level of conduction defect in cases of suspected myelopathy and is particularly useful in clinical scenarios where patients have multiple lesions or multiple clinical conditions that cause similar clinical manifestations.

P398
Classification of Wilson's disease on the basis of neurophysiological data using artificial neural networks
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Introduction: According to the clinical symptoms in Wilson's disease at time of manifestation classification considers neurological and non-neurological types. However, results of evoked potentials reveal disturbances in various pathways of the central nervous system. A classification on the basis of neurophysiological parameters has been failed so far because of the limited possibilities of conventional statistics.

Methods: We measured acustic (AEP), visual (VEP), somatosensory (SSEP) and motor evoked potentials (MEP) in 37 patients with Wilson's disease (28 patients with neurological and 9 with non-neurological type) beeing on long-term treatment. Controll group consisted of 24 healthy people. For correlation of all results a Growth-Self-Organizing-Map-System with Ward Clustering was used.

Results: As a result of the Growth-Self-Organizing-Map-System with Ward Clustering two pathological clusters of patients with a neurological form of Wilson's disease and two clusters consisting of controll group respectively patients with a nonneurological form could be separated. Clusteranalysis was most influenced by the results of motor evoked potentials. However, there was no correlation between clinical classification and the results of clusteranalysis.

Discussion: By means of clusteranalysis it is possible to correlate very complex data like neurophysiological parameters in order to get a correlation in more than one dimension. Thus, a classification of Wilson's disease on the basis of neurophysiological results is possible. But clinical classification and classification based on the neurophysiolgocial results are not congruous.

P399
Neuromuscular transmission disturbances in patients with mitochondrial diseases
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Introduction and objectives: Because the test of neuromuscular transmission in patients with mitochondrial diseases (MD) have not been clearly defined, we have reviewed our experience in the patients with this condition.

Material and methods: Conventional EMG, nerve conduction studies and SFEMG were per- formed in 18 patients with various phenotypes of MD, 11 females and 7 males aged 14–75 years.

Results; 14 cases showed findings consistent with mild myopathy, 2 patients signs of sensory-motor axonal neuropathy and 2 cases a mixture of myopathy and axonal neuropathy. Motor unit fiber density was mild increased in 8 out of 13 tested cases. Jitter was abnormal in 10 out of 18 tested patients. Jitter abnormalities were not related to phenotype, myopathic or neurogenic features in the EMG study, and may be observed in muscles without clinical weakness.

Conclusion: The results suggest the existence of neuromuscular transmission disturbances in patients with MD.

P400
Comparison of data recorded from two different muscles innervated by the same nerve in motor nerve conduction studies
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In motor nerve conduction studies of the median and ulnar nerves abductor pollicis brevis (APB) and abductor digiti quinti (ADQ) are generally used as recording muscles. On the other hand lumbrical and interossei (L/I) method is known to be convenient in which median and ulnar nerve conduction studies can be performed from the same recording site. We used these two methods to know their characteristics and the intraexaminer measurement error. Subjects were 157 patients with diabetes mellitus, having 10±9 years' diabetic history. All the measurements were done by the same examiner. The same stimulation sites were used in the conven-

tional and L/I methods. PNI-R (polyneuropathy index-revised), calculated as a mean percentage of the normal of 8 velocity or latency measurements on 4 motor nerve conduction studies, was used to indicate the severity of diabetic neuropathy. Median nerve conduction velocity in the forearm segment was 51.5 ± 4.2 m/sec recorded from 2nd lumbricalis (2L) and 51.4 ± 4.2 m/sec from APB, respectively. There was a high coefficient of correlation (0.89) between these measurements. Standard deviation of the difference of each measurement was 2.0 m/sec, so the coefficient of variation (CV) was calculated as 3.9 %. Ulnar nerve conduction velocity in the forearm segment was 49.0 ± 5.2 m/sec recorded from 2nd interossei (2I) and 49.7 ± 5.4 m/sec from ADQ, respectively. High coefficient of correlation (0.93) was observed between these measurements. Standard deviation of the difference of each measurement was 2.0 m/sec and CV was calculated as 4.1 %. These values of CV were almost the same as previously reported. Compound muscle action potential (CMAP) amplitudes of median nerve-innervated muscles were 14.4 ± 5.1 mV in APB and 3.9 ± 1.4 mV in 2L, respectively. The coefficient of correlation between them was 0.45 and CMAP of APB was larger in general, but in the advanced stage of muscle atrophy CMAP amplitude of APB became zero before 2L. Perhaps not only the fiber position in the carpal tunnel but also the length of the distal nerve segment will concern to this fact. Distal motor latency was 3.2 ± 0.4 msec in 2I and 3.7 ± 0.7 msec in 2L in the same 9 cm segment. This will be due to the conduction delay across the carpal tunnel. CMAP amplitude was decreased only moderately along with the reduction of PNI-R and coefficient of correlation between them was 0.4 or 0.5. In diabetic neuropathy hand muscles are less apt to be wasted than foot muscles.

P401
Clinical significance of autonomic neuropathy in type 1 diabetic patients
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To investigate clinical significance of autonomic neuropathy as a predictive factor for the development of retinopathy in 118 normotensive and normoalbuminuric patients, autonomic tests based on standard, vector and spectral analysis of heart rate variation (HRV) and 24 h blood pressure (BP) measurement were performed.

Incidence of autonomic neuropathy (9.5 ± 5.5; 59.6 %) was significantly higher in group of 43 patients with retinopathy in comparison with group of 75 patients without retinopathy (5.29 ± 4.9; 16 %), ($p < 0.05$).

Patients were similar regarding age, sex, HbA1c, 24 h urinary albumin excretion (UAE). Group of patients with retinopathy had significantly higer duration of diabetes.

Maximal night systolic, mean night and day diastolic blood pressure was significantly higher in patients with retinopathy (116.84 ± 10; 63.32 ± 8.1; 73.3 ± 7.4) compared to patients without (114.32 ± 9.1; 58.72 ± 7.3; 70.95 ± 4.6) ($p = 0.03$).

Maximal night systolic BP was inversely related to power HF ($r = –0.28$, $p = 0.05$) and CV deep breathing ($r = –0.23$, $p = 0.02$). Mean night diastolic BP was inversely related to power MF ($r = –0.21$, $p = 0.03$), HF ($r = –0.32$, $p = 0.005$), CV deep breathing ($r = –0.27$, $p = 0.005$) and MCR deep breathing ($r = –0.24$, $p = 0.003$); mean day diastolic BP to power HF ($r = –0.22$, $p = 0.02$). In multiple regression analysis retinopathy was associated with the duration of diabetes ($b = 0.53$) and autonomic neuropathy ($b = 0.28$) ($p < 0.001$).

Autonomic neuropathy is related to BP elevation and retinopathy in normotensive and normoalbuminuric type 1 diabetic patients. We conclude, in order to predict the development of complications, autonomic testing should be routinely performed in type 1 diabetics at the normotensive and normoalbuminuric stage.

P402
Reversible non-metabolic triphasic waves
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Triphasic waves (TW) are usually described in relation with toxic and metabolic disturbances, mostly hepatic encephalopathies. They have been described as synchronous, bilateral, symetrical waves of high amplitude, of 300ms duration, with anterior dominance and arising from a slow dominant activity. Other less frequent etiologies include anoxia, hyperosmolality, hyperazotemia and hyperthyroïdism.

TW of non-metabolic origin are uncommon. They seem to be related to lesions in brainstem and/or thalamus, most often secondary to neoplasia or ischemia.

We report a case of TW secondary to intracranial hypertension and hydrocephaly which could be reversible after appropriate treatment. A 51 year-old man was admitted to emergency department for acute confusion and left sided weakness. Neurological examination showed a global aphasia and left hemiplegia. Brain CT disclosed a large right fronto-parietal hematoma dissecting into the lateral ventricule. Presumed etiology was systemic hypertension. The patient initially recovered from motor and phasic deficits, but within a month developed progressive obtundation and confusion (GCS 11/15). Brain CT revealed a communicating tertaventricular hydrocephaly. The EEG disclosed a theta-delta background activity with TW mostly in the left hemisphere, partially reactive to light and sound. Any metabolic disturbance was excluded. Repeated lumbar punctures improved the clinical status.An EEG done 4 days later was normal.

Although the mechanism remains unexplained, the relief of compression of the thalamus and brainstem by increased pressure, may have played a role in the resolution of the EEG abnormalities.

P403
Clinical EEG in the evaluation of patients with headache
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Introduction: It was stated a few years ago that Electroencephalography (EEG) is not indicated in the routine evaluation of patients presenting with headache (Gronseth and al; Neurology 1995; 45;1263–67). The emergence of the several antiepileptic drugs (AEDs: for instance, Valproic acid, Topiramate) as antimigranous agents raises the issue whether the clinical EEG may play a role in for instance selecting the best headaches candidates for the AED.

Purpose: to evaluate the EEG features in a headache patients sample in order to identify the headache subgroups who are most likely to benefit from this test and to define grounds for a prospective study aiming at identifyng the best headache candidates for AEDs.

Material and Methods: We reviewed EEG findings in a sample of 45 patients referred for headache to our EEG lab in Hospital S. João General Hospital (Porto, Portugal) during 2003, during which 1986 EEG recordins and about 500,000 outpatients visits were performed.

Results: Headache was an indication for clinical EEG in a small proportion of patients (about 2 %). The EEG findins were as follows: normal recordings in 16 patients (36 %), generalized or focal slowing in 16 patients (36 %) and epileptiform activities (EA) in an additional 13 subjects (28 %). The patients presenting EEG EA were mostly males (sex ratio: 5 females/8 males) and significantly younger (mean age * S. E.M: 16.3 * 3.5 yrs) as opposed to normal EEG patients (13 females/3 males; 31.7 * 3.7 yrs; $p = 0.002$) and EEG slowing subjects (14 females/3 males; 31.5 *4.3; $p = 0.004$). A final diagnosis of Epilepsy was done in 4 patients with EA (31 %) in contrast with none in the other two groups.

Conclusion: The EEG was not considered to be a clinically useful test in the evaluation of patients with headache in our General Hospital, as may be inferred from the low figure for the EEG recordings requested because of headache. However, the EEG was at least useful in the young male, in whom epilepsy should be considered a pertinent diagnosis. A larger sample in a prospective blinded study the EEG may help to select the patients amenable to have the best AEDs efficacy, by comparing clinical response among the EEG subgroups.

Cerebrovascular disorders

P404
Early versus delayed thrombolysis in embolic stroke in rats: effects on blood flow, DC potential and infarct morphology
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We sought to study the effect of tissue plasminogen activator (TPA) treatment on recanalization rates, on periinfarct depolarizations (PID) as an important mechanism of injury, and on infarct patterns comparing early versus delayed thrombolysis. Rats were submitted to middle cerebral artery (MCA) clot embolism and treated with TPA 1.5 hours and 3.5 hours postocclusion. Occlusion and reperfusion patterns were monitored by using cortical laser-Doppler flowmetry; the direct current (DC) potential was recorded to detect periinfarct depolarizations. Following an observation time of 6 hours, animals were sacrificed to obtain histology. Volumes of complete infarction and scattered neuronal injury were separately determined. TPA treatment induced (delayed) reperfusion in 58 % of treated animals. The probability of reperfusion did not differ significantly between

the groups of early (54 %) and delayed TPA treatment (64 %, $p > 0.05$). TPA treatment lead to a 3fold reduced frequency of PID if successful reperfusion was observed ($p < 0.001$). The volume of complete infarction was significantly reduced in TPA treated animals with successful reperfusion (34 ± 9 qmm, mean ± SEM, $n = 14$) compared with vehicle treatment (88 ± 21 qmm, $p < 0.05$). TPA treatment without successful reperfusion did not lead to reduced infarct volumes. Scattered neuronal injury as percentage of the total ischemic lesion was 22 ± 4 % in vehicle treated and 37 ± 5 % in successfully reperfused rats, respectively ($p < 0.05$). In summary, successful thrombolysis – whether applied early or delayed – inhibits periinfarct depolarizations, reduces total ischemic lesion volume, but increases the percentage of scattered neuronal injury.

P405

Middle cerebral artery stenosis morphology and risk of recurrent ischaemic stroke, a transcranial colour-coded Doppler study

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Background: patients with intracranial symptomatic atherosclerotic stenosis have a rate of recurrent cerebrovascular ischemic events, coronary hearth disease and death. Trancranial doppler ultrasound (TCD) is a useful method for measuring blood flow velocities in the intracranial vessels and for detecting occlusion and stenosis of the basal cerebral arteries. Transcranial Color Doppler ultrasonography (TCCD) is a recent tecnique for visualizing the intracranial arteries and for evaluating the intracranial haemodynamics. We investigated the relationship between the middle cerebral artery stenosis morphology and clinical recurrence by TCCD and angiopower transcranial ultrasonography.

Patients and methods: 43 patients (33 male, 10 female; mean age 65.53 ± 10.7) with first ischemic stroke admitted to our Neurological Department between January and December 2002 presented intracranial stenosis. The middle cerebral artery (MCA) stenosis was evidenced in 20 patients. The MCA stenosis were classified into severe (> 50 %) and mild (< 50 %) following the Baumgartner criteria (1999) on the basis of the mean velocity and the systolic and diastolic peak velocity. Moreover, we studied MCA stenosis morphology by TCCD and Angiopower transcranial doppler using the contrast agent (SonoVue, Bracco SA) and we defined 3 types of stenosis: monofocal with or without post-stenotic dilatation and tubular. Clinical and TCCD recordings were performed at 3th, 6th and 12th month from the discarge.

Results:a new ischemic event during the follow up in the territory supplied by the stenosed MCA occurred in 6 (30 %) out of 20 patients. In all 6 patients MCA haemodynamic study evidenced a severe MCA stenosis; the MCA morphological study showed 4 tubular stenosis and 2 monofocal stenosis without post-stenostic dilatation. Out of the other 14 patients 8 presented a severe monofocal stenosis with post-stenotic dilatation and the other 6 patients had a mild stenosis with tubular or monofocal morphology.

Conclusion: our preliminary data suggest that a severe MCA stenosis with tubular or monofocal without post-stenotic dilation morphology may be considered a predictive factor of ischemic stroke recurrence. We suppose that in patients with tubular or monofocal without post-stenotic dilation stenosis a loss of wall vessel reactivity may be the cause of the reccurrent stroke with an haemodynamic or prothormbotic mechanism. Futher studies are needed to confirm our preliminary findings.

P406

The association of plasma angiotensinogen and angiotensinogen gene polymorphism with ischaemic cerebrovascular diseases

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Objective: To investigate the association of plasma angiotensinogen (AGT) level and its gene polymorphism with ischemic cerebrovascular diseases.

Methods: In 57 cases of ACI, 52 cases of lacunar infarction, 43 cases of essential hypertension and 65 healthy controls, the T704C and C521T mutations at exon2 of AGT gene were analyzed by the methods of PCR-RFLP. The plasma levelss of AGT in ACI patients and controls were measured by means of radioimmunoassay.

Results: The plasma AGT level in the acute phase of ACI patients (194.47 ± 43.83 ng/L) was significantly higher than that in the recovery phase of the patients(163.45 ± 42.64 ng/L) and that in the controls(159.34 ± 45.24 ng/L)($P < 0.05$, respectively). The frequencies of 704C allele in ACI were significantly higher than that in the controls. The 704C allele was associated with increased plasma AGT level. The frequencies of 521T allele were significantly higher only in the patients with lacunae infarction.

Conclusion: The event of cerebral infarction can result responsively in the increased level of plasma AGT, which may be related to the degree of ischemic brain damage. There is a significant correlation between 704C allele of AGT gene and ACI, while 521T allele associates with lacunar infarction.

P407

Morphological features and clinical outcome in hemihydranencephaly

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Occlusion of one carotid artery between week 20th and 27th of gestation is thought to be the underlying mechanism of hemihydranencephaly, a rare brain damage lacking one complete hemisphere. Only seven cases have been reported so far.

We performed MRI and a variety of standardized tests (Wolf Motor Function Test (WMFT), Motor-activity-Log (MAL), 2 point discrimination (2pd), Purdue Pegboard and documentation of mirror movements) for quantitative assessment of sensorimotor skills in a 36 y/o patient suffering from hemihydranencephaly.

MRI demonstrated nearly complete absent of the left hemisphere replaced by CSF with a remaining small residual hippocampus, a small rim of the occipital cortex and a small left cerebral peduncle. The cerebellum was completely normal. There was no left internal carotid artery.

Clinical testing demonstrated impairment due to reduced speed and/or precision of the performed task and limited fine motor control with a threshold of 10 mm in the 2pd leading to 64 of 85 of all possible points (75 %) at the WMFT and the impossibility to perform the Purdue pegboard with the affected hand. Although natural prehension movements were almost unimpaired, only some skills requiring fine motor control were impossible with the disabled hand (MAL). Strong mirror-movements were found in movement of both hands.

Even though there seems to be no compensation by the arch of Willis or leptomeningeal collaterals, the immature brain may compensate for neuronal injury by cortical reorganisation. Because of the subtotal damage of the "dominant" hemisphere, assumed to harbour speech areas, a severe hemiparesis, aphasia or dysphasia or severe intellectual impairment would have been expected, whereas speech was not impaired in our patient who completed school and is fully integrated in social live. Disabilities in the clinical tests were caused by deficits in fine motor control as predicted in the MAL. Maximum points were not reached because of reduced speed and/or reduced precision of the performed tasks. As fine motor control requires unaffected 2-point discrimination, he was unable to perform the Purdue Pegboard with his affected right hand. Morphology cannot predict clinical impairment. Axonal migration or sprouting, development of new connections or activation of already existing pathways may be responsible to achieve almost normal skills, whereas the later seems to be most likely executing the lacking functions of the destroyed hemisphere.

P408

Increased frequency of white matter lesions in patients with osteonecrosis (WMLeON) of the femoral head

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White matter lesions (WML) are commonly seen in cerebral MR imaging in normal and demented elderly people or young people suffering from migraine. We present, data showing that WML are detected in an unexpectedly high frequency in patients with non-traumatic osteonecrosis of the femoral head compared to age and sex-matched controls. We designated the coexistence of WML and osteonecrosis as WMLeON (white matter lesions in osteonecrosis). We examined the possible association of WMLeON with hyperlipidaemia and other risk factors for WML or osteonecrosis of the femoral head.

The patients group with WML ($n = 29$) was compared to the patients without WML ($n = 22$) for each continuous variable (age, age at onset, duration, total cholesterol, HDL, LDL, Lpa, ApoB, ApoA1, triglycerides) using the t-test for two independent samples. The proportions of the two groups were compared for each categorical variable (sex, daily smoking, hypertension, diabetes, migraine, history of vascular disease, history of corticosteroid treatment, and SLE) using a chi-square test with Yates correction. The three groups (A, B, or C according to the grade of WML) were com-

pared for the different continuous variables (total cholesterol, HDL, LDL, Lpa, ApoB, ApoA1, triglycerides) using one-way anova. Individual comparisons between the groups (A vs B, A vs C and B vs C) were carried out using post-hoc tests with Bonferonni's correction.

Clinical neurological examination was normal in all patients. WML were detected in 29 (29/51; 56.9%) patients with osteonecrosis of the femoral head. The frequency difference of WML between control group (2.3%)and group of patients with osteonecrosis was statistically significant ($p < 0.0001$). At the time of the brain MRI examination the mean (± SD) age and duration of disease of patients with non-traumatic osteonecrosis in whom WML were revealed was 33.6 ± 10.3 years and 31.7 ± 25.3 months whilst that of patients in whom WML were not demonstrated was 33.1 ± 11.7 years and 30.6 ± 22.6 months respectively. The frequency of history of corticosteroid treatment was statistically lower in patients with WMLeON (58.6%) compared to those without (90.1%) ($p = 0.03$). We found no association of WMLeON with diabetes, stroke, hyperlipidaemia, migraine, smoking, alcohol consumption, hypertension, atrial fibrillation or systemic lupus erythematosus.

Further studies are needed in order to clarify the clinical significance of WMLeON.

P409

A study of serum angiotensin-converting enzyme activity in ischaemic stroke

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Objective: To study the relationship between the ischemic stroke and serum angiotensin-converting enzyme (ACE) activity.

Methods: The serum ACE activity in 47 cases of vascular dementia (VD), 43 cases of cortical infarction (CI) and 30 healthy controls was measured by means of capillary electrophoresis-ultraviolet detection.

Results: Compared with that in healthy controls (22.62 ± 5.44 U/L), the serum ACE activity was significantly lower in CI patients (19.26 ± 5.11 U/L), particularly in those patients with hypertension (18.42 ± 5.20 U/L) and male ones (19.71 ± 4.99 U/L). There was a slight reduction of serum ACE activity in VD patients(21.95 ± 7.19 U/L), but not significantly.

Conclusion: The serum ACE activity decreases in the event of ischemic stroke, and is related to the degree of cerebral tissue damage.

P410

Blink reflex as a complementary test for MRI in early detection of brain stem strokes

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Objectives: Early detection of vertebro-basilar insufficiency is of paramount importance. Brain MRI was the only method of diagnosis for many years, but in addition to high cost and delay in report, it may not detect all brain stem lesions. In this study Blink reflex (BR) was evaluated as a complementary test for MRI.

Methods: Fifty-five patients were studied [27 anterior circulation stroke patients (ACSP) and 27 posterior circulation stroke patients (PCSP)]. MRI was performed within the first week of the onset. Nineteen age and sex matched healthy people enrolled as controls. BR was performed within the first 24 hours of the onset. Frequency of abnormal responses in ACSP and PCSP was compared with MRI findings. Then abnormal responses in two groups were compared by chi-square test.

Results: In both ACSP and PCSP two patients had normal BR responses, and in 25 patients R1 or R2 responses were absent or prolonged (92.5%). R1was absent or delayed in 16 PCSP, but it was abnormal in only two ACSP ($P < 0.0001$). Abnormal R2 responses were detected in 22 PCSP and 24 ACSP.

Conclusion: BR abnormalities had high correlation with MRI findings in PCSP (92.5%). BR was performed in all of our patients within the first 24 h of onset, and its results were available immediately. This test is easy and comfortable for the patient, has low cost and is available every where. Therefore we introduced BR as a complementary (but not replacing) test for MRI in early detection of brainstem infarctions.

In comparison of BR responses in ACSP and PCSP, abnormalities of R1 responses had high accuracy in differentiation between anterior and posterior circulation strokes ($p < 0.0001$). we concluded that BR responses not only can detect brainstem infarctions rapidly and readily in its early stages, but also can differentiate ACSP from PCSP with high accuracy.

P411

Transcranial Doppler sonography evaluation of anterior cerebral artery variations

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Transcranial Doppler sonography (TCD) is useful to evaluate intracranial arteries, however, interpretation of the TCD results in anterior cerebral artery (ACA) is sometimes difficult due to hypoplasia or aplsia. Comparing with MRA, we try to define useful TCD indices and cut-off values to determine the variations of ACA. Consecutive patients who underwent TCD and MRI/MRA were included. Patients with cerebrovascular abnormality or inadequate temporal windows were excluded. ACA status was classified as normal (NL), hypoplasia (HP), and aplasia (AP) according to MRA. TCD indices of mean flow velocity (MFV), pulsatility index (PI), ACA/MCA flow velocity ratio, and asymmetry index of ACA (AI) were blindly compared with MRA between NL, HP, and AP group. Two hundred and forty one patients (male 51%, mean age; 58.5 years) were included, and 193 patients (80%) were classified as NL, 34 (14%) as HP and 14 (6%) as AP. MFV was 52.8 ± 16.3 cm/s, 41.2 ± 15.8 cm/s, 20.0 ± 19.0 cm/s in NL, HP, and AP ($p < 0.05$). PI and ACA/MCA flow velocity ratio was not significantly different. AI was 21.5%, 50.4%, 105.2% in NL, HP, and AP($P < 0.001$). Using AI criteria, sensitivity and specificity was 50% and 92% for the diagnosis of HP (AI > 50%), or 43% and 98% for AP (AI > 100%). In conclusion, ACA velocity should be interpreted with caution and AI is useful to differentiate hypoplasia and aplasia from normal ACA.

P412

Intracranial stenosis as a risk factor for ischaemic stroke

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Background: intracranial stenosis is considered the cause of approximately 8% of all stroke in white patients. Up to now the diagnose of intracranial stenosis has been based on invasive imaging technique that has probably underestimate its real prevalence. We investigated by Transcranial Color Doppler ultrasonography (TCCD) the presence of intracranial stenosis in a series of patients with ischemic stroke. Moreover distribution of some cerebrovascular risks factors was studied in patients with and without intracranial stenosis.

Patients and methods: 134 patients (106 male; 28 female, mean age 63.99 ± 9.51) with first ever ischemic stroke admitted to Neurological Department of Reggio Emilia Santa Maria Hospital between January and December 2002, were studied by extracranial and intracranial ultrasonography. On the basis of the intracranial stenosis presence, patients were divided in two groups. Demographic data (age, sex), diabetes mellitus, hypertension, cigarette smoking, hypercholesterolemia, lipoprotein (a) (Lp(a)), atrial fibrillation and cardiac disease were assessed in each patient.

Results: intracranial stenosis were found in 43 (33 male, 10 female; mean age 65.53 ± 10.7) out of 134 patients; all intracranial stenosis were confirmed by neuroradiological investigations (cerebral angiography, angio-magnetic resonance (MRA)). The other group of 91 patients didn't present intracranial atherosclerosis. In the two groups a similar distribution for demographic data, diabetes mellitus, hypertension, cigarette smoking and cardiac disease was observed. High serum level of Lp(a) was more frequent in the group with intracranial stenosis compared with patients without intracranial atherosclerosis (13.95% versus 3.29%, $p = 0.03$). Moreover hypercholesterolemia was higher in patients with intracranial disease but it didn't reach a statistical significativity ($p = 0.06$). Conclusion: in our group of patients a high prevalence of intracranial stenosis was found; this datum could be explained by the non invasive technique used. A positive correlation between intracranial stenosis and Lp(a) was evidenced. Intracranial atherosclerosis may be considered an important risk factor for ischemic stroke and it should be taken in mind for primary and secondary prevention therapy.

P413

Influence of spirapril on hemodynamics of cerebral circulation in hypertensive patients

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Objective: To assess the effect of spirapril (6 mg once a day) on cerebral blood flow (CBF) parameters in hypertensive pts.

Design and Methods: Twenty pts with mild to moderate hypertension (47.9 ± 6.2, 15 males) treated spirapril within two months in dose 6 mg

daily and 10 healthy (normotensive) controls were studied. 24 hour ambulatory blood pressure monitoring and doppler ultrasonography were performed at the end of wash-out period, after 4 and 8 week treatment. Doppler-derived parameters from CBF velocity wave was tested. The cerebrovascular resistance (CVR) and CBF index were calculated using measurements from Doppler ultrasonography of internal carotid artery and systemic blood pressure. Statistical analysis were performed by pair variant method.

Results: Spirapril significantly decreased systolic, diastolic and mean blood pressure. We observed that in the group of hypertensive pts mean velocity of internal carotid artery (Vm) was lower compared to the controls (23.5 ± 3.9 versus 34.3 ± 2.7 cm/s, $p < 0.05$). CVR was significantly lower in controls compared to hypertensive pts (4.9 ± 0.4 versus 2.6 ± 0.2 mmHg/cm/s, $p < 0.05$). Under 4 weeks of treatment Vm has not changed significantly(23.5 ± 3.9 versus 26.0 ± 3.1 cm/s) and after 8 weeks of treatment Vm has not changed significantly as well (23.5 ± 3.9 versus 26.2 ± 2.2 cm/s), but CVR lowered in hypertensive pts (4.9 ± 0.4 versus 4.0 ± 0.4 mmHg/cm/s, $p < 0.05$) and CBF index increased respectively (12.8 ± 1.4 versus 16.1 ± 2.1, $p < 0.05$).

Conclusion: Our findings suggest that pts with mild to moderate hypertension had significantly low Vm in comparison with healthy normotensive pts. Spirapril (6 mg once a day) beneficially decreased CVR and increased CBF index in comparison to parameters before and after 8 week treatment. Comparing the effect of treatment to the value of parameters obtained from healthy controls we concluded that spirapril was able to improve the hemodynamics of cerebral circulation.

P414

Papillary fibroelastoma, a rare but treatable cause of ischaemic stroke

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Background: Papillary Fibroelastoma (PFE) is a rare benign cardiac tumor, located mostly on valvular surfaces. PFE are associated with embolic complications, particularly ischemic stroke. Symptomatology may be connected to either tumor embolization or cruoric emboli. We report a case of recurrent transient ischemic attacks (TIA) caused by a PFE located on the mitral valve.

Case Report: A healthy 31-year-old man presented with three TIAs (ataxia of the right arm during 1mn, paresthesis of the left hand during 30s, right ataxia and dysarthria during 10 hours) over a two month period. MRI showed several ischemic lesions in the right parietal lobe and in the right cerebellar hemisphere. Routine blood chemistry, coagulation profile, ECG, transthoracic echocardiography (TTE), trans-cranial and cervical doppler were normal. Transesophageal echocardiography (TEE) revealed a small lesion attached to the mitral valve. The lesion was surgically resected with a conservative valve-sparing approach. Macroscopic examination revealed a small friable tumor and histological examination confirmed the diagnostic of PFE. No new embolic events occurred and no evidence of regurgitation or recurrence was seen on TEE at follow up.

Conclusion: PFE is a rare etiology of strokes in young patients, but confirms the importance of systematic TEE. Despite their benign histological characteristic, surgery is required because of their high embolic potential and because there is no recurrence of embolism after surgical excision. Anticoagulation should not be an alternative.

Poster session 3

Peripheral neuropathy

P415

Pegylated alpha interferons (PEG-IFNs) peripheral neurotoxicity: prospective study in chronic hepatitis C

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Background: Alpha-interferon (IFN) is currently used in chronic hepatitis C. Its use is, however, limited by central nervous system side effects. There are reports of both improvement and worsening of neuropathy during alpha-IFN treatment, but the possible neurotoxicity on peripheral nervous system has never been consistently investigated. Moreover, despite the well-known autoimmune potential of IFNs, the occurrence of antibodies against peripheral nerve antigens has never been evaluated.

Objective: To assess whether pegylated IFNs (PEG-IFNs) treatment is associated with occurrence, worsening or improvement of neuropathy and/or with the occurrence of antibodies against peripheral nervous system antigens in patients with hepatitis C virus (HCV) infection.

Patients and methods: Twenty-six HCV patients (19 male, 7 females, median age 41.5 ± 9.6 years) have been treated with PEG-IFNs (alpha-2a 180 µg weekly or alpha-2b 1.5 µg, weekly) and ribavirin for 6–12 months. Eleven patients had peripheral neuropathy at recruitment. Before therapy (T0) all patients underwent quantitative viral RNA determination, HCV genotype analysis, liver biopsy, neurological and electrophysiological evaluation. Antibodies to peripheral nerve antigens (gangliosides, sulfatides) were assessed by ELISA at the beginning and at every follow up visit. Response amplitude and conduction velocities of median, ulnar, sural, and peroneal nerves were recorded. During therapy (T1) (mean follow-up 7.8 ± 4.0 months), patients were neurologically and electrophysiologically re-evaluated. Eighteen HCV patients (11 males, 7 females, median age 47.4 ± 9.6) with comparable viral load, not in IFN treatment, were studied as controls.

Results: During therapy with PEG-IFNs, no significant differences of all electrophysiological parameters were detected between T0 and T1 evaluations (repeated measures ANOVA) in all 44 treated and not treated patients, also in those with neuropathy at recruitment. No correlations were found between electrophysiological parameters and length of therapy (Spearman's Rho). Some patients developed antibodies to peripheral nerve antigens during treatment.

Conclusions: Peripheral neuropathy seems not to complicate PEG-IFNs therapy in patients with chronic hepatitis C. An ongoing follow-up study on a larger group of patients will help confirm these results.

P416

Gene expression profiling in CIDP

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Objective: To compare gene expression in sural nerve biopsies from patients with chronic inflammatory demyelinating polyneuropathy (CIDP) to normal nerve (NN) or vasculitic neuropathy (VAS).

Background: DNA microarray technology allows for simultaneous analysis and comparison of gene products expressed in normal and disease tissues. Such analyses could provide information about disease pathogenesis and identify potential biological markers or therapeutic targets.

Design/Methods: Gene expression in archived frozen sural nerve biopsies of patients with CIDP ($n = 8$) was compared to that in VAS ($n = 3$) or NN ($n = 3$). 100ng of total RNA was converted into biotin labeled complementary RNA (cRNA), hybridized to the Affymetrix human U133 microarray set (Santa Clara, CA) and processed on the fluidics station under the control of the Microarray Suite software. The data was analyzed using Microarray Analysis Suite v5.0 and GeneSpring™ v6.1 (Silicon Genetics, Redwood City, CA).

Results: 3 genes, Stearoyl-CoA desaturase (SCD), NADPH dehydrogenase, quinone 1 (NQO1) and eukaryotic translation initiation factor 1A (EIF1A) were significantly upregulated in CIDP in comparison to NN or VAS (Welch t-test with log transformed data; p 0.05, fold change 2.0, genes present in at least one sample). SCD is a rate-limiting enzyme in the biosynthesis of monounsaturated fatty acids that are present in myelin, which has been implicated in the demyelination-remyelination process and neonatal myelin development. NQO1 is an antioxidant that may be neuroprotective in conditions of oxidative stress. It catalyzes the two-electron reduction of various quinones, preventing their participation in redox cycling and subsequent generation of reactive oxygen species. Other genes that were overexpressed in CIDP vs NN included the chemokine receptor 4 (CXCR4) and the MHC class II DQ beta 1 antigen (HLA-DQB1).

28 genes were overexpressed in both CIDP and VAS compared to NN, most of which are involved in immunity and inflammation. These included the early T-cell activation gene CD69, the allograft inflammatory factor (AIF1) that is upregulated in vascular damage and CD44, which has a postulated role in matrix adhesion and lymphocyte activation.

Conclusions: Several upregulated genes were identified by differential gene expression in nerve biopsies from patients with CIDP or VAS. These could provide clues to pathogenesis, or serve as potential disease markers or therapeutic targets.

P417

Number of Langerhans immune cells in painful and painless neuropathies in human skin biopsies

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Background: Langerhans cells (LC) make contact with epidermal neurites and, when activated, synthesize molecules with the ability to sensitize axons. We speculated that the number of LC in human skin is increased in patients with long lasting painful neuropathy, comparable to increased numbers of LC in skin biopsies of rats after nerve injury.

Methods: In the present prospective study we investigated the correlation of numbers of Langerhans immune cells to pain in peripheral neuropathies. Twenty-one patients were studied. All patients underwent 1) a clinical examination, 2) quantitative sensory testing, and 3) sural nerve biopsy and a skin biopsy on the same side where sural nerve biopsy was performed. Eleven patients had a painless and 10 patients had a painful neuropathy. Sural nerve and skin biopsy specimes were processed according to established methods.

Skin biopsy was stained with two different standard macrophage/monocyte markers, CD1a and HLA-DR, and were labeled by avidin-biotin peroxidase procedure with DAB as a chromogen. Numbers of LC were counted in 2 sections per patient and the epidermal area was measured using Image Pro Plus 4.0 software.

Results: The average age was 58.6 ± 12 years. Nine patients had chronic axonal neuropathy, 7 patients presented with CIDP, and 5 with vasculitis. Ten patients suffered from a painful neuropathy with burning dysaesthesias. The average number of LCs in the biopsies of patients with painful neuropathy was 63.7 ± 39.2/mm^2 compared to 64.7 ± 44.3/mm^2 in painless neuropathy. The mean numbers of LC were in the same range in the different histological groups (CIDP 74.3/mm^2, vasculitis 51.4/mm^2 and chronic axonal neuropathy 59.6/mm^2).

Conclusions: Thus, the numbers of LC were unrelated to etiology of the neuropathy and the presence of pain in neuropathy. This may indicate that LC are not involved in the sensitization of nerve fibers, or that their involvment is not associated with long-term changes in cell numbers.

P418

Severe Guillain-Barré syndrome in a patient with POEMS syndrome shortly after treatment with mabthera (Rituximab), an anti-CD20 monoclonal antibody

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Mabthera, a murine/human chimeric monoclonal antibody specific for the CD20 surface marker on B cells, has recently been proposed to treat patients with neuropathy associated with IgM monoclonal gammopathy.

A 71 y. old woman with POEMS syndrome developed a Guillain Barré syndrome within 24 h after the first course of mabthera.

In 2001 this patient experienced paresthesiae of the feet that affected the hands a year later, without functional impairment. In April 2003, diffuse oedema with scleroderma-like skin thickening appeared in the lower limbs (LL), the hands and face along with maculopapular eruption, periorbital erythema and facial telengiectasias. A skin biopsy was not contributive. Serum biclonal IgMk IgGk gammopathy, without anti-myelin antibodies was found. Bone marrow aspiration showed mild increase of lymphoplasmacytic cells. Skeletal radiological survey was normal. Body CT scan showed mild hepatomegaly. She was seropositive for HHV-8. Electrophysiological studies showed a slight increase of distal latencies (DL), normal motor conduction velocities (MCV) with severe reduction of the amplitude of compound muscle action potentials amplitudes in the LL. In the the left peroneal nerve: DL: 4.6 ms, MCV: 39m/s, ampl. 1.1 mV. A POEMS syndrome was suspected and a treatment by mabthera undertaken.

One day (Day 1) after infusion of mabthera (600 mg/d.), the patient experienced numbness in the feet, weakness in the LL and progressive walking difficulty. Motor deficit gradually worsened and 4 days later weakness had extended to the upper limbs and the trunk. CSF studies showed increased protein content 0.66 g/dL, 5 cells/mL. She developed swallowing difficulties and was admitted in the Intensive Care Unit. On Day 6, she had flaccid tetraplegia, with strength graded 1/5 in LL (MRC scale), 2/5 in UL, weakness of neck flexors and diffuse areflexia. Position sense was impaired in distal LL and she had stocking hypoesthesia. Electrophysiological studies showed diffuse motor demyelinating polyneuropathy with increased DL, decreased MCV and reduction of CMAPs amplitude in UL and LL. For the left peroneal nerve: DL: 10 ms, MCV: 24m/s, CMAP: 1.1 mV.

A biopsy of the superficial peroneal nerve was performed. The density of myelinated fibers was nearly normal. Many fibers were undergoing an acute, macrophage mediated, demyelinating process, with increased endoneurial cellularity. Teased fiber preparations confirmed the acute demyelinating process and EM examination showed microvesicular degeneration of the myelin sheath and macrophage stripping the myelin sheath, characteristic of GBS. The patient's condition required respiratory assistance. IgIV were given.

Conclusion: This is the first case of severe adverse neurological side-effect of treatment of patients with monoclonal neuropathy and gammopathy, with mabthera, which calls for more study of the role of CD20 + lymphocytes in this setting.

P419

Toxic neuropathies presenting with "swollen axons"

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Peripheral neuropathy is a side effect of a wide variety of pharmaceutical, occupational and environmental agents. Among these agents n-hexane, disulfiram and thallium share similar histopathological aspects. They specifically affect the neurofilaments in such a way as to disrupt their normal orientation. These disorganized neurofilamentous bundles form swollen regions. As most human toxic neuropathies show non-spesific histological changes, this unusual pathological feature may serve as a diagnostic clue. We studied the clinical, electrophysiological and histopathological aspects of 3 patients showing swollen axons in sural nerve biopsy. Patient 1, was a 20 year old shoe-maker who had been utilising n-hexane containing glue in a poorly ventilated workplace. He developed a distal symmetrical sensorimotor neuropathy. Patient 2, was a 29 year old man who showed a subacute painful neuropathy with alopecia. He had been criminally exposed to thallium containing rat poison. Patient 3, was a 23 year old alcoholic man who also showed a subacute sensorimotor neuropathy after a detoxifying treatment with disulfiram. Clinicopathological and electrophysiological details of all the patients will be discussed in detail.

P420

Electrophysiological changes in predialytic patients with polyneuropathy treated with erythropoietin

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Introduction: Neuropathy develops approximately in two thirds of patients with advanced chronic renal failure characterized by demyelination and axonal degeneration. The mechanism is unknown but may be related to accumulation and deposition of toxic substances. Erythropoietin (EPO) is a major determinant of tissue oxygenation, performing this function through the regulation of proliferation and differentiation of erythroid progenitor cells. EPO receptors were demonstrated on a wide variety of non-erythroid cells, but their specific functions in these nonhematopoietic sites are not fully understood.

Aim of study: To evaluate the effect of EPO therapy on peripheral polyneuropathy in predialytic patients.

Methods: Electrophysiological studies were performed in 46 predialytic patients without neurological complaints before and five months after subcutaneous EPO therapy.

Results: Neuropathy was detected in 22/46 (48 %) patients. 12/22 (54 %) had no diabetes mellitus. Fifteen patients completed the study.

Motor nerve conduction velocity (MNCV) and compound muscle action potential (CMAP) of ulnar nerve was normal before and after five months of EPO therapy. MNCV was reduced in median, peroneal and tibial nerves and improved significantly ($p = 0.04$, $p = 0.03$, $p = 0.04$ respectively) after five months of EPO therapy. CMAP was reduced in median, peroneal and tibial nerves. It increased significantly to normal range ($p = 0.01$) only in the median nerve. No significant improvement of CMAP was recorded in peroneal and tibial nerves. Sensory nerve action potential (SNAP) and sensory nerve conduction velocity (SNCV) were reduced in all sensory nerves: ulnar, median and sural and did not improve significantly after five months of EPO therapy. The improvement in MNCV after EPO therapy was found only in non-diabetic patients. No correlation was found between the increase in hemoglobin levels and the electrophysiological improvement.

Conclusions: The significant improvement in MNCV in all affected nerves that was not correlated with the increase in hemoglobin levels may be related to direct action of EPO through specific receptors on human neuronal cells. Moreover, the improvement of MNCV may suggest re-

myelination through activation or induction proliferation of Schwann cells.

P421
Rituximab therapy in IgM-paraproteinemic neuropathies
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Four cases of IgM paraproteinemia associated neuropathy (one Chronic Inflammatory Demyelinative Polyneuropathy – CIDP, three demyelinative sensorimotor neuropathies) were treated with Rituximab and various responses were noted. All the patients were tested for antibodies against GM1, GM2, GD1a, GDI, Sulfatide (ELISA) and glucolipid extracts of bovine Cauda Equine (TLC). Two out of four had anti-SGPG, -SGLPG antibodies (cross-reacting with MAG). An excellent response was noted in the CIDP patient with extranodal marginal zone lymphoma producing monoclonal IgM. The two anti-MAG neuropathies differed in response. The first patient with Waldestrom macroglobulinemia and anti-MAG neuropathy demonstrated slightly improvement of neuropathy along with partial response of the underlying lymphoma. The other anti-MAG patient with IgM-MGUS (monoclonal gammopathy of undetermined significance) was stable durign Rituximab therapy. Two months later his condition deteriorated and the patient finally responded to a combination of Fludarabine and Cyclophosphamide. The fourth patient (Waldestrom – not identified antigen) was slightly improved.

In conclusion Rituximab is a useful therapy of paraproteinemic neuropathies but further studies are needed to determine the specific clinical and immunological parameters of the Rituximab responsive paraproteinemic neuropathies.

P422
Characterisation of neuropathies associated with elevated IgM serum levels
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The significance of quantitative IgM levels in evaluation of neuropathy is unclear. We reviewed a cohort of neuropathy center patients with elevated IgM levels with regard to clinical phenotype, electrodiagnostic features of demyelination, presence of IgM monoclonal gammopathy based on serum immunofixation, and autoantibody activity.

Elevated IgM levels were found in 45 (11.5 %) of 391 patients that had been tested. Of the 45 patients, 24 (53 %) had polyclonal gammopathy and 21 (47 %) had an IgM monoclonal gammopathy. Anti-nerve antibodies occurred in 14/21 (67 %) of patients with monoclonal gammopathy with the following distribution: anti-Myelin Associated Glycoprotein (MAG) 11 (52 %); anti-sulfatide 3 (14 %); anti-GM1 1 (5 %); anti-GD1b and disialosyl 1 (5 %). Two patients had sulfatide and MAG antibodies. Only 1 patient with polyclonal gammopathy (6 %) had autoantibody activity (anti-sulfatide). The percentage distribution of phenotypes among the groups was as follows (monoclonal gammopathy: polyclonal gammopathy): predominantly large fiber sensory neuropathy (53, 46), a different sensory pattern (14, 21), and sensorimotor (29, 33). One patient had a pure motor neuropathy and she had a mononoclonal gammopathy and GM1antibodies. Of the 30 patients that underwent electrodiagnosis, features of demyelination were found in 18/30 (60 %), including: 77 % of the monoclonal gammopathy patients, 47 % of the polyclonal gammopathy patients, 40 % of patients without a specific autoantibody, and 100 % of patients with a specific autoantibody. The 3 monoclonal gammopathy patients that did not have autoantibodies all had axonal electrodiagnostic findings.

Conclusions: The most common clinical phenotype of patients with elevated IgM levels is a predominantly large fiber sensory neuropathy (49 %). Patients with monoclonal or polyclonal gammopathies had a similar distribution of clinical phenotypes. Autoantibody activity occurred in approximately 67 % of IgM monoclonal gammopathies, most often against MAG, but was only rarely associated with polyclonal gammopathy. GM1 antibody activity was associated with motor neuropathy, whereas other autoantibody activities were associated with a predominately sensory or sensorimotor phenotype. 60 % had electrodiagnostic features of demyelination. Serum testing for quantitative IgM and immunofixation may help identify patients with autoantibody activity, demyelinating neuropathy, or immune mediated neuropathies.

P423
Trauma complicating catamenial sciatica
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Endometriosis is the result of an actively growing endometrial tissue in sites outside the uterus. The cyclic sciatica secondary to endometriosis is a rare condition. We report a woman with catamenial sciatica (CSc) who had an exacerbation of her symptoms after a local trauma.

A 48-year-old female complained pain in the lateral surface of her right leg and foot since June 1996. This painful burning symptom occured exclusively in the catamenial periods. Hormonal supression of menstruation was performed with complete recovering of the symptoms. She had been asymptomatic for over three years. In July 1999 after a trauma over the right hip, with hematoma formation on the upper right anterolateral thigh, she began to feel paresthesias on the dorsolateral surface of the right foot and difficulty for walking. She had a right anterolateral leg atrophy, weakness graded 0/5 for the eversion and dorsiflexion and 3/5 for the inversion of the right foot. Right ankle jerk was reduced and there was hypoesthesia on the superficial peroneal nerve territory. Electrodiagnostic evaluation disclosed slowed motor nerve conduction velocity with reduced CMAP amplitude and absent F-wave in the right peroneal nerve. Electromyography showed an incomplete lesion of the right sciatic nerve involving more intensively the peroneal division. MRI revealed a high signal intensity on T2-weighted images in the right sciatic nerve trunk beside piriformis muscle. No improvement was obtained with prednisone. Surgical exploration was not accepted.

Our patient had complicating CSc with trauma, that had not been previously reported. We think that the direct or indirect trauma could complicate catamenial sciatica. An ectopic endometrious tissue is rich in blood vessels, the trauma resulting in increasing symptoms, as occurred in our patient. We believe that recommendations to avoid trauma mainly over the hip regions, should be considered in all patients with CSc.

P424
Three cases of severe Guillain-Barré syndromes treated by intravenous cyclophosphamide and corticosteroids
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We report 3 cases of severe Guillain-Barrè Syndrome (GBS) not responder to plasma exchange (PE) and IV immunoglobulin (IVIg), positively treated with IV Cyclophosphamide and prednisone. First case: 47-year old women admitted to our Neurological Department for progressive numbness and pain in hands and feet, distal muscle weakness in limbs presented at neurological examination severe muscle weakness in lower limbs and in arms. Deep tendon reflexes were absent. Electrophysiological evaluation revealed signs of demyelinating polyradiculoneuropathy and cerebrospinal fluid (CSF) showed an albuminocytological dissociation. Diagnosis of GBS was postulated and she was submitted to 5 PE but become paraplegic. She was treated with IVIg therapy (0.4 g/kg/day for 5 days) associated with IV metilprednisolone (1 g/day for 5 days) without benefits. After 1 month IV cyclophosphamide (300 mg/m^2/day for 4 days) and prednisone (40 mg/m^2/day for 5 days) were started and a slow improvement was noted. Cyclophosphamide and prednisone were administered every month for 3 months. After 18 months from the onset she walked without assistance. Second case: 50-year old men was admitted to our Neurological Department for a progressive onset of numbness in hands and severe weakness in lower limbs. Diagnosis of GBS was formulated. He was treated with PE and then with IVIg, but developed tetraplegia with motor cranial nerves involvement and needed ventilation. After 2 months he was treated with IV cyclophosphamide and prednisone and slowly improved. This therapy was given for 3 month and after 8 months he walked without assistance. Third case: 70 years old man admitted to Piacenza Neurological Clinic for a progressive weakness and numbness in lower limbs presented a quadriparesis. The diagnosis was of GBS. 5 PE and then IVIg were administered. In spite of an initial improvement he become paraplegic. After 2 months from the onset IV cyclophosphamide and prednisone were administered and he slowly improved. After 6 months of this therapy he walked without assistance. In all 3 cases the electrophysiological study at recovery evidenced a chronic inflammatory demyelinating polyneuropathy (CIDP). Conclusions: these cases may be considered GBS with a chronic persistent transformation or CIDP with a GBS onset. We suggest to consider a therapy with IV cyclophosphamide and prednisone in severe case of GBS unresponsive to conventional therapies and/or with electrophysiological CIDP features.

P425

Residual fatigue, fitness and quality of life after training intervention in patients with Guillain-Barré syndrome or chronic inflammatory demyelinating polyneuropathy: 2 to 3 years follow-up

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Background: Despite apparently good physical recovery after adequate therapy, 80 % of patients with immune-mediated polyneuropathies is suffering from severe fatigue and endurance intolerance. It was recently demonstrated that physical training intervention in patients after Guillain-Barré syndrome (GBS) or during the stable phase of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is feasible and results in significant decrease of fatigue and significant increase of physical fitness, functional outcome, and quality of life. The training, a 12-week during cycling program, 3 times a week 45 minutes, was performed in 16 GBS, and in 4 CIDP patients. In this follow-up study, we examine the 'long-term' effects of this physical training program on 'lifestyle', fatigue, physical fitness, functional outcome, and quality of life.

Methods: All 20 GBS and CIDP patients were contacted, and asked to participate again in the current follow-up study, consisting of the same questionnaires, maximal exercise testing and muscle strength measurements. Results will be compared with questionnaires and physical measurements before and after the training intervention, 2 to 3 years ago. Outcome measures are categorised to patients' lifestyle, fatigue (Fatigue Severity Scale), physical fitness and muscle strength: cardio-respiratory fitness (maximal cycle ergometer test), isokinetic muscle strength arms and legs, and muscle strength hands (hand dynamometry), functional outcome: impact of fatigue (Fatigue Impact Scale), and functional disability (GBS-Disability Score), anxiety and depression (Hospital Anxiety en Depression Scale), handicap (Rotterdam Handicap Scale), and quality of life (SF-36 Health Survey, Euroqol Health Questionnaire).

Results: 14 GBS and 3 CIDP patients returned a written authority for participation. Baseline data: mean age of 54 years (range 30–69), mean 6.5 years after diagnosis, and 35 % male patients. Before this follow-up measurements, most patients reported to "feel better" and still having benefits from the training study. Other data are presently collected.

Conclusion: The physical training intervention was well tolerated and effective for treatment of severe fatigue and impaired physical fitness in 'recovered' GBS and CIDP patients. Presently, the long-term effects of the training intervention, using the same assessment scales and performing the same physical measurements, are evaluated. The final results will be presented.

P426

Treatment of chronic inflammatory demyelinating polyneuropathy with interferon beta-1b

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Background: Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune mediated disorder of the peripheral nervous system, clinically characterized by symmetrical motor and sensory involvement. The effectiveness of corticosteroids, intravenous immunoglobulin (IVIG) and plasma exchange in the treatment of CIDP has been established in various randomized trials, however some patients do not respond to these treatment modalities.

Case report: In June 2001 a 41-year old male Caucasian developed a progressive, symmetrical, distaly stressed weakness in both upper and lower limbs and minor sensory symptoms. Based on clinical, laboratory, as well as electrophysiological grounds the diagnosis of CIDP was made and confirmed by sural nerve biopsy in November 2001. The clinical course of the disease was unresponsive to corticosteroids, IVIG, cyclophosphamide, mitoxantrone, and mycophenolate mofetil. Plasma exchange did slow down disease progression for only 2 weeks after repetitive exchanges, thus it could not be considered as a definite therapeutic solution. Therefore, in August 2002 we started therapy with interferon beta-1b s. c. every other day. Under this therapeutic regime disease progression was stopped and the patient showed a remarkable improvement of his clinical condition as well as electrophysiological parameters up to the present.

Discussion and conclusion: Current treatment regimens leave 4 % to 30 % of patients with CIDP with moderate or severe disability, thus further treatment modalities are needed. Interferon beta formulations are known to be clinically effective in multiple sclerosis (MS). Because of clinical similarities between MS and CIDP interferon beta appears to be an attractive drug to study in the inflamed peripheral nervous system. A recently published placebo-controlled trial in treatment resistant CIDP revealed that interferon beta is safe but not efficacious. In contrast, a recent preliminary study suggests that interferon beta might be beneficial in CIDP.

Our case report underlines that interferon beta-1b can be beneficial in CIDP patients not responding to other immunomodulatory and -suppressive therapies. Thus, large placebo-controlled trials are warrented to further evaluate the efficacy of interferon beta for the treatment of CIDP.

P427

Neuromuscular complications of jejunoileal shunt for morbid obesity: case report and literature review

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Intestinal malabsorbtion by jejunoileal bypass has been used to treat morbid obesity. Although procedure was considered safe, several long-term neurological complications have been described This report outlines the potential risk of jejunoileal bypass associated with chronic malabsorbtion.

A 47-year-old man was evaluated because of increasing gait difficulty five years after jejunoileal bypass performed when aged 42.Neurological examination showed extremity proximal and distal weakness, distal sensory loss for touch, pin-prick, vibration and position. Deep jerks were absent.

Gait was broad based and Romberg test positive. Blood tests revealed microcitic anemia (Hb 9 gr/dl), low blood iron (15 ug/dl). CK, thyroid and liver function tests, tumour marker titer, immunological and viral screenings were negative as well as seach for antibodies to gliadin and to gangliosides. Vitamin A was 1.12 umol/l (n. v. 0.56–4.25), vitamin E was 10.7 umol/l (n. v. 11.5–31). B12, folate levels were within range of normal.

Electrophysiology revealed an axonal sensorimotor neuropathy.Patient was treated with parenteral supplement of vitamin and iron e. v. with mild improvement of motor signs and of sensory symptoms after five months. A 42-year-old obese man had similar surgery. Two years later he developed an acute confusion, unsteadiness and coma due to lactic acidosis, from which he recovered. Fifteen years after jejunoileostomy patient was firstly evaluated neurologically because of muscle cramps, paraesthesias, progressive imbalance. On examination, mental state was normal; there were proximal and distal muscle weakness,trunk and extremity severe ataxia, distal muscle atrophy. Deep reflexes were diminished; all sensory modalities but especially vibration and position were affected. Blood tests showed macrocitic anemia, GFR = 50 ml/min, low free calcium (3.7 mEq/l),increased PTH (367pg/ml, n. v. 10–65), low serum level of vitamin A, D3 (OH)2, E and negative search for antibodies to gliadin. Electrophysiology confirmed a sensorimotor axonal and demyelinating neuropathy. Brachial biceps biopsy showed neurogenic changes. Patient general conditions progressively deteriorated because of repeated episodes of dehydration and recurrent metabolic acidosis. Terminal uremia occurred 27 years after the jejunoileal bypass.

P428

Chronic ataxic neuropathy initially diagnosed as ataxic variant of Guillain-Barré syndrome

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Acute ataxic neuropathy is characterized by acute onset of ataxia, loss of tendon reflexes, normal or mildly impaired sensation. Patients usually experience antecedent infections as in typical Guillain Barré Syndrome.

Clinical course is either monophasic or relapsing with high titre of antiganglioside antibodies, namely GQ1b and GT1a. A 40 year old mildly hypertensive man was admitted because of paraesthesias in UE, LE, dysarthria, swallowing difficulties, imbalance. On first admission patient exhibited diplopia on lateral gaze, scanned speech, bifacial weakness, dysphagia, tremor. The Romberg sign was present. Ataxia on finger-nose and heel-shin test was seen.There was mild distal impairment of touch, pinprick, position and vibration. Deep reflexes were absent throughout. CT and MRI scans were normal. Electrophysiology showed delayed F waves in LE. CSF revealed albuminocytologic dissociation (protein 167 mg/dl, NR 45–80). Patient was treated with plasmapheresis and had transient benefit. One month later, because of progression of cerebellar signs patient was newly admitted; a course of plasma exchanges was repeated, without benefit. On electrophysiology there were denervation changes and a polyradiculopathy both axonal and demyelinating. CSF protein content was 330 mg/dl. Search for anti Purkinjje cells and antiglycolipid antibodies was negative. Patient was treated with IVIg (0.4 g/kg for 5 days) without improvement. A trial of methylprednisolone e. v. (1 g daily for 3 days, and 500 mg for 2 days) switched to oral prednisone was administered. Chlorambucil was added (10 mg daily for ten days monthly) and repeated

six times. Patient transiently improved. Nine months after first onset, cerebellar signs progressed in absence of extremity weakness. Cranial nerves were normal; there were tremor, scanned speech, generalized areflexia. Laboratory results included negative search for IgM paraproteinaemia and cold agglutinins. CSF revealed 149 mg/dl proteins. Electrophysiology confirmed severe polyradiculopathy with conduction blocks. A renal biopsy obtained because of nephrosic proteinuria (4.5 g/day) showed focal segmental glomerulosclerosis with negative immunefluorescence. No antibodies against gangliosides GM2,GM1, GM1b, GD1a,GalNAc-GD1a,GD1b, GT1a,GQ1b could be detected. High dose of methylprednisolone e. v. (1 g daily for 3 days, and 500 mg for 2 days) were repeated. Cyclophosphamide was added (1 mg/m^2 monthly)

P429

Antiglycolipid antibodies in hereditary motor sensory neuropathy

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Chronic Inflammatory Demyelinative Polyneuropathy (CIDP) in Hereditary Motor Sensory Neuropathy (HMSN) patients has been occasionally referred. The purpose of this study is to detect a possible immune response to specific glycolipid antigen, in HMSN patients.

Twenty patients with HMSN neuropathy were tested for antiglycolipid antibodies to GM1, ASGM1, GD1b, Sulfatide SGPG, SGLPG, (ELISA, TLC). Positive findings were detected in two out of twenty patients. The first of these two patients showed increased titers to GM1, ASGM1 (800/1,600, 1,600/3,200) of IgM isotype and slightly lower of IgG isotype verified also by TLC overlay. Clinically presented severe mixed demyolinative and axonal neuropathy. The second patient showed strong immunostaining to SGPG, SGLPG, in IgM isotype (TLC overlay) associated with increased antibody titers to MAG (1453 Buhman units > x+3SD) and clinically presented a mixed mainly demyelinative neuropathy. Both patients belong to CMTX type and molecular genetic analysis (SSCP and nucleotide sequencing revealed point mutation in gjb1 gene coding for Connexin 32 in both patients. Our data argue for the immune involvement in some HMSN patients and a search for specific antibodies is needed.

Neurorehabilitation

P430

Impact on mental symptoms of botulinum toxin type A therapy in patients affected by focal dystonia and spasticity: preliminary results

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Object: We performed a prospective study in 48 patients to evaluate the impact of botulinum toxin (BT) therapy on mental symptoms in patients affected by spasticity and focal dystonia.

Method: 21 patients affected by spasticity (I group) and 27 patients affected by focal dystonia (II group) were included in the study. The patients were evaluated at baseline and 3 and 6 months after treatment; we studied the clinical effect of BT with Tsui and Columbia test in II group and with Medical Research Council Scale (MRC) and Modified Ashworth Scale in I group; all the patients were evaluated by center epidemiological study depression (CES-D), brief symptoms inventory (BSI) and attachment style questionnaire (ASQ); the II group by IIP-64, family apgar score (FAS), global clinical rating scale (GCRS), while the I group by short form-12 health survey questionnaire (SF-12); spastic patients' caregivers were examined by CES-D and CBI. A total of 17 patients (10 with dystonia and 7 with spasticity) completed the follow up. Patients were treated with BT type A (Botox-Allergan USA, Dysport-Ipsen UK) at dosage ranging from 350 to 1,000 mouse Units (mU) for Dysport BT and 10 to 100 mU for Botox BT.

Results: in patients with spasticity a positive trend was observed in CES-D whilst no differences were observed in caregivers before and after BT treatment. In dystonic patients we observed a reduction in global stress index in BSI after BT and no difference in CES-D while neurological scales showed an improvement after therapy.

In conclusion psycopathological assessment is crucial in evaluating BT therapy benefits in addition to neurological evaluation.

P431

Effects of muscular discoordination of the lower limb on gait in Parkinson's disease

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Objective: To quantify the activation profiles of the proximal muscular groups of the lower limb and their effect on the energy cost of the parkinsonian gait.

Background: Common abnormalities included augmented activities of the proximal muscles during single support, narrow angular displacement, shortened stride, slow speed and brief single support period. The co-contraction of the muscles is not finalised, with structural stiffness and, as a consequence, it causes the reduction of the muscular visco-elastic coefficient. The study with gait analysis provides data that is potentially useful for designing personalized treatment protocols.

Methods: 24 patients (15 males, 9 females; age range: 61–77 yrs), classified according to Hoehn and Yahr, were tested at the Laboratory of Gait Analysis of the Don Gnocchi Foundation -Onlus-Parma, Italy. A total of 9 tests were carried out using the EL. I.TE. 3-D opto-electronic system (BTS) following S. A. F.Lo. protocol, 1 1/2 hours after administration of the levodopa. EMG signals from gluteus medius, rectus anterior, biceps femoris and adductor muscles were recorded. Two dynamometric platforms allowed the calculation of articular moments of force and mechanical powers produced. The control group was composed of 62 healthy adults (age group: 50–78 yrs).

Results: The dynamic electromiography profiles differ in timing, with increased reciprocal overlapping and width compared to the controls during mid and terminal-stance.

The kinematic profile shows an increase of the hip flexion during the stance phase; besides this, the average range of flexion-extension is 24° as against 49° in the controls.

The maximum extensory moment at the hip takes place in advance, in the mid-stance, with an average value of 0.7 as against 0.2 Newton × meter/Kg of the controls. The maximum flexory moment is on average 0.1 as against 0.7 Newton × meter/Kg of the controls. The maximum "energy waste" in the parkinsonian hip is on average 0.4 watt/Kg.

Conclusions: The parkinsonian subject moves forward with hip movements through the reduction of posterior semi-step. The altered anatomic axis of the lower limb reduces the visco-elastic coefficient of the muscles, by not allowing the physiological alternation of the reciprocal moments of flexion-extension of the limb in stance with consequent instability.

P432

Positive effects of interferon-beta-1-a therapy on attention and cognition

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Cognitive deficits are common in multiple sclerosis (MS). They are only weakly associated with physical disability but substantially correlated with supratentorial lesion-load as well as with measures of general brain atrophy. The aim of our study was to evaluate possible cognition-related effects of IFN-beta-1a treatment in MS-patients for a 1-year-period by using measures of attention, learning and memory as outcome parameters.

We studied a clinical population of altogether 12 MS-patients and also 15 education-matched healthy controls [Group CTRL]. The patient group consisted of 4 male and 8 female participants with a mean age of 39.4 yrs and a mean EDSS-score of 3.3. Control subjects (6 male/9 female) had a mean age of 38.2 yrs. During the study period patients were treated with 30 um p. w. IFN-beta-1a (AVONEX). The cognitive performance of the MS-patients was evaluated at baseline (before starting IFN-beta-1a medication), after 12 weeks and again after 52 weeks. Controls were evaluated at baseline and after 52 weeks. Both groups were compared on the basis of their scores on a variety of cognitive tests of general intellectual abilities, attention and memory.

There were no statistical differences between mean scores of patients and controls on general intellectual performace. A slight attenuation of reaction-time latencies in the MS-group could be detected between baseline and week 52. Moreover, there was also a significant enhancement of the alertness-response for the MS-group during the same period.

There was no difference in span-measures but significant differences were found in total number of recalled items (5th trial) as well as interference and delayed recall (all measures $p > 0.05$). Significant intra-group differences in the interference trial were also found within the MS-group between baseline and week 52.

Since disturbances of attention and memory have a strong impact on activities of daily living one might expect that a IFN-beta-1a induced sta-

bilization of these core functions may also have an overall benefical effect on quality of life in MS-patients.

P433
Effects of whole-body vibration in rehabilitation of spinal cord injury patients
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Introduction: It is a well known fact that vibrations applied to the human body become effective on multiple physiological levels. The most prominent phenomenon is a special muscular activation pattern which is called tonic-vibration-reflex (TVR). In rehabilitation this effect can be used effectively since the voluntary contraction loop can be bypassed. Some studies speculate that this could be an advantage in the treatment of patients with spinal cord injury (SPI). Based on data and experience in rehabilitation of other nerval injuries and diseases the guiding question of this study was to analyse whether whole-body-vibration could be an effective method to improve motor control of SCI patients.

Methods: Altogether 40 incomplete SCI patients participated in this study. In order to compare different treatment strategies patients were subdivided in two groups (20 subjects each). In the control group therapy was based on a traditional rehabilitation procedure. Patients in the experimental group were treated with WBV (average freq. 4 Hz, ampl. 3 mm) additionally. Experimental treatment was performed daily consisting of 5 series lasting 60 seconds each. Some patients had to be supported at the beginning since they were not able to keep up whole body weight. In order to get huge information about the performance of the patients different tests were performed e. g. qualitative and quantitative gait analyses, balance tests, interviews that were focused on motor control in daily live.

Results: After a period of three month patients of the experimental group were superior to patients of the control group in several but not all tests. Prominent group differences that became statistically significant were found in balance tests, 10 meters walking test and whole walking pattern. This better performance of the experimental group in balance and gait was also confirmed in the interviews that showed higher safety in daily tasks and locomotion.

This data can be explained on several levels. One can speculate that additional reflex activity of leg muscles achieved by WBV improves fundamental aspects of motor control like sensory behaviour or strength. Further more there is evidence that the oscillating character of the stimuli leads to an activation of a spinal nerval network called central pattern generator (GPG).

Conclusions: Whole-body-vibration can be an effective method in rehabilitation of SCI patients, but further studies are necessary.

P434
National Institute of Health Stroke Scale (NIHSS) is correlated with electrophysiological impairments of the damaged brain
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Background & purposes: The national Institute of health Stroke Scale(NIHSS) is a commonly used neurological impairment measure. It was correlated with stroke volume, determined by computed tomography (CT), but not compared with the elecrophysiological outcome, measured by transcranial magnetic stimulation (TMS). TMS is non painful, and non invasive tool for estimating cortical function. This study aimed to investigate whether the relationship between the NIHSS scores and cortical electophysiological values after stroke, detected TMS.

Materials and methods: Forth six subjects with the middle cerebral artery ischaemic/hemorrhagic stroke (16 ischemic, 30 hemorrhagic) underwent NIHSS and TMS. According to the MEPs in the affected muscles, subjects were divided into 2 groups: Group 1 was 26 subjects with absent and group 2 was 20 subjects with MEPs responses to TMS of the affected hemisphere. NIHSS scores were expressed as sum of NIHSS scores, NIHSS subscore for the hemiplegic arm & leg. Statistical analysis was performed by means of Student's test when comparing the two groups and Spearman's test when correlating with TMS measures and NIHSS scores.

Results: In comparison with the two groups, the total NIHSS scores and NIHSS subscore for hemiplegic arm were significantly different($p < 0.01$, respectively), but not in NIHSS subscore for hemiplegic leg ($p > 0.05$). There were moderately correlated between resting threshold of TMS and NIHSS subscore for hemiplegic arm ($r = 0.49$, $p < 0.05$).

Conclusions: The NIHSS is correlated with the cortical electrophysiological impairments in the affected cerebral cortex in subjects with stroke.

P435
Early rehabilitation after pontine infarction with special consideration to neurogenic dysphagia
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Objective: The rehabilitation progress of 34 patients after pontine infarction with special consideration to neurogenic dysphagia is been presented. Relevant videoendoscopic pictures of swallowing will be shown and management of therapy will be demonstrated. The influence of neurogenic dysphagia on the rehabilitation prognosis will be analysed.

Methods: It is a retrospective study of 34 patients with pontine infarction. The average age was 64.4 years (34–77), the comparison in sex men/women 20/14. On admission to early rehabilitation there were 3 cases (8.8 %) of oculomotor paresis with hemiparesis and in one case (2.9 %) an isolated hemiataxia. 9 patients (26.5 %) had a severe hemiparesis and another 9 cases (26.5 %) had severe hemiparesis combined with dysphagia. 12 patients (35.3 %) who had a bilateral pontine infarction had a tetraplegia with dysphagia.

Results: The average stay in the early rehabilitation clinic after a bilateral pontine infarction (N = 12) was 165.7 (49–352) days, the average functional independence measure (FIM) on discharge 36.3 (18–63) points. We saw 7 cases (58.3 %) of pneumonia. In single cases the removal of the tracheal canula and an increased oral intake of food was possible. After one-sided pontine infarction with isolated hemiparesis (N = 9), the average duration of stay was 30.9 (18–61) days and the average FIM on discharge 118.3 (97–126) points, and in accordance the results after a hemiparesis with dysphagia (N = 9) was 83.1 (22–198) days and 79.8 (38–124) points. Here despite severe dysphagia, pneumonia only occurred in 2 of 9 cases, at least partial oral intake of food was possible in 7 cases (78.8 %).

Conclusions: Basically the presence of a neurogenic dysphagia after a one-sided pontine infarction is a negative predicative factor for the rehabilitation prognosis. However a videoendoscopic examination of swallowing and the resulting coordinated therapy management in cases of severe neurogenic dysphagia after pontine infarction is an important contribution to the reduction of complications and to the improvement of the rehabilitation prognosis.

P436
Analysis of fine motor deficits following traumatic brain injury
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Introduction:Most patients after head trauma car accidents are known to present deficits of motor coordination and sensory motor.Thus incidence of head trauma is in 40 % of cases followed by hand function deficits including plegia and paresis. Although deficits in fine motor control are one of the most and longest lasting sequelae of head trauma, correlation between the severity of the trauma and the development of posttraumatic deficits has yet not been characterized in more detail.Thus the analysis and quantification of sensory motor performance was the aim of our study.

Methods: Elementary finger force and movement control: For the examination of basic deficits of finger force control we measured maximum grip force and fast force changes in a precision grip; sensory function was assessed by resistance to perturbation.To analyse functional force control we tested grip force control during daily object manipulation. We used an instrumented hand held object supplied with force and acceleration sensors. The anticipation of grip force to inertial and gravitational loads during object movements was examined.

Results: We examined 14 patients suffering from head trauma including 8 multiple trauma patients, as well as 14 healthy age and gender matched control subjects.In the elementary tasks, the frequency of fast force changes and the reaction to perturbation were prolonged in the patients. In contrast, maximum finger force was only slightly reduced. In functional force control concerning grip force, a moderate increase of the grip force especially during dynamic tasks was recognizable. The time used for grasping and transporting of the object was significantly prolonged although the modulation of grip force with dynamic load forces was found to be largely preserved. Concerning the hands, both hands typically yielded disturbed function. An augmented grip force was observed in both hands. Concerning aspects of time, significantly more asymmetry on the disadvantage of the affected hand was shown.

Conclusion: In patients after head trauma, various aspects of fine motor control are affected. The patients have preserved capabilities in basic tasks but seem to be increasingly impaired in more complex tasks.

In fact the grip force was increased, but not to the same degree as known for stroke patients.

Finally the degree of dysfunction concerning fine motor object control

was not related to the overall degree of severity, so that each case has to be considered individually.

P437
Oxcarbazepine treatment of behavioural disorders in brain-injured patients
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After severe head injury many patients continue to experience major cognitive and behavioural problems, even after good physical recovery. Amongst the post-traumatic patients hospitalised in our Rehabilitation Institute in 2002, 5 young patients were selected who had severe disorders, in particular aggressive problems. Carbamazepine is used in the treatment of aggressive behaviour in schizophreniform disorder and personality disorder. We decided to determine the effectiveness of oxcarbazepine, a keto-analogue of carbamazepine, in the treatment of behavioural problems because it is thought to have fewer side effects and to be safer than carbamazepine. Moreover, it has less drug interaction than carbamazepine, which renders this substance interesting for the treatment of affective disorders. It exhibits an antidepressive-like effect and has an antimanic activity. Substitution of oxcarbamazepine for carbamazepine was associated with improved cognition and alertness in some patients with epilepsy.

Oxcarbazepine was markedly effective in all 5 patients and was well-tolerated. A mean oxcarbazepine dose of 1,320 mg/day was administered and the mean follow-up time was 18.6 months. One patient had received carbamazepine, 800 mg/day, as prophylactic drug, and he was able to switch to oxcarbazepine, 1,200 mg/day, with good relief of aggressive symptoms. One patient stopped treatment after 7 months for symptomatic hyponatremia. Substitution of carbamazepine for oxcarbazepine was associated with increased anxiety.

We conclude that further studies are needed to validate the mood-stabilizing effect of oxcarbazepine in brain-injured patients.

P438
Persistence of cognitive deficits following paediatric head injury without professional rehabilitation in rural East Coast Malaysia
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Objective: To use data from a prospective, longitudinal study to determine whether psychomotor functions in a rural area of Malaysia improves spontaneously without modern rehabilitation facilities during the first year following paediatric traumatic brain injury.

Method: 36 pediatric patients who were referred for neurosurgical management for mild to severe head injuries over were studied a period of 2 years. All patients had neither orthopaedic or surgical trauma. Assessment of patients occurred at 3 and 12 months respectively and subjected to Bender Gestalt Test (BGT), Weschler Intelligence Scale for children-revised (WISR-II) and sub tests from the Weschler Preschool and Primary Scale of Intelligence (WPPSI). All these patients did not receive professional rehabilitation due to absence of facilities, only traditional treatment was given during this period.

Results: There was no significant changes in all parameters except in integration error after a period of one year. Cognitive function improved in thirty percent of these patients after 1 year follow up. Despite the increase relationship of caregiver to the patient in the first year of trauma there was no general improvement compared to western literature.

Conclusion: Lack of community modern resources, low ratio of general practitioner to patient and no availability of inpatient or outpatient rehabilitation despite good interfamily support does not improve spontaneously the psychomotor condition of all our patients. These are important findings for the future restructure of psychological service in Malaysia.

Neuro-opthalmology

P439
Prevalence of benign paroxysmal positional vertigo: a population-based study
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Background: Benign paroxysmal positional vertigo (BPPV) is nowadays the most successfully treatable cause of vertigo. In specialized dizziness clinics BPPV is the most common vestibular disorder accounting for about 20 % of referrals, however, its prevalence in the general population is not known.

Objective: To determine the prevalence of BPPV in the general adult population.

Methods: A nationwide computer-assisted telephone interview (CATI) survey was conducted with a representative sample of 4,869 men and women aged 18 years and older residing in Germany. The CATI identified 1,403 subjects with a history of moderate or severe dizziness or vertigo, 1,157 of whom were willing to participate in a detailed dizziness interview conducted via telephone by medical students thoroughly trained in a dizziness clinic. Diagnostic criteria for BPPV were: at least five attacks of vestibular vertigo lasting less than 1 minute provoked by changes of head position such as lying down and turning over in bed. In a concurrent validation study, 61 patients were interviewed by telefone and independently examined by a neurologist specialised in neuro-otology. BPPV was detected by telefone interview with a specificity of 92 % and a sensitivity of 88 %.

Results: From the original sample (n = 1,157) 1003 interviews were completed (response rate 87 %, n = 154 could not be reached or refused to participate). Vestibular vertigo was reported by 243 participants (178 women and 65 men), of whom 80 fulfilled the criteria for BPPV (24 men and 56 women). The proportion of BPPV in the dizziness group varied with age: 2.3 % (men 2 %; women 2.4 %) in the age group 18–39 years, 10.6 % (7.8 %; 12 %) in the age group 40–59 years and 14.9 % (14.6 %; 15 %) in the age group > 60 years. The estimated lifetime prevalence of BPPV in the general population in the three age groups was 0.5 %, 1.6 % and 3.6 % in men and 1 %, 3.8 % and 5.7 % in women.

Conclusions: BPPV is a common cause for vertigo in the general population. The prevalence of BPPV increases with age and has a female preponderance.

P440
Correlation of nicotine-induced nystagmus, vertigo, nausea and imbalance with nicotine plasma concentrations
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Introduction: Nicotine acts through different cholinergic receptors in the peripheral and central vestibular system and may cause nystagmus, postural imbalance, vertigo and nausea. The inter-relationship of these signs and symptoms as well as their dependence on the blood nicotine concentration has not yet been studied. Therefore, the aim of this study was to investigate the correlation between the nicotine (NIC) plasma-concentration and (a) nicotine-induced nystagmus (NIN), (b) imbalance, (c) vertigo and (d) nausea in healthy volunteers. Vertigo and nausea were estimated at rest and during vestibular and optokinetic stimulation.

Methods: A total of 50 healthy volunteers (20 female, 30 male, age 27 ± 6 years, all non-smokers) were included. The subjects were tested before NIC (once) and after NIC (six times) with the following test protocol: First, a blood sample was drawn to determine the NIC-concentration. Next the subject was stimulated first with rollvection (60 sec) and then with head-shaking (60 sec). Eye movements were then recorded using 2-D-video-oculography (VOG) to detect vertical and horizontal NIN (30 sec). Simultaneously with the VOG, the total sway path (tSP) was measured during upright stance with the eyes closed using a Kistler platform (30 sec). At each time-point of the investigation, the subject evaluated nausea and vertigo on a visual analogue scale (0–10). The duration of each cycle was 4.5 minutes, the total duration of all 7 cycles was 31.5 minutes. The subjects were randomized into 5 groups (10 subjects in each): (1) nicotine nasal spray (NIS) 1 mg without stimulation, (2) NIS 1 mg with stimulation, (3) NIS 2 mg without stimulation, (4) NIS 2 mg with stimulation, and (5) stimulation only.

Results: Our investigation showed a significant positive correlation between NIC-plasma-concentrations and (a) NIN, (b) imbalance, (c) vertigo

and (d) nausea. Subjects, who were stimulated by rollvection and headshaking complained significantly more about vertigo and nausea.

Conclusion: The significant correlation of occurrence, intensity and time-course of nicotine-concentrations and nicotine-induced nystagmus, body sway, vertigo and nausea can all be explained by a common, transient, nicotine-induced vestibular tone imbalance. Nicotine appears a feasible substance for perturbing the vestibulo-ocular and vestibulo-spinal system.

P441

4-aminopyridine restores visual ocular-motor function in upbeat nystagmus

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To evaluate the potential beneficial effect of the potassium-channel blocker 4-aminopyridine (4-AP) on primary position upbeat nystagmus (ppUBN), we used the search-coil technique to measure fixation in different gaze positions and smooth pursuit in a patient before and after ingesting 4-AP. Brainstem auditory evoked potentials suggested a mesencephalic lesion. The 3-D eye movement recordings showed that 4-AP reduced slow phase velocity (SPV). of ppUBN with gaze straight ahead from 8.6 ± 0.2 deg/s (mean ± SD) before treatment to 2.0 ± 0.1 deg/s 90 min after treatment when the target remained visible, but not during attempted fixation of a flashed target. Vertical smooth pursuit was highly asymmetrical before medication (gains: pre, downward 0.74, upward 0.38) and improved 90 min after medication (upward 0.89, downward 0.86). These findings suggest that 4-AP improves the function of damaged vestibulocerebellar pathways, mediating gaze holding and smooth pursuit by intensifying the excitability of Purkinje cells.

P443

The importance of subjective sensation and interpretation of physiologic vertigo states for the pathogenesis of somatoform vertigo syndromes

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Thirty percent of patients with vestibular lesions develop a somatoform vertigo syndrome (SVS). In another 50 % vertigo is caused by psychiatric, e. g. phobic and anxiety disorders. It was postulated that patients with high anxiety and phobic anxiety may have a higher sensitivity to complex visual environments and thus a higher sensitivity to "physiological" vertigo sensations. Beside different psychopathological dimensions, the subjective sensation and interpretation of vertigo seems to be important for the pathogenesis and chronification of SVS. The purpose of our study was the improvement and differentiation of a pathogenetic model of SVS, and to enable an early diagnosis and the development of a differentiated interdisciplinary therapy for patients with SVS.

In an interdisciplinary study 80 patients with vertigo syndromes (1. organic disorders caused by peripheral vestibular lesions, 2. somatoform vertigo caused by phobic and anxiety or 3. by depressive disorders) underwent a structured neurological, neurootological, and psychosomatic diagnostic; results were compared with those of 20 healthy volunteers. Sitting in front of a hemi-spherical dome, they looked at a moving random dot pattern that induced the perception of body tilt. The amount of state-anxiety was assessed (STAI-X2 State) before and after exposition. Further instruments for measuring relevant psychosocial dimensions (Vertigo-Symptom-Scale & -Handicap-Questionnaire, Yardley et al.; HADS, Herrmann et al.; AVK, Ehlers et al.; SOMS, Rief et al.) and a structured diagnostic interview (SKID-I) were used.

We found different levels of state-anxiety, somatization, emotional distress, and handicap in the subgroups. The patients with SVS showed higher state-anxiety after exposition than the patients with organic vertigo and the controls. They showed higher emotional distress, handicap, and intensity of complaints and had a higher psychopathological comorbidity. Over all, they experienced much more stress as a result of the vertigo symptoms than patients with organic vertigo.

Our preliminary results show that patients with SVS have higher scores of anxiety after the experimental induction of physiological vertigo sensations (roll vection). They cope with physiological vertigo sensations in a catastrophicating way. They have a much higher risk of developing a complex chronified vertigo syndrome. An early prophylactic intervention seems advisable.

P444

Ultra-short vestibular time constants in the congenitally blind

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Congenitally blind subjects are dependent upon non-visual mechanisms for navigating in everyday life. Sighted humans accurately utilise vestibular signals for navigating in the dark but the presence of such ability in the congenitally blind is unknown. Vestibular navigation may also be influenced by a brainstem mechanism called the 'velocity storage' integrator which prolongs the duration of the peripheral vestibular signal. We studied vestibular navigation and quantified the perceptual vestibular velocity storage time constant in congenitally blind and sighted subjects in the dark. Vestibular navigation was assessed by having subjects (6 blind vs. 12 sighted) steer a motorised Baranyi chair in response to imposed angular displacements for two tasks, 'Go Back to Start' (GBS), a path reproduction task and 'Complete the Circle' (CTC) a path completion task. For GBS both sighted and blind subjects were accurate (stimulus vs. response displacement regressions: r2 range 0.61–0.94) with no difference between both groups' performance ($P > 0.05$ for slopes and r2 of grouped regressions). In contrast, for CTC, blind subjects performed worse than sighted subjects ($P < 0.05$ for comparison of regression slopes and r2). Vestibular velocity storage was measured by subjects (5 blind vs. 31 sighted) turning a tachometer wheel to indicate instantaneous angular velocity perception following velocity steps of 90 deg/s. The averaged velocity storage time constant of the congenitally blind was significantly shorter than in normal controls (5.34 s vs. 16 s; $P < 0.001$). Our findings agree with animal data suggesting that vision is necessary for the development of the velocity storage mechanism. Two congenitally blind subjects had ultra-short time constants (2.39 s and 3.30 s) which were associated with superior angular path completion performance. These two subjects participated throughout childhood and adulthood in spatial activities involving whole-body movements. We conclude that whilst congenital blindness does not interfere with simple path reproduction navigation, it is associated with impaired path completion task performance. Early and prolonged physical spatial activities in childhood and adulthood may however, be of value in improving vestibular navigation in the congenitally blind.

P445

Reliability of history-taking in the diagnosis of benign paroxysmal positional vertigo

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Background and Objectives: Patients with benign paroxysmal positional vertigo (BPPV) usually have typical history. They usually complain of vertigo that lasting a few seconds to a minute. It usually occurs in the morning after awaking and provoked by typical positional change such as head turning, sitting, and lying down. However, some patients may describe their vertigo in a rather atypical way, so there is no absolute reliability of a diagnosis based on history taking. To evaluate the reliability of a diagnosis based on history taking, we performed prospective studies. Materials and Methods: We obtained structured history from all the patients with BPPV. Total of 408 patients were diagnosed as having BPPV. The diagnosis was based on typical findings of vertigo and nystagmus by Dix-Hallpike maneuver and head turning in supine position. Results: Ninety cases (22 %) of patients complained of their vertigo lasting more than 10 minutes. Position-precipitating factors were not spontaneously reported by 37 % of cases. Sixty-five cases(16 %) complained of non-spinning vertigo. In 155 cases (38 %), they could not tell the side to which the spell occurs. In 83 cases (20 %), it was impossible to diagnose BPPV based upon a typical history. Conclusion: We conclude that non-paroxysmal, non-positional vertigo dose not rule out BPPV. The provocation test is mandatory in those complaining of dizziness regardless of history since BPPV can be quickly diagnosed by provocation test and easily treated.

P446

Leber hereditary optic neuropathy and exercise intolerance

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Objective: to describe a case of Leber hereditary optic neuropathy (LHON) associated with exercise intolerance.

Background: vision loss is the main clinical picture of LHON and associated neurological symptoms are rare.

Material and methods: a 44-year-old patient, without family history, was referred for myalgias and fatigue which occured during exercise and

gradually increased. In his past history, he had presented with sudden bilateral vision loss when he was 18 years of age. Neurological examination was normal except areflexia of lower limbs and contracture of vertebral muscles. Fundus examination revealed an optic atrophy. A mitochondrial cytopathy was suspected.

Results: routine blood tests, echocardiography and cerebral MRI were normal. A raised lactate/pyruvate ratio was found after exercise on ergometric bicycle. Muscle biopsy only showed one ragged-red fiber on trichrome stains and histoenzymology was normal. Biochemical studies of muscle revealed a mitochondrial complex I deficiency and T144844C mutation of mtDNA was found by molecular genetics study.

Discussion: LHON is a disease which occurs in young people and is characterized by sudden, bilateral and isolated optic atrophy. Associated neurological symptoms are exceedingly rare and consist of peripheral neuropathies and dystonia. The mutation found in our case is one of the main mutations of LHON and affects mtDNA encoding for complex I subunit 6 of mitochondrial respiratory chain. Pathological abnormalities of muscle have been described in LHON but without clinical symptoms. To our knowledge this is the first documented case of exercice intolerance.

Conclusion: LHON may be added to the list of mitochondrial cytopathy with muscular expression.

P448

Benign paroxysmal positional vertigo predominantly affects the right labyrinth

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Background: Benign paroxysmal positional vertigo (BPPV) is caused by freely moving particles that have entered a semicircular canal and cause short attacks of vertigo whenever the head is turned in the plane of the affected canal.

Objective: The aim of the study was to clarify whether BPPV manifests equally in both labyrinths or whether there is a preponderance for one side.

Methods: PubMed literature search of BPPV case series which specify the affected side and retrospective chart review of 80 consecutive patients with BPPV of the posterior canal who presented to our dizziness clinic.

Results: Eighteen previous studies with 3,426 patients were identified. In our own series the right side was affected in 54 of 80 patients (ratio right/left 2.08). Altogether, in 3,506 patients the right labyrinth was involved 1.41 times more often than the left (95 % CI 1.37–1.45).

Conclusions: We speculate that the predominant involvement of the right ear in BPPV can be explained with the habit of most patients to sleep on the right side.

P449

Isolated bilateral abducent nerve palsy due to a spontaneous left-side dural carotid cavernous fistula, type Barrow C

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Carotid cavernous fistulas (CCFs) are commonly associated with congestive orbito-ocular features such as chemosis, exophthalmus, loss of visual acuity, ophthalmoplegia and orbital bruit. We describe, as a rare entity, a case of an isolated bilateral abducent nerve palsy due to a spontaneous left-side CCF.

A 63-year old woman developed acute horizontal diplopia associated with nausea, without preceding trauma or illness. The symptoms disappeared within a few hours, reappeared again 10 days later and persisted thereafter. Her medical history included an essential hypertension for several years and an intermittent, pulsatile left-side tinnitus for about 6 months. Physical examination showed a bilateral, left-dominant abducent nerve palsy and a pulsatile bruit over the left carotid arteries. The funduscopic examination and the visual acuity were normal. T2-weighted magnetic resonance (MR) images of the brain revealed small flow voids adjacent to the cavernous segment of the internal carotid artery, suggestive for an arteriovenous fistula. MR digital subtraction angiography (DSA) showed a filling of the cavernous sinus during the early arterial phase, proving the presence of a CCF. On conventional DSA an exclusive filling of the fistula by branches of the external carotid artery was observed (CCF Type Barrow C). The embolization with microparticles of the major feeding branches arising from the maxillary and the middle meningeal artery (one small branch could not be reached) resulted in a marked reduction of fistula flow. A few hours after embolization the pulsatile tinnitus disappeared and within about 10 weeks the bilateral abducent nerve palsy gradually regressed. Follow-up MR DSA 6 weeks after embolization showed signs of a slightly persistent fistula and follow-up conventional DSA 18 weeks after embolization disclosed a complete occlusion of the fistula.

Uni- and rarely, as in our case, bilateral abducent nerve palsy might be caused by a CCF. The presence of a pulsatile tinnitus in a patient with an abducent nerve palsy is suggestive for a CCF. MR DSA as a non-invasive technique might show this fistula directly and should be incorporated into the imaging protocol of these patients.

P450

Congenital fibrosis of extraocular muscles type 1 (CFEOM1) with progression of ophthalmoplegia and ptosis

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Congenital fibrosis of the extraocular muscles type 1 (CFEOM 1) is a developemental disorder characterized by a congenital non-progressive bilateral external oculomotoric nerve palsy with ptosis and autosomal-dominant inheritance due to mutations in the KIF21A gene, encoding a kinesin motor protein.

Serial sections over 23 years in a 60-year old patient with the common C2860T mutation in the KIF21A gene revealed not only congenital, but additional further progressive bilateral external ophthalmoplegia and ptosis.

Clinical examination and electromyographic examination of the extraocular muscles showed isolated involvement and aberrant innervation of residual oculomotoric nerve fibers.

Additional abnormalities as pes cavus, a slight kyphoscoliosis, and neurogenic EMG pattern in 2 of 5 muscles might reflect a more widespread involvement of a-motoneurons due to the KIF21A mutation.

Progredient chronic external ophthalmoplegia might be caused by either a continuous disease progression due to the kinesin defect or the consequence of an overuse of the reduced number of oculomotoric brain stem a-motoneurons.

P451

Tolosa-Hunt syndrome: neuroimaging and steroid treatment correlations in five cases

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Objective: To evalute correlations between clinical evolution, neuroimaging and steroid treatment in patients (pts) affected by Tolosa-Hunt syndrome (THS).

Background: THS is a rare painful ophthalmoplegia often due to nonspecific granulomatous inflammation in the cavernous sinus or superior orbital fissure. Diagnostic criteria are based on oculomotor nerves involvement, steroid responsiveness and/or demonstration of granuloma by MRI or biopsy and exclusion of other causes(tumrors, vasculitis, basal meningitis, sarcoidosis, aneurysm, diabetes and opthalmoplegic migraine), according to International Headache Society (IHS 2004).

Methods: We report 5 pts (3 males, 2 females, age range: 35–65 years) affected by THS according to IHS inclusion criteria. All pts underwent general, neurological and ophthalmologic examinations, routine blood tests, serum inflammatory and infectious tests, autoantibodies, angiotensin converting enzyme, tumor markers and gadolinium enhancement brain MRI. Cerebral angiography and cavernous sinus biopsy were performed in 1 pt, CSF examination was performed in 1 pt.

Results: In 3 pts laboratory data and neuroimaging were normal at onset of symptoms; high dose steroid therapy was promptly started (desamethasone 16 mg bid i. m. tapered in 4 weeks) within 5 days from onset of symptoms. Pain disappeared within 60 hours, ocular palsies whitin 5 days from onset therapy. Two other pts had cavernous soft-tissue mass at gadolinium enhanced brain MRI and lightly increased sedimentation rate. Cavernous sinus mass biopsy was performed in 1 case showing nonspecific inflammatory abnormalities. These 2 pts underwent high dose steroid therapy only after 1 month from the onset of symptoms and showed slow improvement with complete recovery within 2 months. Cavernous sinus mass disappeared after 6 months on brain MRI. All pts did not show any clinical relapse during follow-up (from 3 to 10 years, mean 6 years).

Conclusions: Our report confirm that steroid treatment has to be started early during the course of the disease to obtain a more rapid resolution of symptoms and signs possibly preventing anatomical damage. MRI coul have a positive prognostic value predicting steroid efficacy and clinical outcome.

Multiple sclerosis

P452

Neurotrophic factors and clinical recovery in relapsing-remitting multiple sclerosis

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Background: Although immune responses contribute to the formation and maintenance of multiple sclerosis (MS) lesions, an increasing body of experimental evidence supports a potentially beneficial effect of inflammation, at least partly mediated by the release of neurotrophic factors, that may help to minimize neuronal damage. Activated human T cells, B cells and monocytes cells were proved to secrete bioactive brain derived neurotrophic factor (BDNF) in vitro and studies in Relapsing Remitting (RR)MS patients demonstrated that BDNF production by peripheral blood mononuclear cells (PBMCs) was significantly higher during relapses and recovery phases compared with values detected in the stable phases of the disease.

Objective: The aim of this study was to determine neurotrophin (BDNF; glial cell line-derived neurotrophic factor, GDNF; nerve growth factor, NGF; neurotrophin 3, NT3; neurotrophin 4, NT4) production by PBMCs in RRMS patients at different phases of disease in order to evaluate whether clinical recovery is correlated with different levels of neurotrophic factor production.

Methods: We studied 21 patients affected by RRMS in different phases of disease (stable, relapse, post-relapse). All patients were treated with high dose corticosteroids during relapse phase. Neurotrophin production was assayed by enzyme-linked immunoabsorbent assay (ELISA) in supernatants of unstimulated PBMCs.

Results: In the post-relapse phase 15 patients obtained complete recovery from new symptoms, 6 showed a progression in disability as compared with the pre-relapse phase. The two groups of patients did not differ for any of the clinical characteristics studied – sex, age, relapse rate in the past two years, baseline EDSS – except for disease duration, with a longer history of disease in subjects who obtained only partial recovery in post-relapse phase as compared with patients with complete remission. The BDNF production by PBMCs was significantly higher during relapse phase only in the group of patients with complete recovery after relapse. There was no main variation of the other neurotrophic factors studied at relapse time. An increase of NGF, GDNF, NT3, and NT4 production was observed in the post-relapse phase only in the group of patients with complete recovery.

Conclusion: Our data bear out the neuroprotective effect of inflammation in the early phases of MS. A reduced neuroprotective potential of immune cells is associated with accumulation of disability.

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Impaired maturation of plasmacytoid dendritic cells in multiple sclerosis

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Background: Dendritic cells (DCs) are considered as key regulators of the immune response. There are at least two major subsets of DCs present in human peripheral blood – myeloid and plasmacytoid DCs. Plasmacytoid DCs (pDCs) represent a distinct subpopulation of DC which exerts divergent functions in T cells including induction of immunoregulatory responses and maintaining tolerance. Thus, in multiple sclerosis (MS) alteration in pDCs function may play a role in the loss of immune tolerance towards putative autoantigens. We assessed the phenotype of pDCs freshly isolated from the blood of MS patients as well as their maturation in culture.

Materials and methods: Ex vivo phenotypic analysis was performed by flow cytometry on blood samples obtained from 32 clinically stable, untreated MS patients with relapsing-remitting disease and 22 healthy controls. pDCs were characterized as BDCA2 positive cells and counterstained with antibodies specific for a panel of surface antigens including DC subset markers, major maturation antigens and co-stimulatory molecules. For maturation experiments, pDCs were isolated by magnetic sorting from leucapheresis material obtained from 18 MS patients and 12 controls and than cultured for 96 hours with IL3 and soluble CD40 ligand. Every 24 hours, cultured pDCs were assessed by flow cytometry for the expression of maturation markers and co-stimulatory molecules.

Results: pDCs in MS had features of immaturity compared to pDCs of healthy subjects. The expression of co-stimulatory molecules CD86 and 4-1BBL on pDCs was significantly lower in MS samples than in controls (22 % vs. 47 %, $p < 0.0001$ and 11 % vs. 35 %, $p < 0.0001$, respectively). pDCs of MS patients, when cultured with IL-3 and CD40L, also showed delayed and inefficient maturation as demonstrated by significantly lower or delayed upregulation of CD86, 4-1BBL, CD40, and CD83.

Conclusions: In untreated MS patients we observed a lower expression of two major co-stimulatory molecules on blood pDCs as well as an impaired maturation of pDCs in culture. These findings suggest functional abnormalities of pDC in MS which may play a role in the pathogenesis of the disease.

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P454

Early abnormalities of evoked potentials predict long-term disability in patients with multiple sclerosis

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Background and goal: While the decisive role of evoked potentials (EP), especially of visual evoked potentials (VEP), for diagnosis of multiple sclerosis (MS) is widely accepted it is still under debate whether pathological alterations of evoked potentials may help to predict the future disease course in MS.

Patients and Methods: To determine the prognostic value of EPs, 94 patients who were examined clinically and by electrophysiology at first presentation with follow-up after 5 and 10 years were included into this retrospective study. Patients were further divided in relation to the time point of first presentation: Group 1 had their first examination within two years after disease onset ($n = 44$, mean disease duration 1.2 years) and Group 2 was first examined at later time points ($n = 50$, mean disease duration 9.6 years at first presentation).

Results: For patients examined early after disease onset (Group1) a predictive value for EPs was found: Single parameters like delayed latencies of somato-sensory (SEP) and motor evoked potentials (MEP) at baseline were associated with higher degrees of disability (EDSS > 3.5) after 5 years. Baseline MEP as well as SEP scores significantly correlated with EDSS after 5 years ($r = 0.5–0.55$, $p < 0.003$) and baseline MEP score with changes in EDSS over five years ($r = 0.75$, $p < 0.001$), while the VEP score was not correlated with clinical disability as expressed by EDSS. The cumulative number of pathological EPs at baseline was indicative of higher degrees of disability after 5 years: 1 resp. 3 pathological EPs indicated a mean EDSS after 5 years of 2.4 resp. 4.8. The combination of altered SEP and MEP at basis best predicted clinical disability after 5 years (Odd's ratio 11).

Conclusion: Combined testing of EPs at early disease stages in MS may be useful as predictor for later clinical disability. Together with clinical data and MR imaging EP may help the neurologist to identify MS patients at high risk of clinical deterioration and thereby guide in making decisions as to early immunomodulatory treatment.

P455

Brain MRI characteristics of relapsing-remitting MS patients who respond to glatiramer acetate therapy

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To determine brain MRI abnormalities including godolinium (gd) enhancement in RRMS patients who clinically respond to glatiramer acetate (GA).

Background: In clinical practice, brain MRI scan including Gd enhancing lesions are often considered along with clinical history to recommend a particular immunomodulatory therapy (IMT) in RRMS. Beta-interferons are known to have a robust reduction of Gd enhancement in contrast to GA therapy which has a relatively modest effect. This practice tends to favor recommending beta-interferon over GA therapy in RRMS patients who have Gd enhancing lesions. It is unknown if this leads to a clinical response of similar magnitude in clinical practice.

Methods: Clinical records of patients treated and followed at the Wayne State University MS Clinic were reviewed (September 1, 2003). Data from all clinically definite RRMS patients who received GA therapy for at least one year was reviewed. Annual relapse rate (ARR) before and after starting therapy with GA was determined. Non-responders were identified as patients having an identical or higher ARR on GA compared to the ARR prior to starting GA therapy. Brain MRI scans prior to onset of GA therapy were examined for the presence of Gd enhancing lesions and T2 lesions.

Computerized volumetric analyses or brain atrophy could not be because a substantial number of scans were performed at different MRI machines in the community and only hard copies were available for review.

Results: 265 patients qualified for analysis. Mean duration of therapy with GA was 28.1 months. 209 (79 %) of 265 patients were responders. The total number of Gd enhancing and T2 lesions did not distinguish responders from non-responders to GA therapy. Sub-analyses by stratifying the number of gd enhancing lesions at onset of GA therapy by categorizing to 1, 2 to 3, 4 to 5 or greater than 5 Gd enhancing lesions did not distinguish between responders and non-responders. Similar observations were made when stratifying by the number of T2 lesions (5 to 10, > 10 but < 15, > 15 but < 20 or > 20). Clinical results will be presented separately.

Conclusions: Presence of single or multiple Gd enhancing lesions does not distinguish between responders and non-responders to GA therapy. Until, MRI techniques can be standardized in clinical practice and serial brain MRI scans can be performed, recommendation of IMT therapy should be largely based on the clinical profile of patients with RRMS.

P456

Can MEG be used to monitor multiple sclerosis?

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Purpose: Currently, monitoring the course of the disease in multiple sclerosis (MS) patients is based on a combination of clinical measures, such as EDSS, and MRI measures, such as new lesion counts. In this pilot study, we investigated the possible usefulness of magnetoencephalographic (MEG) assessment of interhemispheric connectivity in MS. Loss of interhemispheric connectivity in MS patients has been assessed by other means including neurophysicological testing, functional and structural MRI [1, 2], EEG [3] and transcranial magnetic stimulation [4]. However, none of these assessments indicated a promising marker for MS.

Method: Ten MS patients (EDSS 1.0–3.5 RR) and 11 healthy controls were scanned for the pilot study. Five minutes of eyes closed data was acquired while each subject was seated comfortably in a 151 channels CTF (Vancouver, Canada) MEG scanner. We selected an artefact free 16 s interval from each subject's data set. We then calculated the interhemispheric correlation measure over each 16s interval for each of 5 frequency bands (1–4 Hz, 4–8 Hz, 8–12 Hz, 12–30 Hz, 30–48 Hz).

Results: When ranked by interhemispheric correlation measure, the pilot study showed a highly significant ($p = 0.00011$) difference between the two groups in the alpha band (8–12 Hz). By this ranking, of the 21 subjects, the highest 9 were all healthy controls and the lowest 7 were MS patients. The other 4 frequency bands showed little or no statistical significance differences.

Conclusion: Most likely, the loss of interhemispheric correlation in MS patients reflects widespread white matter dysfunction including connectivity loss, in particular of transcallosal commissural fibres. Determination of interhemispheric correlation with MEG is a promising marker for overall assessment of brain function in MS.

References

1. Pelletier, et al. (1993) Arch Neurol 50:1077
2. Barkhof, et al. (1998) J Neurol 245:153
3. Leocani, et al. (2000) J Neurol Neurosurg Psychiatry 69:192
4. Boroojerdi, et al. (1998) Electromyogr Motor C 109:230

P457

Qualitative deficits of cognitive performance in relapsing-remitting multiple sclerosis correlate with T1 and T2 lesion burden on MRI

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Background: The pattern of cognitive impairment in MS patients often includes deficits in the areas of executive functioning, verbal and spatial learning and recall, organizational skills and abstract reasoning. Very little is known about the quality of these defective areas of performance, including semantic clustering ability during the learning process and recognition vs free recall upon retrieval and their correlation to whole brain or regional lesion load on brain MRI.

Methods: We studied eighteen RRMS patients (mean age 32 ± 8.5 yrs; F/M 13/5) with a disease duration of 7.5 ± 3.8 yrs and an EDSS score of 1.8 ± 1.3. They were all administered a neuropsychological test battery assessing working memory, controlled attention, manual dexterity, verbal fluency, visual scanning, spatial recall and verbal learning. All patients underwent brain imaging on a NMR 1.0 Tesla system and T1 and T2-lesion volume was calculated according to Ormerod et al. (1987). Statistical analysis was carried out using Spearman's rank correlation matrix.

Results: Deficits in executive functions, working memory, manual dexterity, and visual exploration were observed. Impairment of visual-spatial organization and semantic clustering ability were also documented, supporting the notion of a "frontal" pattern of cognitive dysfunction in MS patients. Whole brain and frontal lobe T1 lesion load values inversely correlated with recognition ability on CVLT (r –0.742, p 0.009, whole brain; r –0.688, p 0.003, frontal lobe) and on Rey's copy (r –0.612, p 0.01 and r –0.695, p 0.003). Whole brain and frontal lobe T2 lesion load also correlated with selective cognitive aspects such as performance on visual scanning (r 0.516, p 0.04) and number of perseverations on CVLT (r 0.537, p 0.03). Both T1 and T2 lesion load correlated to manual dexterity on 9-hole-pegs and executive ability on PASAT.

Conclusions: Our data confirm a predominant involvement of executive functions in RRMS patients. Furthermore, qualitative cognitive defects such as semantic clustering and strategic abilities correlated to both whole brain and frontal lobe T1 lesion load on MRI, suggesting that the loss of executive skills in MS may derive from severe tissue damage preferentially localized in the frontal lobes.

P458

Safety and tolerability of 500 mcg versus 250 mcg interferon beta-1b: first phase of the BEYOND programme

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Objective: To evaluate the safety and tolerability of 500 mcg versus 250 mcg interferon beta-1b (IFNB-1b; Betaferon(r)/Betaseron(r)) given subcutaneously (sc) every other day (eod).

Background: The efficacy of IFNB treatment in patients with relapsing-remitting multiple sclerosis (RRMS) is greater with high-dose, high-frequency administration. Treatment with 250 mcg IFNB-1b is the current gold standard, and whether a dose higher than any currently available IFNB dose will result in greater efficacy with continued tolerability in RRMS is not yet known.

Methods: A multicentre, randomised, double-blind, parallel group study comparing IFNB-1b 500 mcg with 250 mcg, self-administered sc eod for at least 12 weeks. Patients were instructed to use auto-injectors to give consistent injection technique. Study drug was escalated over the first 6 to 12 weeks, and then maintained at full-dose. Temporary interruption or dose-reduction of IFNB-1b treatment was allowed in patients experiencing tolerability problems or other adverse events. Non-steroidal anti-inflammatory drugs were used to minimise flu-like symptoms. Primary outcomes were safety and tolerability, defined by the proportion of patients in each treatment arm experiencing flu-like syndrome, fever, myalgia, injection site reactions, asthenia, headache, and liver and bone marrow function abnormalities.

Results: IFNB-1b 500 mcg was well tolerated and there were no new or unexpected adverse events. An effect of dose on the occurrence of some adverse events, such as flu-like symptoms and related adverse events, lymphopenia and liver function elevation was observed, but this was not seen in others, such as injection site reactions. The dose escalation scheme was successful in the 500 mcg group and the 250 mcg group: over 90 % of patients attained the full 500 mcg dose during the course of the study. Dose interruptions were similar for the two groups (4 patients in each treatment arm), but transient dose reductions were more common in the 500 mcg treatment arm.

Conclusions: This study is the first phase of the BEYOND programme and provides support for safely administering 500 mcg IFNB-1b sc eod to patients with RRMS. The second phase of BEYOND is a 3-arm comparative study to evaluate the efficacy, safety, and tolerability of 250 mcg and 500 mcg IFNB-1b and glatiramer acetate in patients with RRMS. BEYOND will examine relapse-related, disability-related and other clinical and paraclinical outcomes.

P459

The immunosuppression (IS)-responsive secondary-progressive multiple sclerosis (SPMS). Experience from cyclophosphamide- and mitoxantrone-treated SPMS patients indicates the clinical profile of the IS-candidate patient

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Multiple Sclerosis (MS) is currently considered immune-mediated disease of the Central Nervous System. Immunomodulatory agents, such as interferon beta and glateramer acetate, are used to slow down disease activity in the relapsing remitting form of the disease (RRMS), but are substantially ineffective in modifying the progressive phase of the MS. Moreover, a relevant portion of RRMS patients do not respond to IMA, and enter rapidly the so-called secondary progressive phase. Immunosuppressive therapy may be the best available chance to treat both SPMS and IMA-non responsive RRMS, but a better classification of patients candidate to immunosuppressive therapy is needed in order to optimize therapy benefit. We have previously observed that cyclophosphamide (Cy) was able to stabilize rapidly deteriorating SPMS (J.Neurol. 2003, 250:834–838). Here, we report our experience using Mitoxantrone (MT), compare the effect of Cy and MT on disease activity and progression, and further characterize the profile of IS-responsive patients. Thirty SPMS patients were treated with MT (8 g/m^2 every other month for 2 years) and were compared with an equal number of Cy-treated SPMS patients (0.8–1.2 g/m^2 monthly for one year, and every other month in the second year). Both Cy and MT were equally effective in stopping disease progression in the majority of treated patients, but the effect of both drugs was highly significant in a subgroup of patients experiencing rapidly deteriorating disease, characterized by frequent and severe relapses as well as rapid progression (defined by a confirmed increase of more than 1 EDSS point in a period of 1 year). After two years of therapy, in this subgroup of patients the relapse rate was almost set at zero, and the EDSS significantly improved ($p < 0.01$). However, the relapse rate within the first six months from therapy initiation was higher in the MT-treated patients compared to Cy-treated patients. These drugs, however, did not modify disease evolution in slowly-progressive or non-relapsing SPMS, further suggesting that IS should be initiated at the beginning of the progressive phase of the disease. Both drugs were well tolerated. Taken together, our data further confirm that the ideal MS patient for a successful immunosuppressive therapy is characterized by short duration of the progressive phase, rapid progression, and frequent relapse with rapid deterioration of clinical condition.

P460

Screening for cognitive impairment in multiple sclerosis – the MUSIC approach

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Introduction: Cognitive dysfunctions are known to affect about 50 % of MS-patients. Since cognitive disturbances have been recognized to have a significant impact on the ability to maintain employment there is a strong need to develop neuropsychological tests to assess cognitive functioning in MS. We present a cognitive-screening instrument (MUSIC = Multiple Sclerosis Inventory of Cognition) which is aimed to evaluate mental disturbances in MS-patients on a basis of 5 subtests covering the most compromised areas of cognition.

Patients and Methods: A sample of altogether 238 subjects (Ctrls = 158; MS-patients = 80) matched for age, education and gender was evaluated with a cognitive test-battery consisting of 5 subtests (attention, working-memory, flexibility and long-term memory) and an additional 3-item fatigue questionnaire. The raw scores of the individual subtests were weighted according to their respective sensitivities and specificities derived from discriminant-analysis and then transformed into weighted test-scores on the basis of means and standard-deviations of the norm population. The weighted subscores were added to a total sum-score with a maximum of 30 pts.

Results: A between-group-comparison yelded significant differences between ctrls. and patients in the individual subtests and the total score (all p's < 0.01). On the basis of the mean and standard-deviation of the weighted total-score it was able to determine cutoff-scores, thus classifying individual overall-test-performance into 4 categories (normal performance; mild cognitive dysfunction; moderate cognitive dysfunction; severe cognitive dysfunction).

Comments: Cognitive dysfunctions are common in MS. While some comprehensive batteries have been developed there ist still a lack of cognitive screening instruments to identify individuals in need of further assessment. The MUSIC is a valid and reliable test to identify patients with MS with cognitive dysfunctions.

P461

Pregnancy and multiple sclerosis therapies

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Introduction: Multiple sclerosis (MS) is a common neurological disorder affecting young adults, and most of them are women. Previous research have shown that maternal MS has no apparent effect on birth outcomes compared with the general population. However,there is lack of information about the safety of MS-modifying therapies in pregnancy and brest-feeding.

Goals: To determine whether women with MS who become pregnant while they are on disease-modifying therapies are more likely to have poor birth outcomes or pregnancy or delivery complications than those who discontinue therapy before pregnancy.

Method: We have reviewed our European database for multiple sclerosis (1,100 patients) from January 1995 to January 2004, looking for pregnancies in women on disease-modifying therapies. They were assigned to one of two groups: those who discontinued therapy before pregnancy (planned pregnancy) and those who did not (unplanned pregnancy). Pregnancy course, birth outcomes and MS course were reviewed.

Results: We have found 160 fertile women on disease-modifying therapy and 18 of them became pregnant.There have been 20 pregnancies:15 planned and 5 unplanned.

Whithin the planned ones,there have been one miscarriage, 10 normal deliveries, one miscarriage followed by a normal delivery, and one abortion because of an ectopic pregnancy.None of them did brest-feeding.One is still pregnant. Another 4 patients have discontinued therapy but they have not become pregnant yet; and 3 discontinued treatment but went on without becoming pregnant. Whithin the unplanned group, there have been 2 normal deliveries whithout brest-feeding and 2 abortions,both because the patients were concerned about the risks for the newborn. One of them was an ectopic pregnancy. The fith is in her first month of pregnancy.

Discussion: The incidence of miscarriage was higher in the planned group.Given the theoretical abortive potential of these treatments, one would expect this to happen whithin the unplanned pregnancies. Nevertheless, this was not higher than the expected in the normal population. There were no differences in terms of birth outcomes.

We are concerned this is a small group,so a statistical analysis is not possible. We think it is imperative to perform a longitudinal study in a wider population to stablish the effects of MS therapies on pregnancy and brest-feeding.

P462

Cognitive impairment in patients suffering from secondary progressive multiple sclerosis

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Objectives: To study cognitive function of subjects affected by secondary progressive multiple sclerosis (SPMS).

Methods: Fourty two SPMS patients according to Poser and Lublin criteria, treated with interferon beta 1-b, were submitted to a wide neuropsychological battery, including Mini-mental state examination, verbal IQ (WAIS-III), FAS and SET tests to fonetic and semantic language, Wechsler Scale for short and long term memory, Wisconsin Card Shorting Test, Trail Making Test A and B, Stroop color/word interference test, Abbreviated Boston naming test and Benton Visual Retention Test. They also underwent Beck Depression Inventory, Anxiety scale of Hamilton and neurological examination (EDSSS and MSFC). Two or more tests affected was considered as cognitive impairment.

Results: 42 SPMS patients, 73.8 % females and 26.2 % males, mean EDSS 5.38 (3–7.5), mean disease duration 13.57 years (3–38), mean treatment duration 34.5 months (4–80). 23.8 % patients presented one test affected, 21.4 % two tests, 16.7 % three, 16.7 % four, 16.7 % five and 4.8 % six tests affected, thus 72.2 % patients were considered to have cognitive impairment. PASAT correlated significantly ($p < 0.01$) with minimental state examination, verbal IQ, FAS, Boston and Benton, but didn't correlate to the other tests. There was no correlation between EDSS, MSFC nor illness duration and cognitive impairment.

Conclusion: Subcortical cognitive impairment was frequent, and it did not correlate to EDSS nor illness duration. PASAT correlated with many of

the items examinated, but not with memory tests nor Stroop. We suggest that a basic neurological examination should include these items in order to determine the presence of cognitive impairment in these patients.

P463

Th2-cytokines in multiple sclerosis: IL-4- and IL-10 production correlates with disease progression

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Introduction: Th1-/Th2-imbalances play an important role in pathogenesis of multiple sclerosis. In the present study we looked for the relation between clinical parameters (EDSS, disease duration, index of progression, exacerbation frequency) and immunologic parameters. As important pathogenetic immunologic parameters we measured IL4, IL10, IFNg, IL4R and IFNgR by flow cytometry. IFNgR was examined in this connection the first time.

Methods: We present a prospective, non-randomized study with 58 multiple sclerosis patients (female = 40; male = 18; age: 38.2 ± 11.2 years). Intracellular cytokines and membrane-bound cytokine receptors in peripheral blood leucocytes were detected with monoclonal antibodies and measured by flow cytometry. Results are given as percentages of CD3 + populations (intracellular cytokines) or as relative fluorescence intensity (membrane-bound cytokine receptors). These methods have shown good quality results in other studies (Petereit et al., 2000, Kraus et al., 2000). As statistic methods multidimensional non-parametric analyses of variance (MANOVA) and Spearmans coefficient of correlation were used.

Results: An influence of the age or sex on the expression of the examined immunological parameters could be excluded statistically. The progression index (defined as EDSS-Score/disease duration) correlated negatively with percentage of IL-4-positive-CD3+ cells ($r = -0.29$; $p < 0.03$), IL-10-positive-CD3+ cells ($r = -0.26$; $p < 0.05$) and IL-10-positive-CD3+CD8+ cells ($r = -0.27$; $p < 0.05$). The evaluation of the further clinical parameters showed that the examined cytokine and cytokine receptors were independently expressed of the duration of the disease, exacerbation frequency and increased EDSS.

Conclusion: For the first time a negative correlation between the progression index and the by flow cytometry detected IL-4- and IL-10-expression was shown. The negative correlation between disease progression and Th2-cytokine-expression confirms the investigations of Petereit et al. (2000), which demonstrated a positive correlation between handicap degrees and the proinflammatoric cytokine IFN-α in multiple sclerosis patients.

P464

Cognitive impairment in secondary progressive multiple sclerosis. A longitudinal one-year follow-up study

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Objective: To study the evolution of cognitive impairment in an homogeneous secondary progressive multiple sclerosis (SPMS) patients cohort.

Patients and methods: We have selected 27 patients with clinically definite SPMS according to Poser and Lublin criteria (77.8 woman, mean age 46 years, mean EDSS 5.1, mean evolution time 13.7 years and mean time with beta-interferon treatment 37.7 months). In order to avoid byass by a possible effect of immunomodulatory treatment, only patients under beta-interferon 1b along all the periode have been studied. EDSS, Functional Composite MS scale (FCMS), and a selected battery of neuropsychological test including WAIS-III, Wechsler Scale for short a long term memory, FAS and SET tests to fonetic and semantic language, Wisconsin targe, Stroop test, TRAIL A and TRAIL B test, Boston vocabulary test and Benton visuospatial perception, were administrated at the same moment an one year after. The same neurologist and neuropsychologist performed the clinical and neuropsycological explorations. Cognitive impairment was considered if two or more of the following tests was affected (WAIS-III, Wechsler Scale for short memory, FAS, Wisconsin targe, Stroop, Boston vocabulary test or Benton test). Tests were considered abnormal according to the normal values published in spanish population (results was adjusted by age and educational years). Patients also underwent Beck Depression Inventory (BDI) and the Hamilton test to anxiety.

Results: At the basal evaluation 77.8 % of patients fullfilled CI criteria, this percent raised to 85.2 % one year after (two new patients reached CI criteria). In the follow up, 6 patients worsened in the number of test, 9 patients improved (in Wechsler memory scales and TRAIL making tests A and B) and 12 remained with the same number of test affected. No patient with CI in the basal evaluation improved to no CI. No correlation between BDI, Hamilton test nor EDSS and the neuropsychological tests was proven.

Conclusion: CI in SPMS is a frequent and progressive condition, not related to the depression state or anxiety. Improvement observated in Wechsler memory scales and TRAIL making tests A and B may be due to a training effect. We think that the CI criteria we have considered in this study is robust, as all patients that fullfilled CI criteria at the basal evaluation remained equal or worsened in the follow up.

P465

Putable prognostic biological markers of "benign" multiple sclerosis

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The clinical course of multiple sclerosis (MS) is characterised by an extreme variability of disease progression which makes difficult to individualise prognostic information. Some patients remain fully independent even after 10–20 years from disease onset and the term "benign" MS (BMS) commonly indicates this form. Nevertheless, there is disagreement on the clinical meaning of the term, on the method to evaluate disability, and on the number of required follow up years to define a BMS. Some clinical factors seem to predict a favourable prognosis, but a biological assay predicting a BMS is lacking. In fact, MS is a highly variable and dynamic disease, and destructive and repair mechanisms are often simultaneously active, making difficult to assess suitable predictive biological markers. Although MS is considered a T-cells disease, new evidences support a major pathogenic role of humoral immunity. In isolated ON and clinically isolated syndromes CSF oligoclonal(OC)IgG are strongly predictive of the future development of MS. Moreover, the presence of CSF OCIgM is associated to an increased probability to reach higher EDSS scores.

In order to assess a CSF antibody panel having prognostic value in early MS, we determine the presence of OC IgG and IgM bands, as well as IgG and IgM indexes in a group of 23 BMS (EDSS < 3 after 10 yrs; mean age at onset: 27.4 yrs; mean follow up yrs: 15.4) compared to 20 MS with a severe course (SMS) (EDSS > 4 after 10 yrs; mean age at onset: 26.3 yrs; mean follow up yrs: 14.5). CSF OC bands were determined by mean of agarose isoelectric focusing followed by immunoblotting with specific anti human IgG and IgM antibodies. CSF OCIgG were absent in 8/23 (34.8 %) BMS and in 1/20 (5 %) SMS ($p < 0.05$). Furthermore, the bands number was significantly lower in BMS (mean: 3 bands), respect to SMS (mean: 6.25 bands) ($p < 0.01$). OC IgM bands were absent in 17/23 (73.9 %) BMS and in only 2/20 (10 %) SMS ($p < 0.01$). IgG and IgM indexes were not significantly different between the two groups.

Our findings suggest that OCIgG and OCIgM negative patients have a better prognosis than OCIgG and OCIgM positive ones. If these results will be confirmed in a larger cohort of patients, the OC IgM bands may be a suitable prognostic marker, together with the clinical features. Early predictions of MS outcome will have an impact on counselling and will allow the patient to plan for his future and to make optimal use of medical, family, and community resources.

P466

The levels of chemokines CXCL8, CCL2 and CCL5 in multiple sclerosis patients are linked to the activity of the disease

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Chemokines are small cytokines with selective chemoattractant properties. They contribute to the T cell-mediated pathogenesis of multiple sclerosis (MS). Recent studies have reported presence of chemokines in the cerebrospinal fluid (CSF) and serum of MS patients mainly during the active phase of the disease.

In order to ascertain if a different types and stage of disease correlates with a varying level of chemokines, the levels of chemokines CXCL8, CCL2 and CCL5 were measured in serum and the CSF of the MS patients.

The patients group included 56 people with definite MS according to Poser's criteria and 29 patients with other neurological diseases. Depending on clinical symptoms of MS, the MS-patients were divided into tree sub-groups: stable stage of the relapsing-remitting multiple sclerosis (20 subjects), relapse stage multiple sclerosis (18 subjects) and progressive multiple sclerosis (18 subjects). Control serum and CSF samples were available from 15 patients with non-inflammatory neurological disease and from 14 patients with inflammatory neurological diseases.

ELISA method was used to determine the levels of the chemokines.

The levels of CXCL8 and CCL2 in both groups were higher in CFS than in serum whilst the level of CCL5 measured higher in serum than in CSF. A significant rise in the levels of CXCL8 and CCL5 was observed in CSF during relapse ($p < 0.05$ and $p < 0.001$, respectively), as against the level of CCL2 which was getting lower when compared to the control group as well as other MS groups ($p < 0.05$). During relapse, high levels of CCL5 were observed in serum of the MS patients as well. The levels were significantly higher than in other MS-group and non inflammatory control group ($p < 0.001$). No significant differences were observed in the levels of chemokines between the stable relapsing-remitting MS and progressive MS.

The different levels of chemokines are linked to relapse of the disease. No separate, specific pattern of chemokine production dependent on the type of MS could be ascertained.

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Usefulness of a portable device in the psychomotor assessment of relapsing remitting multiple sclerosis: preliminary data

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Introduction: Objective measurement of psychophysical performance is of capital importance in the longitudinal evaluation of motor and cognitive function in Multiple Sclerosis (MS) for clinical trials and therapeutic decisions.

Objectives: to evaluate the usefulness of a new portable device in assessing psychomotor performance in Multiple Sclerosis patients (MS).

Methods: Thirtyfive right-handed patients with relapsing-remitting MS (25 females; age 39 ± 7 years; EDSS 2.1 ± 1.5) underwent a 10 min battery of tests on a portable device allowing to administer visual stimuli on a LCD screen and to measure responses of the index finger on a response button: simple, cued, go/no go visual reaction times (sRT, cRT, chRT), finger-tapping, motor coordination (reproducing a sinusoidal movement on the device screen), fatigue at a series of 20 maximum voluntary contractions. All tasks were performed with the dominant hand. Reaction time, movement duration, velocity and force, frequency and phase shift were compared with a group of 35 age and sex-matched normal subjects. Patients and subjects were also administered the Nine Hole Peg Test (NHPT) and the Fatigue Severity scale.

Results: In the RT tasks, MS patients showed slower reaction times in all RT tasks compared with normal subjects, with significant differences for the cued ($p = 0.007$) and choice RT ($p = 0.01$), pushed the button with a significantly reduced force ($p < 0.007$) and at a lower speed ($p < 0.0001$ for simple and choice RTs, n. s. for cued RTs). Patients also had a slower finger tapping (2.3 ± 0.7 Hz) compared to normals (3.0 ± 0.7 Hz) ($p = 0.0004$). At the fatigue test, patients showed a reduced maximum force both at the beginning ($P = 0.03$) and at the end of the task ($P = 0.04$) compared with normal subjects, while the force decay ratio did not significantly differ between the two groups. MS patients had a higher FSS score than normals ($P = 0.0003$) and performed worse at the NHPT ($P = 0.0001$). No correlation was found between objective fatigue and the FSS.

Conclusions: The abnormal findings obtained in MS patients in measures of speed and force suggest the possible usefulness of the measures obtained through a portable device in the assessment of psychomotor function. The lack of abnormal objective fatigue, together with increased subjective fatigue in these patients, suggests that independent factors may underly the two phenomena.

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Does fatigue in early relapsing-remitting multiple sclerosis correlate with brain atrophy?

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Introduction: Fatigue is a common symptom of relapsing remitting multiple sclerosis (RRMS) even in the early phase of the disease when neurological disability is not prominent. Previous studies found no correlation between the severity of fatigue in RRMS patients and the extent of lesions as assessed by conventional and quantitative MRI techniques. However, functional imaging studies indicate that fatigue in RRMS is associated with dysfunction in frontal cortex and basal ganglia. The aim of our study was to evaluate the correlation between fatigue and brain compartment proportions, measured by brain parenchymal fraction (BPF), volumes of white matter (WMF) and grey matter (GMF).

Methods: We studied 16 patients with RRMS (mean EDSS 1.63 ± 0.7) showing no mood disorder as measured by Beck Depression Inventory (BDI < 17) and receiving no immunomodulatory treatment. Fatigue was assessed using Fatigue Severity Scale (FSS). MRI scans including a volume-rendering MP-RAGE data set were acquired on a 1.5T clinical MRI scanner, and BPF analysis was performed using a previously described standardized and automated protocol.

Results: All patients presented with fatigue with mean FSS of 51.3 (SD 15.2, range 25–76), using a cut-off of 25. Mean BPF was 0.7934 ± 0.0242 with a mean grey matter fraction (GMF) of 0.5286 ± 0.0187 and mean white matter fraction (WMF) of 0.2651 ± 0.0121. There was no statistical significant correlation between the severity of fatigue and BPF, GMF or WMF although patients with higher FSS scores tended to show decreased GMF values.

Conclusion: The data showed no correlation between the severity of fatigue and the values of brain atrophy measured by BPF, the GMF and the WMF in early stages of MS. We confirmed results of previous studies, reporting no morphological correlate for fatigue. Fatigue might be due to functional changes in cortical and subcortical structures.

P469

Illness representations, symptomatology, marital satisfaction and quality of life in patients with multiple sclerosis and their caregivers

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Introduction: Multiple sclerosis (EM) is a inflammatory disease of myelin from the Central Nervous System of cause unknown, chronic, that affects young people's quality of life. This study's goals include: assessment of disease representations, psychological morbidity, marital satisfaction and quality of life in patients with EM and their caregivers.

Methods: Sample – A group of 100 ambulatory patients with criterions of Poser defined EM, age mean of 39.19 years, Expanded Disability Status Scale (EDSS) of 1.8, and a group of respective caregivers participated in this study.

Instruments. The instruments used for patients were: Illness Perception Questionnaire (IPQ Weinman & Petrie, 1996), Sickness Impact Profile (SIP – Delyo et al. 1982, 1983), Hospital Depression and Anxiety Scales (HADS – Zigmond & Snaith, 1983), Multiple Sclerosis Quality of life Questionnaire (MSQOL-54 – Vickrey, Hays, Harooni, Myer & Ellison, 1995) and the Index of Marital Satisfaction (IMS – Hudson, 1990). The instruments used for caregivers were: Caregivers Reaction Assessment (CRA – Given et al. 1992), Beck Depression Inventory (BDI – Beck, Mendelson & Mock, 1961), State Trait Anxiety Inventory (STAI – Spielberger, Grush, Lushene, Vagg & Jacobs, 1983) and the Index of Marital Satisfaction. (IMS – Hudson, 1991).

Hipothesis 1: We expect differences in patients with index of severity (EDSS) > 4 when compared with EDSS < 4 in all psychological variables

Hipothesis 2: We expect differences in caregivers from patients with index of severity (EDSS) > 4 when compared with caregivers from patients with EDSS < 4 in all psychological variables

Results

- The results showed that patients with a higher severity index present lower quality of life, and lower adjustment to disease when compared with less severe patients. In terms of illness representations, those with higher severity perceive their disease as having worst consequences, and themselves as having lower personal and treatment control. Patients with higher severity index also manifest more depression.
- Those caregivers from patients with higher severity index have a higher impact on their schedules, higher lack of family support and higher impact in their health.

There were no significant differences in all other psychological variables. Implications for intervention with this population are discussed.

P470

Disease duration and self-image, level of depression and anxiety in patients with multiple sclerosis

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Aim: In this study we investigated the correlation between disease duration and certain features of self-image, level of depression and anxiety in patients with multiple sclerosis.

Subject: Subjects were patients with clinically defined multiple sclerosis according to McDonald criteria (n = 42, M/F = 19/23 = 45.2 %/ 54.8 %;mean age = 36.02 ± 9.94 years, mean EDSS = 3.01 ± 1.31). Subjects were patients of Neurological Department od Military Hospital in Lublin.

Methods: Patients were investigated with the use Beck Depression Inventory(BDI), State Trait Anxiety Inventory (STAI), Adjective Check List by Gough and Heilbrun(ACL) and a questionnaire especially designed for the study.

Results: Our results show that there is positive correlation between disease duration and level of anxiety as a trait, level of depression and certain features of present self-esteem of investigated patients.

Conclusions:

1. The longer the disease duration the higher level of depression and anxiety the patients have.
2. In a group of women the longer the disease duration the more sympathizing, cooperating with other people and taking care they are, the more they look for stabilization and safety and avoid risky situation.
3. In a group of men disease duration is positively correlated with strong need of life changes. The longer they are ill, the more often they look for new experiences and life changes.

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COMparative study FOR Two high-dose interferons in MS: COMFORT

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Objective: To compare injection site pain (ISP) and injection site reactions (ISR) in healthy volunteers receiving either subcutaneous (sc) interferon beta-1b (IFNB-1b; (Betaferon(r)/Betaseron(r)) 250 mcg every other day (eod) or sc IFNB-1a (Rebif(r)) 44 mcg three times a week (tiw).

Background: Evidence demonstrates that high-dose, high-frequency sc IFNB (Betaseron® 250 mcg eod or Rebif® 44 mcg tiw) is more effective than once-weekly intramuscular IFNB-1a (AvonexTM) in the treatment of relapsing-remitting multiple sclerosis (RRMS). However, there has been no direct comparison of the two high-dose, high-frequency IFNB regimens. IFNB therapy can be associated with specific adverse events, such as ISRs and flu-like symptoms, but anecdotal evidence suggests that sc IFNB-1a is accompanied by greater ISP than sc IFNB-1b. A comparison in healthy volunteers will help to clarify the position.

Methods: A 4-week, randomised, single-centre, rater-blinded, phase I study to examine the tolerability of IFNB-1b (250 mcg sc eod) and IFNB-1a (44 mcg sc tiw) in healthy volunteers. During Week 1, subjects in each group received a 50 % dose as dose titration. Sterile technique and standard autoinjectors were used. Subjects assessed each injection for ISP at 5 and 30 minutes post injection using a visual analogue scale (VAS) ranging from 0 mm (no pain) to 100 mm (worst pain imaginable). Two days after each injection, an investigator blinded to drug allocation examined ISR severity using a 4-point categorical rating scale. Safety was monitored weekly.

Results: IFNB-1a administration was more frequently associated with ISP than IFNB-1b (43 % versus 13 %, respectively; $P < 0.0001$). This effect was consistent at 5 and 30 minutes post injection for the duration of the study. At 5 and 30 minutes post injection, the pain associated with injection was also more severe in the IFNB-1a group than in the IFNB-1b group. IFNB-1b was associated with a greater proportion of ISR-free injections compared with IFNB-1a (71 % versus 47 %, respectively; $P < 0.0001$). Additional pain data will be presented. Any adverse events noted were typically mild.

Conclusions: IFNB-1b was consistently better tolerated than IFNB-1a in terms of ISP and ISR in healthy volunteers. The acidic pH of the Rebif(r) preparation may, partially, explain this observation. These data will enable patients and physicians to make an informed choice when selecting an appropriate disease-modifying therapy for RRMS.

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Core hypothermia as relapses in multiple sclerosis

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A 41 year old man with multiple sclerosis (MS) presented 6 neurological relapses associated with hypothermia. He had a clinically definite relapsing progressive MS which started 10 years before with a Kurtzke disability scale at 7. Hypothermic relapses were severe (30–33 degrees Celcius) and associated with worsening of neurological signs. They lasted 2 weeks to 2.5 months and required invasive ventilatory assistance. Laboratory findings excluded a primary cause of hypothermia (infection, hypothyroidism, and adrenal insufficiency). T2 weighted MRI images revealed hypersignals bilaterally in the hypothalamic area. The patient recovered after intravenous corticosteroid injection, but he eventually died of respiratory failure in another hospital. Autopsy was not performed.

Acute relapses with hypothermia are not common in MS, although 13 cases of both recurrent and chronic hypothermia have already been reported. In most cases, the mechanism of hypothermia was thought to be caused by hypothalamic demyelination, even if it is rare in MS (less than 1 %). However, postmortem examination were performed only in 2 cases. Other CNS locations are known to be associated with hypothermia, and their possible involvment in hypothermia is discussed.

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Mitoxantrone in secondary progressive multiple sclerosis: after or with interferon-beta or glatiramer acetate

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In 13 patients with secondary progressive multiple sclerosis (MS) (7 F, 6 M), aged 38.7 + 9.3 years (28–53; median: 41), mitoxantrone was administered. All the patients had received at least one form of disease modifying drug previously (mostly interferon beta [IFN-b]); however, they still had progressive disease. In six of them the previous disease modifying drug was continued (6 had IFN-b, and one had glatiramer acetate [GA]). Mitoxantrone was given according to a protocol: 8 to 12 mg/m^2 every 3 weeks for 6 times, and later every 3 months. At any indication, deviations from this protocol were permitted. Peripheral blood-counts were performed on post-infusion days 7, 10, 13, 18 and 21. If there was any National Cancer Institute (NCI) Grade 3 (eg, leucocyte count: > 1000–< 2000/mm^3) or more toxicity, the next dose was decreased by 25 %. Echocardiography was performed at baseline and every 6 months. Treatment duration ranged between one single dose (where it was stopped due to toxictiy) and 24 months (2 cases): mean duration was 8 months. All the cases had at least mild (Grade 1) hematotoxicity. However, in most of the cases Grade 3 neutropenia (neutrophil count: > 500–< 1000/mm^3) was seen (4 cases had Grade 4 neutropenia, one with fever). Thrombocytopenia and lymphopenia were rare and were usually Grade 1. One patient had Grade 2 nausea without vomiting, and another patient had Grade 1 diarrhea during neutropenia. None of the cases had cardiac toxicity; EF remained the same. Pretreatment EDSS ranged from 4.5 to 7.0 (mean: 6.0 + 0.8; median: 6.25), posttreatment EDSS also ranged from 4.5 to 7.0 (mean: 5.95 + 0.8; median: 6). EDSS mostly remained the same. Mitoxantrone was discontinued in one patient due to severe toxicity after one infusion, and in another due to inconvenience, after 4 infusions. Although the numbers are small, this preliminary data suggests that mitoxantrone, alone or with IFN-b or GA, could be well tolerated, and it seems that it might arrest the disease at the pretreatment level.

P474

Follow-up studies during a median of 6 years of posterior spinal cord plaques in multiple sclerosis. Application in first and subsequent demyelinating episodes

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Background. There is no information on MRI follow-up of one unique plaque in MS and its relationship with the corresponding clinical manifestations.

Objectives. To improve the understanding of the natural history of the new spinal cord plaques (SCP) located in the posterior columns and to assess the usefulness of new diagnostic criteria for MS in patients with clinical isolated syndromes (CIS).

Methods: A total of 15 patients with clinically definite MS (CDMS) presenting acute propioceptive troubles related to a CIS (6 patients) or to a new SCP (9 patients) were followed for a median of 6 years. They underwent clinical, electrophysiological (in 7 patients), spinal cord MRI (MRIs) and CSF studies. MRIs were applied within 2 months of their first attack (weekly in 8 patients) and again each year later. Brain MRI (MRIb) at baseline and at follow-up was also studied. The CDMS was established in all patients following the application of new McDonald criteria (incorporating MRI).

Results: At 20 months, the 6 patients with CIS had CDMS. A weekly follow-up of the SCP at the cervical (11 patients) or at the dorsal (4 patients) level demonstrates a blood-SC breakdown barrier (inflammation) in the second and third weeks but not in the fourth week after the beginning of symptoms. The plaque appearance became static since the eighth week.

Neurophysiological findings, particularly somatosensory evoqued potentials (SEP) showed also a block of conduction (demyelination) between the first and the third weeks. At present, 13 among the 15 patients present a EDSS inferior or equal to 1.5.

Conclusions: The blood-SC breakdown barrier appears to become restaured between the second and the fourth week after the clinical revealing symptoms. The variability of clinical symptoms correlates strongly with the MRIs and SEP data indicating that inflammation and demyelination are strongly related. The MS in patients with this lesions are much more frequent in women and have a good prognosis.

General neurology

P475

Clinical and radiological characteristics of posterior leukoencephalopathy

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Purpose: To investigate clinical and radiological variables related with clinical spectrum of posterior leukoencephalopathy (PLE).

Methods: We reviewed protocol-based medical records and radiological studies of 36 patients who were diagnosed as PLE during the period from 1998 to 2003. All patients had MRI. Patients were divided into two groups according to the presence and absence of following variables; hypertension, arterial spasm, reversible clinical outcome, involvement of cerebral cortex,and high signal intensities on diffusion weighted imaging (HSI-DWI). Comparative analysis of each variables for their correlations was conducted by using t-test and Fisher's exact test.

Results: Mean age was 36 yr-old and 29 patients were female.Associated illnesses were quite diverse but acute or chronic renal diseases, eclampsia, and postpartum cerebral angiopathy were most common. Hypertension was found in 75 %, irreversible neurological deficits in 25 %, involvement of cerebral cortex in 39 %, HSI-DWI in 50 % of patients. Arterial spasm was found in 9 of 15 patients (60 %)who had vascular studies. Comparative analysis of each variables revealed a significant correlation of (i) irreversible neurological deficits with age ($P = 0.017$) and high signals on DWI ($P = 0.015$), (ii) hypertension with predominant involvement of cerebral white matter ($P = 0.04$), and (iii) arterial spasm with absence of hypertension ($P = 0.028$).

Conclusion: PLE is not necessarily a benign illness and often involve wide cerebral regions including cortex. Arterial spasm is an important pathogenetic factor in patients without hypertension.

P476

Treatment of episodic ataxia type 2 with the potassium channel blocker 4-aminopyridine

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Episodic ataxia type 2 (EA2) is an autosomal dominant hereditary disorder caused by mutations of the calcium channel gene CACNA1A on chromosome 19p13, which is clinically characterized by recurrent attacks of ataxia which last for several hours to several days and are provoked by stress or exercise. Associated findings during the interval between the attacks include central ocular motor and vestibular dysfunction, mainly downbeat nystagmus (DBN). Based on the functional changes of the P/Q-type calcium channel mutations which lead to a reduced calcium current as it was shown in an animal model of EA2, it can be assumed that the inhibitory effect of Purkinje cells is reduced. Threfore we evaluated the effects of the potassium channel blocker 4-aminopyridine (4-AP) (4 mg tid) on the occurrence of attacks in three patients with EA2, in whom sequence analysis of the CACNA1A gene demonstrated in two of three mutations in the CACNA1A gene (one truncating and one missense mutation), who had become non-responders to acetazolamide after 1 to 2 years of treatment. The occurrence of attacks of ataxia could be completely prevented in two patients with EA2 and markedly reduced in one. Removal of the treatment led to a reoccurrence within one to two days. Subsequent therapy with 4-AP alleviated the symptoms (mean follow-up time: 6 months). Based on animal studies it is assumed that the effects of 4-AP in EA2 can be explained by improving the impaired function of Purkinje cells, thereby increasing the Ca2+ dependent release of the inhibitory transmitter GABA.

P477

Bimanual coordination: is it influenced by handedness?

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Introduction: Involuntary synchronization of both hands is a well known phenomenon during execution of bimanual antiphasic movements. However, functional imaging studies of left- (LH) and right-handers (RH) have shown differences in the cerebral lateralization of motor control. This raises the hypothesis that interlimb coupling could be influenced by handedness (Haaland and Harrington, Current Opinion in Neurobiology 1996, 6:796–800; Kim et al. Science 1993, 261:615–617).

Subjects and methods: Grip forces of 17 healthy LH and 17 RH matched by age, gender, and motor practice were measured continuously. Subjects grasped two identical force transducers and had to perform repetitive grip force changes with both hands in a symmetric (in-phase) or an asymmetric (out-of-phase) manner. Tasks were performed with slow (1.5 Hz, triggered by acoustical signal) and maximal speed. A correlation analysis was performed to estimate the correspondence of the grip forces of both hands in time. In addition, force amplitudes and frequency of the grip force changes were compared.

Results: Statistical analysis of the grip force amplitudes and frequencies did not show any differences between LH and RH ($p > 0.05$, U-test). Also the correspondence between the both hands found in the various tasks differed not between the groups ($p > 0.05$, U-test). In the in-phase-condition, LH reached correlation coefficients of at mean $r = 0.82$ during the fast and of $r = 0.98$ during the slow performed grip force changes. RH had coefficents of $r = 0.68$ (fast) and of $r = 0.97$ (slow). In the out-of-phase condition, mean correlations varied from $r = -0.28$ (slow) to $r = -0.49$ (fast) in the LH, and from $r = -0.25$ (slow) to $r = -0.46$ (fast) in the RH.

Conclusion: As expected, performance of asymmetric grip force changes was characterized by a significant interference between the hands in both groups indicated by correlation coefficients of > -1. However, no substantial influence of the handedness on the extent of that synchronization tendency could be detected.

P478

Secondary reconstruction in facial paralysis

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The etiology of facial paralysis is various. Aim of this presentation is to describe the clinical as well as the electrophysiological prerequisites for an operative treatment as well as to represent the different operative treatment options.

If the paralysis consists clinical (no visable activity in voluntary muscles) and electrophysiological (electromyographic no motor unit action potential (MUAP), no reinnervation potentials, electroneurographic no compound muscle action potential (CMAP)) longer than one year, reconstructive techniques must be used to attempt some type of movement and support.

The therapeutic options consist in static techniques like sling plasties (Mc Laughlins technique) and dynamic techniques like free muscle grafts.

In Mc Laughlins technique we place in first step a cartilage anchor in a subdermal layer anterior to the affected nasiolabial fold. The second step consists in the sling plasty with static and dynamic slings, animated by the temporal muscle.

In free muscle grafts, as first step, a cartilage anchor is placed in in a subdermal layer anterior to the of the affected nasiolabial fold and a crossface nervegraft is anastomosed to the facial nerve of the uneffected side. After a period of 9 months the gracilis muscle is transplanted free microvascular and the nerve is anastomosed at the crossface nerve transplant.

Between 1991 and 2003 86 patients have been operated for facial reanimation. All of them had cartilage anchor for smile-reanimation. 59 had sling plasties alone, 14 had free muscle grafts alone and 13 had a combination of both techniques.

Free muscle grafts can achieve spontaneous symmetric smile but synkinesis with other facial movements especially orbicularis oris function is frequent.

The combination of sling plasties and free muscle transfer is appropriate in case of severe static asymmetry and gave the best results on the long run.

P479

Idiopathic acute transverse myelitis. A clinical study and prognostic markers in 45 cases

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Introduction: Idiopathic acute transverse myelitis (IATM) is a disease involving focal inflammation of the spinal cord of unknown aetiology. It is not associated with multiple sclerosis (MS) nor with other nosologic entities (postinfectious, systemic disease, ischaemia, post-radiotherapy and spinal cord compression) and constitutes 16.5 % of all non-compressive myelopathies. New criteria have recently been proposed for IATM diagnosis.

Objective: The principal aim of the study is to analyse a historic cohort of patients with IATM who meet the new criteria, and to evaluate the usefulness of the criteria in differentiating between myelitis associated with the onset of MS and that of IATM. Secondly, to determine the clinical or laboratory findings that may be useful as prognostic markers.

Material and Methods: A retrospective review of all patients diagnosed with myelitis at the Hospital Universitari de Bellvitge Barcelona between 1989–2003, selecting patients who meet the new IATM diagnostic criteria. Data on epidemiologic features, follow-up period, prodromes, functional outcome (using Modified Rankin Scale at the time of admission and on terminating study) and number of cases that developed MS were collected. In addition, the number of levels affected in the spinal magnetic resonance image (MRI), cerebrospinal fluid (CSF) pleocytosis and biochemical characteristics, and response to treatment data were also recorded.

Results: During a mean follow-up period of 3.5 years (range: 8–5,415 days), 11.1 % of the total number of patients meeting new IATM diagnostic criteria developed MS, and 44.4 % presented in autumn. There were also significant differences between the group that developed MS and that which continued to present IATM in terms of age of onset and the number of spinal levels affected. Cases with elevated CSF glucose and pleocytosis, more than two spinal MRI affected levels, sphincter dysfunction, older and short maxim deficit reaching time presented a worse functional prognosis. Elevated CSF glucose levels was the only independent factor in the multivariate analysis.

Conclusions:

1. 11.1 % of the patients who meet the new IATM diagnostic criteria will progress to MS.
2. Initial elevated CSF glucose levels is a prognostic factor in terms of functional recovery at the end of follow-up period.

P480

Audit of neurological diagnoses in a national referral centre

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Aims and Objectives: Access to neurological care in Ireland is limited by a relative shortage of neurologists. There is currently no accurate information with respect to in-patient management of neurological conditions in Ireland. The aim of this study was to determine the commonest conditions requiring admission, the length of stay and cost per diagnosis.

Methods: We collected demographic data, suspected diagnosis on admission and diagnosis on discharge for all the patients admitted to a 30 bed specialist neurology unit in the National Neuroscience centre. The audit took place from January 1 2003 to November 30 2003.

Variables collected included number of investigations done whilst in hospital, length of stay, suspected diagnosis and secondary diagnosis. We further refined the data and used the top four diagnoses and analysed the length of stay according to international norms. In addition, we compared admissions from various sources (elective v transfers from secondary referral centres v emergency admissions).

Results: Data were obtained from 599 patients. The top ten diagnosis comprised 72 % of the total data bass. In descending order these were: Epilepsy, Multiple Sclerosis (MS), Stroke, Amotrophic Lateral Sclerosis, Chronic Inflammatory Demyelinating Polyneuropathy, Lumbar Disc Disease, Parkinson's Disease, Meningitis, Non-epileptic seizures, Unruptured Cerebral Aneurysms and Myasthenia Gravis.

The mean duration of stay for Epilepsy was 11 days ±2, for MS patients was 11 days ±1, for Stroke patients was 23 days ± 4 days and for ALS was 12 days ± 1.

Epilepsy patients were equally divided between emergent and non-emergent cases. The majority of MS and stroke patients were admitted through the emergency department, and the majority of ALS patients were admitted as urgent electives. Stroke was the most common diagnosis among patients that were transferred from another referral hospital.

Conclusions: Our data reflect the changing nature of in-patient neurologic care in Ireland. The majority of patients were admitted as emergencies or urgent electives for acute management of symptom exacerbation. Lengths of stay were broadly reflective of international norms. Further analysis of our data will provide an accurate cost basis for management of the commonest neurological problem, and will permit the generation of patient pathways to improve efficiency.

P481

Report of two young females with severe Hyperemesis gravidarum presenting as acute Wernicke encephalopathy

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Acute wernicke's encephalopathy is a neurologic emergency resulting from thiamine deficiency. It's triad of confusion, ataxia, and ophthalmoplegia is well known but a classic triad is seen in only one third of cases.

It is a misconception that wernicke's encephalopathy occurs exclusively in alcoholics. Every medical condition leading to malnutrition and so thiamine deficiency can culminate in it. Recurrent vomiting from hyperemesis gravidarum and chemotherapy are among well known causes.

We present two young female pregnant women with history of severe hyperemesis gravidarum presenting with symptoms and signs suggestive for acute wernicke encephalopathy and dramatic response to IV thiamine.

The first case a 19 yrs old female in her second trimester of pregnancy referred with the classic triad and the second a 23 yrs old pregnant presented with ophthalmoplegia and mental dullness. Brain MRI in both of them was normal.

We conclude that wernicke's encephalopathy should be considered in every pregnant woman with hyperemesis gravidarum presenting with confusion, ophtalmoplegia and ataxia, with different combinations.

P482

The variety of aetiologies of meningeal thickening and enhancement

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There is a broad spectrum of differential diagnoses of meningeal thickening and enhancement observed on MRI scanning. With three case reports we want to illustrate this spectrum and discuss the diagnostic and therapeutic procedures.

It is helpful to divide the pattern of enhancement in the two types of (1) dural and (2) leptomeningeal enhancement. (1) In dural enhancement, which is uncommon, the meninges appear linear or nodular thickened along the inner surface of the calvaria. Dural enhancement can follow subdural hemorrhage or be caused by infectious inflammatory, noninfectious inflammatory, and neoplastic processes, or intracranial hypotension. (2) Leptomeningeal enhancement follows the convolution of the gyri and is in most cases a presentation of infectious meningitis. Among the infectious processes, an epidural abscess is mostly seen in patients with risk factors for chronic bacteremia or an immunodeficiency state. Chronic meningitis includes tuberculous and syphilitic pachymeningitis, Lyme disease, nocardiosis and different mycosis. In the category of noninfectious inflammatory processes neurosarcoidosis, autoimmune pachymeningitis and idiopathic hypertrophic pachymeningitis deserve consideration. Infiltration of the meninges by metastatic tumors is an underrecognized complication of cancer. Other neoplastic processes contain meningiomas en plaque, lymphomatous meningitis and plasma-cell disorders involving the dura. Finally, diffuse, homogenous pachymeningeal enhancement on MRI may be due to intracranial hypotension, which may occur spontaneous or after lumbar puncture, head trauma or shunt placement.

We present an overview of the differential diagnosis of meningeal enhancement and illustrate rare causes or pitfalls with own cases.

P483

Familial hyperhydrosis: an overactive, emotional sweat pathway and a new channelopathy?

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Familial hyperhydrosis (FH) is a disabling condition, causing difficulties with manual skills such as writing and socially when shaking hands. FH is an autosomal dominant condition with variable penetrance, characterised by excessive sweating of the palms, soles and sometimes axillae and face. Four cases of FH are presented. These cases hightlight the role of emotion in exacerbating palmar and plantar eccrine sweating, in contrast to the physiological role of thermoregulation of these glands. It is hypothesised

that FH patients possess emotional sweat pathways which are continuously overactive and easily excited into signalling excessive sweating by certain emotions. Ion channelopathies provide possible mechanisms for hyper-excitable neuronal pathways. Voltage-gated potassium channel antibodies have been identified in Morvan's syndrome and hyperhydrosis in Morvan's syndrome has been improved with plasmapheresis. This points to a possible role of potassium ion channel abnormalities in hyperhydrosis and thus a possible potassium channelopathy in FH. Further research into FH is needed to identify the gene and test this hypothesis.

P484
Clinical features of non-specific white matter lesions
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Background/objectives: Magnetic resonance imaging (MRI) is very sensitive for the detection of white matter lesions. White matter abnormalities are non-specific and the etiology includes a wide variety of entities: the hereditary leukodistrophies and a number of aqcuired disorders. Objectives: to describe clinical features, diagnosis and outcome of a series of patients with white matter lessions.

Material and methods: retrospective study, from october-2002 to january-2004, of young adults with white matter abnormalities comparing the initial MRI with a control one performed 3 to 6 months later.

Results: we present 14 patients (7 women, 7 men). Mean age: 37.4 years old. Diagnosis: epilepsy (2), tinnitus (3), tension type headache (1), paresthesias (3), cramps and paresthesias (1), positional vertigo (1), dizzines/anxiety (1), isolated fasciculations (1), transient bilateral VI nerve palsy (1). Multimodal evoked potentials, pro-trhombotic and immunologic studies and cerebrospinal fluid analysis, when performed, were all within normal ranges. No one had past history of focal neurologic episodes nor major vascular risk factors were recorded. MRI showed periventricular and centrum semiovale small white matter hyperintensities. In all patients an MRI performed 3 to 6 months later showed no changes. Conclusions: white matter abnormalities are casual findings in these patients and are not related to diagnosis. According to our findings in young adults with these lesions, if no major vascular risk factors are recorded, and they do not have clinical features of multiple sclerosis, it would not be necessary to perform a second MRI because no differences have been found between them.

P485
A patient with neurologic complications of celiac disease (case report)
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Celiac sprue is a chronic disease of the digestive tract that interferes with he absorption of nutrients from food. The prevalence in european population is about 1 in 300 persons. The age of patient is bimodal, at 8–12 months and in the third to fourth decades. Immune responses to gluten and genetic factors are common causes of disease. GI tract is the primary target organ but systemic disease is an important consequence in many patients. The later consist of anemia, osteopenia, dermatitis herpetiformis, amenorrhea, bleeding diathesis and neuropsychiatric symptoms including encephalopathy, myelopathy, peripheral neuropathy, cerebellar ataxia,motor weakness, seizure, depression, korsakov syndrome, frank psychosis.

The diagnosis is made by detection of serum IgG and IgA antigliadin antibodies, serum IgA antiendomysial antibodies and intestinal biopsy. When these are done in laboratories that are not experienced, the sensitivity may fall to as low as 50 %. Indeed if the biopsy is negative gluten alergy has not been ruled out. The most significant test of gluten intolerance is remission of symptom when grains are eliminated for period of 3–6 weeks. The primary treatment for celiac is gluten-free diet. In patients who are refractory, corticosteroids might be helpful.

The neurologic complication have been reported to improve in patients who receive multivitamins (A – B – E) or calcium.

We report a 34 year old man who was admitted to neurologic ward with convulsion, confusion, disorientation, irritability, sphincteric disturbances, anemia, weight loss, nausea & vomiting, abdominal pain & tenderness and icter.

Serum IgA & IgG antigliadin antibodies, abdominal sonography & CT-Scan, intestinal & stomach biopsy, bone marrow aspiration and biopsy were done. Except antigliadin antibodies & nonspecific findings in brain MRI other evaluations were normal. Before complete laboratory tests, treatment was started beacause of poor condition of patient due to respiratory distress & decreased level of consciousness. He was treated with gluten-free diet and corticosteroids. After 2 weeks almost all of symptoms and signs subsided and consciousness is retained.

P486
Assessment of patients with erectile dysfunction using SPECT
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Aim: Erectile dysfunction is an important problem not only for physical health of men but also for the social life and quality of life. Various diseases have been associated with erectile dysfunction. The identified reasons are neurological, vascular, endocrine, surgical and traumatic disorders, various drugs, and psychiatric problems. Erectile dysfunction are reported to occur as a result of temporal lobe lesions and bilateral pallidofugal section. The aim of this study was to evaluate the presence of alterations in regional cerebral blood flow in patients suffering from erectile dysfunction.

Material and Method: Sixteen patients with erectile dysfunction and 16 control subjects were included in this study. There was no recognizable primer pathology causing impotence in these patients. Brain SPECT was performed after injection of 20 mCi of Tc-99m HMPAO perfusion of 19 different cerebral cortical regions, pons, right-left caudate nuclei and right-left hemi-thalamus, totally 24 regions of brain were analysed by semi-quantitative technique using transverse scan sections. Data from patients and control group were compared statistically.

Results: There were statistically significant differences between control and patient group in parietal and temporal lobes. The blood perfusion on the right superior parietal gyrus ($p < 0.03$), right and left inferior temporal lobe ($p < 0.05$) were decreased in patients with erectile dysfunction with regards to control group.

Conclusion: Regional cerebral perfusion changes may exist in the patients with erectile dysfunction which might shed light on etiology of erectile dysfunction with no identifiable cause.

P487
Dynamic neurologic, psychiatric, neuropsychologic investigation in patients with postcommotional syndrome
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Mild BI is an important medical and socioeconomic problem due to its extremely high prevalence and incidence of its related posttraumatic disorders. In most patients with mild BI, recovery of brain functions was complete, but occurs more slowly than that early considered, namely within several months. The postcommotional (PCS) syndrome that occurs with mild BI resulted from the complex interaction of organic changes in the brain and social and psychological factors whose role ratio changes in the pathogenesis with time.

The purpose of our work is to study the PCS with the help of neuropsychological analysis.

We investigated 32 patients (28 male, 4 female) with age from 22 to 41 at the acute period of mild brain injury (BI), in 3 weeks, in 3 months and in one year after injury. Patients did not have any associated diseases. Studied group was investigated by neurologist, psychiatrist, neuropsychologist before BI and revealed no pathology.

There were concentration disorders, short-term memory, and behavior control difficulties in 25 (78 %) patients at the acute period (5^{th} day after BI). The same symptoms were founded in 15 (60 %) patients in 3 weeks and in 13 (52 %) patients in 3 months after BI. In 4 (16 %) patients revealed a chronic postcommotional syndrome (CPCS): headache, dizziness, chronic cervicalgia, sleep disturbance, decrease of workability, anxiety. Grounds for the development of CPCS were premorbid personality traits, frequent stress, hypochondriac mood, social problems. We did not reveal any personality disorders caused by BI.

Conclusion: Evaluation of BI consequences is required complex approach which includes neurologic, psychiatric, neuropsychologic investigation in dynamic for choosing of optimal treatment and elaborating rehabilitation programs.

P488
Treatment of severe progressive hereditary chorea with acquired dystonia
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Intrathecal baclofen has been used to treat severe spasticity along with other treatments including botulinum toxin, whilst intrathecal bupiva-

caine has been used for post-operative and refractory chronic pain. Although there have been isolated reports of baclofen used in some forms of chorea, we report a case of successful treatment of refractory chorea related to intrathecal bupivacaine and possibly botulinum toxin.

A previously independent 60 year old female with a hereditary chorea presented with a late-onset rapid deterioration, mainly affecting her lower limbs and trunk, with no objective cognitive decline. After a poor response to oral medications, she underwent a left posteroventral pallidotomy which failed to control her chorea and also caused a mild right hemiparesis with severe right hip and knee flexion dystonia. The severity of her impairments resulted in rapid physical, mental and social decline necessitating nursing home care.

Intrathecal baclofen was initially used as treatment for her severe dystonia, with some initial improvement in her dystonia and surprisingly, her choreiform movements as well. She quickly became refractory, however, and had increasing doses over 8 months to 800 mcg/day but the dystonia and chorea continued to progress. Intrathecal bupivacaine was then added to control pain from lower limb spasms, which again surprisingly controlled her chorea. Intrathecal baclofen was gradually ceased due to poor treatment response, and Botox® was administered to her right hamstrings and hip flexors to treat the dystonia.

Her movements have remained well controlled for the past 18 months with intrathecal bupivacaine and she is able to fully extend her right hip and knee with preservation of lower limb power. Following a rehabilitation program, she has become fully independent again to be able to live at home. We are presently weaning the maintenance dose of intrathecal bupivacaine to see if it is still a factor in controlling her chorea.

Extrapyramidal disorders

P489

Oculomotor impairment correlates with basal ganglia metabolic dysfunction in presymptomatic Huntington's disease

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Background: Several studies have reported oculomotor, memory and prefrontal deficits in presymptomatic Huntington's disease (pre-HD), but others have failed in demonstrating cognitive dysfunctions in these subjects.

Objective: To investigate the presence of neuropsychological deficits and brain metabolic abnormalities in pre-HD subjects.

Patients and Methods: We studied 14 genetically proven pre-HD (mean age 32.86 ± 8.82) and 9 age-matched controls (mean age 35.33 ± 6.30) with a similar educational level. The neuropsychological battery comprised memory (Rey's auditory-verbal learning, Rey's complex figure), visuomotor speed (WAIS-III symbol search), oculomotor (The 15-objects), premotor (Luria's motor alternances), frontal (WAIS-III digits, Stroop, Trail Making, phonetic and semantic verbal fluency) and visuospatial (Judgment of Line Orientation) tests. Proton MR Spectra (PRESS, TR = 1500/6000, TE = 30) were obtained in the basal ganglia and frontal cortex in all subjects. Quantization of absolute metabolite concentrations and metabolite ratios was performed using the LC-Model. Statistical assessment was carried out by T-test with independent groups and ANOVA with repeated measures.

Results: Pre-HD subjects did only show a significant slowing in the oculomotor test scores (The 15-objects test) compared with controls ($t = 3.35$, $p = 0.004$). Slowing correlated with increased choline/creatine ratios in the basal ganglia ($r = 0.59$, $p = 0.005$), but not in frontal cortex.

Conclusion: Our results suggest that oculomotor impairment may be the first abnormality in pre-HD subjects. This seems to be related to metabolic impairment in the basal ganglia, which may result in functionally altered connections between basal ganglia and frontal cortex.

P490

Altered regulation of ghrelin in Huntington's disease

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Huntington's disease (HD) is an inherited neurodegenerative disorder characterized by progressive motor, cognitive, and psychiatric deficits. HD results from a CAG expansion in the first exon of the IT15 gene, located on chromosome 4p16.3, that encodes a 350 kDa protein called huntingtin (htt). The size of CAG expansion is one of the factors determining the course of the disease but clinical aspects such a higher body weight have been associated with a slower progression of the disease.

Weight loss with a normal or increased food intake is reported at early stage of Huntington's disease, but its cause is unknown and probably multifactorial. Ghrelin is a recently discovered endogenous ligand for the growth hormone secretagogue receptor (GHSR). In animal models intracerebroventricular administration of ghrelin generates a dose-dependent increase in food intake and body weight. Recently, it has been shown that circulating ghrelin levels in humans rise shortly before and fall shortly after every meal. Thus ghrelin, in addition to its role in regulating GH secretion, plays a pivotal role in energy balance. Since ghrelin affects body composition as well as food intake we investigated whether ghrelin regulation is altered in HD patients.

We studied 7 HD patients (3 pre-symptomatic patients, 4 symptomatic patients-stage I and II) and 7 healthy control matched for age, sex and body mass index. All patients were clinically characterised through UHDRS, neurophysiological studies, and MRI and were not taking any medications. Bone mineral content, bone mineral density, fat mass, and lean body mass were measured by dual-energy x-ray absorptiometry. Overnight circulating fasting IGF-1, fT3, fT4, TSH, ghrelin, and ghrelin levels 30 and 120 min. after a standard meal were evaluated.

No statistical difference was present in IGF-1, fT3, fT4, TSH and fasting ghrelin levels between HD patients and controls (mean fasting ghrelin: 1,401.0 ± 275.0 pg/ml and 1,188.7 ± 51.4 pg/ml, respectively; p = NS). Ghrelin levels were decreased by meal in control subjects (after meal, 30 min: 967.3 ± 14.9 pg/ml, $p < 0.01$; 120 min: 972.2 ± 57.5 pg/ml, $p < 0.05$ vs. baseline), but meal failed to suppress ghrelin levels in all HD patients (after meal, 30 min: 1,274.7 ± 177.4 pg/ml, p = NS vs. baseline; 120 min: 1,145.7 ± 97.2 pg/ml, p = NS vs. baseline). In conclusion, failure of meal to decrease circulating ghrelin concentrations would reflect an impaired energy metabolism in Huntington's disease.

P491

A functional magnetic resonance study in patients with Parkinson's disease and visual hallucinations

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Background: Several prospective studies indicated that hallucinations, mainly of visual nature, affect as many as one quarter of patients with Parkinson Disease (PD). Although hallucinations are commonly considered to be a side effect of dopaminergic treatment, several additional factors including cognitive and motor status, sleep disorder and depression may influence. Neuropathological studies have demonstrated increased densities of Lewy bodies in the temporal lobes among demented and non-demented hallucinating PD patients. However, the functional brain correlates of these areas in PD patients with visual hallucinations (VH) have not been studied to date.

Objective: To investigate brain regions involved in complex visual processing in patients with PD and VH by means of functional Magnetic Resonance Imaging (fMRI).

Methods: Subjects: The sample of patients was composed by six patients with idiopathic PD without VH (PD) and five patients with PD who had manifested complex VH during a minimum of two weeks (PDVH). None of the patients was demented. The control sample consisted on 5 subjects with no evidence or history of neurological or psychiatric disorders. The patients and healthy subjects were matched for gender, age and years of education.

Magnetic Resonance Imaging: Subjects were explored by fMRI while they were performing a visual task, which consisted on visualising two alternating blocks of stimuli (abstract patterns and pictures of human faces). Functional images were analyzed using SPM2. Threshold for statistical significance was set at $p < 0.005$ (uncorrected). Age was included in the statistical analysis as a covariate.

Results: When brain activation derived from visualisation of abstract patterns was subtracted from that observed during face processing, patients with PDVH exhibited increased brain activity in the boundaries of the fusyform and lingual gyri bilaterally (all significant clusters at p uncorrected < 0.0001) compared to controls. There were not differences between PD and PDVH group, and between PD group and controls.

Conclusion: These results suggest an abnormal function of the temporo-occipital areas supporting complex visual process among PDVH. This dysfunction could predispose to presence of visual hallucinations in these patients, and to be related with the presence of Lewy bodies in these regions.

P492

An Italian family with autosomal recessive ataxia, extrapyramidal features and dementia

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Objective: to report a family with ataxia, extrapyramidal features, dementia, and autosomal recessive transmission.

Background: only few cases of autosomal recessive ataxia associated with parkinsonian features have been described. Mild gait ataxia has been exceptionally reported in patients with parkin mutations.

Methods: we examined three brothers with an early-onset progressive disorder characterized by cerebellar ataxia, extra-pyramidal features, and dementia. Their parents were first cousins. Available family members were examined and blood samples for DNA analysis have been obtained after informed consent. A simulation analysis using SLINK has been conducted to evaluate the power of the pedigree, assuming autosomal recessive inheritance and complete penetrance.

Results: the proband, a 34 year old man, since the age of 24 years showed gait ataxia, dystonic posturing of the neck and the arms, and dysarthria. Later, he developed arm and head tremor. Disease progression was fast and he was wheel-chair bound at the age of 32 years. His 38 year old brother presented gait ataxia, dysarthria and dystonic posturing of the right arm since age 15. Disease progression was slow and he is still autonomous in walking. Their 30 year old sister has a milder phenotype with gait ataxia occurring since age 22. In all patients neurological examination showed gait and limb ataxia, coarse nystagmus in both horizontal and vertical planes, saccadic pursuit and hypermetric saccades, severe dysarthria, abnormal tapping, rigidity, reduced vibration sense at lower limbs, marked cognitive impairment (WAIS scores < 49). The clinical picture was more severe in the proband, who also showed severe resting, postural and intentional arm tremor and tremor of the head. Vitamin E, hexosaminidase and ceruloplasmin serum levels were normal; brain MRI showed cerebellar atrophy, associated with pontine atrophy in the eldest sibling. Levodopa, dopaminergic and anticholinergic drugs, gabapentin, and propanolol did not improve clinical signs in the proband. Simulated LOD score was 1.64.

Conclusions: the absent response to levodopa, normal level of ceruloplasmin and absence of "eye of the tiger" sign at MRI exclude Parkinson and Wilson diseases and neurodegeneration with brain iron accumulation. Consanguinity and absence of affected members in early generations are against autosomal dominant spino-cerebellar ataxia. Further families with similar phenotype may allow genome wide scan.

P493

Reduction of sleep fragmentation and improvement of nocturnal and early morning bradykinesia in parkinsonian patients after nocturnal transdermal slow-release apomorphine treatment

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Introduction: sleep in Parkinson's disease is frequently disrupted and may present periodic limb movements, prolonged tonic contractions of limb muscles during NREM sleep, reduction of normal body shifts during sleep. These disorders may lead to arousals and may be related to an increment of electroencephalogram cyclic alternating patterns (CAP), reflecting sleep instability.

Objective: in this study we evaluated macrostructure and microstructure of sleep (CAP analysis, micro-arousals) and diurnal motor performances in a group of patients with severe Parkinson's disease after one night treatment with a new microemulsion-based formulation of apomorphine, administered by an epicutaneous-transdermal route (APO-TD), able to provide a constant release of the drug for several hours.

Patients and methods: 12 patients affected by Parkinson's disease (mean age 59.5 ± 12.4 years; mean Hoehn-Yahr score: 3.4 ± 1.8) were submitted to standard polysomnography on basal conditions (T0) and during a night-time treatment with 50 mg of APO-TD applied to a 100 cm^2 cutaneous area over the chest, from 22 p. m. until 8.00 a. m. (T1). During this period blood samples were collected at regular intervals from 22 p. m. for 14 hours; apomorphine concentration was analysed by high performance liquid chromatography. Motor performances were evaluated at regular intervals during the day on basal condition and the day after APO-TD treatment, using UPDRS scale.

Results: pharmacokinetic analysis confirmed the constant absorption of apomorphine (mean Cmax: 42.81 ± 11.67 ng/ml; mean Tmax: 5.1 ± 2.24 hours). Polysomnography analysis showed on T1 compared to T0: 5 % reduction of sleep onset latency, 11 % increment of sleep efficiency ($p = 0.04$), 16 % increment of stage 3 and 4 NREM ($p = 0.04$), reduction of periods with elevations of muscle tone, 8 % increment of body shifts during sleep, 15 % reduction of awakenings ($p = 0.03$), 34 % reduction of CAP rate/NREM ($p = 0.001$). Motor evaluation showed 32 % reduction of UPDRS-III score on awakening the morning after APO-TD treatment compared to baseline ($p = 0.03$) and 57 % reduction of off periods from APO-TD application until 12 a. m. the following day.

We concluded that night-time APO-TD administration is able to reduce nocturnal anomalous movements, akinesia and sleep maintenance instability typical of parkinsonian sleep and could be a useful add-on treatment in patients with prolonged and not completely controlled nocturnal and early morning off periods.

P494

Weight gain and pramipexol in Parkinson's disease

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Objective: Some PD patients experience significant weight loss, even early in the disease course. The pathogenesis of this phenomenon is unknown, but it may be related with underlying disease proceses or dopaminergic therapy, including dopamine agonists.

Methods: Twenty-five PD patients with stable treatment (8 female, mean age 63.4 ± 7.8; mean duration of PD 7.0 ± 5.0 years) were studied. Twenty-four were receiving L-dopa with mean dosage 564.1 mg ± 278.4 mg. No patient had received dopamine agonists during the previous month. Clinical evaluation included: UPDRS, Hoehn and Yahr (H-Y), Schwab-England (S-E) and weight control. The Hamilton depression scale (HDS) was also applied at the same visit. All the clinical procedure was repeated after three months under stable pramipexol doses (mean dose: 2.1 ± 0.3 mg/day).

Result:Motor symptoms improved significantly (UPDRS; 16.1 ± 4.5 vs 8.6 ± 4.5, $p < 0.001$, H-Y; 1.9 ± 0.4 vs 1.4 ± 0.4, $p < 0.001$, S-E; 85.6 ± 5.8 vs 96.4 ± 4.9, $p < 0.001$). Pre-pramipexol four patients had dyskinesia on-treatment (mild in 3, moderate in one). Post-pramipexol, seven patients had dyskinesia (mild in 5, moderate in 2). Eleven patients had wearing-off pre-pramipexol, which disappeared in nine of them on pramipexol. When all patients are considered, there was a significant increase in weight after pramipexol (74.1 ± 12.3 vs. 77.5 ± 12.8, $p < 0.001$). Specifically 20 patients increased their weight (range 2–8 Kg) associated with an increase in appetite, three experienced weight loss (range 1–1.5) and two did not change their weight. The HDS score decreased after pramipexol (6.6 ± 5.1 vs 2.7 ± 3.4; $p < 0.001$) although no patient was considered depressed at any time in the study. Twenty-three patients reported improvements in mood, with more interest in daily life activities, in talking or in doing homework.

Conclusion: Pramipexol causes weight gain in PD patients. The cause of this effect is unknown but seems to be associated with an improvement in mood. We speculate that pramipexole's greater affinity for D3 receptors, which predominate in the limbic system, might explain this improvement in mood and increase in weight. We cannot exclude an effect of pramipexol on the hypothalamic centers that regulate feeding.

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P495

Accuracy of 123 I-ioflupane (DaTSCAN™) in the diagnosis of patients with clinically uncertain parkinsonism: a two-year follow-up study

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Objective: To assess the diagnostic accuracy of 123I-Ioflupane (DaTSCAN) SPECT imaging in patients with clinically uncertain parkinsonian syndromes.

Methods: A group of patients previously enrolled in a study assessing the clinical utility of 123I-Ioflupane in the diagnosis of patients with uncertain parkinsonism, has been followed-up 24 months after study entry. At this follow-up visit, patients were re-examined and an updated clinical diagnosis was made. A new DaTSCAN was performed in those cases with disagreement between clinical diagnosis at follow up and result of imaging at study entry as well as in those patients in whom a firm diagnosis could not be established.

Results: 85 out of 118 patients who entered the study were evaluated in the 24-month follow-up. At this time, the updated diagnosis was in agreement with the initial 123I-Ioflupane image in 69 patients. was discordant in 8 and remained inconclusive in other 8 patients, with a rate of agreement of 90 % (95 %CI: 80.6 %, 95.4 %), negative predictive value of 96 %, and positive predictive value of 87 %.

At the 24 month follow up, a second DaTSCAN was performed in 14 pa-

tients. In 6 of them, in which there was disagreement between clinical diagnosis and imaging results, the new SPECT imaging led to confirmation of diagnosis in 4, while in the other 2 diagnosis remained discordant with the results of the image.

The follow-up DaTSCAN helped to establish diagnosis in 7 out of 8 patients with an inconclusive diagnosis (87.5 % of cases).

Conclusion: This study in patients with clinically uncertain parkinsonism shows a high degree of agreement between DaTSCAN image result and available clinical diagnosis after 2 year follow-up. It further suggests an added value of a second scan in patients where doubt remains about diagnosis despite prolonged follow up.

P496

Severe "off" anxiety may benefit from deep brain stimulation in Parkinson's disease

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Objective: To determine whether severe "off" anxiety improves following deep brain stimulation (DBS) for motor complications of Parkinson's disease.

Background: Anxiety is a risk factor for PD, and therefore in some patients may be a primary manifestation of the disease. Anxiety occurs in over 33 % of PD patients, affects quality of life, and is often difficult to treat. After several years of levodopa therapy, anxiety often fluctuates with motor symptoms. It may be the most common non-motor "off" phenomenon, occurring in up to 66 % of patients with motor fluctuations. Although DBS of the subthalamic nucleus (STN) has been shown to improve motor performance during "off" periods, the effects on "off" anxiety are not known.

Methods: This is a retrospective analysis of seven subjects with dramatic "off" anxiety, who then underwent DBS for motor complications of PD. After chart review, 2/7 subjects were excluded due to insufficient documentation, and 1/7 because "off" depression occurred without overt anxiety. The four remaining subjects received STN DBS, and in three the procedure was bilateral. "Off" anxiety and motor symptoms following DBS were then categorized by reviewers as greatly improved, minimally affected, or worse.

Results: All four subjects greatly improved with well-documented reduction in "off" anxiety. An independent reviewer found identical results. One subject had transient benefit in "off" anxiety that improved again with increased voltage. The single patient with unilateral DBS (left) no longer feared he would die during an "off" period, and ceased the frequent emergency room visits. All subjects also had improvement in motor "off" symptoms. Two subjects had less painful "off" periods. Of note, the excluded subject with depressive "off" periods received motor benefit from DBS, but required levodopa for management of "off" depression.

Conclusion: Severe "off" anxiety may improve with DBS of the STN. Clearly, a larger, prospective trial would more sufficiently challenge this hypothesis. Stratified analysis could then help to separate out the effects that are due to improvements in motor symptoms. Quantification of the subjective experience of anxiety in this population would make results easier to interpret. In the end, patients will benefit from improved understanding of "off" anxiety in PD, and in the process scientists can learn more about the neurocircuitry that links these two disorders.

P497

The effect of quetiapine in psychotic parkinsonian patients with and without dementia – an open study of 6 months duration

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Objective: To study the effect of quetiapine (QTP) in drug-induced psychosis (DIP) in Parkinson's disease (PD) patients with and without dementia.

Background: QTP has been recently introduced in the armamentarium for the treatment of psychosis in PD. Dementia in PD patients with DIP may influence the outcome of treatment.

Methods: Thirty-five consecutive PD patients with DIP (19 of them demented [DSMIV criteria]) were examined. Assessment included Mini-Mental State Examination (MMSE), UPDRS (motor part), Brief Psychiatric Rating Scale (BPRS), Hamilton score for depression (HT) (performed only in non-demented patients) and Clinical Global Improvement Scale (CGIS).

T-paired test and Anova were used to analyze the effect of QTP treatment. Responders were considered patients in whom the psychotic symptoms disappeared or diminished in a way that improved their quality of life.

Results: Out of the 35 patients included in the study, 24 responded to treatment with QTP (14 demented and 10 without dementia). Eleven patients dropped out (5 demented). The reasons for dropping out were: 7 – lack of response, 1 – severe somnolence, 1 – headaches, 3 – both lack of response, somnolence (2) and orthostatism (1).

In the non-demented groups, BPRS improved almost significantly ($p = 0.06$, paired T-test) and a time effect was also found ($p = 0.06$, Anova). Among demented patients, BPRS did not change. MMSE and HT did not change significantly during the trial. According to CGIS, a good improvement was observed in over 50 % of demented patients (4/7) and 40 % of non-demented (4/10).

Optimal QTP dose achieved was higher in the demented groups (150.9 + 90.2 mg vs 76.3 + 59.1 in the non demented). The motor features of PD patients worsened mildly within time ($p = 0.03$, Anova,) but not significantly (paired T-test).

Conclusions: QTP treatment in PD with DIP seems to be effective in about 50 % of patients. The effect of QTP does not seem to be significantly influenced by the presence of dementia. BPRS examination improved only in the non-demented group.

P498

Levetiracetam as an anti-myoclonic agent

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Objective: To evaluate the tolerability and efficacy of levetiracetam (LEV) for the treatment of myoclonus.

Background: There are currently no approved therapies for myoclonus, and antiepileptic medications such as valproic acid and clonazepam remain the mainstay of treatment. LEV, an antiepileptic approved as adjunct therapy for partial-onset seizures, is structurally similar to piracetam, a medication with proven efficacy in the treatment of cortical myoclonus. We reviewed our single-institution experience treating myoclonus patients with LEV, and compared it to published cases in the literature to provide preliminary data to guide a placebo-controlled, double blind trial.

Methods: Clinical data of 12 patients followed at our movement disorders center and 30 patients reported in the literature were collected. Etiologies of myoclonus included posthypoxic myoclonus, progressive myoclonic epilepsy, spinal myoclonus, and myoclonus occurring as the result of trauma or degenerative illness. Drug-induced or transient forms of myoclonus lasting less than one month were not included. Age at treatment initiation ranged from 16 to 85 years. The dose of LEV ranged from 250 mg to 4,000 mg per day and the duration of treatment from 2 weeks to 2 years. Clinical effect was summarized on a 0 to 3 scale: 0 = no benefit noted by the patient or examiner; 1 = mild benefit with subjective improvement noted; 2 = moderate benefit with obvious improvement; 3 = excellent response with near-complete resolution of myoclonus.

Results: LEV was well tolerated, with the most common side effect being sedation. Side effects requiring the discontinuation of the medication usually occurred at low doses early in the course of treatment. The mean clinical effect score was 1.6 ± 1.2 in our 12 patients. In the literature, 83 % of patients had a clinical effect score of 2 or 3. Patients with cortical myoclonus experienced more benefit than other forms of myoclonus. Partial response at low dose appeared to predict a more robust response at higher doses.

Conclusions: LEV should be considered as a potential therapeutic option for patients with myoclonus. It appears most effective in cortical myoclonus, but it may also be effective in subcortical and spinal myoclonus. Most patients tolerate the drug, and serious adverse events related to treatment are rare. The time for a double blind, placebo-controlled, multi-center trial has arrived.

P499

[123I] beta-CIT SPECT imaging in the differential diagnosis of juvenile onset dystonia

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Introduction: Juvenile Onset Dystonia (JOD) clinical distinction required long term following. Early differential diagnosis between dopa-responsive dystonia (DRD), Juvenile Parkinsonism Disease (JPD) and other dystonias … supposed a diagnostic challenge. Actually, functional neuroimag-

ing with [123I] Beta-CIT SPECT (SPECTIo) could provide an early diagnosis and prognosis.

Objectives: To present 8 unrelated patients with JOD and their clinical, therapeutical and diagnosis data, including patterns of SPECTIo.

Material and Methods: Eight patients with JOD who fullfilled following criteria: early onset dystonia witnessed by us, preceding or ocurring at onset of parkinsonim (if it was present at time consultation) while still dopa naive, and intact basal ganglia in neuroimaging with a high or high-moderate levodopa responsiviness. We record demographic, clinic and therapeutic data and results of diagnosis test: laboratory data, DNA analysis,conventional neuroimaging and SPECT Io.

Results: 3 men and 5 women with mean age at initial symptoms was 11.1 years (range 3–31 years). Presenting complaint: focal dystonia and gait disturbance (8), with pakinsonism signs at consultion time (3). 50 % have diurnal fluctuation of symptoms. Initial doses of levodopa: 112.5 mg (50–300). Four patients had dyskinesias at the beginning of dopa-therapy and 5 required moderate increases in dopa doses. All patients have normal laboratory results and neuroimaging studies (CT scan, cerebral MRI). DNA studies for GTP-cyclohidroxylase I mutation (3) and Torsin gene (1): all negatives. Phenyalanine-loading test (2): pathological results (1). The mean delay from consultation and SPECTio was 10.75 years (range 2–26 years). The pattern of imaging was: normal striatal [123I] Beta-CIT binding (50 %) and decreased striatal binding (50 %) with next pattern: bilateral putamen (2), one-sided putamen and caudate (1) and bilateral putamen and caudate (1). Definitive diagnosis was DRD (3), JPD (4), and secondary parkinsonism (1).

Discussion: The results of SPECTIo modified initial diagnosis in five patients: EPJ (3) DRD (1). These patients had negative phenyalanine-loading test and negative mutation. And confirm one case of secondary parkinsonism. The use of SPECT imaging of dopamine transporter ([123I] Beta-CIT SPECT) could facilitate early differential diagnosis in Juvenile-onset Dystonia, establishing adequate therapy and early functional prognosis.

P500

Typing cramp: task dystonia or communication disorder?

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Background: Task dystonias are focal dystonias related with specific repetitive movements. Their pathophysiology is controversial and mostly unknown.

Objective: To present the case of a patient with hand dystonia brought on by typewriting.

Case report: A 45 year-old man has been working for more than 20 years typing eight hours every day copying official reports. He had reached an average of 500 taps per minute without problem. But seemingly coinciding with some changes in his last computer program, he began experiencing a sort of painless contracture in his left hand when typing, becoming unable to carry out his job; other manual activities were unaffected and he was otherwise healthy. He was naturally left-handed corrected in childhood. Examination was normal, but when we observed him typing on a keyboard trying to copy a text, a dystonic posture appeared in the left hand, preventing him from typing. With the keyboard removed, he was able to type extremely quickly on the table in a random way with both hands. Intriguingly however, if asked to imagine himself trying to copy a text on a virtual keyboard, the left dystonia reappeared immediately. Electromyography during an attempt at typewriting confirmed a co-contraction of the left forearm agonist and antagonist muscles. Brain and cervical spine magnetic resonance imaging was normal. He underwent a functional training program, but several months after he remained unable to type. Botulinum toxin was not administered.

Conclusion: In this patient, typing dystonia seemed related with exceptionally rapid finger movements in his most probably dominant hand. But we suggest that in fact the dystonia appeared just when he was trying to "speak" with his fingers. Writers and musicians suffer task dystonias also when communicating with a specific language. Consequently, investigations into these movement disorders should perhaps explore cerebral structures modulating primary speech and language.

P501

Evaluation of a concept to improve postural instability in Parkinson's disease

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Introduction: Postural instability (PI) is one of the cardinal symptoms in Parkinson's Disease (PD). A marked postural disturbance can lead to a higher risk of falling and traumatic injuries respectively. An essential problem consists in the fact that PI can not be treated satisfactorily by medication. Further more it is speculated that chronic L-DOPA treatment leads to worsen of PI. Based on the results of earlier experiments the aim of this study was to analyse the effects of whole-body-vibration on postural control in PD.

Methods: 40 PD patients participated in this study. Overnight all subjects were withdrawn from L-DOPA to exclude the influence of the medication. Several parameters of postural control were analysed by a complex biomechanical test battery. One test is based on standing on an instable platform lasting 30 seconds each series. Another test consisted of generating a standardized, ballistic anterior shift of the platform. Pre and post treatment 3 series of all tests were performed. Platform shifts were quantified by the use of acceleration sensors. EMG analyses of various muscles were registered additionally. The treatment consisted of 5 series of randomised whole-body-vibration (ampl.: 3 mm, freq. 6 Hz) lasting 60 seconds each.

Results: Patients show spontaneous changes in their ability to maintain equilibrium. The improvement in postural control became evident in less body and platform sway respectively which was statistically significant. Moreover electromyographic analyses showed reduced muscular activation in the post test which seems to be connected with a more efficient motor control. This hypothesis is confirmed by the results of spectral analysis that identified a change of the predominant peak in some patients. However, the results are characterized by a high interindividual variety.

Discussion: Different functions could be responsible for these results since vibration stimuli become effective on various physiological levels. One hypothesis deals with an improvement of the neuromuscular system. An adaptation of motor control is possible by selecting relevant from irrelevant information more quickly. It can be speculated that this process influences the pathologically changed information selection in PD. Based on the results of animal experiments changes of neurotransmitter concentrations could be another explanation.

Conclusion: Whole body vibration can be regarded as an additional device in balance training in PD.

P502

The effectiveness of pergolide and cabergoline as an adjunct to levodopa in Parkinson's disease

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Objective: The aim of this double blind study is to compare the efficacy and safety of adjunct pergolide therapy versus cabergoline in patients with Parkinson's disease suffering from the complications of levodopa therapy.

Method: 40 patients with PD and motor complications using levodopa (mean dose 975 mg), disease duration 5–7 years, Hoehn & Yahr stage II–IV were enrolled to the study and were divided into 2 groups, each group consisting of 20 patients who were evaluated by a blind physician every week for the first month, and monthly thereafter for 12 months after initiation of the adjunct therapy.The patients were evaluated according to UPDRS, Global Clinical Impressıon scale(GCIS). The primary end point is the degree of levodopa reduction and secondary end points are duration and severity of dyskinesias, and "off" time.

Results: The time patients spent "off" was reduced by 2.1 hours with pergolide compared to 1.2 hours with cabergoline($p < 0.001$). Dyskinesia developed or detoriorated in 59 % of pergolide treated compared with 51 % cabergoline treated patients($p = 0.05$). The excess in in dyskinesia prevalence and severity resolved with levodopa dose reduction. Levodopa dose was reduced more in those receiving pergolide (225 mg), compared to cabergoline 175 mg) ($p < 0.05$).Pergolide produced significant improvement in Hoehn & Yahr stage ($p < 0.05$) and both the motor activities in UPDRS (both $p < 0.001$). Side effects were similar in both treatment groups, although nusea and hallusinations were more frequent in pergolide treated group, but the results were not ststistically significant ($p = 0.05$).

Conclusion: The results of this double blind study revealed that pergolide reduces "off" time and improves impairment and disability due to PD and allowing a marked reduction in levodopa dose more significantly compared to cabergoline. Further trials are required to compare pergolide with newer dopamin agonists.

Epilepsy

P503

Atypical seizure semiology in temporal lobe epilepsy

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Background: Typical seizure semiology in temporal lobe epilepsy (TLE) is characterized by abdominal, psychic, experiential or auditory auras followed by oroalimentary and hand automatisms. We present 13 patients with temporal lobe epilepsy with atypical seizure semiology.

Methods: All admissions to our EMU between 1997 and 2003 were reviewed; patients with temporal lobe epilepsy and atypical seizure semiology were selected. RESULTS: Of a total of 579 patients recorded, 353 (60.9 %) were considered to have temporal lobe epilepsy. 13/353 (3.6 %) patients with atypical seizure semiology were identified. These have been seizure free for at least one year after temporal lobectomy (8) or have a clearcut lesion in the temporal region in addition to typical temporal EEG patterns on surface EEG (5). Ten patients had right and 2 had left TLE; one patient had left temporal seizures on surface EEG and right MTS. Ten patients had complex motor/hypermotor seizures (vigorous truncal and axial limb movements as pedaling or flying arm movements in 9 patients and pelvic thrusting in 1). Prolonged screaming preceded seizures in 6/10 patients. Whistling and blowing, or singing a song were observed in 2 patients. Complex visual hallucinations including well formed human images and metamorphopsias were seen in 1. Interictally, 8 patients had right temporal and 3 bilateral temporal sharp waves. Ictal EEG was regional right temporal in 10 and left temporal in 3. Radiological findings were right MTS (4), neocortical cavernous angiomas (3), amygdala low grade tumors (2), neocortical MCD (2) and parahippocampal gliosis (2). Eight patients underwent surgery; 6 are seizure free and 1 is having rare auras. One patient declined monitoring with FO electrodes and 4 patients declined surgery after being offered a standard temporal lobectomy.

Conclusions: Complex motor behaviours (similar to the ones observed in frontal lobe epilepsy) as well as complex visual hallucinations can be seen in patients with TLE. In our series, this semiology was more frequent among patients with right TLE. It is possible that these complex motor behaviours/visual hallucinations are the result of a rapid propagation of the epileptic activity to extratemporal regions. Atypical seizure semiology does not necessarily imply the need for invasive recordings if all other EEG and MRI data point to the temporal region.

P504

EURAP: European registry of antiepileptic drugs and pregnancy – German experience

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Background: All old-generation antiepileptic drugs (AEDs) are considered to be teratogenic. The teratogenic potential of newer AEDs is even less known, a situation that prevents a rational approach to AED treatment in women of childbearing potential. EURAP is a prospective international multicentre study of pregnancies with AEDs. The primary objective of EURAP is to evaluate and determine the comparative risk of major foetal malformations following intake of AEDs during pregnancy. So far more than 300 reporting physicians from 37 countries have contributed 1,701 prospective pregnancies to the Central Registry. A total of 98 cases with major birth defects have been identified, representing an expected malformation rate of 6 %. Outcome in relation to exposure to specific drugs will only be assessed after 5,000 pregnancies are included. In order to identify national differences with respect to management standards we analyse the German registry separately.

Methods: EURAP is a prospective observational study. Women taking AEDs at the time of conception are included in the prospective risk assessment (within week 16 of gestation). The final classification of malformations is the responsibility of an outcome assessment committee, which is kept blinded with respect to the type of exposure.

Results: In Germany the project was started in 2001 and so far 220 pregnancies have been enrolled by 71 reporting physicians. The enrolment rate is 2 % (80 out of 4,000 pregnancies with AEDs reported annually). 164 of the 206 prospective pregnancies in Germany had been followed until the end of the first trimester. The classification of epilepsy was generalized in 45 % and focal in 48 % of the women. The maternal age was 29 ± 5.0 years (mean ± SD), ranging from 15 to 44 years. 79 % of the women were using a single AED. The most common AEDs in monotherapy were lamotrigine, valproic acid and carbamazepine. 80 pregnancies had been followed until 3 months after delivery. There were 3 stillbirths, 8 induced and 15 spontaneous abortions reported. Only one major malformation has been identified (prenatally diagnosed neural tube defect leading to an induced abortion during the 15th gestational week). The registry reflects shortcomings in management standards of pregnant women with epilepsy in Germany. 25 % of the women did not have a sufficient folate prophylaxis during the first trimester. We also will present data on prenatal ultrasound, breast feeding and vitamine K prophylaxis.

P505

A Spanish family with partial epilepsy, myoclonus and photosensitivity: clinical and genetic analysis

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Background: Benign adult familial myoclonic epilepsy (BAFME) is an autosomal dominant disorder characterized by nonprogressive postural and action finger tremor and seizures. Linkage to chromosome 8q24 has been described in Japanese families. and to chromosome 2p11.1-q12.2 in European families. A possible allelism with the syndrome of autosomal dominant cortical myoclonus and epilepsy (ADCME) has been suggested. The aim of this study is to characterize the clinical features of a three generation Spanish family with 11 affected members with a phenotype similar to BAFME and ADCME and to study if there is linkage to the BAFME and ADCME loci.

Methods: We identified a family with 44 members, including 11 individuals presenting partial epilepsy and myoclonus. Personal interviews and DNA samples were obtained from 18 individuals. Microsatellite markers localized in chromosomes 8q24 and 2p11.1-q12.2 were genotyped and linkage analysis was performed.

Results: Age of seizure onset ranged from childhood to adulhood. The epilepsy was characterized by focal motor, secondary generalized tonic-clonic, myoclonic seizures and photosensitivity. Neurological examination revealed action tremor. Electroencephalograms showed both focal and generalized epileptiform discharges. Neuroimaging studies were normal. The mode of transmission was consistent with an autosomal dominant pattern with incomplete penetrance. Linkage analysis excluded linkage to the BAFME and ADCME loci.

Conclusions: We describe a family in which affected members present several common features to both BAFME and ADCME. Linkage to regions previously linked with these disorders was excluded. We suggest that this family may represent a previously undescribed form of familial partial epilepsy.

P506

A new doublecortin gene mutation in a woman with resistant partial epilepsy and normal low resolution brain MRI scan

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Introduction: we describe a woman with resistant partial epilepsy, in whom MRI examination suggested a genetic origin, as confirmed by sequence analysis of the X-linked doublecortin (DCX) gene. Brain malformations due to a neuronal migration defect have been associated with mutations of the DCX gene in sporadic and familial cases. Main clinical features are mental retardation and epilepsy with phenotypic and morphological heterogeneity in a wide spectrum from subcortical band heterotopia(SBH) of variable degrees in heterozygous females to diffuse lyssencephaly in hemizygous males.

Patient and Methods: a 29 years old female without family history of epilepsy and/or mental retardation presented from childhood with occasional generalized tonic-clonic seizures, complex parzial seizures with oroalimentar automatisms and simple partial seizures with right arm motor and sensitive symptoms. Antiepileptic politheraphy achieved only partial seizure control. EEG, cerebral MRI (axial T2-weighted, coronal IR, FLAIR and T2), Chromosome analysis, Wechsler Adult Intelligence Scale (WAIS-R),Minnesota Multiphasic Personality Inventory (MMPI), sequence analysis of DCX gene (Xq22.3) have been performed.

Results: general and neurological examination were normal; EEG showed sharp waves and delta slow waves on temporal regions; cognitive level at WAIS-R was within normal limits (Full Scale IQ 85, Verbal IQ 81, Performance IQ 87), while the personality profile (MMPI) showed interictal disturbances characterized by viscosity, dependence and affected be-

haviour. Low resolution cerebral MRI was reported as normal; repeated brain MRI detected a partial bifrontal and left posterior parietal SBH. Sequence analysis of DCX gene revealed a nucleotidic substitution (c781 C > T), causing a premature protein truncation.

Conclusions: MRI findings led us to suspect a genetic basis for a previously defined "cryptogenic" epilepsy and prompted genetic testing.

Discussion: We underline the indication to repeat MRI selective focusing on cortical dysplasias when EEG and clinical evidence of focal dysfunction, polymorphic and uncontrolled seizures indicate a possible symptomatic epilepsy. Otherwise genetic confirmation in a woman is recommended, considering the risk of lyssencephaly in male subjects in subsequent generations.

P507

Perivascular clustering – Oligodendroglial cells of unknown function

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Background: Marked perivascular clustering (PC), i. e. groups and rows of small round cells along white matter vessels, is seen in temporal lobe epilepsy (TLE) specimens obtained by surgery. This study focusses on constituting cell types, clinical significance and pathogenesis of PC, which are unknown so far.

Methods: In a series of 59 nonlesional TLE surgical specimens, we characterized PC by immunohistochemistry and correlated the amount of PC with clinical parameters.

Results: PC cells were variably positive for galactocerebroside, myelin basic protein and S-100 protein, while glial fibrillary acidic protein, vimentin, nestin and neuronal antigens were not expressed. There was no correlation between amount of PC to any clinical feature, including age at surgery, age at epilepsy onset, duration of epilepsy, preoperative seizure frequency, childhood febrile convulsions, family history of epilepsy and postsurgical outcome.

Conclusions: Our findings suggest oligodendroglial differentiation of PC. Wether it represents a primary (dysplastic) or secondary (reactive) tissue feature remains unresolved.

P508

Levetiracetam normalises Connexin 43 expression and intercellular communication in rat primary astrocytes

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Background: Astrocytic gap junctions (GJ) are comprised of Connexin 43 and account for the astrocytic syncytium in the central nervous system which is a major component of the metabolic homeostasis, e. g. uptake and distribution of potassium, neurotransmitter dissipation etc. Inflammatory conditions result in restricted intercellular communication in cultures of primary rat astrocytes. Levetiracetam (LEV) is an antiepileptic drug which exhibits anticonvulsant features, the mechanism of which are still not clearly understood. We investigated the effect of LEV on Connexin 43 expression and intercellular communication in astrocytes under inflammatory conditions.

Methods: Inflammatory conditions were elicited by high concentrations of microglial cells (30 % – M30) in rat astrocyte/microglia cocultures. Control cultures contained 5 % (M5) microglial cells which keeps them in a resting phenotype. M30 cocultures were treated with 50 and 100 µg/ml LEV for 24 h. Cx43 expression was investigated by western blotting using a Cx43 polyclonal antibody. Membrane resting potential was measured by patch clamp technique and gap junction communication (GJC) was simultaneously tested by Lucifer Yellow dye-application. Amount and phenotype of microglia was determined with a monoclonal ED1 – antibody by immunocytochemistry.

Results: 50 µg/ml LEV caused a significant increase in Cx43 expression. Membrane resting potential (MRP) depolarised from – 80.10 mV in M5 (median value) to – 61.4 mV in M30 cultures ($p = 0.0080$). Normalised MRP was achieved after LEV application [–79, 85 mV ($p = 0, 0026$)]. Number of coupled cells increased in LEV treated M30 cultures to 77.5 ($p = 0.0031$) after significant decrease in untreated M30 cultures [15 ($p = 0.01459$]. The amount and phenotype of microglia cells in M30 cocultures treated with LEV was not significantly changed compared to untreated M30 cultures.

Conclusion: Based on these results we suppose an antagonising effect of LEV on impaired intercellular communication and Cx43 expression in inflammatory affected astrocytes. This could indicate an anti-inflammatory component in the antiepileptic mechanism of LEV. This work was supported by UCB-Pharma

P509

Seizure frequency and number of concomitant antiepileptic drugs do not limit the efficacy of pregabalin as add-on treatment of partial seizures

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Background: Epilepsy severity can be characterized, in part, by seizure frequency and number of concomitant antiepileptic drugs (AEDs). Pregabalin is a novel ligand for the alpha2-delta subunit of voltage-gated calcium channels that has antiepileptic, analgesic, and anxiolytic activity. This report describes an analysis performed to determine whether seizure frequency and number of concomitant AEDs influenced the degree of patient response to add-on treatment with pregabalin. Data here reported were from a randomized, double-blind, placebo-controlled, add-on study, consisting of 8-week baseline and 12-week double-blind phases.

Methods: Patients were refractory to 2 AEDs at maximally tolerated doses, experienced at least 6 partial seizures during baseline with no 4-week seizure-free period, and were currently receiving 1–3 AEDs. Patients were randomized to placebo or 50, 150, 300, or 600 mg/day pregabalin, BID. Efficacy was assessed by seizure-frequency reduction and responder rate (> 50 % seizure reduction from baseline). Baseline seizure rate was divided into quartiles or used as a continuous variable. Seizure reduction (ANOVA or ANCOVA, 2-sided, $a = 0.05$) and responder rate (logistic regression, 2-sided, $a = 0.05$) were analyzed by dose, with refractoriness in the models as explanatory variables to determine if efficacy varied with refractoriness.

Results: 28-day baseline seizure-rate quartiles were 5 or fewer, > 5 to 10, > 10 to 23, and > 23, with mean seizure rates for each quartile of 3.9, 7.4, 15.3, and 66.9. Approximately 30 % of patients were on one AED, 50 % on two, and 20 % on three. Baseline seizure rate by dose interaction ($P = 0.1569$ for seizure reduction; $P = 0.6838$ for responder rate) was not significant; efficacy remained consistent within effective doses. Number of concurrent AEDs does not affect seizure reduction within doses of pregabalin (AED by dose interaction, $P = 0.4833$) or responder rate ($P = 0.5202$).

Conclusions: In this refractory population, pregabalin's efficacy was not a function of epilepsy severity as measured by baseline seizure rate and number of concomitant AEDs.

P510

MRI and video-EEG findings in encephalocraniocutaneous lipomatosis (Fishman syndrome)

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Encephalocraniocutaneous lipomatosis is a rare, congenital neurocutaneous syndrome characterized by lipodermoids of the eye, cutaneous and intracraneal lipomas, and non progressive brain abnormalities, ipsilateral to the skin lesion. Seizures and mental retardation are usually present. We report a 24 year old woman with Fishman syndrome who was evaluated for epilepsy surgery.

Case report: A 24 year-old left-handed women was admitted to the adult EMU. She had a large soft subcutaneous mass (lipoma) within the left fronto-temporal scalp, with overlying alopecia. Two epibulbar dermoids of the left eye associated to iris colobomata were seen; she had a right upper homonymous cuadratanopsia. She started to have seizures at the age of 1, with aura of dizziness followed by loss of consciousness, oral and hand automatisms. There was no postictal confusion or aphasia. Seizures were pharmacorresistant. A brain MRI showed an extensive MCD in the basal left temporo-occipital region along with an extensive leptomeningeal angiomatosis and brain calcifications. Other findings were a left cerebellopontine angle lipoma, an arachnoid cyst in the left middle cranial fossa and left hemisphere atrophy. Automotor seizures characterized by prominent oral and left hand automatisms associated to dystonic/fixed posture of the right arm were recorded. Ictal-EEG pattern was characterized by a paroxysmal fast activity over the left temporo-parietal region evolving into a theta rithmic pattern over the left posterior quadrant. SISCOM revealed an area of hyperperfusion in the posterior and basal temporo-occipital region surrounding the MCD. Her IQ was normal and no deficits were found in denomination, speech fluency as well as in verbal memory. fMRI showed right hemisphere dominance for language.

Discussion: Epileptic seizures often happen in patients with Fishman syndrome (19 out of 33 patients reported to date). Seizures tend to be focal and are usually pharmacorresistant. In our patient, seizures arose from the surroundings of the dysplastic tissue in the temporooccipital region as showed by surface EEG and SISCOM, and she is a potential surgical candidate. Our patient had a normal IQ and did not displayed any verbal or visual memory deficits, showing that a reorganization and restoration of

cognitive functions including memory and language functions may happen in the setting of extensive malformations.

P511
Efficacy of levetiracetam in drug-resistant epilepsy
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New broad-spectrum antiepileptic agents play a major role in the treatment of severe drug-resistant epilepsy. Levetiracetam has been proposed as a well-tolerated drug with improved efficacy against refractory seizures. It has a reasonable adverse-effect profile that has contributed positively to its acceptance. In this open study we evaluated the efficacy and safety of levetiracetam in adults suffering from severe epilepsy.

Fifteen patients (age: 38–52) suffering from generalized tonic-clonic (11) or complex partial (4) seizures were treated with levetiracetam at a dose of 2,000–3,000 mg daily. The neurological, electroencephalographic and neuroimaging data were analysed in all cases. The drug was given as an add-on therapy.

A full control of seizures was achieved in 9 patients (60 %). Seizure frequency was reduced by more than 50 % in 3 patients (20 %), while in the remaining 3 patients there was no effect. Electroencephalographic recordings showed a normalization of background activity in 85 % of cases. The frequency of adverse reactions was 3 %. These mainly consisted in mild asthenia and somnolence, while 1 patient developed a reversible ischaemic enteritis.

According to our findings levetiracetam has a marked efficacy as an adjunctive therapy for drug-resistant epilepsy. Its potential usefulness as a monotherapy remains to be evaluated.

P512
Myoclonic epilepsy and cerebellar tumour in children: considerations on a clinical case
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Cerebellar astrocytoma is one of the most common posterior cranial fossa tumors in infantile age, it is histologically benign and is associated to a favorable prognosis. At onset the clinical picture is usually characterized by endocranial hypertension, gait disorders with ataxia, nystagmus and abducens paralysis.

The clinical case of a female patient is reported, aged 2 years and 9 months, with familiarity for epilepsy from the paternal line, who was referred to our Institute for psychomotor delay, language delay, palpebral myoclonias, episodes of lower limb tremor which caused her to fall to ground and inability to resume ambulation. The electroencephalogram (EEG) in wake and spontaneous sleep revealed discharges of bilateral epileptiform abnormalities, which were diffuse, synchronous and asynchronous over the two hemispheres, sometimes isolated over the posterior regions. The EEG tracing also showed the epileptic nature of these phenomena.

A brain magnetic resonance revealed the presence of a round mass located in the right cerebellar deep median and paramedian regions with solid aspect compatible with pilocytic astrocytoma.

The patient received neurosurgery and the histological exam confirmed the radiological hypothesis. Upon complete resection of the mass the patient showed an improvement of her motor skills. Her cognitive higher functions and language abilities remained defective. Epileptic discharges significantly diminished but did not disappear. A Valproate therapy allowed a fair control of the fits.

According to some studies, epileptic discharges and progressive myoclonic phenomena are due to cerebellar tumor lesions.

In our study, the lack of complete regression after neurosurgery poses a diagnostic problem questioning the etiological relationship between epilepsy and cerebellar tumor.

Cerebrovascular disorders

P513
Cerebellar infarcts – Clinical features and outcome
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Background: cerebellar infarcts is relatively infrequent and accounts for 2–2.5 % of all strokes.

The aim of this study was to estimate the risk factors, clinical features, causes and mechanisms, neuroimaging patterns, complications and outcome in cerebellar infarcts.

Patients and methods: we included 71 consecutive patients with territorial and nonterritorial cerebellar infarcts from a total of 3,432 stroke patients (2.06 %) in 3 year period (2001–2003). All infarcts were confirmed by CT-scan or magnetic resonance imaging. We consider as nonterritorial infarcts cerebellar infarcts less than 2 cm in diameter.

Results: 52 were men (73.23 %) and 19 women (26.76 %) and the mean age was 63.4 ± 13.4 years. From total of 71 patients 61 had territorial infarcts and 10 nonterritorial infarcts. Risk factors included: hypertension 69.01 %, coronary artery disease 53.52 %, previous stroke 8.45 %, diabetus mellitus 15.49 %.

Arterial territory: superior cerebellar artery territory 36 (59.01 %), posteroinferior cerebral artery territory 16 (26.22 %), superior cerebral artery + posteroinferior cerebral artery 5 (8.19 %), inferior cerebellar artery 4 (6.55 %), the remaining 10 cases had nonterritorial infarcts.

Etiopathogenic mechanisms for the 2 groups (territorial vs nonterritorial): cardio-embolic 29.5 % vs 20 % (p = NS), large artery occlusive disease 11.47 % vs 10 % (p = NS) nonatherosclerotic vasculopathie 11.47 % vs 10 % (p = NS), haematologic abnormalities 4.91 % vs 0, cryptogenic 42.62 % vs 60 %. Clinical exam: cerebelos signs 56 (78.88 %), vestibular signs 63 (88.73 %), brainstem signs 37 (35.21 %). Dysarthria and ataxia, ipsilateral dysmetria are more severe in superior cerebellar artery territory infarcts and vertigo and dizziness are more often in posterior inferior cerebellar artery territory infarcts.

The outcome – 66 (92.95 %) patients were favourable and 5 patients die (7.04 %) because of acute complications – acute hydrocephalus 2 patients and brain stem compression 3 patients.

Conclusions: nonterritorial infarcts have to same risk factors like territorial infarcts with more cryptogenic mechanisms. In general cerebellar infarcts have a favorable outcome.

P514
Homeostasis maintenance in acute ischaemic stroke. Impact in infarction size and outcome
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Background: Body temperature (BT^a), glycemia and blood pressure (BP) prognostic influence in acute ischemic stroke (AIS) have been demostrated one by one in previous studies. However these variables have not been evaluated all together as a whole physiological condition. Our aim is to study the influence of homeostasis maintenance on infarction size and on functional outcome at 3 months.

Methods: Prospective study during 2002. Patients with AIS (< 24 hours) were included. Exclusion criteria: TIA, haemorrhagic stroke, previous dependence, unconsciousness at admission or severe concurrent disease. Homeostasis was defined as the maintenance of $BT^a \leq 37.5$ °C, glycemia ≤ 140 mg/dl and systolic blood pressure (SBP) 130–180 mm Hg. Analyzed parametres: T^a, glycemia and SBP at admission and every 8 hours during first 48 hours, infarction size (TC 24 h-7 day) and modified Rankin Scale (mRS) at 3 months. Stadistical analysis: t-student, U-Mann Whitney, chi-square.

Results: 118 AIS patients included. Three of defined homeostatic patterns were present in 6 patients, two in 51, one in 53 and none in 8. The maintenance of three or two of these patterns within the first 48 h was significatly associated to lower infarct size (p = 0.018) and better functional outcome (p = 0.035) at 3 months.

Conclusions: A tight control of homeostasis during the first 48 hours from AIS onset conditions a lower infarction size and a better outcome. Therefore it, we recommend a precise surveillance of these physiological parametres in the AIS managment.

P515

Protein S-100 beta in subarachnoid aneurysmal haemorrhage

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Background: Protein S-100 Beta (PS-100 B) is a calcium binding protein, most abundant in glial cells of the nervous system. High levels of serum protein are correlated to brain damage in several neurological diseases, specially in brain ischemia. However, only few reports focused on PS-100 B in subarachnoid aneurysmal hemorrhage (SAH).

Method: PS-100 B was measured in 40 patients with acute SAH (admission delay lower than 48 h) during the ten first days.

Results: At admission, PS-100 B was higher in severe SAH according to both World Federation of Neurosurgeon (WFNS) and Fisher radiological score, but correlation was better for the Fisher score. After day 6, PS-100 B was higher in patients presenting arteriographic criteria of vasospasm. PS-100 B was correlated to outcome assessed by the Glasgow outcome score. PS-100 B was higher in operated patients as compared to patients who underwent coiling.

Conclusion: PS-100 B, a marker of brain damage, is correlated to severity, vasospasm and outcome in SAH. It could be used for gravity stratification at admission, follow-up of vasospasm therapy, and evaluation of treatments-induced ischemia.

P516

Determinants of poor outcome after ischaemic stroke – predictors for death and dependency in Warsaw

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Background and purpose: We undertook this study to identify the possible predictors of poor outcome after the ischemic stroke (IS) in Warsaw, Poland. We studied risk factors, apolipoprotein E (ApoE) genotype and initial stroke severity in relationship to death and dependency within a year after the event.

Methods: We investigated 496 patients (260 women, 236 men) with ischemic stroke consecutively admitted to the 2nd Department of Neurology, Institute Psychiatry and Neurology, Warsaw. All patients were subjected to investigations regarding risk factors. Stroke severity was evaluated with the Scandinavian Stroke Scale (SSS), dependency was defined according to the modified Rankin Scale (mRS). Multivariate regression model were used to analyze predictors of death and dependency. The following independent variables were used: age > 70 years, male gender, hypertension, congestive heart failure, atrial fibrillation, ischemic heart disease, myocardial infarction, diabetes mellitus, intermittent claudication, former TIAs, former stroke, symptoms of infection within 1 week before stroke, current or ex-smoking of any kind of tabacco, daily alcohol consumption, ApoE genotype and initial stroke severity.

Results: The 1-year mortality was 37.9 %. After 1 year, 29.2 % of the survivors were dependent. Death within 1 year was associated with age > 70 years (OR = 1.79), heart failure (OR = 1.97), atrial fibrillation (OR = 1.96), stroke severity (OR = 1.07). Dependency was predicted by: former stroke (OR = 3.97), stroke severity (OR = 1.15) and lack of alcohol consumption (OR = 5.13). On our IS population we did not noticed any impact of ApoE genotype on poor outcome.

Conclusions: In addition to stroke severity and age, heart diseases seem to have impact on mortality. Finding and, when possible, treating these heart disturbances may affect stroke mortality. Dependency after stroke is very close associated with former stroke so proper secondary prevention remains very important and should be individualized to achieve optimal results.

P517

Spontaneous carotid or vertebral arteries dissections: Prevalence of dermal ultrastructural connective tissue abnormalities in Spanish population

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Background/Objective: The etiology of spontaneous cervical artery dissection is unknown. Cutaneous ultraestructural abnormalities have been described in more than 55 % of patients with non-traumatic cervical artery dissections in central European population. We assessed the prevalence of this ultraestructural abnormalities in our environment (Mediterranean area).

Methods: From 1999 to 2003, we prospectively evaluated 30 patients with spontaneous cervical artery dissections without signs of connective tissue disorders (internal carotid artery n = 19 and vertebral artery n = 11) from two neurology departments in Barcelona (Clinic Hospital n = 16 and Germans Trias i Pujol Hospital n = 14). In all patients, skin biopsies were obtained from 4 mm punch in the upper non-paretic forearm and fixed in glutaraldehyde. We examined the variation of calibers, irregularities of the contours an electron-dense inclusions in collagen and elastic fibers by electron microscopy.

Results: We have observed dermal ultraestructural abnormalities in 40 % (n = 12) of patients: variation in calibre of collagen fibers (n = 7), irregularities of the contours(n = 4), and electron-dense inclusion in elastic fibers(n = 4). There were non-statistical differences in age, presence of vascular risk factor and affected artery when patients with normal or abnormal ultraestructural findings were compared.

Conclusion: Dermal ultraestructural connective tissue abnormalities in spontaneous cervical artery dissection are also frequent in Spanish population.

P518

Ischaemic stroke – comprehensive imaging by means of multisection CT

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The primary purpose of imaging in the evaluation of a stroke patient is to differentiate between haemorrhage and ischemic stroke. However, it is also essential for the further patient care to obtain information about irreversibly damaged brain as well as "tissue at risk" and to show stenosis or occlusion of major arteries. This study presents a protocol used for comprehensive imaging of stroke including non-enhanced CT (NECT), CT-perfusion (CTP) and CT-angiography (CTA) as a first investigation performed in patients with suspected ischemic stroke.

We investigated 100 patients with the admission diagnosis "ischemic stroke" using multisection CT (MSCT). The protocol included NECT, CTP and CTA of the carotid and intracerebral arteries. We measured the time needed to perform the study including the initial post processing. Moreover, we evaluated the findings recorded immediately, in this emergency setting.

The average time to complete the study including post processing was 12 minutes. The carotid arteries could be evaluated in 96 patients. In four patients artifacts prohibited adequate evaluation. In 23 patients severe extracranial stenosis of at least one internal carotid artery was found, in 7 patients one vessel was occluded. Occlusion of a large cerebral artery was seen in 26 patients. CTP detected areas of diminished perfusion not seen on NECT in 27 patients. In 6 patients who were admitted within two hours after onset of symptoms, areas without perfusion were detected on CTP, while NECT showed no "early" signs of stroke.

MSCT allows a fast comprehensive imaging of stroke in less then 15 minutes. Thus, this method is suitable for a rapid and thorough evaluation of patients with acute neurologic deficits as it provides precise information about haemorrhage, brain perfusion and brain vasculature.

P519

Isolated cortical vein thrombosis and cerebral amyloid angiopathy

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Background: Cortical vein thrombosis (CVT) has only rarely been reported which is probable due to the difficulties of diagnosis. The etiologic mechanisms in isolated CVT or sinus dural thrombosis are commonly thought to be the same and coagulation abnormalities, infection, pregnancy, autoimmune disease, Hodgkin's disease have been reported in association with CVT.

Case-report: We report on a 74-year-old woman with an unremarkable medical history, presenting with recurrent sensory focal seizures of the left body. Physical examination and CSF analysis were normal. CT showed a slight subarachnoid hemorrhage in the right central sulcus with a striplike enhancement after contrast application. On MRI a narrowing of the sulci of the right central region was found on native T1w images with an enhancement of the corresponding regional medullary and superficial veins after application of gadolinium. T2*-weighted gradient-echo sequence confirmed the subarachnoid hemorrhage but disclosed three microbleedings in the subcortical white matter (two in the ipsilateral frontal, one in the contralateral temporal lobe). Coagulation parameters (including antithrombin III, protein C, protein S, lupus anticoagulant, factor V leiden mutation), borrelia and syphilis serology, rheumatoid factor, antiphospholipid antibodies, and antinuclear antibodies were within the normal range.

Differential diagnosis included CVT but also a meningeosis why a stereotactic leptomeningeal and cortical biopsy was performed. Histopathological examination disclosed a cerebral amyloid angiopathy without signs of meningeosis or vasculitis. Seizures stopped under valproate treatment.

Conclusion: Cerebral amyloid angiopathy is characterised by deposition of congophilic material composed of β-amyloid in the walls of small and medium-sized arteries and less often veins passing from the leptomeninges into the superficial cortex. To the best of our knowledge, isolated CVT in association with CAA has not been reported previously, which may partially be due to the difficulties to diagnose isolated CVT. In our patient, other known causes of CVT have been excluded and CAA seems to be the most probable etiology. However, because CAA is present in about 8 % of individuals in the 7th decade of life, a definite conclusion is not possible. Due to the increased bleeding risk in CAA oral anticoagulant therapy of CVT must carefully be weighted against the increased bleeding risk associated with CAA.

P520

Plasma homocysteine levels in patients with mild or moderate ischaemic stroke

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High levels of homocysteine (Hcy) enhance atherosclerosis and may predispose to ischemic stroke. We decided to find out whether Hcy levels increase in patients with ischemic stroke and whether they correlate with stroke severity, risk factors, outcome,or recurrence. We measured plasma Hcy levels in 102 consecutive likely-to-survive patients with ischemic stroke on admission, at 1 week, 1 month, and 3 months after stroke and 102 control subjects once only. At each sampling, the patients underwent a complete neurological evaluation. The patients were contacted 3 years later for prognostic determination. Plasma Hcy level in patients was significantly lower than of control subjects on admission, but were not different at later time points. No correlation was found between Hcy levels and stroke etiology, risk factors, severity, outcome, or recurrence, except that Hcy levels correlated with MMSE at 3 months. We were not able to demonstrate a role of Hcy in ischemic stroke. Our patients consisted of mildly and moderately ill patients due to study design.

P521

Restenoses after carotid stenting: incidence, diagnosis and treatment

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Background: Carotid stenting is developing as an alternative to carotid endarterectomy. Because restenosis after endovascular treatments as coronary or peripheral vascular interventions are common, the restenosis rate in carotid stenting is of high interest. We report about incidence, diagnosis and treatment of carotid restenosis in our series.

Incidence: Since 1993 carotid stenting was performed in 412 consecutive procedures. 18 (4.4 %) of the patients developed a restenosis of more than 50 %. In 8 patients a re-angioplasty had to be performed. Other series report about a re-stenosis rate between 2.3 and 4.9 %. Re-stenoses most frequently occur within 6 to 12 months after the intervention (10 ± 8 months). According to our experience they can be seen within the stent or more often at the distal end of the stent.

Diagnosis: Carotid ultrasound should be performed after 6 and 12 months and thereafter yearly after the initial procedure, so re-stenoses can be discovered early. In our experience the grade of restenosis is often overestimated by ultrasound compared to angiography which is probably due to a higher velocity level in stented vessels. So we recommend performing an angiography before a second intervention. The design of the stents restricts the use of MR Angio.

Treatment: During repeated carotid angioplasty the same devices as in conventional procedures can be used. Embolic protection was performed in 6 out of 8 patients. Re-stenosis within the stent usually can be treated by balloon angioplasty. Only a new stenosis at the distal end of the stent may require an additional stent.

Complications: Within 30 days no complications occurred. During follow-up (18 patient-years) one patient developed a second re-stenosis of 60 % after 8 months. One patient suffered from ischemic stroke after 42 months.

Conclusion: Restenoses after Carotid stenting are rare. If occurring they can be detected easily by ultrasound. Repeated angioplasty is a successful method for treatment.

P522

Erdheim Chester disease with symptomatic involvement of the cervical arteries

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Erdheim Chester disease (ECD) is a rare non Langerhans cell histiocytosis characterized by a diffuse infiltration of long bones, retroperitoneal space, lungs, kidneys, brain, retro-orbital space and heart. The only pathological arterial process which have been already described is a profuse periaortic fibrosis surrounding the whole thoracic and abdominal aorta.

We report the case of a 41-year old man who developed amaurosis fugax in the left eye; four similar episodis had occured over a 6-month period. ECD had been diagnosed by the association of hypogonadism, diabetes mellitus, retroperitoneal infilration, periaortic fibrosis and osseous condensations with typical bone isotopic pattern 6 years before. Arterial hypertension has been diagnosed one year before. An angioplasty for iliac-artery stenosis had been performed in 1998. The neurological examination was normal as well as ophtalmological and fundoscopic examinations. Electrocardiogram, cardiac echocardiography, biochemetry were normal. Cerebral magnetic resonance imaging (MRI) showed retrochiasmatic infiltration without any ischemic lesion, carotid duplex ultrasonography and extracranial MR angiography revealed a 90 % stenosis in diameter of the left internal carotid and a 50 % stenosis of the right internal carotid with a concentric thickening of the artery wall. Intracranial MRI angiography also revealed intra-cranial stenosis of the left middle cerebral artery. A high-spacial-resolution MRI revealed a distinctly and unusual image of layers in the artery wall.

This is to our knowledge the first case of ECD suggesting that xanthogranulomatous process can encircle large and intra-cerebral blood vessels and can lead to recurrent episodes of amaurosis fugax of hemodynamic mechanism.

P523

Concomitant echocardiographic findings in ischaemic stroke patients: relation to stroke aetiology?

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Background: The percentage of unknown etiology of ischemic stroke depends on how much investigation is undertaken. The generalization of stroke etiology research contributed to a higher number of patients with multiple etiologies. Since treatment options differ according to stroke etiology, and concomitant cardiopathy is common in these patients, we compared the prevalence of changes observed by transthoracic echocardiography (TTE) in ischemic stroke and non-stroke patients.

Methods: We studied a hospital sample of 531 consecutive patients (279 male, 52.5 %), referred to TTE, including 177 consecutive first ever ischemic stroke patients (95 male). Median age was 72 years (15–93). TTE was performed according to AHA guidelines and Henry et al. normograms for weight and age. Ischemic stroke patients were studied according to a protocol including Triplex scan and TTE. We excluded patients with technically unsatisfactory TTE. Statistical methods included multifactorial analysis, Chi-square test and Pearson's correlation.

Results: From 531 patients, 177 (33.3 %) had an ischemic stroke. The occurrence of ischemic stroke was associated with the presence of left atrium enlargement ($c = 0.131$, $p = 0.002$), posterior left ventricular wall enlargement ($c = 0.136$, $p = 0.002$), diminished left systolic ventricular function ($c = 0.095$, $p = 0.028$), diminished left diastolic ventricular function ($c = 0.288$, $p = 0.000$), pericardial suffusion ($c = 0.134$, $p = 0.048$) and pleural suffusion ($c = 0.125$, $p = 0.004$).

Discussion: In our patients referred to TTE, presence of ischemic stroke was associated with echocardiographic findings that are not traditionally described as related to stroke occurrence, like posterior left ventricular wall enlargement, diminished left systolic ventricular function or left diastolic ventricular function, pericardial or pleural suffusions. Probably, closer attention should be paid to evaluate if these echocardiographic findings reflect new correlations between heart and brain.

P524

Embolic protection in carotid stenting with eccentric filters

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Background: Carotid stenting is a developing technology to treat carotid stenosis. There are several different embolic protection devices to prevent

ischemic events during the intervention. We report about our results with eccentric filters.

Methods: Since January 2001, we have treated 114 consecutive high-grade lesions of the internal carotid artery using eccentric filters for embolic protection. The following filters were used: Filterwire XP and EZ (Boston Scientific) in 63 patients and TRAP or Spider (Microvena) in 51. 116 stents were implanted. Follow-up investigations included a neurological examination and duplex ultrasound after 6 and 12 months, thereafter annually.

Patients: The age ranged from 46–90 years (69 ± 9 years). 66 patients had a contralateral stenosis or occlusion. 54 % of the patients suffered from coronary heart disease, 81 % from hypertension, 29 % from diabetes, 63 % from hyperlipidemia and 44 % were previous or current smokers. Mean percentage of the lesion was 76 ± 10 %, mean length of lesion 8.2 ± 5.6 mm.

Results: The procedure was technically successful in all interventions. 4 patients (3.5 %) had one of the following acute or subacute (< 30 days) complications: Major stroke leading to death in 2, non-fatal major stroke in 1, minor stroke in 1, non-cerebrovascular death in 0 patients. During follow-up (77 patient years) 1 non-cerebral death and 1 major stroke occurred. 3 patients had a second angioplasty due to restenosis.

Conclusion: Carotid stenting under embolic protection with eccentric filters is a successful method for preventing stroke in patients with a carotid stenosis. Most neurological events occur during acute follow-up. Complications and restenosis during long-term follow-up are rare.

P525

The link between stress-induced hyperglycaemia after acute ischaemic stroke and poor clinical outcome

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Background: Diabetes mellitus (DM) and stress-induced hyperglycemia occur in about 20–45 % of stroke patients and are associated with worse stroke outcome. It is generally accepted that hyperglycemia aggravates cerebral ischemia and could be associated with increased mortality and poor recovery in diabetic and non-diabetic patients after stroke.

Objectives: To determine the impact of stress-induced hyperglycemia in patients after acute ischemic stroke on the clinical outcome and mortality.

Design: One year follow up study of patients with acute ischemic stroke.

Results: 375 patients with ischemic stroke was enrolled in study, among them: 157 (41.9 %) patients had hyperglycemia at admission (93 (59.2 %) with DM and 64 (40.8 %) – without previously established DM). In general, clinical outcome was similar in surviving patients with and without DM. However, the stress-induced hyperglycemia at admission was associated with poor functional recovery up to 3 months after stroke in non-diabetic patients ($p < 0.05$). In patients without DM, stress-induced hyperglycemia (> 7.0 mmol/l) was associated with a 2.5-fold increased risk of mortality after stroke (pooled relative risk, 2.51; 95 % CI, 2.15 to 3.37). In patients with DM hyperglycemia was not tightly associated with a significantly higher risk of short-term mortality after stroke (pooled relative risk, 1.39; 95 % CI, 0.45 to 3.32). Our preliminary results suggest that early administration of human recombinant insulin improves at least the clinical outcome of acute stroke associated with stress-induced hyperglycemia.

Conclusions: Stress-induced hyperglycemia increases risk of poor functional recovery in patients without DM. Increased glucose levels at admission independently increase mortality caused by stroke in non-diabetic but not in diabetic patients. This finding provide us opportunity to suggest that the intensive insulin therapy could have beneficial effect on clinical outcome and mortality in non-diabetic patients with stress-induced hyperglycemia, however further investigations have to be carry out.

P526

VII–XII cranial nerves palsies – another presentation of cerebral vein thrombosis

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Introduction: The clinical manifestations of Cerebral Vein Thrombosis (CVT) are protean, being isolated cranial nerves palsies a rare occurrence. Its fisiopathology remains to be clarified.

Clinical case: A 33 years old woman, under oral contraceptives, was admitted for surgical drainage of a retropharyngeal abcess. On the 3nd day after surgery, the patient complained of dysphagia and vertigo. The neurological examination disclosed a peripheral paralysis of the left VII cranial nerve; a horizonto-rotary rightward jerk nystagmus and left postural deviation consistent with a left VIII cranial nerve lesion, and a ipsilateral Collet Sicard syndrome (paresis of the left IX, X, XI and XII cranial nerves). Magnetic Ressonance Imaging (MRI) and Angio-MRI confirmed a left lateral sinus and jugular vein thrombosis. The electromiographic study revealed peripheral VII and IX palsies. The patient was started on anticoagulation. Besides the local infectious process, the surgical trauma and the oral contraception, the etiological investigation revealed no other risk factor for the thrombosis. Twelve months later, there was an almost complete recovery, remaining a left tongue hemiatrophy and a slight leftward tongue deviation. The Angio-MRI showed parcial recanalization of the previously occluded vessels.

Discussion: This is, to our knowledge, the first case of CVT presenting as isolated VII-XII cranial nerves palsies. The manifestation of a CVT as isolated multiple cranial nerves palsies has been recently reinforced and should be considered in the differential diagnosis. Several cranial nerve lesion mechanisms have been proposed on CVT. The first reports favoured a mechanism of pressure palsy, by direct compression of the occluded vein on the nerve. More recently, venous stasis, either inducing transient conduction abnormalities or more permanent ischemia, has been suggested. Our case, given the cranial nerves affected and the irreversibility of the hypoglossal nerve lesion, points out to a mechanism of cranial nerves ischemia secondary to venous stasis.

P527

Coexistence of dural arteriovenous fistulae and factor V Leiden mutation

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Background and Goals: Dural arteriovenous fistula (DAVF) is a vascular lesion of unclear aetiology. Some authors thought to be of congenital and others of acquired origin. This is based on a coexistence between DAVFs and cerebral venous thrombosis (CVT).

Methods: We report a 61-year-old man who presented with headache, vomits and vertigo because of cerebellar hematoma. Five years ago, the patient was diagnosed of DAVF of left transverse sinus associated to CVT. Diagnostic was made by conventional angiography performed as study of acuphens. Subsequently, the fistula was embolized. Later, fistula became patent and required two additional embolizations. One month following the diagnosis of fistula the patient presented a venous thrombosis in left leg. He was treated with oral anticoagulants for six months. Study of the thrombotic risk demonstrated resistance to activated protein C (APC) secondary to heterozygot Factor V Leiden mutation (FVLM).

Results: Magnetic resonance imaging (MRI) disclosed left cerebellar hematoma invading arachnoideal and tentorial spaces. Small permeable vessels were visible, corresponding to DAVF. There was absence of outflow from the left transverse-sigmoide sinus on MR Angiography.

Conclusions: CVT seem to be a predisposing factor for DAVFs. Several authors reported an increased prevalence of APC resistence in patients with DAVF. The aim of the treatment is the complete obliteration of the lesion, but the persistent thrombophilic condition favors the fistula recurrence. FVLM could explain the persistence of DAVF despite endovascular treatment. Therapy of DAVF and FVLM is controversial, because of coexistence of thrombophilic state and a vascular malformation with high risk of bleeding.

Poster session 4

Sleep disorders

P528

Role of CSF hypocretin-1 determination in the diagnosis of narcolepsy and other hypersomnias

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Introduction: Narcolepsy is a disease characterized by excessive daytime sleepiness (EDS) and symptoms of REM sleep disregulation (cataplexy, sleep paralysis and hallucinations). Narcolepsy is diagnosed based on the presence of EDS and cataplexy/sleep onset REM periods (SOREMs) in the

MSLT test. However, cataplexy is not always present and SOREMs may be unspecific.

Narcolepsy is related to a loss of hypocretinergic neurons in the posterior hypothalamus. Hypocretin-1 (Hcrt-1) may be measured in the CSF as a biological marker of the function of the hypocretinergic system, and typically, is absent in narcolepsy.

Objective: To determine the diagnostic value of CSF Hcrt-1 determination in patients with ESD diagnosed as narcolepsy-cataplexy, narcolepsy without cataplexy and idiopathic hypersomnia based on the clinical picture and electrophysiological tests.

Methods: Nocturnal polysomnography followed by MSLT, HLA determination for DQB1*0602 and measurement of CSF Hcrt-1 levels by direct radioimmunoassay.

Results:

1. Narcolepsy-cataplexy: 31 patients, mean age 42.5, disease duration 22.9; mean sleep latency 2.15 minutes, > 2 SOREM in 26; HLA DQB1*0602 in 30 patients; undetectable CSF Hcrt-1 in 28 patients (all HLA positive), low in 1 HLA positive patient and normal in 2 patients.
2. Narcolepsy without cataplexy: 8 patients, mean age 35.75, disease duration 14.25; mean sleep latency 2.25, > 2 SOREM in all the patients; undetectable CSF Hcrt-1 in 2 patients HLA positive for DQB1*0602, normal in 6 patients (3 HLA positive).
3. Idiopathic hypersomnia: 8 patients, mean age 55.6, disease duration 20.25; mean sleep latency 4.22, no SOREMs in MSLT; low CSF hcrt-1 in 1 HLA positive patient, normal in 7 (3 HLA positive patients).

Conclusion: The measurement of CSF Hcrt-1 in patients with ESD may help in the diagnosis of narcolepsy. In patients with cataplexy it may select a small subgroup of patients with a different physiopathology. In patients without cataplexy, the determination is useful in finding narcoleptic patients with a partial clinical expression or with doubtful cataplexy. Overall, in our experience the test is only useful in HLA DQB1*0602 positive patients.

P529

A comparison of polysomnographic and actigrafic evaluation of periodic leg movements in sleep

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Periodic leg movements in sleep (PLMS) represent a quite common sleep disorder characterized by recurrent motions ranging from triple-flexion in hip, knee and ankle through big toe extension similar to Babinski's sign to mere electromyographic (EMG) activity of anterior tibial muscles. Such activity must happen at least 4 times in a row lasting from 0.5 s to 5 s and intervals between individual movements have to be from 5 to 90 s. The number of kicks per hour of sleep (PLMI) of 5 and more is regarded as significant PLMS occurrence. The disease is often associated with the restless legs syndrome (RLS). A standard method of PLMS detection is polysomnography, including surface anterior tibial muscles EMG. Since 1995 there have been efforts to record the actual movements by means of high-resolution actigraphy which is more convenient for the patient and cheaper and easier for evaluation. However, limited data are available on specificity and sensitivity of this method. The aim of our study was to compare results obtained be simultaneous polysomnographic and actigraphic recording and thus estimate the specificity and sensitivity of actigraphic evaluation.

We recorded 50 nights in 45 consecutive patients in sleep laboratory, of those 14 referred to have RLS symptoms and in 15 sleep apnoea syndrome (SAS) was diagnosed. Using the same periodic leg movement criteria for both methods and the cut-off PLMI > 5, we proved the specificity of 66 %, sensitivity 69 %, positive predictive value 64 %, negative predictive value 72 % and total diagnostic accuracy of 68 %. A close correlation between PLMI resulting from either recordings (Pearson's coefficient r = 0.73) was observed, but actigraph PLMI proved to be significantly lower. This finding suggests, the cut-off value for actigraphy should be reviewed, to increase the sensitivity, so that actigraphy could serve as a screening method as it was formerly proposed. Further, we found no out-of-trend differences between the studied procedures in SAS patients. In RLS patients we proved more non-periodic leg movements, but the PLMI remained in close correlation. So regarding these two most prevalent sleep disorders – SAS and RLS, actigraphy and polysomnography seem to produce comparable results while detecting PLMS.

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P530

Quality of life in restless legs syndrome – influence of daytime sleepiness and fatigue

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Introduction: Restless legs syndrome (RLS) is a frequent neurological disorder characterised by leg paraesthesia and motor restlessness. Discussion still goes on about the effect of the disease on daytime sleepiness and quality of life. The presented study intended to evaluate the daytime problems by different scales.

Patients and Methods: 28 RLS patients with RLS (9 men, 19 women, age: 58.6 ± 11.9 years) were investigated with the following instruments:

Epworth Sleepiness Scale (ESS), which prescribes the chance to doze off in some daily situations, severity from 0 to 3, score > 11 indicates daytime sleepiness.

Fatigue Severity(FSS) Scale (FSS by Krupp et al.) Estimation of fatigue in various situations with severity from 1 to 7, score > 37 indicates fatigue.

Short Form-36 from Health Survey (SF-36). Evaluation of health related quality of life on eight dimensions, predominantly describing physical and mental/emotional impact.

19 patients staged their complaints in the International Rating Scale for restless legs syndrome (IRLS), 0 to 40 points.

Results: 17 patients presented an ESS > 11. Significant correlations regarding the SF-36 with ESS could be demonstrated in 6 terms judging physical deficits ($r = -0.399$ to $r = -0.550$, $p < 0.05$ to $p < 0.01$) and in 12 terms judging emotional problems like depression and anxiety ($r = -0.320$ to $r = -0.637$, $p < 0.05$ to $p < 0.01$).

17 patients scored > 37 in the FSS. Significant correlations regarding the SF-36 with FSS could be demonstrated in 8 terms judging physical deficits ($r = -0.339$ to $r = -0.550$, $p < 0.05$ to $p < 0.01$) and in 6 terms judging emotional problems ($r = -0.324$ to $r = -0.497$, $p < 0.05$ to $p < 0.01$).

In the 19 patients with available RLS-Severity-Scale the severity was correlated with problems described in the SF-36 ($r = -0.413$ to $r = -0.636$, $p < 0.05$ to $p < 0.01$). They were affected in the same amount with physical problems (8 terms) and emotional problems (9 terms).

Conclusions: RLS-patients suffer as a consequence of their disease from daytime sleepiness and fatigue. These symptoms have to be distinguished with different scales as daytime sleepiness causes emotional problems and fatigue predominately causes physical impairment (FSS). Follow up studies will evaluate therapeutic effects. It has to be decided if antidepressant or stimulants have to be added to dopaminergic medication.

P531

Insomnia associated with Whipple encephalopathy

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Whipple disease (WD) is a relapsing systemic illness characterized by migratory polyarthralgias, chronic diarrhea and fever. Central nervous system (CNS) involvement may occur in 5–40 % of all patients. In 15 % of cases, cerebral WD may occur without evidence of gastrointestinal infection.

We report the case of a 48-year-old man, with severe insomnia, dysarthria, myoclonic jerks of right limbs and complete ophthalmoplegia. His history included migratory non-deforming recurring arthritis and lymphadenopathy. He had been followed for 2 years for fever spikes of unknown origin. There was no history of gastrointestinal symptoms. Magnetic resonance imaging (MRI) of the brain showed abnormal hyperintensive signal in the area of basal ganglia. WD of the CNS was suspected as findings were consisting with the diagnostic criteria proposed by Louis et al.

The results of polymerase chain reaction (PCR) analysis of blood and stool confirmed the diagnosis. The patient received antibiotic therapy. He showed improvement as myoclonic jerks subsided and horizontal saccades – but not vertical – were partially restored. Six months later a new MRI of the brain was obtained which revealed resolution of the lesions in the basal ganglia. Despite antibiotic therapy, insomnia persisted. Polysomnography showed 110 min total sleep and no rapid-eye movement (REM) sleep. Hypnotics and neuroleptics had no effect. Carbamazepine was administered (600 mg/day) based on the findings in a similar case by Voderholzer et al. The total duration of sleep increased up to 389 min after 4 months under Carbamazepine treatment.

Hypothalamic manifestations occur in 31 % of CNS WD. Involvement of the pontomesencephalic area, supported by the presence of vertical ophthalmoplegia, may play a role in the regulation of the sleep cycle and of REM sleep, although no lesions were detected in MRI scan.

CNS WD without treatment follows a fulminant course. Because the disease is rare, has an insidious onset and sometimes lacks the characteristic gastrointestinal signs, diagnosis might be missed or reached quite late in its course, when antibiotic treatment may be less effective. Our case also supports the finding that Carbamazepine might be useful in the treatment of insomnia associated with CNS WD. To the best of our knowledge, this is the second case of severe insomnia due to CNS WD that resolved with Carbamazepine treatment.

P532
Does sleep apnoea predict outcome in neurorehabilitation (NR) after stroke?
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Background: Recent publications focus on the role of sleep in brain plasticity resp. in learning and memory. Two hypotheses receive experimental support: 1) REM sleep serves an important role, 2) REM sleep serves no role in memory processing and consolodating.

Setting: Inpatient NR.

Measurements: Barthel Index (BI); Basic activities of daily living (BADL); Rivermed Motor Assessment (RMA); Tinetti Test (TT); Apnea-Hypopnea-Index (AHI); Percentage of REM sleep (REM%).

Population: Consecutive cohort of 20 stroke patients:

12 patients severe disabled (BI ad admission beyond 30), 8 men.

Median age 64 years (26–79).

Time since onset of signs and symptoms to beginning of NR 7 weeks (2–14).

11/20 patients: REM depressant drugs (selective serotonin reuptake inhibitors) in low dose.

Statistics: Significant correlations are calculated using spearman's rank.

Multiple regression analysis. Descriptive data of cohort: median/mean – as appropriate.

Results and conclusion: Correlation analysis between sleep parameters (AHI, REM sleep, central apneas) and motor outcome parameters (TT, RMA, BADL): $p > 0.05$; n. s.

1.) Amount of all types of apneas/hypopneas (AHI) does not predict outcome.

2.) Amount of central apneas/hypopneas is not associated with outcome.

3.) Amount of REM-sleep is not associated with motor learning measured by TT, RMA, BADL.

Peripheral neuropathy

P533
Topiramate differentially influences cytokine expression after peripheral nerve injury
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Topiramate (TPM) is an antiepileptic drug with a wide spectrum of actions and is currently being investigated for potential neuroprotective properties. Here we investigated whether TPM influences injury induced cytokine regulation in the peripheral nervous system (PNS). We measured mRNA expression of the proinflammatory cytokines tumor necrosis factor-alpha (TNF), interleukin (IL-)1 beta, IL-6, of the anti-inflammatory cytokine IL-10 and of TGF-beta 12 and 24 hours after a sciatic nerve crush lesion in the nerve itself and in the L4 and L5 dorsal root ganglia (DRG) using quantitative real time PCR. In addition, an enzyme linked immuno assay (ELISA) was used to quantify IL-10 protein, since mRNA expression of IL-10 often differs from protein-levels. Immunohistochemistry was used to identify the cytokine-producing cells. In the sciatic nerve distal to the crush lesion, mRNA levels of all cytokines were increased with a peak 12 hours after surgery except for IL-6 which peaked 24 hours after crush. Under TPM-treatment, the mRNA of the proinflammatory cytokines was further upregulated (TNF $\times 3$, IL-6 $\times 2.2$, and IL-1beta $\times 1.4$) whereas IL-10 was reduced (x 0.7). TGF-beta levels were not altered under TPM-treatment. Schwann cells could be identified as the major cytokine producing cells for both pro- and anti-inflammatory cytokines. In the DRG, mRNA expression peaked later (at 24 h for TNF, IL-1beta, and IL-6) except for IL-10 which peaked at 12 hours. Treatment with TPM increased expression of IL-6 and – contrarily to the sciatic nerve – IL-10. Protein levels for IL-10 in the sciatic nerve but not the DRG were found to be nearly 2 times higher under TPM compared to saline treatment 12 hours after crush. Differences between nerve and DRG may be caused by the type of cells producing the cytokines, which are mainly Schwann cells in the peripheral nerve and mainly neurons in the DRG. Furthermore, the effect of TPM on IL-10 gene expression and post-transcriptional or post-translational regulation seem to be distinct.

P534
The use of targeted nerve and muscle biopsy in the diagnosis of vasculitis
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Previous studies suggest that combined nerve and muscle biopsies (usually of the superficial peroneal nerve and peroneus brevis muscle) produce a higher diagnostic yield when compared to nerve biopsy alone in the investigation of vasculitis. We have reviewed our own experience in the use of targeted nerve and muscle biopsy in the diagnosis of vasculitis. We interrogated our data base of nerve and muscle biopsies between the years 1999 and 2004 to identify cases of vasculitis and used case records to provide clinical and electrophysiological data. In each case electrophysiology was performed prior to biopsy. If the sural nerve sensory action potential (SAP) was either reduced or absent, this nerve was biopsied, if not an alternative affected nerve was chosen. All muscle biopsies were taken from the quadriceps muscle. Nerve pathology was defined as showing either definite or probable vasculitis and all cases included in the study had a clinical diagnosis of vasculitis. 93 nerve biopsies (81 of sural nerve) were performed for suspected vasculitis, 26 showed evidence of vasculitis (15 definite and 11 probable). 46 muscle biopsies were also performed, of which 4 showed evidence of vasculitis and in all these cases vasculitis was also present in nerve. We identified 10 cases of isolated peripheral nerve vasculitis and 16 cases of vasculitis as part of multi-system disorder, including: Rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, polyarteritis nodosa, Wegener's granulomatosis, Churg-Strauss syndrome, paraneoplastic disorders and infection with Hepatitis B, C and HIV. 15 patients presented clinically with mononeuritis multiplex, 8 with symmetrical sensory or sensorimotor neuropathy and 3 with asymmetrical sensory or sensorimotor neuropathy. Electrophysiology showed evidence of mononeuritis multiplex in 12 patients, an axonal symmetrical sensory or sensorimotor neuropathy in 7 cases, and axonal asymmetrical sensory or sensorimotor neuropathy in 5 cases. 2 patients had mixed axonal and demyelinating features. In agreement with previous series we find that 60 % of patients have vasculitis as part of a multi-system disorder and 40 % have isolated peripheral nerve vasculitis. However we have not found that combined muscle and nerve biopsy improves diagnostic yield compared to nerve biopsy alone. This may reflect differences in the use of electrophysiology to target suitable nerves to biopsy, differences in biopsy site or referral population.

P535
Motor involvement in herpes zoster
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Background: Herpes Zoster(HZ) is well known as a benign viral infection affecting the sensory nerves. But this disease may also cause motor paralysis is less well known. However motor involvement is hard to detect clinically, because most lesion of HZ is located in thoracic spinal level.

Goals: We performed this study to evaluate the exact prevalence of motor involvement and to compare the extent of EMG abnormality with that of skin lesions.

Methods: Ninety patients (male:female; 39:51, mean age 52.3 years old) with HZ who did not show clinical motor weakness except 4 patients with Ramsay-Hunt syndrome were studied prospectively for 2 years using EMG which is generally known to be very sensitive method for detection of motor involvement. We did paraspinal needle EMG means 11.9 days after pain or skin lesion. We try to find denervation potentials (Fibrillation potentials and positive sharp waves).

Results: Most common location of HZ was thoracic segments (59/90) and motor involvement

(Denervation on EMG study) was 56.67 % (51/90 patients) and subclinical motor involvement was 54.65 % (47/86 patients). And there was no statistically significant difference in the rates of motor involvement among the cranial (7/14), cervical (2/3), thoracic (33/59) and lumbosacral lesions (9/14) or in the rate of motor involvement between the male (24/39) and female (27/51), although the positivity were higher in male. The subclinical motor involvement was gradually increased by aging, as seen in clini-

cal motor paralysis of other report. There was significant statistic difference between the number of dermatome involved by skin lesion (mean 1.88) and that of myotome with motor involvement (mean 2.55).

It was suggested that subclinical motor involvement in HZ is rather frequent and extensive than generally expected.

P536
Effects of neuropeptides on sudomotor function
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Some neuropathic pain states are accompanied by a dysfunction of the sympathetic nervous system, e. g. exaggerated sudomotor function. The aim of our study was to investigate possible interactions between primary afferent and sudomotor efferent neurons.

Neuropeptides may be candidates since the concentration of CGRP (calcitonin gene related peptide) is increased in CRPS (complex regional pain syndrome) which is often associated with sweating abnormalities. Up to now only a few studies have shown that CGRP influences sweat rate, but these results were conflicting.

For this reason we investigated the effect of different concentrations of CGRP on nicotine induced sweating on 8 subjects (5 females, 3 males, age: 25 ± 1) who participated in 14 experiments.

Nicotine and CGRP were applied via intradermal microdialysis using fibers with a cut-off of 3,000 kDalton. With this technique all substances were applied without time related skin trauma, which would itself increase the concentration of neuropeptides in the skin. Nicotine (10–4 mol) alone always elicited a sweating response. When nicotine was combined with high concentrations of CGRP, sweating was reduced by about 65 % (CGRP 10–5) and 15 % (CGRP 10–6 mol). However, when lower concentrations of CGRP were used (10–7 and 10–8 mol) sweating was enhanced by 110 % (CGRP 10–7) and 12 % (CGRP 10–8).

We conclude that CGRP enhances the sweating response in physiological lower concentrations, whereas higher concentrations of CGRP have a different effect. Higher concentrations of CGRP induce a local vasodilatation which might lead to a faster clearing of local nicotine and therefore reduced sweating.

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P537
Tactile C-fibres may have interoceptive roles
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Cutaneous receptors are regarded as exteroreceptors with close connections to somatosensory brain areas, which underlie the perception of the detailed physical characteristics of external objects. Recently, however, various types of thinly myelinated and unmyelinated cutaneous afferents have been linked to the concept of interoception due to their potential to signal the physiological condition of the body. Such afferents have been proposed to be the afferent limb in a network controlling homeostasis and the well-being of the individual, with the autonomic nervous system being the efferent limb. The thin afferents activate posterior insula where the physiological condition of the body may be represented (i. e. interoceptive cortex).

Recently, we showed that the human hairy skin is equipped with unmyelinated (C) fibres responding to light touch. Findings in a rare patient lacking large myelinated afferents demonstrated that tactile C (CT) afferents activate posterior insula and signal a weak and spatially indistinct, but pleasant, sensation suggesting a role for CT afferents in interoception.

We have now investigated another patient (I. W., age 51) with selective large-fibre sensory neuropathy, and control subjects (n = 4). Testing, performed on the forearm, included psychophysical detection and galvanic skin response (GSR) to stroking with soft water-colour brush, and functional magnetic resonance imaging (fMRI, 1.5 tesla, BOLD protocol) during manual caressing (alternating epochs of 10 s caressing and 10 s rest).

A pure CT stimulation (brush stroking in the patient) gave a barely noticeable sensation that could be detected in a two-alternative forced-choice situation. A CT stimulation (caressing in the patient) evoked fMRI activation in posterior insula and somatosensory area two (S2), whereas a combined A and CT stimulation (caressing in normals) activated S1. Further, a pure CT input evoked a GSR response even in tests when the patient did not perceive the stimulation.

We have confirmed that CT afferents activate posterior insula and may evoke a barely noticeable sensation. We also demonstrated that a pure CT stimulation can evoke a sympathetic (GSR) response even in the absence of stimulus perception. These findings support the idea that CT afferents constitute a specific system through which tactile stimulation can affect homeostasis and general well-being of the individual, i. e. a system for sensual touch.

P538
Vascular endothelial growth factor serum concentration and diabetic neuropathy
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The prevalence of diabetic neuropathy ranges from 7 % within one year of diagnosis to 50 % for those with diabetes for more than 25 years. The pathogenesis of diabetic neuropathy has remained enigmatic even though microangiopathic abnormalities with impaired blood flow and ischemia have been implicated. Angiogenetic factors, with preminence of vascular endothelial growth factor (VEGF), appear to play a pivotal role in the development of microvascular complications. VEGF has already been proved to be a major mediator of the intraocular neovascularization present in diabetic retinopathy while a possible role in diabetic neuropathy is suggested by the increased nerve conduction velocities induced by VEGF gene transfer in neuropathic animals with experimental diabetes.

We evaluated the VEGF serum concentration in three populations, 42 type II diabetic patients including 11 with neuropathy, 176 patients with other neurological disorders (OND) and 55 healthy subjects, in order to investigate if there is any correlation between the VEGF serum concentration and the presence of diabetic neuropathy. Patients included in the study were required to have normal platelet count and no clinical evidence of tumor or metastases. VEGF serum concentration was measured in duplicate using a commercial ELISA kit. For type II diabetic patients the mean of the VEGF serum concentration was 302.07 pg/mL ± SD 246.69; for OND patients mean 409.93 pg/mL ± SD 281.88; for healthy controls mean 370.92 pg/mL ± SD 184.32 (diabetic populations versus control pvalue = 0.07, versus OND pvalue = 0.009. Control population versus OND pvalue = 0.09). Among diabetic patients VEGF levels tended to be lower in those with neuropathy (mean 244.24 pg/mL ± SD 139.26) than without (mean 324.79 pg/mL ± SD 276.72).

In this preliminary small-scale study serum VEGF concentration was reduced in type II diabetes even if its correlation with the presence of neuropathy needs to be confirmed in larger cohort of patients.

P539
Efficacy of pregabalin in patients with painful diabetic neuropathy: a pooled analysis of three clinical trials
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Aims: To evaluate the efficacy and safety of pregabalin administered three times a day (TID) in three clinical trials in patients with painful diabetic peripheral neuropathy.

Methods: Pregabalin was studied in three randomized, double-blind, placebo-controlled, fixed-dose, parallel-group trials with a 1 week baseline phase followed by a double-blind treatment phase ranging from 5–8 weeks in duration: 1008-14 (150 and 600 mg/day; 6 week duration), 1008-29 (75, 300 and 600 mg/day; 5 week duration), and 1008-131 (300 mg/day; 8 week duration). The primary efficacy parameter was the endpoint mean pain score from the daily pain diaries (recorded daily using 11-point numerical rating scale). Secondary efficacy measures included 50 % and 30 % responder analyses, Short Form McGill Pain Questionnaire (SF-MPQ), sleep interference diary, and Patient and Clinical Global Impressions of Change (PGIC, CGIC).

Results: The ITT population comprised 729 patients (164 received 600 mg/day pregabalin, 157 received 300 mg/day, 79 received 150 mg/day, 77 received 75 mg/day, and 252 received placebo). Both the 300 and 600 mg/day pregabalin doses were effective in reducing endpoint mean pain scores (each p-value ≤ 0.0001). Forty-three percent of patients in the 300 mg/day dose group and 44 % in the 600 mg/day dose group were 50 % responders compared to 16 % of placebo patients (both comparisons p = 0.001). Similarly, significantly more patients showed a 30 % reduction in pain in the 300 and 600 mg/day doses compared to placebo. Statistically significant improvements were also seen in sleep interference scores, SF-MPQ scores, PGIC and CGIC. The efficacy of the 300 and 600 mg/day pre-

gabalin doses was evident by week 1 on the weekly mean pain and sleep scores and SF-MPQ scores, and efficacy was maintained through study end. Pregabalin was generally well tolerated. Dizziness and somnolence were the most commonly reported adverse events. Eighty-nine percent of patients completed the studies, and 88 % entered the follow-on open-label studies.

Conclusions: Pregabalin at doses of 300 and 600 mg/day produced statistically and clinically significant improvements in patients with painful diabetic peripheral neuropathy.

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Inflammatory small fibre neuropathy observed in patients with HTLV-I/II- infection

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Inflammatory chronic sensory neuropathies are usually related to infectious diseases such as HIV infection, leprosy, and others. In several cases vasculitis is observed in superficial nerve biopsy. Nevertheless, inflammatory small fiber neuropathy (SFN) with vasculitis is an uncommon finding in association with HTLV-I infection. We describe the clinical, electrophysiological and hystopathological findings of SFN observed in patients with HTLV-I/II-infection.

We analyzed the clinical, electrophysiological and hystopathological findings of 14 HTLV-I-infected patients presenting a SFN. Sural nerve biopsy revealing inflammatory changes was seen in all cases. Concurrent causes of peripheral neuropathy were ruled out. The mean age of HTLV-I-infected patients was 44.4 years (range: 31–72 y.). The mean time follow-up was 3 years. Sensory symptoms were present in all patients: numbness or tingling without pain (3 cases), numbness or tingling with pain (8), only burning-feet (3). These symptoms were present mainly in the distal lower extremities. Pinprick and temperature sensations were the compromised sensory modalities in the neurological examination. Reflexes were preserved or reduced at the ankle. In 4 HTLV-I patients there were signs indicating a mild involvement of the spinal cord. Autonomic involvement was verified in 6 HTLV-I/II patients. A careful neurological examination revealed a summated effect of multiple mononeuropathy producing a distal, asymmetric polyneuropathy observed in 6 HTLV-I. Nerve conduction studies were normal in 10 patients, and fulfilled criteria for axonal neuropathy in the others. CSF examination showed protein within normal limits in all cases, and HTLV-I ELISA and W. blot tests positivity for HTLV-I/II virus. Sural nerve biopsy disclosed an axonal neuropathy with lymphocytic epineural microvasculitis in 11 cases, but in 3 there was necrotizing vasculitis. Prednisone therapy was beneficial for the majority of patients. Pain intensity decreased with gabapentin.

This study provides evidence that an inflammatory SFN can be associated with HTLV-I/II infection. A distal asymmetric polyneuropathy, due to inflammation in the nerves, seems to be the most common pattern of SFN in this infection. Facing a patient with a SFN in an endemic region, we should consider HTLV-I/II as a possible cause.

P541

Inflammatory polyradiculoneuropathy with quadriplegia in a patient with Chediak Higashi syndrome

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Chediak-Higashi syndrome (CHS) is a rare autosomal recessive lysosomal disorder associated with albinism, increased susceptibility to infections during infancy due to defective macrophage activation and immunedeficiency, occasionally associated with mild chronic neuropathy. Most patients die during childhood from infection. Some patients improved after early bone marrow transplantation.

We report on a 22-year-old man with CHS who developed complete quadriplegia, while under treatment with ciclosporin. The diagnosis of CHS was made at 16 years of age when he had a "Guillain Barré-like" syndrome following vaccination against poliomyelitis, associated with macrophage activation, recurrent infections, moderate mental retardation and albinism. He was subsequently treated with ciclosporin and antibiotics. Six years later, in May 2003, he complained of walking difficulty. He then had asymmetrical mild distal motor deficit in lower limbs, abolished deep tendon reflexes, mild distal hypoesthesia, dysarthria, cerebellar ataxia, memory disturbances with normal MRI. A biopsy of the right peroneal nerve biopsy showed only minor axonal lesions. In September 2003 he had improved and could walk with assistance. He then stopped taking ciclosporin. In December 2003, he became febrile and developed severe weakness and amyotrophy of both lower limbs within a few weeks and asymmetrical deficit of the upper limbs, with mild distal hypoesthesia. Electrophysiological testing showed diffuse sensorimotor axonopathy. CSF protein was 7.75 g/L (N < 0.40 g/L), with 39 cells/mL. The biopsy of the left superficial peroneal nerve showed massive Wallerian degeneration, endo- and epineurial infiltration by mononuclear cells made of lymphocytes and macrophages, with multifocal "attacks" of nerve fibres. On EM examination the unmyelinated fibres were also affected. No other organ was affected. The patient became quadriplegic within a few days, with proximal and distal strength at 0/5; the cranial nerves and respiration were preserved. He was treated with ciclosporin, VP16 and dexamethasone. He remained stable within the next three months.

This catastrophic polyneuropathy was the only manifestation of macrophage activation in this patient. We assume that interruption of treatment with ciclosporin by the patient may have induced a sudden rise of macrophage activation.

P542

Genotype-phenotype study of Charcot-Marie-Tooth disease type 1A

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Background: Charcot-Marie-Tooth-disease (CMT) is the commonest inherited neurological disease. Genotype-phenotype studies have been most extensively studied in CMT 1A secondary to the chromosome 17 duplication (chr 17) but there is no explanation for the variation in disease severity observed with this genetic abnormality. GOALS The aim of this study was to describe the phenotype in patients with chr 17 CMT1A and to identify environmental phenotype modifiers.

Methods: This was a retrospective study of case notes of patients who have attended the National Hospital for Neurology, with chr 17 CMT1A. A detailed proforma was used to obtain the relevant information. Each patient was assessed retrospectively using a nine-point functional disability scale (FDS), a modified sensory scale, the CMT neuropathy scale and nerve conduction studies.

Results: Of the 83 patients identified 40 were male and 43 female. Disease onset was in the 1st decade in 65 % of cases and in the 2nd decade in 21.3 %. All patients had signs. The most important clinical signs were distal wasting and weakness in the lower limbs. The lower limbs were always affected to a greater extent than the upper limbs although both were affected in over 80 % of patients. In 35 cases some reflexes were depressed and in 48 patients areflexia was present. Sensory loss was evident in 63 patients. It affected the lower limbs only in 46 cases. Pes cavus was present in 53 patients. Scoliosis was present in 9 cases. Nerve enlargement was detected in 18 patients. Functional disability was

mild or absent in 58.8 %. Motor nerve conduction velocities (MNCV) were uniformly reduced in all nerves; the mean MNCV was 19.6 m/s in the median nerve and 18.3 m/s in the ulnar nerve. Sensory action potentials were reduced or absent in all cases. The only environmental factor found to influence phenotype was smoking, which increased the severity of the phenotype regardless of age but as the numbers were small this finding needs to be interpreted cautiously.

Conclusions: As previously reported, clinical severity with CMT 1A ranges from being severely affected in early childhood to being completely asymptomatic in later life and neurophysiological data suggested marked uniformity in the slowing of the MNCV. No significant environmental influences on phenotype were found except smoking which needs further study.

P543

Changes in the neuromuscular synapses of the mouse induced by the chronic application of an IgM monoclonal antibody against the terminal moiety of GM2, GalNAc-GD1a and GalNAc-GM1b gangliosides

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We use a monoclonal IgM antibody from a patient with a pure motor chronic demyelinating polyneuropathy which binds specifically to the complex gangliosides GM2, GalNAc-GD1a and GalNAc-GM1b whose common epitope appears to be – (GalNAcbeta1-4Gal(3–2alphaNeuAc)beta1), first, to reproduce an animal model of that pathologic condition. Second, to localize these gangliosides in specific cellular components of the NMJ. Third, to describe the antiganglioside antibody-induced structural and functional changes in the NMJs relating gangliosides and synaptic function. By immunofluorescence techniques, we found that these gangliosides are only located in the presynaptic component of the motor endplates,

both in nerve terminals and Schwann cells. After two weeks of continued passive transfer of the mIgM over the mouse Levator auris longus muscle, electromyography showed an axonal or NMJ transtorn. Morphology shows demyelination changes in the intramuscular nerves and important nerve terminal growth and retraction changes. By intracellular recording electrophysiology, we found neurotransmitter release alterations including quantal content reduction and an immature expression of VDCCs similar to that occurring during NMJ development and regeneration. These results show that these gangliosides are involved in the reciprocal Schwann cell-nerve terminal interactions including structural stability and neurotransmission.

P544

Clinical and neurophysiological patterns of GBS patients in Kuwait

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Background: Being a tertiary neurology care center, our hospital receives almost all cases of Guillain-Barre Syndrome (GBS) in Kuwait. The study was carried out to analyze the clinical and Neurophysiological patterns of GBS in our population.

Methods: The clinical records of 41GBS patients admitted between 1997 and 2003 were retrospectively analyzed.

Results: There were 30 males and 11 females and age ranged between 16 to 72 years. 59 % of our cases occurred in the winter months (November to March). 18 patients (44 %) had preceding respiratory infection, 6 patients (15 %) had diarrhea and 2 patients (5 %) had both. 3 patients (7 %) had Miller-Fisher syndrome (MFS).

Predominant proximal weakness (90 %) was noted in Lower Limbs (LL), while in the upper limbs both distal and proximal muscles were equally involved (57 %). Respiratory failure (7 patients/17 %), bulbar weakness (6 patients/15 %) and autonomic disturbance (8 patients/20 %) occurred together in 5 patients (13 %) who required plasma exchange (PE). Nerve conduction studies (NCS) revealed demylination in 28 patients (70 %), axonal pattern in 6 patients (15 %), mixed type in 2 patients (5 %) and was normal in 2 patients (5 %). As for treatment, 30 patients (77 %) improved with 1 course of Intravenous Immunoglobulin (IVIg), 4 patients (10 %) received a 2nd course of IVIg and 5 patients (13 %) had PE, while 2 patients didn't receive any treatment.

Mean recovery time (MRT), (time at which patient improves by 1 grade from nadir in modified objective scale published by Miller et al.), was 4.4 weeks. MRT was 3.8 weeks in patients who improved after one course of IVIg, 6 weeks for patients who needed a 2nd course of IVIg, and 7 weeks for patients who had PE.

Delayed recovery (MRT more than 5 weeks) was common in female gender, if the plateau phase last more than 2 weeks, predominant distal weakness in LL and proximal weakness in UL, bulbar weakness, autonomic disturbance, respiratory failure and axonal type in NCS. Early recovery (MRT 3 to 3.3 weeks) was associated with descending type of motor weakness, MFS and mixed type in NCS. Surprisingly, older patients (more than 70 years of age) showed a faster recovery. There was no mortality in our series.

Conclusion Although our group of patients is generally similar to those described in literature, however their response to treatment is different depending on pattern of disease progression, distribution of weakness, and gender.

P545

Measuring outcome in chronic inflammatory demyelinating neuropathy using quantitative muscle testing

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Background: Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is an immune mediated disorder characterised by motor and sensory dysfunction. The time course may be relapsing – remitting, progressive or monophasic with long periods of disability. Intravenous immunoglobulin (IVIg) is one of the treatments advocated and has been demonstrated to have good results when compared to placebo and other therapeutic interventions.

Muscle weakness is one of the major manifestations of CIDP and the importance of quantitative and reliable tests to assess the outcome of therapeutic and pharmacological intervention on muscle strength has been well established. While manual muscle testing and functional assessment are effective in determining the response to therapy in most patients, objective clinical response may be difficult in some cases.

Methods: We have used MVIC as an objective measure of change in muscle strength before and after treatment in a cohort of patients with CIDP (n = 15). Patients are assessed prior to treatment and within 2–4 weeks post infusion. Muscle strength is measured in 10 muscle groups (neck flexion, upper limbs: shoulder abduction and adduction, elbow flexion and extension and hand grip, lower limbs: hip and knee flexion, knee extension and ankle dorsiflexion) and compared to age matched normative data generated from the Irish population. Each member of the cohort has been followed for a minimum of 6 months

Results: The degree of response and intervals between required treatments, varies considerably between patients. In some patients, differences between the mean of pre- and post treatment MVIC results does not differ significantly. However in these cases individual strength results often demonstrated a significant increase post-treatment, which was concurrent with the patients' subjective reports. In these cases comparison to normative data demonstrated the extent of the strength deficit.

Conclusion: MVIC testing is a useful adjunct to the medical management of patients with CIDP. It allows precise estimation of the extent of muscular weakness and accurate analysis of treatment intervention.

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Heat pain hyperalgesia in patients with Bell's palsy

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Background: Patients with facial palsy often report sensory symptoms over the paretic part of the face. To test for the presence of sensory disturbances we applied a battery of sensory tests according to the Quantitative Sensory Testing (QST) protocol of the German Research Network on Neuropathic Pain (GNNP) over ipsi and contralateral parts of the face.

Methods: Sixteen patients with idiopathic facial palsy and 32 controls were studied. All patients were investigated within 3 days after onset of symptoms. Seven tests were performed determining 13 variables over ipsi and contralateral cheek and forehead including thermal (cold and warm perception threshold, thermal sensory limen, paradoxical heat sensations, cold pain and heat pain thresholds) and mechanical stimuli (von Frey filaments, pinprick stimuli, vibration threshold using a tuning fork, and pressure pain thresholds using a handheld algometer).

Results: Heat pain threshold was lowered by 1.3°C over ipsilateral face ($p = 0.036$; ANOVA; LSD post hoc-test) without a significant cheek-forehead difference. All other pain thresholds were not reduced ($p > 0.16$). Additionally thermal and mechanical perception thresholds tended to be increased over the affected side of the face. However, this effect was only significant for cold perception threshold ($p = 0.02$; ANOVA; LSD post hoc-test), again with no cheek-forehead difference. These findings were not related to the presence of dysaesthesia (6 out of 16 patients).

Conclusion: Our finding of heat pain hyperalgesia in patients with facial palsy is consistent with peripheral rather than central sensitization of nociceptive neurons, probably due to a trigeminal affection. This result also contributes to the old concept of polyneuritis cranialis rather than mononeuritis facialis in patients with idiopathic facial palsy (Adour et al., Arch Otolaryngol 1976; 102:262–264).

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Autoimmunity in painful sensory neuropathy

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Painful sensory neuropathies consist of a wide range of neuropathies that can involve large as well as small nerve fibres. Even if most cases remain of unknown cause, some of them may be associated with an underlying disorder such as diabetes, HIV, infections, amyloidosis, Sjogren's syndrome. Since in some cases an autoimmune mechanism has been postulated, we investigated a panel of circulating autoantibodies including anti-gliadin (AGA), anti-endomysium (EmA), anti-transglutaminase (tTGA) and anti-nuclear (ANA) antibodies in the sera of patients with unexplained painful sensory neuropathies in order to identify other potentially treatable disorders. We tested the sera of 10 patients (4M: 6F) previously investigated for other causes of neuropathies, including anti-nerve, onconeural, anti-extractable nuclear, anti-neutrophil cytoplasmatic, anti-thyroglobulin (TgA) and anti-peroxidase (TPOA) antibodies. We found the presence of AGA positivity in 4 patients (40 %), ANA in 6 (60 %) and AGA+ANA in 4 (40 %), two of whom were negative for celiac disease by gastrointestinal biopsy. None of the patients had EmA positivity. Three (30 %) had TgA and TPOA and none had anti-nerve or onconeural antibodies. Whether the presence of circulating autoantibodies in patients with unexplained painful neu-

ropathy, reflect a autoimmune involvement which may be amenable to immune therapy and not only to symptomatic treatment, remains to be established.

P548
Intraneurial perineurioma – a systemic disease?
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Intraneurial perineurioma is a rare clinical entity causing peripheral neurological deficit.

We present the case of a 29-year-old man referred because of progressive weakness and sensory deficit of his right lower extremity. Electrophysiological examinations revealed absence of the F wave of the right peroneal nerve, the right H reflex and the right sural nerve potential. The muscle action potential of the right peroneal nerve was reduced. Electromyography showed acute and chronic denervational changes localizing the lesion to the right sciatic nerve at the thigh. By MRI, post-gadolinium enhancement of the sciatic nerve was found, the common, superficial, deep peroneal nerve, tibial nerve and sural nerve being unsuspicuous. Sural nerve biopsy was performed because of supposed vasculitic mononeuropathia multiplex.

Histological examination revealed intraneurial perineurioma by finding loss of nerve fibers, disorganization of the fascicular pattern with compartimentalization of the endoneurium, proliferation of elongated cells forming concentric pseudo onion-bulb like structures and exhibiting positive immunoreactivity for epithelial membrane antigen EMA.

This multilocal presentation of intraneurial perineurioma has not so far been reported. By now, no consensus has been made on proper treatment of this entity. Focal surgical resection and sural nerve grafting often has only poor clinical and electrophysiological outcome.

Our finding of the sural nerve being affected too could be a possible explanation and indicates intraneurial perineurioma being a systemic disease.

We therefore recommend diagnostic sural nerve biopsy in case of intended surgical resection of the lesion with or without nerve grafting.

Pain and headache

P549
Pre- and postoperative correlation of high-resolution magnetic resonance imaging and microvascular decompression of the trigeminal nerve in patients with trigeminal neuralgia
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Background: Microvascular decompression of the trigeminal nerve is successfully performed in patients with trigeminal neuralgia (TN) if pharmacological therapy fails. Many attempts have been tried to visualize a neurovascular conflict at the nerve root entry zone preoperatively by magnetic resonance imaging. A correlation of pre- and postoperative MRI with the clinical status and intraoperative findings in a prospective series was performed.

Methods: In 20 patients with TN, which were considered for neurovascular decompression, high resolution imaging was performed using a 1.5 Tesla MRI-scanner (Symphony, Siemens, Erlangen, Germany). The examinations were performed 1–3 months before the operation and 3–6 months postoperatively. On both dates a clinical neurological status was achieved. The intraoperative findings were documented by video recording or photography.

Results: In all examinations a volumetric analysis of the trigeminal nerve in the cerebellopontine angle could be achieved. A significant side difference could be detected in the volumetry of the trigeminal nerves. In patients with TN the involved nerve was significantly thinner than the opposite side ($p < 0.0001$; 0.070 versus 0.085 cm^3). In the postoperative measurements the relationship of the trigeminal nerve, former vascular compression and decompressive effect of the interposed gore-tex sheet could be visualised. In two patients with recurrent neuralgia MRI revealed a dislocation of the interposed material. This was positively correlated with the intraoperative findings.

Conclusion: High-resolution MRI of the cerebellopontine region allows volumetric measurement of the trigeminal nerve. In cases of TN and neurovascular compression a significant unilateral atrophy of the nerve can be found. High-resolution MRI becomes more interesting in clinical diagnosis and indication for operative treatment, also in cases of recurrent pain after successful microvascular decompression.

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P550
Lamictal as add on therapy in the treatment of 100 Iranian patients with trigeminal neuralgia
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This study has been done to investigate the efficacy of Lamictal in reduction of frequency of painful attacks of trigeminal neuralgia.About 70 % of patients with idiopathic trigeminal neuralgia responds favorably to recommended drug (Carbamezipine, Phenytoin, Baclofen and Clonazepam) for this syndrome on monotherapy or in combination. A novel anticonvulsant, Lamictal blocks voltage sensitive sodium channels and inhibits the release of glutamate and aspartate.There have been anecdotal reports of efficacy of Lamictal in the treatment of painful neuropathy and trigeminal neuralgia. We conducted a single-blind, crossover, placebo contolled, multiple center clinical trial in patient with treatment resistant trigeminal neuralgia. A total of 100 patients from all over Iran received the lamictal (50 mg), Lamictal (100 mg a day) or placebo for up to six months after titration. For assessment of the primary outcome, patients had to complete the present pain intensity (PPI) questionnaire forms and pain frequency report before and every two weeks after the treatment. Among 100 patients in comparison of three groups crossed over the best result was in 100 mg/day Lamictal person ($P < 0.001$). In two group there was no statistically significant ($P < 0.05$). There were 62 % reduction in the severity and 58 % reduction in frequency of attacks in patients who were placed on Lamictal so treatment with 100 mg/day Lamictal as add on therapy is effective for patients with intractable trigeminal neuralgia.

P551
Bradykinin-induced inflammation in human forearm skin is enhanced after surgical sympathetic block
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Background: The endogenous peptide bradykinin (BK) is an inflammatory mediator that induces nociceptor activation and sensitization on the one hand, as well as plasma protein extravasation and vasodilation on the other hand. A pro-inflammatory involvement of sympathetic post-ganglionic neurons in the BK-induced neurogenic inflammation has been suggested.

Methods: To test this hypothesis dermal microdialysis was employed on the volar forearm in 10 patients (22–41 years) with palmar hyperhidrosis preoperatively and 3 months after surgical block of the sympathetic chain at the T2 or T3 level and in 8 healthy volunteers (22–36 years). After 60 min perfusion with Ringer's solution microdialysis fibers were perfused with BK 10(–7)M and 10(–5)M for 30 min followed by 30 min Ringer's solution again. To assess protein extravasation dialysate protein content was measured photometrically using Coomassie blue dye, and Laser-Doppler imaging was used to quantify axonreflex vasodilation.

Results: Mean flux values at almost every time point were significantly higher after sympathetic block as compared to controls and preoperative values ($p < 0.05$, MANOVA), regardless if perfusion with Ringer's solution or with BK. Neither BK 10(–7)M nor BK 10(–5)M lead to significant axonreflex vasodilation in any group. After perfusion with BK 10(–7)M no protein extravasation was found and dialysate protein concentrations did not significantly differ pre- (0.39 ± 0.05 mg/ml) and postoperatively (0.43 ± 0.04 mg/ml) in patients and in healthy controls (0.31 ± 0.04). Bradykinin 10(–5)M, however, lead to significant protein extravasation in all groups, but protein concentration after sympathetic block (0.91 ± 0.09 mg/ml) was significantly enhanced as compared to preoperative values (0.61 ± 0.05 mg/ml, $p < 0.05$) and to controls (0.53 ± 0.08, $p < 0.05$).

Conclusions: Our results show that forearm skin perfusion is increased after surgical sympathetic block on the T2 or T3 level. They further show that protein extravasation induced by BK 10(–5)M is significantly higher postoperatively, and thus clearly speak against the hypothesis that the sympathetic nervous system enhances bradykinin-induced inflammation.

P552

How patients' preferences lead to early termination of a randomised trial comparing surgical and non-surgical treatment in patients with sciatica and herniated lumbar disc

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Objectives: No clear criteria exist for an evidence-based decision between conservative and surgical treatment of acute sciatica and a disk herniation without functional relevant neurological deficits. The main objective was to compare the outcome of a conservative multimodal treatment with or without additional surgery.

Methods: DISK ("Deutsche Interventionsstudie radikulärer Kreuzschmerz") was designed as a prospective, randomized, controlled clinical trial. According to a sample size estimation it was planned to include 200 patients with acute sciatica and correlating disk herniation. Initially, patients received 14 days of standardized conservative inpatient treatment (consisting of non-steroidal analgetic-antiinflammatory drugs, muscle relaxants, opioids, steroids, physiotherapy based on the concepts of Maitland and McKenzie, physical therapy and relaxation techniques). Thereafter, patients were randomized into conservative and surgical groups. If marked improvement occurred or if exclusion criteria applied, patients were not been randomized but assigned to an observational follow-up group.

Results: Between October 2002 and November 2003 all patients with sciatica due to a herniated disk admitted to the inpatient service of the Department of Neurology Guenzburg were screened according to defined inclusion/exclusion criteria. 54 patients were included in the study. After the first 14 days of standardized conservative treatment, 18 patients (33 %) were markedly improved and one patient refused to further participate. The remaining 35 patients (65 %) were randomized. More than 80 % of the 17 patients randomized into the surgical treatment group preferred to continue non-surgical treatment. Only 3 patients randomized into the non-surgical group asked for surgery. As a result, after randomization 6 patients had a standardized microdiskektomy and 29 patients continued conservative therapy. Because of these methodological difficulties the study was terminated. In the following, the patients were interviewed about their reasons for refusing surgery. Mainly, the patients reported fear of suffering severe side effects from surgery and having improved by non-surgical treatment.

Conclusion: Multimodal medical treatment is an important approach for sciatica. Randomized studies in patients with acute sciatica are difficult to perfom in Germany.

P553

Headache and spontaneous cervical artery-dissections: time-course and follow-up

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Background: Headache is very common at the acute phase of cervical artery-dissection (CAD). However, the relationship between these 2 conditions are complex and the course of headache in patients with CAD is not well known.

The aim of this study was to evaluate the course of various types of headache in patients who had had spontaneous CAD.

Patients and methods: We conducted a telephone interview with a structured questionnaire about headache in all consecutive patients hospitalized for spontaneous CAD in our stroke unit between 1998 and 2001, confirmed by a mural hematoma on MRI.

Results: forty two patients had had a spontaneous CAD during this period. Twenty two had had headache in the past: 9 migraine without aura, 5 migraine with aura and 8 with episodic tension-type headache. Twenty one (95.5 %) improved their headache after the spontaneous CAD. Of 14 patients who were migrainers, 13 (92 %) had fewer migraine attacks after the CAD. Only 7 patients, without previous headache developed new headache after CAD: 3 migraine without aura, 3 episodic tension-type headache and one chronic tension-type headache.

Conclusion: Most patients improve their pre-existing headache after spontaneous CAD. A few patients only developed new headache after CAD.

P554

Effect of epidural blood patch for chronic orthostatic headache without typical MRI findings of intracranial hypotension

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The aim of this study is to shed light on the clinical entity of cerebrospinal fluid (CSF) leakage without typical MRI evidence of intracaranial hypotension (IH). We retrospectively evaluated 16 patients admitted to our institute with suspected IH. There were 5 men and 11 women with age ranging 16–65 years old. All had orthostatic headache associated with other miscellaneous symptoms and underwent MRI and radioisotope (RI) cisternography. Symptoms were relieved only by bed-rest in 3 patients and epidural blood patch (EBP) was attempted in 10; EBP was markedly effective in 7 and partly effective in 2. Of the 7 patients successfully treated with EBP, 4 manifested no definite MRI abnormalities indicative of IH. However, all shared the early appearance on RI cisternograms of tracer in the bladder suggestive of CSF leakage. Our radioisotope findings and the efficacy of EBP suggest that these patients had mild but persistent CSF leakage from the spinal dural sac. Therefore, it is necessary to widen the spectrum of the clinical presentation of CSF leakage and to recognize that EBP may be an efficacious treatment modality in patients with orthostatic headache who manifest no, or only subtle findings of IH on MRI and have no history of lumbar puncture.

P555

Is prolonged whiplash-associated disorder a result from cerebrospinal fluid hypovolaemia?

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Whiplash-associated disorder (WAD) after extension-flexion injury of the neck is benign and self-limiting in many cases, although some patients manifest various symptoms that can last for a long time. Starting in 2003, we postulated that posture-related symptoms in patients with WAD is attributable to persistent cerebrospinal fluid (CSF) leakage from spinal dural sac caused by mechanical impact. We examined 11 patients with WAD who experienced orthostatic headache or neck pain and other symptoms with 111In-DTPA radioisotope (RI) cisternography and the cisternograms resulted in the early detection of tracer in the bladder and/or tracer leakage from the dural sac in 7. Spinal epidural blood patch (EBP) was attempted in 7 and pains were successfully treated in 5. While CSF leakage can be related to traumatic impact, little has been reported on the relationship between CSF leakage and WAD. Our results suggest that some WAD patients may actually have CSF leakage causing CSF hypovolemia syndrome and that this treatable condition should not be overlooked in patients presenting with trauma to the head and neck.

P556

Motor cortical brain mapping in patients with complex regional pain syndrome type I

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Previously changes in sensory cortical representation in patients with complex regional pain syndrome (CRPS) were found. Therefore, we measured motor cortical size using transcranial magnetic stimulation in CRPS patients.

Thirteen patients participated (9 female and 4 male) and were compared with seven healthy subjects. Patients were divided into two subgroups: acute (8 with duration of < 6 month) and chronic (5 with duration of > 12 month). Using a figure-of-eight magnetic coil and a Magstim 200, the size of motor cortical representation and its volume for the affected (AC) and unaffected cortex (UC) were determined. Using a surface-EMG, the motor hot spot and resting motor threshold were detected. The coil was then systematically moved around until no further responses could be released and the size (cm^2) was marked on a plastic cape worn by the patients. Using amplitudes (mV), recorded at each stimulation site, the cortical volume could be calculated.

Seven acute (out of 8) and four chronic (out of 5) patients showed a smaller cortical size and volume for the AC. This was significantly different to the UC ($F(1/30) = 16.3$, $p < 0.001$), whereas no difference was found between acute and chronic patients. Size was 9.3 cm^2 for the AC and 14.6 cm^2 for the UC; volume was 26.1 (AC) and 37.3 (UC). In healthy subjects there were no significant differences between both cortices, but data were systematically smaller than in patients; size/volume: 5.6 cm^2/16.4 for the left and 6.1 cm^2/21.3 for the right.

CRPS patients showed significantly smaller motor cortical representation for the AC compared the UC. In acute patients the reduced usage, muscle weakness, and other symptoms would explain these findings. Chronic patients had nearly normal hand usage again, so this would not explain our findings. Pain as one main symptom in CRPS was discussed as possibly inducing changes in motor cortical excitability. With the close connection between sensory and motor cortical neurones and its high potential for plastic changes this would provide a hypothetical explanation for our findings of lasting changes.

An unexpected result were the smaller values in healthy subjects. There were no differences between the two sides and the difference to patients was not significant, but existent. The described reduced motor cortical inhibition in CRPS patients might point to a generally reduced inhibitory activity and could be one cause of an enlargement of motor cortical representation.

P557

Spontaneous intracranial hypotension treated with epidural blood patch

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Background and goals: Spontaneous intracranial hypotension (SIH) syndrome is characterized by orthostatic headache in conjunction with reduced cerebrospinal fluid (CSF) pressure. Epidural blood patch (EBP) has emerged as one of the most important nonsurgical treatments for spontaneous CSF leaks. We review our own experience with patients admitted to our department diagnosed of SIH and treated with EBP.

Methods: Six patients were admitted to our neurological unit for SIH between January 1998 and January 2004. Four of them, three women and one man (aged from 24 to 47 years) required EBP. In addition to gadolinium (Gd)-enhanced brain magnetic resonance imaging (MRI), spinal MRI with and without Gd-enhancement was performed in all patients and all of them underwent Indium-111 radionucleotide labelled cisternography.

Results: Brain and spinal MRI showed diffuse pachymeningeal Gd-enhancement in all subjects. Two of the patients had subdural hematomas and hygromas. In one patient radicular spinal cysts were seen on MRI. In none of the subjects Gd-enhanced spinal MRI identified the site of the leakage. Radioisotope cisternography identified CSF leakage sites in two patients at the thoracic spine level. Although exact site could not be identified in other two patients, cisternography showed an important CSF leakage. All the patients failed initial period of conservative, noninvasive management (from two to four weeks). Three patients significantly improved on first EBP. One patient required a second EBP and later became asymptomatic.

Conclusions: EBP showed to be an effective and safe nonsurgical treatment of SIH in all our patients.

P558

1 Hz rTMS increases intracortical facilitation and reduces intracortical inhibition in motor cortex of patients affected by migraine with aura

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Background: we previosly showed paradoxical facilitatory effects of low-frequency rTMS on striate and extrastriate cortex of patients suffering migraine with aura.

Objective: the aim of the present study was to evaluate the effects of 1 Hz rTMS on excitability of intracortical inhibitory (ICI) and facilitatory (ICF) circuits of motor cortex to explore if abnormal pattern of excitability extend beyond sensory cortex involving also motor areas in migraine with aura.

Methods: 9 patients affected by migraine and 9 healthy controls entered in the study. The hot-spot for activation of right abductor pollicis brevis (ABP) was checked by mean of a figure-of-eight coil and motor threshold (MT) on this point recorded. 600 magnetic stimuli at 1 Hz frequency and 90 % MT intensity were delivered at the hot-spot. Before and after rTMS, excitability of ICI and ICF circuits was assessed by mean of paired pulse paradigm with a conditioning subthreshold stimulus (80 % MT) followed by a suprathreshold test stimulus (120 % MT). Two different interstimulus intervals (ISI) were used: inhibitory: 2 msec and facilitatory 10 msec. Amplitude of motor evoked potential (MEP) after paired stimulation was expressed as percentage of MEP induced by test stimulus alone (test MEP).

Results: in basal condition migrainers showed reduced excitability of ICI circuits (2 msec ISI), not significantly different as compared with controls. 1 Hz rTMS significantly reduced the size of test MEP in healthy controls but not in migrainers. Moreover, 1 Hz rTMS decreased ICF circuits in controls while increased ICF and decreased ICI circuits in migrainers.

Conclusions: our results showed that motor as well as sensory cortex of migraine patients show an abnormal excitability pattern, giving raise to paradoxical facilitatory responses at low frequency stimulation.

P559

Prevalence of patent foramen ovale in patients with migraine

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Migraine is a common neurologic disorder whose etiology remains unknown. Migraine has been reported as possible risk factor for ischemic stroke, especially in young patients. The relationship between migraine and stroke is stronger in patients suffering from migraine with aura compared to those with common migraine. Coexistence of migraine and patent foramen ovale (PFO) should be also considered.

The aim of our study was to evaluate the frequency of PFO in patients with migraine with aura (MA) and compare it with the prevalence of PFO in migraine patients without aura (M) and in healthy age-matched control group.

We assessed 62 patients (48 females) suffering from migraine with aura, 60 without aura (53 females) and 65 normal controls (51 females). In order to detect PFO the contrast transcranial Doppler was performed during Valsalve maneuver. The presence of PFO was found in 33/62 (53 %) patients with MA compared to 15/60 (25 %) without aura and 16/65 (25 %) control subjects. The difference between MA patients and M patients and the difference between MA patients and control group was statistically significant ($p < 0.05$). Our findings suggest that at least some attacks of migraine with aura may be associated with paradoxical embolism.

P560

Botulinum toxin type A (DYSPORT) as a prophylactic treatment of migraine: a double-blind, randomised, placebo-controlled study

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Objective: To evaluate the efficacy of botulinum toxin type A (DYSPORT) in the prophylaxis of migraine headache.

Design and Methods: This is a double-blind placebo controlled study of 40 patients with history of migraine headache consistent with international headache society (IHS) criteria for migraine. The patients were randomized to receive a single injection of 125 units of dysport or the same volume of saline. Participants filled out daily diaries including: migraine frequency, severity, number of lost working days due to attacks, attack duration, and number of oral or parenteral analgesics used to treat each attack during a 1-month baseline period and 3-month post injection period of dysport or saline.

Results: Demographic characteristics and baseline efficacy variables in both groups were similar except for sex(male less than female). There was no statistically significant difference between two groups regarding primary efficacy variables including: frequency, mean severity, mean duration, maximum duration, maximum severity of attacks and number of lost working days due to attacks. Changes from baseline in moderate to severe headaches (mean severity and mean duration less than 5) in third month after injection and changes from baseline in frequency of moderate to severe headaches requiring parenteral analgesics in first and third month after injection were significant (p-value = 0.047, p-value = 0.052, and p-value = 0.048 respectively).

Conclusion: It seems the effectiveness of dysport in the relief of migrane symptoms is not more than placebo.

P561

Chronic daily headache. Initial headache, psychological profile and response to treatment

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Mood status specialy anxiety and depression are important factors in the chronification of headache.

Objectives: To study the psychological profile of chronic daily headache (CDH) patients and its relationship to: 1) initial headache, 2) response to pharmacological treatment and 3) medication over-use.

Method: We studied 112 CDH patients (96 women) evolved from 33 chronic migraine (CM) (24 women) and 79 tension tipe headache (72 women). Psychological evaluation was performed with: anxiety scale

(STAI), Beck depression inventory (BDI), Maudsley obssesions inventory and Minnesota Multiphasic Personality inventory (MMPI). Twenty six percent of the patients presented medication over-use and 57 % a good response to treatment (> 50 % CDH reduction).

Results: No psychological diferences between CM and TTH patients or between responders vs non responders patients, were observed. Patients without drug over-use have higer BDI ($p = 0.017$) and paranoia scores (MMPI) ($p = 0.05$). Non responders CM patients showed higer hypocondria score (MMPI) ($p = 0.04$).

Conclusions: Psychological profile does not identify chronic migraine or tension type headache CDH patients neither treatment responder vs non responder patients or patients with pharmacological over-use.

P562

Neurogenic leg claudication caused by occult giant pelvic lipomas

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Leg pain or exercise induced claudication due to an extraspinal cause is uncommon. We describe 3 patients with leg pain due to clinically occult giant pelvic lipomas.

Case 1: a 45-year-old man presented with an unpleasant sensation of pins and needles in the ventral part of the left thigh and the lower leg, mainly provoked by walking. He sometimes experienced weakness or a feeling of heaviness of the left leg. Neurological examination revealed a depressed patellar reflex on the left side and slight hypesthesia in the innervation area of the lateral femoral cutanous nerve. MRI of the lumbar spine was normal. Electrodiagnosis showed a prolonged peripheral latency. CT scan of the pelvis showed a huge pelvic lipoma adjacent to the left psoas muscle, extending into the upper leg through the muscular foramen. The tumor was surgically removed. Histological examination of the tumor showed lipomatous tissue without sarcomatous degeneration. After the operation the patient noticed almost complete relief of his symptoms.

Case 2 and 3 were previously described by us. It concerned two men, aged 60 and 62 years, both suffering from exercise induced sciatica of the leg. neurological exmination in these patients showed only slight sensory loss in the L5 and S1 dermatomes. Electrodiagnosis in one case was normal. CT scans of the lumbar spines were normal, but additional CT scans of the pelvis showed huge lipomas extending from the subgluteal area into the left sciatic foramen in both patients. Removal of the tumor relieved the leg pain in both patients. Histology confirmed the diagnosis of benign lipoma.

Discussion: Only very few cases of extraspinal nerve compression syndromes by a pelvic lipomatous tumor are reported in the literature. The fact that we met 3 patients with huge pelvis lipomas causing neurogenic claudication indicates that such lipomas may be less rare than assumed based on literature.

Neuro-oncology

P563

Induction of glioblastoma regression using skin-derived stem cell

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Diffuse invasion of the brain by tumor cells is a hallmark of human glioblastomas and a major cause for the poor prognosis of these tumors. Current therapies for gliomas fail to address their highly infiltrative nature, resulting in eventual tumor recurrence. Recently, Aboody et al. reported that neural stem cells (NSC) when implanted into experimental intracranial gliomas of adult rodents distribute themselves and surround infiltrating tumor cells promoting the tumor regression. These intriguing results did, however, leave unanswered a number of questions of relevance to construction of clinical trials (i. e. the isolation of human NSC from adult tissues is difficult and ethical problematic are determined for the use of central nervous fetal derivatives; it is necessary to determine whether NSC offers advantages in allogenic transplantation). To develop a new therapeutic strategy we inoculated human skin-derived progenitors into experimental intracranial human glioblastoma allowed in immunodeficient nude adult rodents. Injected cells migrate extensively within the tumor and surround the invading tumor border. Moreover, treated tumors were associated with a significant decrease of vascularization and tumor spread in the area of injected skin-derived stem cells (SDSC) leading to a significant inhibition of tumor growth and prolonged survival of treated mice. When implanted into the controlateral hemisphere the SDSC migrate along the white matter fibers targeting the human glioblastoma. All these data suggest a potential treatment of intracranial glioblastoma by the use of the SDSC from the same patients.

P564

Two cases of intravascular large B-cell lymphoma mimicking disseminated encephalomyelitis and encephalomyelopathy – a rare differential diagnosis

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Intravascular large B-cell lymphoma is a rare neoplastic disorder histologically characterized by the presence of lymphoma cells within small vessels. It is an uncommon disease with a wide range of possible neurological manifestations. This report presents two patients in which the post mortem diagnosis of an intravascular large B-cell lymphoma was made.

Case 1: A 63-year-old man developed sensomotoric transverse spinal cord syndrome, motoric aphasia and fluctuating disturbance of orientation. Lumbar puncture revealed albuminocytological dissociation. MR-imaging showed progression of multifocal infarct-like lesions, partly with parenchymal enhancement in the brain, the thoracic cord and the medullary cone. The patient received immunosuppressive therapy and died 18 months after the onset of symptoms.

Case 2: A 68-year-old man showed fluctuating aphasia, disorientation, and fever for several months. He was first treated on the suspicion of encephalitis due to Lyme disease. Brain MRI-scan, electroencephalography (EEG) and cerebrospinal fluid (CSF) cytology were unconspicuous. Premortal biopsy of lesions in liver and right suprarenal gland showed evidence of a partial intravascular, initially not further characterized, malignancy. The patient died six months after the first occurrence of symptoms. Autopsy revealed an intravascular lymphomatosis with large tumor cells having vesicular nuclei, prominent nucleoli and frequent mitotic figures. Intravascular lymphoma cells were seen disseminated in extranodal site having seized heart, lung, renal gland, spleen, thyroid gland and brain.

Conclusions: An intravascular lymphomatosis should be considered in differential diagnosis when a meningoencephalitic symptomatology is unclear and an encephalitis cannot be proved by liquor diagnosis. A biopsy of different organs including the brain should not be delayed to ensure ante mortem diagnosis and to initiate chemotherapy.

P565

Mesenchymal stem cells and their potential role as vectors in gene therapy of glioma

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Background: Since prognosis of malignant glioma is still very poor, efforts have been made to establish new treatment strategies using vectors which deliver a therapeutic gene to the tumor. One such gene vehicle could be neural stem cells (NSC), because Aboody (2000) could demonstrate a tropism of NSC to glioma, making them migrate into the CNS and towards the tumor. Aim of our study was to test the migratory and invasive patterns of human bone marrow mesenchymal stem cells (MSC) towards glioma. Since MSC are much easier to win without ethical or immunological problems, they would be an attractive alternative to NSC as vectors in gene therapy of glioma.

Methods: Human MSC were isolated from bone marrow biopsies, cultivated and characterised by a fluorescence activated cell sorter. Migration analysis of MSC and rodent embryonal NSC was performed on laminin, tenascin and plastic using cell spheroids in medium without supplement, tumor-conditioned medium and medium supplemented with VEGF. Chemotaxis assay with Boyden chamber was performed with MSC challenged with tumor-conditioned medium, MCP-1 and VEGF. To asses invasion, confrontational cocultures of glioma spheroids and stem cell spheroids were investigated.

Results: Migration of MSC and NSC was fastest on laminin, when compared to tenascin and plastic and was significantly increased by tumor-conditioned medium as well as by VEGF. In Boyden chamber assay tumor-conditioned medium and VEGF, but not MCP-1 showed to be a potent chemotactic factor for human MSC, increasing cell migration five to ten times, when compared to medium without supplement. Furthermore, when cocultured, MSC showed an extensive invasion into glioma spheroids, even more than NSC did.

Discussion: Not only rodent NSC, but also human MSC show strongly enhanced migratory behaviour when challenged with glioma. VEGF, but not MCP-1 seemes to play a crucial role in this process. Since use of MSC has several advantages compared to NSC and their invasional patterns towards glioma seem to be even better, they proof to be hopeful candidates as treatment vectors in gene therapy of this malignancy.

P566
FDG-PET- and MR-imaging in anti-Ma2 positive paraneoplastic limbic encephalitis
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Background: Paraneoplastic limbic encephalitis (PLE) is a rare neurological disorder. The clinical hallmarks of PLE are memory dysfunction, epilepsy, and psychiatric abnormalities. The neuroradiological diagnosis of PLE has to be based on MRI. Findings are hyperintense signals on FLAIR- and T2-weighted images in the medial temporal lobe(s), frequently without enhancement after contrast administration. PET-imaging has only rarely been performed in PLE.

Methods: We performed serial MRI and F-18-Fluorodeoxyglucose (FDG)-PET in a patient with anti-Ma2 positive PLE during a follow-up of 13 months.

Results: FDG-PET showed a focal tracer accumulation in the left medial temporal lobe, which increased during the first 9 months of follow-up and which corresponded with an increase of serum anti-Ma2 antibody titers. MRI revealed a hyperintense signal change in the left medial temporal lobe without contrast enhancement, which remained unchanged over time.

Conclusions: The results of functional and structural imaging in PLE may differ substantially. FDG-PET can demonstrate focal hypermetabolism over a long time, which may indicate therapeutic potential. The etiology of FDG-PET hypermetabolism in PLE is unknown. A prospective study with more patients will be needed to clarify the relevance of PET as possible outcome measure in PLE.

P567
Anti-Ma 2-associated encephalitis with predominant upper brainstem features
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Introduction: Anti-Ma2-associated encephalitis is a paraneoplastic syndrome that usually presents with isolated limbic encephalitis, sometimes combined with diencephalic-hypothalamic or brainstem dysfunction. Neurological symptoms frequently appear before tumour diagnosis, usually testicular germ-cell tumour. The clinical features of the brainstem dysfunction have not been well described. We present a patient with anti-Ma2-associated encephalitis who presented with upper brainstem symptoms.

Patient: A 69-years-old man presented with diplopia followed by unsteady gait with falls, hypophonia, apathy, memory problems, emotional lability and excessive daytime somnolence in the last three months. The neurological examination showed a patient with eyelids closed who had reflex blefarospasm when the examiner tried to open them. He seemed to be sleeping but he adequately responded to commands. His speech was hypophonic, inaudible. He was bradypsychic, forgetful with masked face and frequent crying. Hypokinesia was present without rigidity nor tremor. There was vertical ophtalmoplegia with right internal rectus palsy without nistagmus. Oculocephalic reflexes and pupils were normal. Deep tendon reflexes were brisk and plantar responses were flexor. The gait was unsteady with short steps. Postural reflexes were impaired. Routine blood test and chest X-ray were normal. Brain MRI showed T2-weighted hyperintense lesions in the dorsal aspect of the midbrain, bilaterally around the hypothalamus,in both thalami and medial temporal regions including the amigdala,that did not show contrast enhancement. Lumbar puncture showed normal glucose, increased protein (89 mg/dl) without pleocytosis. Antineuronal antibodies were positive for anti-Ma2. Tumoral markers, testicular ultrasounds, body CT scan, body FDG PET, and colonoscopy did not show any tumour. Treatment with intravenous metilprednisolone and high-dose immunoglobulins was ineffective. The patient died eight months later from progressive neurological deterioration. Necropsy was not performed.

Conclusion: Anti-Ma2-associated encephalitis may present with a rapidly progressive clinical picture predominantly involving the upper brainstem, with vertical gaze palsy and gait-postural abnormalities. The clinical picture may lead an initial diagnosis of progressive supranuclear palsy or Whipple disease. The brain MRI features should rise the possibility of this syndrome that is confirmed by the detection of anti-Ma2 antibodies.

P568
Limbic encephalitis and small cell lung cancer
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Summary: We report the case of a 55 year old man with a subacute onset of nausea, vertigo, vomiting, ataxia, nystagmus, cognitive dysfunction and psychiatric symptoms. The cranial MRI with Gadolinium showed no signal abnormalities. Lambert-Eaton myasthenic syndrome antibodies in serum were tested positive. The patient suffered a subacute limbic and brain stem encephalopathy. This paraneoplastic limbic encephalitis was found to be associated with a small-cell-lung cancer. A small cell lung cancer was confirmed by histology characterisation.

Cerebrospinal fluid composition showed no cells, an increased protein level and negative cytology. The PCR for herpes simplex, varicella zoster virus, and cytomegalovirus were negative.

The indirect immunoperoxidase method and Western blot analysis in serum were used for screening for anti-Hu antibodies often associated with small cell lung carcinoma. Nerve conduction studies demonstrated delayed velocities of motor nerve conduction and absence of sensory potentials. A high resolution Spiral-CT of the lung demonstrated a 4 mm lesion in the right middle lobe suggestive of malignancy. This lesion was subsequently confirmed by histological characterisation as small oat cell lung cancer. Treatment with high-dose corticosteroids was administered with only marginal impact.

Discussion: Limbic encephalitis is a paraneoplastic encephalitis and a particular manifestation of paraneoplastic encephalomyelitis with affinity for the limbic system. Limbic encephalitis is a rare neurological paraneoplastic disorder that usually presents with changes in mental status and behavioral abnormalities. The paraneoplastic neurological syndrome is often associated in patients with small cell lung cancer. The limbic system is also involved in the much more common herpes virus (HV) encephalitis which is the major differential diagnosis. Small cell lung cancer is the extracranial malignancy most commonly associated with limbic encephalitis and has been identified in 2–3 % of cases. The diagnosis is difficult because clinical markers are often lacking, and symptoms usually precede the diagnosis of cancer or mimic other complications. Pathological and imaging findings are nonspecific and indistingiushable from those of HV encephalitis, consisting of bilateral T2-MRI hyperintensities associated with variable postcontrast enhancement in the medial temporal regions, insula-and cingula gyri.

P569
Intramedullary spinal cord metastases in a patient with small-cell lung cancer – MRI findings
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Background: Intramedullary spinal cord tumors are rare comprising only 5 % of spinal cord neoplasms. Intramedullary spinal cord metastases are even rarer accounting for only 1–3 % of all intramedullary neoplasms. In the majority of cases they are single.

Case report: A 60 year-old male smoker was admitted to our department with gait disturbance, lower-limb sensory disturbance and urinary difficulties of a subacute onset and progressive course. He had been diagnosed 10 months previously with limited-stage small-cell lung cancer and had received 4 cycles of cisplatin-etoposide chemotherapy along with thoracic radiotherapy and prophylactic cranial irradiation and was in remission on follow-up. Examination revealed bilateral pyramidal tract signs, a T9 sensory level and loss of vibration and position sense in the lower limbs. A bone scan and brain MRI were normal. A lumbar puncture revealed only mild protein elevation. An abdominal CT showed a small bilateral increase in adrenal size. Gadolinium-enhanced MRI of the cervical and thoracic spinal cord revealed 2 enhancing intramedullary lesions at C2–3 and T9–10 consistent with metastases. The patient received high-dose dexamethasone and was referred for topical radiotherapy.

Discussion: Intramedullary metastases are exceedingly rare accounting for only 3.4–6 % of myelopathies in cancer patients. The presence of multiple metastases is even rarer, two lesions found in only 10 % of patients with intramedullary disease. Furthermore, intramedullary metastasis usually coexists with brain metastasis (57.5 %) or leptomeningeal disease (27.5 %). Gadolinium-enhanced MRI is the investigation of choice. Early

diagnosis is paramount since the greater the deficit upon treatment initiation, the worse the prognosis.

P570
Primary optic nerve meningioma mimicking optic neuritis and demonstrated using FATSAT MRI
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The clinical hallmark of the intrinsic tumors of the optic nerve is progressive loss of vision. We report a 47-year-old woman, who developed a sudden loss of vision in the right eye without other neurological symptoms. The visual field showed a peripheral loss of vision and abnormality of PEV (P100 in the right eye was increased in latency and shortened in amplitude), in the presence of normal fluroangiography and brain MRI. The first diagnosis was one of "retrobulbar optic neuritis" and the patient was treated with steroid iv without improvement. After eighteen month, the vision in the same eye worsened, suggesting a second relapse of optic neuritis. CSF examination, including viral and bacterial screening and research of oligoclonal bands, were unremarkable. A second standard brain MRI with gadolinium showed an unclear enhancement in the right optic tract. The presence of an optic nerve meningioma was demonstrated using a FATSAT-T1 with and without gadolinium sequence, which showed an homogeneous enhancement around the right optic nerve, that appeared markedly atrophic. Although surgical approach was successful, the vision was irreversibly lost because of advanced nerve damage. Primary optic nerve meningioma has a low prevalence in the population (about 0.002 %), but it has to be considered as a possible diagnosis, especially when patients with supposed optic neuritis do not improve after steroid therapy. In these cases a MRI with FATSAT sequences of the orbits has to be performed.

P571
Salvage radiotherapy in oligodendroglial tumours
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Background: There is an increasing tendency to use chemotherapy as initial treatment in oligodendroglial tumors, but the efficacy of salvage radiotherapy is still unknown.

Aim of the study: The objective of the study was to investigate the efficacy of salvage radiotherapy in patients with recurrent or progressive oligodendroglial tumors failing chemotherapy.

Design/methods: Since 1985, 27 histologically confirmed oligodendroglial tumors were treated with salvage radiotherapy: 14 grade II oligodendroglioma, 9 grade III oligodendroglioma, 2 grade II oligo-astrocytoma and 2 grade III oligo-astrocytoma. The patients had been previously undergone partial, sub-total or total surgical resection, and first-line PCV chemotherapy. Second-line chemotherapy was delivered in 20 patients (8 with Carboplatin, 10 with Temozolomide, 2 with intraventricular Tiothepa) and 2 patients were re-operated upon. Focal external radiotherapy with conventional fractionation up to a total dose of 50–60 Gy was employed. Response rate was evaluated according to Macdonald's criteria.

Results: Twenty-five patients were evaluable. Responses were as follows: 1 CR (4 %), 8 PR (32 %), 11 SD (44 %); 5 PD (20 %). Among patients with SD, 2 (4 %) had a reduction of tumor volume of 20–40 % ("minor response"). Overall response rate (CR+PR+ "minor response") was 44 %. Median time to tumor progression (TTP) was 7 months (range: 1–51). Median overall survival was 50 months (range: 23–129). A clinical benefit was observed in 6/20 patients (30 %), consisting in a reduction of epileptic seizures and in improvement of intracranial hypertension. Regarding late neuro-toxicity, we observed 1 patient with cognitive deterioration and 1 patient with lumbo-sacral radiculoneuropathy.

Conclusions: Salvage radiotherapy seems to be effective in oligodendroglial tumors. Further prospective data are needed.

Multiple sclerosis

P572
Magnetisation transfer imaging quantifies pathology in corpus callosum and correlates with cognitive dysfunction in multiple sclerosis
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Magnetisation transfer imaging (MTI) quantifies macro- and microscopic pathology in multiple sclerosis (MS). Decreased magnetisation transfer ratio (MTR) reflects demyelination or/and axonal damage. We aimed to investigate whether MTR in corpus callosum, defined by fibre tracking on diffusion tensor imaging (DTI), correlates with cognitive scores in relapsing-remitting (RR) MS.

Dual-echo, MT and DTI brain scans were obtained from 36 patients with RR MS and 13 age and gender matched normal controls. Voxels from corpus callosum were automatically identified using a tractography based algorithm on DTI. The mean MTR was calculated in corpus callosum by co-registering the DTI to the MTI. The Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk (T25FW), Nine-Hole Peg Test (9-HPT) and Paced Auditory Serial Addition Test (PASAT) were scored.

The mean MTR in the corpus callosum was lower in patients than in controls (0.40 ± 0.02 vs 0.43 ± 0.01, $p = 0.0003$). Multiple regression analysis revealed that the mean MTR was the only significant correlate of PASAT ($r2 = 1.38$, $p = 0.036$), but not of EDSS, T25FW or 9-HPT, of all factors entered into the model. Other variables, including disease duration, global T2-lesion load, T2-lesion load within corpus callosum did not correlate with PASAT.

MTI quantifies pathology in corpus callosum and correlates specifically with cognitive dysfunction in MS.

P573
Disease modifying drugs in childhood-juvenile multiple sclerosis: results of an Italian Co-operative Study
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Background: Immunomodulatory drugs (Interferon-Beta -IFNB- and Glatiramer acetate -GA-) reduce relapse rate and disease progression in relapsing-remitting multiple sclerosis (MS) but extensive data are not available on the effectiveness and tolerability of these drugs in childhood or adolescence.

Objective: to evaluate the impact of IFNB and GA in MS patients treated before 16 years of age.

Methods: a research group (ITEMS = Immunomodulatory Treatment of Early onset MS) was promoted in Italy to collect a large series of patients affected by clinically definite MS according to Mc Donald's criteria and treated with immunomodulatory drugs before 16 years of age. Fourteen centres recognised subjects suitable for inclusion: 76 patients (52 females) were collected with a mean age at onset of 12.4 ± 2.5 years.

Results: as subjects with pre-treatment and treatment duration lower than 4 months were excluded, results are given of 65 patients (45 females): 38 were treated with IFNB-1a 6 million once weekly (Avonex), 18 with IFNB three times weekly (Rebif = 16) or on alternate days (Betaferon = 2), and 9 with GA (Copaxone).

The mean pre-treatment period was respectively 20, 18, and 9.2 months. The treatment duration lasted respectively 23.3, 40.7 and 33.3 months.

The mean annualized relapse rate decreased dramatically during the treatment: from 2.4 to 0.4 in the Avonex group, from 3.2 to 0.8 in the Rebif-Betaferon group, and from 2.8 to 0.25 in the GA group. The mean EDSS score remained stable at the end of the follow-up.

Clinical side effects were recorded in 41/65 subjects (mainly in subjects treated with IFNB), abnormal laboratory findings were observed in 13/65 subjects. IFNB was stopped in 6 cases: in 4 because of inefficacy, in 2 cases because of side effects.

Comment: 65 clinically definite MS subjects were treated during childhood or adolescence with immunomodulatory drugs. The treatment reduced the relapse rate and stopped the progression of MS. Side effects were common in subjects treated with IFNB, but were well tolerated in most cases.

P574

The use of optical coherence tomography to measure axonal loss in multiple sclerosis

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Background: The ability to assess potential neuroprotective therapies in Multiple Sclerosis (MS) is limited by a lack of outcome measures capable of selectively quantitating axonal/neuronal loss. We choose to circumvent this problem through utilization of a commercially available technique to measure the thickness of the retinal nerve fiber layer (RNFL) – a tissue devoid of myelin – following episodes of optic neuritis.

Objective: To determine the sensitivity, reliability and validity of OCT RNFL thickness measurements in relapsing Multiple Sclerosis patients post optic neuritis (ON).

Methods: Patients with relapsing remitting multiple sclerosis, aged 20–50, were recruited from our neurology clinics. They were at least 6 months post-monocular optic neuritis and experienced only one clinical episode of ON. Exclusion criteria included frequent steroid treatments in the 6 months post-ON (> 2), chemotherapy, severe refractive errors or other eye diseases. To test for reliability, 3 OCT tests were performed over a 3 week period. One test was performed at the first visit and two tests at the second. To assess for functional significance and validity, a series of visual function tests were repeated on two separate visits. These tests include the Humphrey visual field, Sloan, FM 100, Morphonome and Landolt C tests. The National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25) and 7-item MS Vision Questionnaire (MSVQ-7) were also administered on these two occasions.

Results: Results so far indicate that the retina post-ON, unlike the contralateral control eye, has an average RNFL thickness measurement in the 1st or 5th percentiles, compared to normal population controls matched by age. This occurs despite near complete recovery of visual acuity in the majority of patients. For Patients tested to date, the overall coefficient of variation within subjects was 3.22 %; intervisit variation accounted for 2.77 % and intravisit variation 0.66 %. Correlations of RNFL thickness measurements with visual function measures will be presented.

Conclusions: Preliminary data indicate that RNFL thickness as measured by OCT is sensitive and reliable and may be used as an outcome measure to assess axonal loss following optic neuritis.

P575

The individual costs of multiple sclerosis in Poland – a cross-sectional prospective multicentre cost-of illness study

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Objective: To estimate the costs of multiple sclerosis (MS) in Poland according to severity of disease.

Method: 148 outpatients with MS were enrolled at 3 centres across Poland. Socio-demographic, clinical and resource utilization data were collected prospectively using a validated questionnaire. Total, direct and indirect costs were compared among three groups categorised by disease severity: stage I (EDSS < 3.5, n = 57), stage II (EDSS 4.0–6.0, n = 56) and stage III (EDSS > 6.5, n = 35). Cost evaluation was performed from the societal perspective and covered the 5-months period. Due to absence of available opportunity costs, tariffs were used as an approximation. Human capital approach was used for calculation of indirect costs. Simple sensitivity analysis was performed by varying the tariffs and valuing caregiving at 40 % of the average wage.

Result: The mean total cost/patient for 5 months was estimated at 10,955, 15,603 and 18,464 PLN for stage I, II and III respectively (1 PLN = 4EUR) ($p < 0.0001$). Regardless of EDSS stage indirect costs exceeded direct costs. Both direct and indirect costs increased with MS progression: for stage I, II and III patients the mean direct cost was 4,069, 5,399 and 6,010 PLN/patient/5 months ($p = 0.04$); the mean indirect cost – 6,886, 10,204 and 12,454 PLN/patient/5 months ($p = 0.001$). For indirect cost the main item was productivity loss. The major direct cost drivers were rehabilitation followed by hospitalization and payable home care for stage III patients and hospitalization for stage I and II patients. Results were sensitive to the variation applied, but the overall trend remained as in the primary analysis.

Conclusion: This study confirms that MS represents a high economic burden, with indirect costs greatly exceeding direct costs. As costs increase with disease progression, treatment efforts should focus on patients in the early stages of MS.

P576

The course of cognitive deficits and fatigue in the very early stage of multiple sclerosis under immunmodulation

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Background: Cognitive deficits and fatigue are frequent symptoms in multiple sclerosis (MS). There are some long-term studies which show stability or slow progression at any time of the course. No study investigated cognitive performance as well as fatigue at the time of diagnosis.

Methods: The cognitive performance of 50 patients with newly diagnosed multiple sclerosis under immunmodulation (IFNb, Copaxone or IVIG) was compared with that of 33 control subjects, matched for sex, age and education. The test-battery included tests of reasoning (LPS-3), verbal and nonverbal memory (VLT, NVLT), alertness, divided and focused attention (TAP). Tests were applied at diagnosis, a half, one and three years later. Fatigue was measured subjectively by the Modified Fatigue Impact Scale (MFIS) and objectively by the test of vigilance (TAP). Physical disability (EDSS) and depression (BDI) were controlled.

Results: Patients had an average age of 35 years, a mean EDSS-score of 1.8. 92 % suffered from a relapsing-remitting MS. At baseline 50 % of the patients were cognitively unimpaired, 38 % showed mild and 12 % moderate cognitive deterioration. Patients performed significantly poorer than controls in nonverbal memory and reaction-time. No differences were found in reasoning and verbal memory. Three years later no improvement in manifestation and severity of cognitive deficits was found. Fatigue was subjectively reported in 63 % at baseline and one year later. After three years only 47 % suffered from it. The long-term fatigue-reduction was confirmed in the vigilance-test. The EDSS-score did not change during the investigation. There were no differences in the BDI-scores between the groups. Throughout testing the BDI-score has been significantly correlated with the MFIS-score.

Conclusions: Cognitive dysfunction and fatigue are frequent symptoms already in newly diagnosed patients with MS. After three years under immunmodulation the manifestation, the severity of cognitive deficits as well as the reported Fatigue did not increase.

P577

Evidence of evolving normal appearing brain tissue diffusion tensor imaging abnormalities in early relapsing-remitting multiple sclerosis

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Background: Diffusion tensor MRI (DTI) is a quantitative imaging tool that has investigated multiple sclerosis (MS) in cross-sectional studies. DTI parameters measure the magnitude (mean diffusivity (MD)) and directionality (fractional anisotropy (FA)) of water movement within a tissue. DTI therefore provides biologically meaningful measures of the normal parenchymal structure of tissues. Studies in well established MS cohorts show widespread MD and FA abnormalities in normal appearing brain tissue (NABT). However, a recent study investigating early relapsing-remitting (RR) MS showed only FA changes suggesting that there are initially structural abnormalities which disrupt neuronal fibre tract orientation (eg. gliosis) in the absence of an increase in tissue fluid spaces (no increase in MD). The natural history of how DTI parameters evolve, and therefore how measurable tissue damage evolves, has not been investigated. We present a two-year study investigating early RRMS subjects with quantitative DTI. The aims were to: (i) determine longitudinal DTI abnormalities in this group; and (ii) infer the nature of the abnormalities affecting the NABT in early MS.

Methods: Sixteen patients with early RRMS (median disease duration 1.9 years; EDSS < 3.0) and 11 controls had DTI yearly for two years. Whole NABT FA and MD maps were analysed from a single shot DTI echo-planar sequence with an automated segmentation clustering algorithm which removes cerebrospinal fluid. Quantitative histograms were generated from this and models correcting for age, gender and brain volume used.

Results: At baseline, FA mean ($p = 0.010$) and peak height ($p = 0.003$) were significantly different in patients in comparison to controls but no significant MD abnormalities were observed. Overall two year analysis revealed persistence of the FA abnormalities (mean ($p = 0.015$); peak height ($p = 0.047$)), but no progressive change. However, there was a significant decrease in MD peak height ($p = 0.045$) over two years. In addition, MD mean ($p = 0.023$) and peak location ($p = 0.024$) were significantly different in MS patients in comparison to controls cross-sectionally at two years.

Conclusions: While the initial abnormality of FA suggests some disruption of fibre tract integrity, the change in MD over time may indicate increased oedema related to inflammatory events in the NABT. Future

studies are needed to address the prognostic role of NABT DTI abnormalities and to investigate their pathological basis.

P578

Early relapsing-remitting multiple sclerosis: a study of gadolinium enhancement and clinical measures over six months

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Background: Multiple sclerosis (MS) lesions which enhance with Gadolinium-DTPA (Gd) on T1-weighted MRI images are correlated with active inflammation, oedema and blood brain barrier breakdown. Most previous studies in established MS show a moderate association with clinical relapse but a poor correlation with long term disability. Evidence exists that lesion inflammation early in MS is associated with more significant amounts of acute axonal loss [1] and that long term clinical outcome may be partly related to T2 lesion volume accumulation within the first 5 years [2]. Thus, Gd enhancing lesions early in MS have potential regarding disease course prediction. We present a 6-month study of Gd enhancement in early relapsing-remitting (RR) MS and its relationship to clinical and MRI outcomes.

Methods: Forty patients with early RRMS (median disease duration 1.7 years; EDSS < 3.5) had pre and post-contrast (triple dose Gd (0.3 mmol/kg)) brain and cord T1-weighted scans. From this, 31 subjects were imaged as above at six months. Associations between Gd enhancement and relapse, EDSS, MS Functional Composite score (MSFC) and pre and post-contrast T1 and T2 lesion load measures were calculated in models correcting for age and gender.

Results: Only two subjects had no Gd enhancement at any stage. Baseline enhancement was weakly associated with relapse rate over 6 months ($p = 0.058$). A significantly improved clinical outcome at 6 months (measured by the MSFC) was seen in subjects with baseline enhancement ($p = 0.022$), whilst in those with no baseline Gd enhancing lesions a worse MSFC 6 month outcome was noted ($p = 0.014$), significant MSFC difference between the groups ($p = 0.002$).

Conclusions: A high overall extent of inflammatory lesions was demonstrated in early RRMS. The weak correlation with relapse confirms previous studies. The noted MSFC improvement associated with enhancement may indicate that subjects with Gd baseline enhancement are more likely to be in relapse near study entry and recover subsequently, or that inflammation may promote tissue repair. The MSFC deterioration in those without enhancement may indicate continued axonal loss following an inflammatory phase prior to study entry, or that disability progression in early MS can be unrelated to inflammation. Long term follow up is needed to investigate whether the extent of early inflammation is related to long term disability.

References

1. Kuhlmann T, et al. (2002) Brain 125:2202–2212
2. Brex PA, et al. (2002) NEJM 346:158–164

P579

Mycophenolate mofetil: a safe and promising immunosuppressant in multiple sclerosis

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Objective: To investigate the short-term efficacy and safety of Mycophenolate mofetil (MM) in patients with Multiple Sclerosis (MS).

Background: MM has been successfully used for treatment of allogeneic transplants and other immune-mediated diseases. Currently approved disease modyfying drugs and several immunosuppressants for the treatment of MS are not always effective in MS patients. There are MS patients who do not respond to them and all these agents carry side effects. The possibility of a new effective and safe immunosuppressant in the treatment armamentarium for MS seems necessary.

Method/Design: In an open-label study, 17 patients with MS (13 female, 4 male, aged 29–60 years, EDSS 3.0–8.0) received MM (CellCept) in a dose of 500 mg twice daily for 6 months. In six MS patients MM was added to Rebif (22 mcg 3×/week, S. C.). We enrolled patients with secondary progressive MS with or without superimposed relapses, with deterioration of 1 or more point in Expanded Disability Status Scale (EDSS) score during 6 months preceding enrolment in the study, and patients with relapsing-remitting MS with 2 or more relapses in the previous 6 months. The primary outcome measures were the change in EDSS and the proportion of patients who improved, remained stable or worsened in disability, defined as a change of at least 1 point in EDSS for patients with baseline EDSS 4.5 or less, and change of 0.5 point if baseline EDSS was 5.0 or more. Safety was assessed by the incidence of adverse events at any time throughout the study.

Results: Benefit from treatment was observed in all patients included in the study. After 6 months on MM, 14 patients (82.3 %) improved presented by a reduction of at least 1 point in EDSS if baseline EDSS was 4.5 or less, and change of 0.5 point if baseline EDSS was 5.0 or more. Three patients (17.6 %) remained stable. No patient deteriorated. This study also showed a significant beneficial effect on relapse rate and on proportion of relapse-free patients. No major side effects were observed and all patients were able to tolerate the drug.

Conclusions: MM may be a promising and potential treatment option for patients with progressive MS. MM has influence on disability progression in MS, and can reduce the relapse rate. Its potential to stabilize the disease course and the safe side effect profile would make MM a useful drug which could be considered in MS patients who do not seem to benefit from one of the established therapies.

P580

Every-other-day interferon beta-1b compared with once-weekly interferon beta-1a in MS. Further analysis of treatment effect on MRI activity and neutralising antibodies (NAbs) in the INCOMIN Trial

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Objective: To correlate MRI activity with NAb status in the INCOMIN Trial.

Background: Controlled trials have demonstrated efficacy of interferon (IFN) beta-1a at the dose of 30 mcg intramuscularly once a week or of IFN beta-1b, 250 mcg subcoutaneusly on alternate day, compared to placebo in patients with relapsing-remitting MS. The INCOMIN Trial was the first study that compared the two drugs in a randomized prospective trial.

Design and methods: 188 patients were randomly assigned to IFN beta-1a (92 patients) or IFN beta-1b (96 patients). MRI scans were performed, at baseline and yearly, on 149 patients (73 treated with IFN beta-1a and 76 with IFN beta-1b). Of the latters, 127 (62 treated with IFN beta-1a and 65 with IFN beta-1b) were tested for Nabs at baseline and yearly. Titers of ≥ 20 neutralizing unit/mL were considered positive. Study duration was of two years. MRI active lesions were identified as: (1) new hyperintense lesions on PD/T2 scans; (2) enhancing lesions on T1- weighted post-gadolinium scans; (3) hyperintense enlarging lesions on PD/T2; (4) T1-weighted acute black holes. In order to control for confounding, the effect of treatment on MRI activity, stratified for Nabs status, was evaluated with Mantel-Haenszl and logistic regression analysis.

Results: Mantel-Haenszl analysis showed that IFN beta-1b significantly reduced the risk of having MRI activity, compared with IFN beta-1a both at the end of second year (RR = 0.43; 95 %CI = 0.26–0.73), and during the whole 2-year study period (RR = 0.69; 95 %CI = 0.5–0.94). No statistically significant difference was found at the end of first year (RR = 0.64; 95 %CI = 0.38–1.07). The logistic regression analysis confirmed these results both at the end of second year and during the whole study period. Nab status did not significantly affect changes of MRI activity after treatment.

Conclusions: INCOMIN study did not establish any clear effect of NAb on MRI and clinical response. INCOMIN study lasted only 2 years, possibly a too short period to evaluate the full impact of NAb. More prolonged studies, in fact, showed a reduced clinical efficacy in Nab positive patients. Other studies, however, demonstrated that NAbs to IFN beta-1b tend to disappear over time. The impact of NAbs on clinical-MRI response to IFN beta is still highly controversial and, at the moment, any treatment decision should be based on the clinical and MRI response to therapy and not only on the occurrence of NAbs.

P581

Quantification of subtle blood-brain barrier disruption in normal appearing brain tissue and chronic non-enhancing lesions in relapsing-remitting versus secondary progressive MS: a preliminary study

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Objective: To find quantitative evidence of blood brain barrier (BBB) disruption in chronic lesions and normal appearing brain tissue (NABT) of patients with relapsing remitting (RR) and secondary progressive (SP) MS, and correlate it with clinical and lesion subgroups.

Background: Leakage of inflammatory mediators from subtle BBB dis-

ruption in NABT and chronic lesions could contribute to ongoing tissue damage. Serial dynamic contrast enhanced MRI is a potentially sensitive method of investigating subtle BBB disruption in these regions.

Methods: Serial T1 relaxation time (T1-RT) maps were obtained before and at 3 time points (20, 40 & 60 minutes) after administering Gd-DTPA (0.3 mmol/kg). Regions of interest (ROI) were placed around non- enhancing lesions, and in contralateral NABT. In addition to this, a template of multiple ROIs of NABT was constructed for each patient. T1-RT in the ROIs was measured at each time point. The shortening of T1-RT in response to contrast was used to infer BBB leakage.

Results: 11 patients were scanned (7 SPMS, 4 RRMS). Greater T1-RT decrease was observed in MS lesions than contralateral NABT at all post contrast timepoints (e. g. median decrease –9.47 % in lesions and –3.5 % in NABT, $p < 0.0001$). No significant difference was observed between lesions in RRMS and SPMS patients. Post-contrast T1-RT decrease in T1 hypointense lesions was greater than in T1 isointense lesions in both clinical subgroups (RRMS $p < 0.05$, SPMS $p < 0.05$). There was a trend for T1-RT decrease in NABT to be greater in SPMS than RRMS at 40 minutes ($p = 0.08$) and the difference was significant at 60 minutes ($p = 0.006$)

Conclusion: In so far as T1-RT decrease post gadolinium indicates BBB leakage, the results show greater BBB leakage in chronic (non-enhancing) lesions than NABT and in T1 hypointense than T1 isointense lesions in MS. There also appears to be more BBB leakage in NABT in SPMS than RRMS, but a larger cohort should be studied in order to confirm these preliminary observations.

P582

Effects of a combined mitoxantrone with methylprednisolone therapy on primary and secondary progressive multiple sclerosis – an interim analysis

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Mitoxantrone (mitox) has been shown an effective treatment in secondary progressive (SP)- and relapsing-remitting multiple sclerosis (MS), (Hartung et al. Lancet 2002). The aim of this open trial was to evaluate the effects of a combined mitox and methylprednisolone (MP) therapy in patients with primary progressive (PP)- and SP-MS.

Methods: Sixty-five patients with PP-MS or SP-MS who had had an impairment of at least 0.5 or more expanded disability status scale (EDSS) points on the Kurtzke scale (mean 0.7 ± 0.4, range 0.5–2.5 EDSS-points) during the preceding 12 months participated in this prospective study. The treatment protocol called for ten courses of a combined, intravenously administered, therapy with MP (500 mg on 5 successive days) and mitox (10 mg/sqm body surface on day 3). The first three courses were given every 3 months. Course 4 was administered after 4 months, course 5 after 5, and courses 6–8 after 6 months; courses 9 and 10 were each given after 1 year. Before each course the patients underwent an EDSS evaluation.

Results: So far 65 patients (39 females, 26 males; age 47 ± 11 years, range 20–69 years) have been enrolled. Three of the 65 patients were excluded (one patient due to new onset of atrial fibrillation; the other two discontinued therapy). Eighteen of the final total of 62 patients suffered from PP-MS, 44 patients from SP-MS. Currently all patients have completed at least four courses of therapy (14 patients completed 4, 9 patients 5, 14 patients 6, 8 patients 7, 17 patients 8 up to 10 courses). Upon entering the study, the PP-MS and the SP-MS groups had a mean EDSS of 5.3 ± 1.4 and 5.6 ± 1.0, respectively. Overall, the EDSS remained nearly unchanged after four courses (PP-MS: 5.1 ± 1.5, SP-MS 5.4 ± 1.1) and after 8 courses (PP-MS: 5.2 ± 1.4; SP-MS: 5.5 ± 1.5) in both groups. The EDSS improved in 21 patients, remained unchanged in 30, and deteriorated in 11 patients by at least 0.5 points. Patients with PP-MS seemed to profit more from therapy than SP-patients, but up to now this was not significant.

Conclusion: The results of our ongoing study indicate that mitox combined with methylprednisolone benefits the progression of disability in patients with primary and secondary progressive MS. Therefore, this therapy regime can be considered a feasible treatment option for these patients.

P583

Assessment of potential cardiotoxic side effects of mitoxantrone in patients with multiple sclerosis – an interim analysis

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Introduction: Several studies have shown that mitoxantrone (mitox) may have beneficial effect on the course of disease in patients with multiple sclerosis (MS). There is, however, concern that its potentially cumulative cardiotoxic side effects may cause cardiomyopathy, reduced left ventricular (LV) ejection fraction (EF), and irreversible congestive heart failure (CHF). Therefore the aim of this study was to investigate cardiac side-effects by repetitive monitoring.

Methods: In this prospective study 73 patients with a rapidly deteriorating primary (PP) or secondary (SP) progressive MS or a severe relapsing-remitting (RR) form were included. The treatment protocol called for ten courses of mitox (10 mg/sqm body surface). Before each course a transthoracic echocardiogram was performed to determine the LV-enddiastolic diameter (EDD) and the endsystolic diameter (ESD); the LV-EF was calculated.

Results: 73 patients (41 females, 32 males; age 48 ± 12 years, range 20–75 years) were enrolled in the study. 25 patients had a PP-, 47 patients an SP-, and 1 patient an RR-form of MS. Three of the 73 patients were excluded (two patients discontinued therapy; one patient with a previous history of ischemic heart disease developed atrial fibrillation after the second treatment with mitox). 70 patients were followed for at least 13 months, i. e., they completed at least four courses of therapy. The mean cumulative dose of mitox was 114.0 ± 33.8 mg. The initial mean-EDD was 47.5 ± 5.7 mm, mean-ESD 28.2 ± 4.7 mm, and the mean-EF 64.7 ± 5.7 %. On follow-up investigations after four courses the mean-EDD was 46.8 ± 4.5 mm, mean-ESD 27.9 ± 3.7 mm, mean-EF 64.3 ± 5.9 %; and after eight courses the mean-EDD was 45.5 ± 3.3 mm, mean-ESD 27.1 ± 4.6 mm, mean-EF 64.0 ± 8.1 %. Thus, up to now there was no significant change of all parameters over time. None of the patients had any regional wall motion abnormalities or experienced CHF.

Conclusion: Mitox (10 mg/sqm) did not cause a reduction of LV-EF or signs of CHF in any of the investigated patients. Further long-term cardiac monitoring is, however, needed to determine the safety of mitox after application of higher cumulative doses.

P584

Attention in multiple sclerosis: evaluation of 115 patients with the relapsing-remitting form

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Introduction: Attention plays a role in the cognitive process and the limitation of this capacity may be a result of deficits at the processing of information and in the working memory, but in patients with relapsing-remitting multiple sclerosis (RRMS) this is not well elucidated.

Objectives: The aim of this study is to investigate attention in patients with MS, through the use of tests that measure specific aspects of automatic and controlled processing of attention.

Methods: Clinically defined RRMS patients were compared with a group of normal volunteers, paired as to gender, age and level of education. The neuropsychological battery included digit span (forward and backward), trail making, cancellation and Stroop tests.

Results: 115 patients and 40 controls were included. In the comparison of the MS and control group, we observed that in the Digit Span test, there was no significant difference between the groups, both in the forward order ($p = 0.077$) and in the backward order ($p = 0.245$). As to the attention tests that involved visual-motor speed, mental flexibility and control of inhibitory responses, we observed significant differences between the performance of the patients and control group. In the Cancellation test, we observed that response speed was inferior in the patients ($p = 0.001$). In the Trail Making test no difference was observed between the groups as to the number of errors, however, the patients presented a poorer performance as to time to complete the test, both in part A ($p = 0.001$) and B ($p = 0.001$). In the Stroop test, the patients required more time to complete the three last stages of the test, with statistical significance for trial 4 ($p < 0.001$) and in the total time ($p < 0.001$).

Conclusions: In conclusion, our results indicate that attention impairment in MS is related to the slowing down of information processing, and may be affected in all of its stages, with alteration in automatic and controlled processing and in the motor program.

P585

The stability of IFNB-1b (Betaferon®/Betaseron®) and IFNB-1a (Rebif®) at different storage temperatures

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Objective: To determine the effects of different storage temperatures on the stability of interferon beta (IFNB) therapies for multiple sclerosis (MS).

Background: Three IFNB products are available for the treatment of

MS. IFNB-1b (Betaferon/Betaseron) and IFNB-1a (Rebif) are high-dose, high-frequency treatments, whilst IFNB-1a (Avonex) is a low-dose, once weekly therapy. The formulations of Betaferon and Rebif both contain albumin for stability. Appropriate storage of IFNB products, as recommended by the manufacturers, is crucial to maintain correct activity. The recommended storage temperature for Betaferon is room temperature (25°C), removing any requirement for refrigerated storage. In contrast, the recommended storage temperature for Rebif is between 2°C and 8°C. If necessary, Rebif can be stored for up to 30 days from manufacture at no more than 25°C. The option of storing MS therapies for prolonged periods at room temperature is an important consideration for patients in maintaining quality of life.

Methods: To test the stability of Betaferon and Rebif, vials of both products, as provided by the manufacturers, were stored at 4°C, 24°C or 37°C for up to 8 weeks. Stability was assessed at baseline, 2 weeks, 4 weeks and 8 weeks, using a new vial at each time point. The extent of degradation was assayed by gel electrophoresis (SDS-PAGE).

Results: The IFNB component of Betaferon and Rebif could be detected without the removal of albumin. IFNB-1b in Betaferon appeared as two well-resolved bands at 18 kDa, whilst IFNB-1a in Rebif appeared as two well-resolved bands at 22.5 kDa. The stability of the Betaferon formulation did not change after 2, 4 or 8 weeks at either 24°C or 37°C. Degradation of the Rebif formulation was observed by week 2 at 24°C, increasing at weeks 4 and 8. The degradation of Rebif at each time point was more pronounced at 37°C. Kinetic analyses revealed that Rebif degradation began after 6 days at 24°C and 3 days at 37°C.

Conclusions: The Betaferon preparation showed no signs of degradation when stored at room temperature in accordance with the manufacturer's recommendations. However, Rebif begins to degrade after just 6 days. It is likely that most of the 30-day room temperature storage permitted by the manufacturer elapses by the time this product reaches the patient. As a result, room temperature storage of Rebif for short periods may exceed this 30-day period, and therefore adversely affect stability.

P586

Correlation of neuropsychological performance with fatigue in multiple sclerosis

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Introduction: Fatigue and cognitive deficits are common in multiple sclerosis (MS) patients. Fatigue may negatively impact cognitive performance, but the association between fatigue and cognition is far from clear.

Objective: This investigation evaluates the interference of fatigue on cognitive performance, identifying its characteristics and correlations with other variables.

Methods: Clinically defined remitting-relapsing MS patients were included. Patients evaluated with depression by Hospital Depression and Anxiety Scales (HAD) were excluded. Fatigue was evaluated using the Fatigue Severity Scale (FSS). The neuropsychological battery included digit span, trail making, memory word list, FAS, Wechsler logical memory, Raven progressive matrices, cancellation, Buschke memory, and Stroop tests. Patients were classified as having fatigue with FSS scores above 28 points. Neuropsychological performance was compared between groups. Correlation between fatigue and neuropsychological performance, age, education, MS duration, and functional disability was investigated.

Results: 75 patients were included, 49 presenting fatigue. There was no difference in age, education, and MS duration between groups. No correlation between fatigue and neuropsychological performance was found, but there was positive correlation between fatigue and MS duration, and fatigue and functional disability.

Conclusions: Fatigue is common in MS. A correlation exists between its severity and functional disability, but this study showed no evidence that fatigue severity has relation to cognition.

P587

Post-receptorial mechanisms underlie functional disregulation of beta2-adrenergic receptors in lymphocytes from multiple sclerosis patients

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Background: The Beta2-adrenergic receptors are over-expressed (two folds) on lymphocytes from Multiple Sclerosis patients (Zoukos et al., 1994) where play a relevant role in the downregulation of the immune response through the induction of cAMP. By contrast, the oral administration of the beta-agonist terbutaline fails to regulate the production of both IL-10 and IL-12 in MS patients (Heesen et al., 2002). Signalling through the Beta2-adrenergic receptors is desensitised by the G-protein coupled receptor kinases (GRK).

Objective: To investigate the signalling pathway and the immunoregulatory functions associated with the beta2-adrenergic receptors in Multiple Sclerosis.

Methods: Fourteen (14) stable Relapsing Remitting (RR) MS patients (MS), six (6) relapsing MS patients (MS relapsing), thirteen (13) MS patients undergoing IFNb-1a (8) or IFNb-1b (5) treatment (MS IFN beta), six (6) patients affected from Other Inflammatory Neurological Diseases (OIND), and eleven (11) age and sex-matched healthy controls (HD) were recruited for this study. We investigated the effects of isoproterenol (10 mM) on the proliferative response and on the secretion of IFNg associated with the anti-CD3+IL-2 stimulation of peripheral blood mononuclear cells (PBMCs) from all the study subjects. We also analysed the expression of the regulatory molecules GRK2/3 and the isoproterenol-induced cAMP formation in the same PBMCs. Finally, we studied the effects of dibutyryl-cAMP (a cAMP analogue) on T cell proliferation.

Results: The isoproterenol-induced inhibition of T cell proliferation and of IFNg secretion were lost in both stable and relapsing MS patients, but not in IFNb treated MS patients ($p < 0.0001$). The expression of GRK2-3 was reduced (–30 %, $P < 0.05$) in both non-treated as well as in IFNb treated MS patients. The isoproterenol-induced cAMP formation was increased in PBMCs from untreated as well as IFNb treated MS patients. Differently, dibutyryl-cAMP strongly inhibited the PBMCs proliferation from HD (–70 %; $p < 0.0001$) and IFNb treated MS patients (–50 %; $p < 0.0001$), but only in a slight manner those from both stable (–30 %; $p < 0.05$) and relapsing MS patients (–30 %, $p < 0.05$).

Conclusions: The intracellular signalling pathway associated with the Beta2-adrenergic receptors is down-regulated downstream the cAMP level in lymphocytes from MS patients. Treatment with IFNb renews the potent down regulatory function of the Beta2-adrenergic receptors on lymphocytes activation.

P588

Visual psychophysical deficit, visual evoked potentials and magnetic resonance imaging in the treatment of secondary progressive multiple sclerosis

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Introduction and objectives: Standard techniques for the evaluation of multiple sclerosis (MS) include pattern-reversal evoked potentials (VEP) and magnetic resonance imaging (MRI) which may not directly relate to overall clinical status. Visual psychophysics provides a sensitive measure of visual sensory deficit, the results of which may be interpreted in terms of two major visual pathways (magnocellular and parvocellular) according to the spatial frequency, temporal frequency and colour of the stimuli used.

Since the effects of any treatment may be detected more easily within a particular functional domain, a combined visual psychophysical, MRI and VEP study was undertaken of MS patients receiving the disease-modifying therapy interferon-beta-1a.

Methods: 20 patients with secondary progressive MS, enrolled in a phase III trial of interferon-beta-1a (Rebif,® Serono International, n = 618 patients) were studied with expanded disability status scale (EDSS), VEP, MRI and visual psychophysics. Measurements were made at enrolment and again after three years of treatment (8 placebo, 7 interferon-beta-1a 22 mcg tiw, 5 interferon-beta-1a 44 mcg tiw).

Results: Over the three years of the study none of the patient groups demonstrated significant changes from baseline in visual psychophysical thresholds, VEP amplitude or P100 latency, There was a significant improvement in burden of disease as measured by MRI sequences which was associated with interferon-beta-1a treatment ($p = 0.02$).

Conclusion: In this small subcohort (3 % of the total enrolled) from a study of patients with SPMS, treatment with interferon-beta-1a did not have an effect on the function of visual magnocellular and parvocellular axons or on signal conduction as assessed by visual psychophysics or VEPs. The improvement in MRI suggests that structural measures of MS disease burden appear dissociated from measures of sensory deficit in the visual pathways.

P589

Relapsing-remitting multiple sclerosis: a long-term observation of immunomodulatory therapy

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In multiple sclerosis (MS) powers of vision is deteriorated due to inflammation of optic nerve and visual pathway, especially during relapses. The function of optic nerve and visual pathway may be assessed by determination of visual evoked potential (VEP). The prolongation of stimulus transport can be measured as prolongation of latent period (P-100), which is the time between visual stimulus and response and which is for healthy persons 100 ms on average.

In a medical care unit specialized in treatment of MS in Lowersaxony patients with relapsing-remitting MS (RR-MS) were retrospectively observed for a long-term period. Aim of this investigation was to determine long-term efficacy of immunomodulatory drugs by measurement of VEP and annual relapse rate (ARR).

Within 8 years data of 178 patients who regularly visited the medical care unit had been collected. A change of immunomodulatory drug within the observation time was not excluded. 90 patients had been treated with interferon (IFN), 91 with intravenous immunoglobulins (IVIG) and 52 with glatiramer acetate (COP); for 39 patients data for periods without any therapy had been available. Data for 225, 289, 99 and 39 years of observation, resp., could be analysed.

For untreated patients a mean prolongation of latent period P-100 of 2.7 ms per year was determined. IVIG therapy resulted in a significant decrease of P-100 of –0.45 ms per year whereas IFN and COP therapy resulted in a mean prolongation of + 0.65 and 0.68 ms, resp.

Within the same period untreated patients experienced a mean of 0.9 relapses per year (ARR) whereas for IVIG treated patients mean ARR was clearly reduced to 0.3. On treatment with IFN or COP ARR was 0.5 and 0.6, resp.

The results of this retrospective long-term investigation confirm the trial-proven efficacy for IFN and COP. Under similar conditions also IVIG improved the course of disease as measured by ARR and P-100. This clearly supports the findings from clinical trials for this immunomodulatory therapy. Additionally long-term follow-up of latent period P-100 might be a suitable marker for course of disease which can be determined by standard equipment without great effort even in a neurologists medical office.

P590

Mitoxantrone therapy in multiple sclerosis and acute leukaemia: a case report out of 644 treated patients

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Background: As a rare complication of mitoxantrone (MITOX) therapy in multiple sclerosis (MS), a therapy related acute leukaemia (TRAL) may develop. The incidence is difficult to estimate, as mostly single cases are reported, up to now a total of eight MS patients.

Method: Here we report a new case out of 644 patients.

Case Report: This is a 45 year old female patient with secondary progressive MS who developed TRAL after a total dose of 48 mg/m^2 MITOX. The TRAL was classified as acute myeloblastic leukaemia (AML) M4eo and showed an inversion of chromosome 16 and a partial trisomy 11. Her TRAL was treated with chemotherapy followed by allogeneic bone marrow transplantation. It responded well to the transplantation, whereas the MS symptoms initially worsened but have nearly returned to the pre-transplantation level. This report brings the published frequency of MITOX-associated TRAL in MS therapy to five in a total of 2,236 treated MS patients, representing an incidence of 0.22 % representing a 100fold increase over background risk.

Conclusion: Therapy related acute leukaemia may occur as a severe complication of mitoxantrone therapy in MS. Obtaining informed consent of the MS patient should also cover this complication.

P591

MRI data in comparison of 500 mcg interferon beta-1b with 250 mcg: first phase of the BEYOND programme

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Objective: To compare the efficacy of 500 mcg and 250 mcg interferon beta-1b (IFNB-1b) using MRI outcomes, in patients with relapsing-remitting multiple sclerosis (MS).

Background: The licensed dose of 250 mcg IFNB-1b subcutaneously (sc) every other day (eod) has unsurpassed efficacy, but higher doses of IFNB-1b have not been evaluated on MRI and might provide improved efficacy. Accompanying data demonstrated that 500 mcg IFNB-1b sc eod, a dose higher than any currently available IFNB, was well tolerated. Whether higher dosing of IFNB-1b will result in greater clinical efficacy is an issue still to be addressed. The first phase of the BEYOND programme compared the effect of 250 mcg and 500 mcg IFNB-1b on various brain MRI measures including the frequency of enhancing lesions and combined unique lesion activity.

Methods: A multicentre, randomised, double-blind, parallel group study comparing IFNB-1b 500 mcg with 250 mcg sc eod for at least 12 weeks. Escalation of the study drug over the first 6 to 12 weeks was followed by administration of the full dose. Primary outcomes were safety and tolerability. T2-weighted and T1-weighted (before and after 0.1 mmol/kg gadolinium-administration) MRI scans were performed at baseline and week 12 for each patient, and these were analysed in a blinded fashion.

Results: IFNB-1b 500 mcg was well tolerated and there were no new or unexpected adverse events. Pre-planned and post-hoc descriptive analyses showed: median percentage change in T2 lesion volume from baseline was –6.9 % in the 500 mcg IFNB-1b group vs –1.8 % in the 250 mcg group (T2 lesion number –8.7 % vs –7.8 %); median Gd-enhancing lesion volume and number at week 12 was 0 in both groups (baseline volume 0 mm^3 vs 13 mm^3; baseline number 0 vs 1). Change in mean Gd-enhancing lesion number was –90 % in the 500 mcg group vs –70 % in the 250 mcg group (volume –96 % vs –93 %). The mean number of newly active lesions at Week 12 was 0.8 in the 500 mcg group and 1.7 in the 250 mcg group.

Conclusions: The small sample size and short duration of the trial mean that the results must be regarded as preliminary, but the findings indicate a trend towards a more positive effect of 500 mcg IFNB-1b on some MRI parameters compared with the 250 mcg dose. The clinical and MRI efficacy, safety, and tolerability of 250 mcg and 500 mcg IFNB-1b, and glatiramer acetate, will be comprehensively evaluated in the second phase of the BEYOND programme.

P592

Cutting the cost and length of clinical trials – the importance of choosing the right outcome measure

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Clinical trials in many chronic neurological diseases have been hampered by the lack of appropriate clinical outcome measures. Using the EDSS MS rating scale as an outcome measure, trials require large numbers of patients followed up for prolonged periods in order to demonstrate effects. Such studies are expensive and prone to high dropout rates, often 10 % per annum, making interpretation of results difficult. In order to develop clinical trials for progressive disease, reduce dropout and assess the long-term impact of treatments in MS we have been comparing outcome measures. We tested the properties of various outcome measures for MS trials by evaluating their responsiveness, intercorrelations and statistical significance of change scores in 77 consecutive patients receiving steroids for MS relapse. We demonstrate that, in order to obtain the same significant clinical effect using the different scales, sample sizes vary substantially. If 100 patients are required for the patient-orientated MSIS-29, the numbers for the other scales are: MSFC = 219; SF-36 = 381; EDSS = 891; UKNDS

LL = 1371. Standardised response means varied from 0.33–1.22 and significance of change scores varied from $p < 0.001$ (MSIS 29 and MSFC) to $P > 0.05$ (UKNDS LL). These findings have important implications for the cost, length and feasibility of clinical trials.

P593
IgG gammopathy as an adverse effect of interferon-beta therapy
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Multiple sclerosis (MS) is a cell-mediated autoimmune disease directed against central nervous system myelin components. Evidence suggests a predominance of Th1 activity in MS relapse and elevated Th2 cytokines during remission.

Interferon Beta (IFN b) is now the most widely prescribed therapy for long-term immunomodulation of MS. IFN b reduces relapse rate, disease activity as measured by MRI, and disease progression. Most studies indicate a suppression of the generation of autoreactive CD4 + Th1 cells and a decrease of Th1 cytokines following interferon-b treatment, but a clear shift from a Th1 network to a Th2 environment has been difficult to be demonstrated. Although the flu-like syndrome is the most common side effect, laboratory abnormalities are frequently observed: lymphopenia, neutropenia, leukopenia and increased liver aminotransferase values.

In two patients (4 %), one affected by secondary progressive form with relapses and one by relapsing-remitting form of MS, of those treated with IFN b 1 b (250 mcg other day sc), three months after the beginning of the therapy, the routine serum protein electrophoresis showed small monoclonal proteins. The immunoelectrophoresis demonstrated heavy chain IgG and K type of light chains. Urine test excluded the presence of light chain excretion. These laboratory data demonstrated the benign nature of the monoclonal gammopathy, a MGUS.

In both patients the IFN b therapy has produced clinical and neuroradiological effects measured as a reduction of either the relapse rate and the disability progression, and no appearance of gadolinium positive areas on MRI.

Two hypotheses could explain the gammopathy: the first is the presence of Interferon neutralizing antibodies (their detection is still under investigation), but it is in contrast with the clinical efficacy; the second one is the activation of B cells by Th2 cytokines. The neurologist has to monitor the gammopathy because the risk of MGUS progression to a malignant plasma cell proliferative disorder is approximately 1 % per year.

P594
Multiple sclerosis presenting as chronic optic neuropathy
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Background: Visual loss in multiple sclerosis is typically the result of acute optic neuritis. Progressive visual loss also occurs but it is very rare for multiple sclerosis to present in this way.

Method: We report two cases of multiple sclerosis that presented with chronic demyelinating optic neuropathy. Both of these cases experienced painless, slow, substantial, bilateral visual loss over a time course of three to twelve months, both cases failed to recover their acuity. There is only one other paper documenting multiple sclerosis presenting in this way and that was prior to MRI scanning and screening for Leber's hereditary optic neuropathy.

Conclusion: From a review of the literature it can be concluded that there is substantial evidence of progressive visual loss in up to 90 % of multiple sclerosis patients. The rarity of cases presenting in this way may well represent a lack of appreciation that chronic demyelinating optic neuropathy can herald the diagnosis of multiple sclerosis. Chronic optic neuropathy is also difficult to appreciate in the early stages as it is asymptomatic. It is important to recognise this condition as chronic optic neuropathy has a significant morbidity in the multiple sclerosis population. It is also crucial to appreciate that multiple sclerosis can present in this way, failure to appreciate this could result in the diagnosis of multiple sclerosis being delayed or missed.

Motor neuron disease

P595
Increased serum VEGF levels in patients with amyotrophic lateral sclerosis
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Introduction: There is evidence that glutamate-mediated toxicity may play a role in the etiopathogenesis of amyotrophic lateral sclerosis (ALS). It is known that vascular endothelial growth factor (VEGF) is a multifunctional cytokine that can protect neurons from glutamate-mediated toxicity. The aim of this study was to investigate serum VEGF levels in ALS patients.

Methods: Fifteen (seven males, eight females) ALS patients with an average age of 56.4 years and 15 (six males, nine females) controls with an average age of 53.8 years took part in the study. The mean duration of the disease was 16.5 years. ALS patients were diagnosed according to El Escorial criteria of the disease and divided according to type of ALS onset (bulbar/limb), clinical state of patients (mild/severe) and ALS duration (short-up to 12 months/long-over 12 months). VEGF was measured by the enzyme-linked immunosorbent assay. Serum VEGF was detectable in all samples. For statistical analysis the Mann-Whitney test and Spearman rank correlation were used.

Results: The study showed that serum VEGF levels are significantly increased in ALS patients compared with controls (median 438.25 pg/ml; range 98.06–936.96 pg/ml and median 239.13 pg/ml; range 71.02–669.72 pg/ml, respectively) ($p = 0.019$). Serum VEGF levels were not dependent on clinical parameters of ALS (type of ALS onset, clinical state of patients, or duration of the disease) ($p > 0.05$). There was also no correlation between serum VEGF levels and clinical state of patients, nor ALS duration ($p > 0.05$).

Conclusions: Data indicates that VEGF may be implicated in the etiopathogenesis of ALS and may suggest a protective role of this cytokine against glutamate-mediated toxicity in this disease. However, serum VEGF cannot be a marker of ALS activity.

P596
Very late onset of X-linked bulbospinal muscular atrophy (Kennedy syndrome)
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Kennedy-Syndrome is a X-chromosomal recessive bulbospinal muscular atrophy (X-BSMA), in some cases associated with endocrinological disturbances such as androgen insensitivity and diabetes mellitus. X-BSMA is characterized by almost symmetrical muscular atrophy, weakness and fasciculations predominantly of bulbar, facial and proximal muscles of the extremities, with typical onset in the third to fifth decade. Disease progression is usually slow and live expectancy normal. Sensory symptoms are clinically rare, but sensory nerve action potentials may be abnormal. Additional symptoms are important for differential diagnosis, and include postural tremor, gynecomastia, testicular atrophy and impotence. X-BSMA is caused by a CAG repeat expansion in the first exon of the androgen receptor (AR) gene on the X-chromosome. The size of CAG expansion significantly influences the age of onset, but neither clinical features nor disease severity. The most frequently early symptoms are gynecomastia, muscle pain, and premature muscular exhaustion.

We report on a 81 year old man presenting with a slow development of bilateral weakness of the proximal muscles of the upper and lower limbs over the preceding 6 years. Neurological examination disclosed a mild paresis and gross muscle atrophy of the small muscles of the hands as well as mild proximal weakness of the legs and arms. Tendon reflexes were depressed and pyramidal signs were absent. Spontaneous fasciculations of the buccal muscles and less pronounced of the limb muscles were observed. There was a slight pallhypaesthesia at the ankles. Additionally, bilateral gynaecomastia was observed. Laboratory results were normal except for a raised creatine kinase and pathological glucose tolerance test. Motor nerve conduction velocities were only slightly reduced whereas sensory action potentials were absent. Electromyograpy showed the typical features of chronic neurogenic denervation in all examined muscles. Motor evoked potentials were normal. The genetic analysis showed 44 CAG trinucleotid repeats within the AR gene (normal 11–34 repeats), which prooved the diagnosis of X-BSMA.

The example of our patient illustrates the heterogeneity of clinical presentation in X-BSMA. A very late onset in the eighth decade complicates the differential diagnoses encompassing amyotrophic lateral sclerosis, spinal muscular atrophy, muscular dystrophies and other types of motor neuron disease.

P597
Amyotrophic lateral sclerosis in the young: clinical and epidemiological features
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Objective: Previous epidemiological studies on amyotrophic lateral sclerosis (ALS) in our province showed incidence and prevalence rates of 2.16 and 4.02/100,000 respectively. No data are present about the clinical features and the epidemiological entity of the disease among young people.

Materials and methods: from 1990 a local register ascertaining cases of ALS in the province of Modena is active, both retrospectively (until 1998) and prospectively (from 1999). All the cases are defined considering the El Escorial Revised Diagnostic Criteria. Among 195 sporadic ALS patients we detected the clinical records of patients aged under 51 at disease onset, in order to show the clinical characteristics of ALS in young people.

Results: During the period considered, 30 residents (13 F, 17 M) were aged under 51 years (from 25 to 50 years) at the disease onset, whereas 165 (83 F, 82 M) were over 50 years. Considering Modena population aged from 25 to 50 years, the mean annual incidence of young ALS was 0.94/100,000 and the mean mortality rate was 0.40/100,000; in the older group, mean incidence and mortality rates were 4.99 and 3.99/100,000 respectively. The average age at onset was 41.14 years in the young and 66.82 years among patients over 50 years at onset. Mean time from onset to diagnosis was longer in younger patients (13.6 months; 12.65 among men, 14.85 among women) than in older ones (10.65 months; 8.34 among men, 12.94 among women). ALS with onset at lower limbs (36.97 %) and bulbar ALS (36.36 %) were the most common clinical forms in the older group, whereas the prevalent clinical forms in the young were the one with onset at higher (43.33 %) and lower (33.33 %) limbs. Bulbar ALS was less represented among young patients. The 56.66 % of young ALS patients were still alive at 31 December 2003, in contrast with the 20 % of older patients. Among patients dead for ALS, the mean disease duration from onset was 30.02 months for the older (30.96 F, 28.95 M) and 39.31 months for the younger (36.00 F, 43.17 M).

Discussion: ALS is five times rarer in young people than in people aged over 50 years, and it is characterized by a ten time lower mortality. The greater survival in younger people may be related to the young age itself, but also to a more benign disease course requiring a longer time to have a diagnosis, and to the less common onset in the bulbar district. The effect of these clinical features should be considered in clinical trials design.

P598
Lack of association between VEGF gene promoter variability and sporadic ALS
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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder involving upper and lower motoneuron with an incidence of about 1:100,000. The large majority of patients are sporadic cases and only 5–10 % show an inherited form. Vascular Endothelial Growth Factor (VEGF), an important angiogenesis citokine, has been described to have pleiotropic effects on neuronal survival, neuroprotective processes, regeneration, growth, differentiation and axonal outgrowth. Specific polymorphic changes within the VEGF gene promoter have been recently associated with lowered VEGF plasma levels, reduced VEGF gene transcription and increased risk to develop ALS.

We tested the involvement of VEGF as a susceptibility gene in ALS screening a portion of the VEGF gene promoter for known SNPs in 60 Italian sporadic ALS patients, randomly enrolled from the Department of Neurology, Policlinico of Milan. Total DNA was isolated from peripheral blood samples and two DNA regions containing specific portions of the VEGF gene promoter were amplified and directly sequenced, according to standard procedures. Two-tailed Pearson's Chi-square and Fisher's exact tests were used to compare genotype or allele frequencies and corresponding Odds Ratios and 95 % Confidence Intervals were calculated. To assess a functional relevance of VEGF SNPs, serum VEGF concentrations were measured according to specific promoter genotypes.

Genetic analysis failed to find different distributions of C (–2,578)A, C (–1,198)T, G (–1,190)A and G (–1,154) A polymorphisms in the ALS population compared to 186 age-matched healthy controls. Serum VEGF levels were not different between ALS patients and controls (365.6 ± 223.70 pg/ml vs 385.4 ± 179.8 pg/ml; $p > 0.05$); moreover, serum concentrations were not correlated to specific VEGF gene promoter genotypes.

In this small-scale study we found a non-significant difference between Italian ALS patients and controls in terms of both VEGF gene promoter variability and VEGF levels; larger numbers of patients are needed to verify that this is a true association.

P599
Epidemiological features of motor neuron disease in Southwestern Greece
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Aim: To evaluate the epidemiological features of Motor Neuron Disease (MND) in a region (835,000 inhabitants) of southwestern Greece.

Patients and Methods: All cases of adult-onset MND, encompassing Amyotrophic Lateral Sclerosis (ALS), Progressive Bulbar Paralysis (PBP) and Progressive Spinal Muscular Atrophy (PSMA), diagnosed from 1990–2003 at the department of Neurology of the University Hospital of Patras, have been retrospectively analysed.

Results: Overall 133 patients were identified, corresponding to an average annual incidence rate of 1.13/100,000 (95 % C.I: 0.95–1.35), 1.47 for males (95 % C.I: 1.18–1.82) and 0.81 for females (95 % C.I: 0.6–1.08), with a male to female incidence ratio of 1.77:1. The annual incidence rate, age and sex adjusted to the Greek population in 2001 was 1.35 cases per 100,000 inhabitants, 1.83 for men and 0.9 for women, while the same annual incidence rate adjusted to the European population was 1.15/100,000 population, 1.54 for males and 0.78 for females. The mean age at the time of diagnosis was 61.5 ± 13.3 years. Annual incidence rates increased with advancing age with the highest peak between ages 59–68 and 69–78 (53 and 28 cases respectively). Indicatively, at the age 59–68, the incidence rate reached the value of 0.45/100,000 population/year. ALS was found to be 5.8 times more frequent than PSMA (0.95/100.000/year vs 0.16/100,000/year) and 37 times more frequent than PBP (0.95/100,000/year vs 0.03/100,000/year).

Conclusions: There was no statistically important difference in the results of the considered epidemiological parameters of our study to those reported by most other similar previously studies.

P600
Clinical features of motor neuron disease in Southwestern Greece
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University Hospital of Patras (Rion, Patras, GR)

Aim: To evaluate the clinical features of Motor Neuron Disease (MND) in a region (835.000 inhabitants) of southwestern Greece.

Patients and Methods: The medical records of all patients diagnosed with adult-onset MND at the Department of Neurology of the University Hospital of Patras from 1990–2003, were reviewed. The medical and demographic background of patients with MND was compared to that of 135 controls patients randomly selected from the case records of our department.

Results: Overall 133 patients were identified, corresponding to an average annual incidence rate of 1.13/100.000 population (95 % Confidence Intervals: 0.95–1.35). 85 of them were men (63.9 %) and 48 were (36.1 %) females having a mean age of 61.4 ± 13.3 years. The most common type of MND was ALS, identified in 111 (83.5 %) patients Two of them had positive family history of ALS. There were 19 cases (14.3 %) classified as PSMA and 3 (2.2 %) cases as PBP. The median age at onset was 60.3 ± 13.5 years, while the mean delay between age at onset and age at diagnosis was 1.3 ± 1.1 years. The site of symptoms onset involved lower limbs in 76 (57.2 %) cases, upper limbs in 32 (24 %) cases, bulbar region in 22 (16.5 %) cases and respiratory muscles in 3 (2.3 %) cases. The patients were followed-up throughout the illness in 62.3 % of cases. Data about long-term outcome were obtained by telephone contact in another 23 (17.3 %) patients. The median survival time after onset of disease was 20.4 ± 8.3 months for ALS, 15.3 ± 4.5 months for PBP and 38.1 ± 26.4 months for PSMA. When compared to controls, patients with MND presented similar rates of positive past medical history. Likewise, data on occupation and toxic exposure factors revealed no association between any of them and occurrence of the disease. The same applied for educational, marital status, lifestyle habits (smoking, alcohol intake). For all the above correlations, x2, p = ns.

Conclusion: The study of patients with MND showed a predominance of ALS patients. No potentially causative clinical associations were found and no relation between occupational exposure, trauma and the disease was noted.

P601
Parieto-occipital atrophy in chronic juvenile ALS with long-term progression of 47 years
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Background: Chronic juvenile ALS is a heterogeneous disease, characterized by age of onset before 25 years, a progressive and benign course, upper and lower motor neuron involvement and the absence of sensory, cerebellar, extrapyramidal and other atypical features. Abnormalities on magnetic resonance imaging (MRI) have been reported in the cortex and corticospinal tract of a subset of typical ALS patients. Little is known about MRI features of ALS patients with long-term progression and survival.

Case report: we report a 71 years old male patient, who at the age of 24 years developed a slowly-progressive upper and lower motor neuron syndrome. After the clinical course of 47 years the patient was wheelchair-dependent and showed a high grade of upper-extremity disability. In the last two years he noticed significant progression of dysarthria and dysphagia. The patient was without need for ventilatory support or sustained nutritional intervention. The ALS Severity Scale was currently 21 of 40. There were no atypical symptoms, and no evidence for dementia. Biochemical workup was negative.

Results: A diagnosis of chronic juvenile ALS was made. The patient fulfilled the criteria for definite ALS by the WFN criteria. T1 and T2 weighted MRI of the brain revealed severe, bilateral cortical atrophy of the parietal-occipital lobes and the pre-central gyrus, followed by cerebral atrophy of the frontal and anterior temporal regions. There was no evidence for signs of corticospinal tract hyperintensity.

Conclusion: We present a case of chronic juvenile-onset ALS with a natural history of 47 years and ongoing disease progression. This patient represents – to our knowledge – the longest reported disease duration of clinically typical and definite ALS. In our patient, MRI of the brain revealed an unusual pattern of severe cortical atrophy of the occipital, parietal lobes and the cingular gyrus. This finding contributes to the notion that chronic juvenile ALS may present with highly variable features of multi-system involvement. The investigation of extended groups of ALS patients with prolonged survival will be important to define MRI abnormalities which are associated with slow disease progression.

P602
ALS and associated conditions: is there any causative relationship?
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Introduction: Although the association of sporadic ALS (SALS) with many disorders and conditions is well known, their frequency has not been precisely determined as yet. A causative relationship between many of these disorders and SALS has not been clearly established. The aim of the present study was to investigate the frequency of other disorders and conditions which are associated with SALS.

Patients and methods: The study included SALS patients who were diagnosed at the Institute of Neurology, Belgrade, Serbia in the period between 1992–2002. All patients fulfilled the criteria of probable or definite ALS according to El Escorial criteria. In this study the SALS patients with associated disorders and conditions which preceded the onset of SALS, were selected and these data were statistically evaluated.

Results: The study population comprised 674 (404 males and 290 females) SALS patients. The mean age of onset was 58.7 ± 11.7. In 162 (24 %) patients associated conditions were found, among which the most common were spinal degenerative changes (5.7 %), trauma (4.8 %) and surgical stress (5 %) occurring less than 3 years before the onset of ALS; intervertebral disc protrusion (4.6 %) and hypertension (3.9 %) ($p < 0.01$). Further, ALS was associated with brain ischemia (2.5 %) and trauma (2.1 %), which occurred shortly before the onset of the disease ($p < 0.05$). Trauma and surgical stress preceding the onset of disease for less than 3 years, as well as intervertebral disc protrusion and spinal degenerative changes were more frequent in patients with spinal onset of SALS ($p < 0.01$). In cases were trauma shortly preceded the onset of ALS the first symptoms appeared in the traumatized limb (83.3 %) ($p < 0.01$). In all patients who manifested the first symptoms immediately after the discectomy, the symptoms of ALS appeared in the priory affected region ($p < 0.05$).

Conclusions: It is not uncommon for ALS to be associated with other diseases and conditions. Surgical stress, as well as trauma seems to precipitate the onset of SALS.

P603
Toxicity of cerebrospinal fluid in patients with amyotrophic lateral sclerosis and level of glutamate
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Objectives: The purpose of this research was to study: Is the cerebrospinal fluid (CSF) in patients with amyotrophic lateral sclerosis (ALS) toxicity or not.

Methods: We studied the level of glutamate in patients with ALS.

Results: 56 patients out of 82 patients under observation in (CSF) showed reliable increase of level of glutamate. The other patients had normal level of glutamate. In the nervous tissue culture we reveal great damage of anterior horn cells and formation of abnormal phosphorylated neuro-filaments there and also anomaly of cytoarchitectonics. Such toxicity of (CSF) concerning neurons in the nervous tissue culture, perhaps is correlated with alfa-amino-3hydroxy-5methylisoxa-zole-4 propionate (AMPA) and kainite receptors activation. This toxicity in our investigation is correla-ted with the amount of glutamate in (CSF): (CSF) with increased level of glutamate caused the marked toxic effect, where as (CSF) with normal level of glutamate did not cause the effect.

Conclusion: We managed to show toxicity of (CSF) in patients with ALS to neurons in tissue crops.The selected subgroups of patients with ALS involving glutamate excitotoxity, who have high level of glutamate in (CSF) may become important while evaluating clinical reaction while using antiglutamate agent- Riluzole (Rilutek).

P604
SPECT evaluation of patients with amytrophic lateral sclerosis
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Aim: The degeneration in the pyramidal motor system is the most characteristic feature of motor neuron diseases. Amyotrophic lateral sclerosis (ALS) is the most common type of motor neuron diseases in which anterior horns of the spinal cord most commonly involved. The exact pathogenesis of Amyotrophic lateral sclerosis is unknown. The aim of this study was to evaluate patients diagnosed as amyotrophic lateral sclerosis via SPECT imaging and determine possible changes in blood flow of these patients and its relationship with several symptoms.

Material and method: Eleven patients (8 male, 3 female) with Amyotrophic Lateral sclerosis whose diagnosis were confirmed by electromyography has been included in the study. The mean duration of the disease was 8.2 years. The mean age of the patients was 53 years. EEG and magnetic resonance imaging results of all patients were within normal limits. Eleven healthy people (4 female, 7 male) with a mean age of 51 years formed the control group for the study. We performed resting brain SPECT to the patients and healthy controls injecting 20 mCi of Tc-99m HMPAO intravenously. SPECT images were evaluated visually. Data from patients and control group were compared statistically

Results: There were statistically significant differences between control and patient group in frontal, parietal and temporal lobes as well as in thalamus. The blood perfusion on the right precentral gyrus, right fronto-parietal lobe and right superior temporal lobe and left thalamus ($p < 0.05$) were decreased in patients with amyotrophic lateral sclerosis.

Conclusion: In addition to clinical and laboratory findings, Regional cerebral perfusion changes may exist in the patients with amyotrophic lateral sclerosis which might shed light on course and etiology of amyotrophic lateral sclerosis.

Infection of the nervous system

P605
Antigen-driven immunoblots and polymerase chain reaction in cerebrospinal fluids from 30 patients with suspected varicella-zoster infection of the nervous system
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Objective: Cerebrospinal fluid (CSF) analysis is a key tool in the diagnosis of central nervous system (CNS) infection with varicella-zoster virus (VZV). Detection of intrathecal synthesis of VZVspecific antibodies and amplification of VZV DNA by polymerase chain reaction (PCR) are well-established techniques. We present a detailed CSF analysis of patients suspected to harbor CNS VZV infection and possible correlations with clinical pictures.

Materials: Thirty patients were included and distinguished in four groups. First one consisted of 23 cases with a rash in one or more dermatomas and clinical suspicion of radiculitis or meningitis. These patients were divided in three subgroups according to the affected dermatomas: trigeminal (N = 8), facial (N = 9) and cervico-thoraco-lumbar (N = 6). Second group contained two patients presenting radiculitis without eruption "zoster sine herpete". Two patients were recorded in third group, who displayed meningoencephalitis signs without eruption. Fourth group contained three patients with generalized rash and encephalitis. A PCR for VZV DNA and the detection of an intrathecal synthesis of VZVspecific antibodies were performed in all cases.

Results: In patients with radiculitis, PCR was negative in 75 % within trigeminal subgroup while positive within facial and cervico-thoraco-lumbar subgroups, 67 % and 50 % respectively. Intrathecal synthesis of oligoclonal antibodies with antiVZV activity was detected in CSF of 39 % of radiculitis group. CSF collected from both patients with zoster "sine herpete" and radiculitis displayed pleiocytosis. Positive VZV PCR and intrathecal synthesis of VZVspecific antibodies were detected in one patient each. Both patients with meningoencephalitis without eruption had positive PCR but CSF analysis detected oligoclonal antiVZV specific antibodies in one of them. CSF PCR was positive in two of three patients with generalized eruption and encephalitis signs. Both produced locally VZVspecific antibodies.

Conclusion: Our findings highlight the diagnostic value of a detailed CSF analysis in VZV infection. This is particularly true in facial palsy and intercostal zona with suspected meningitis because of frequent CSF abnormalities. VZV may be a causative agent in cases with meningitis or radiculitis of unknown origin, even in the absence of skin manifestations. In such patients rapid diagnosis by PCR amplification of VZV DNA and detection of intrathecal antiVZV antibodies allow early antiviral therapy.

P606

Chronic neutrophilic meningoencephalitis due to toxoplasmosis in an apparently immunocompetent woman

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Introduction: An apparently immunocompetent 73 year old woman presented with chronic neutrophilic meningoencephalitis in the absence of cerebral mass lesions. Extensive investigation, including tests for Toxoplasma, failed to identify a cause during life, but at autopsy Toxoplasma gondii meningoencephalitis was discovered.

Case report: A 73 year old woman presented with a six month history of initially non-specific headaches progressively worsening in severity and increasingly associated with meningism. On examination she was mildly confused and pyrexial with neck stiffness. There was bilateral papilloedema but no focal neurological signs. CT brain was unremarkable, but cerebrospinal fluid (CSF) demonstrated a raised opening pressure, predominantly neutrophilic pleocytosis and low glucose. Gram stain, ZN stain and cryptococcal antigen were negative, and cytology normal. Repeated subsequent CSF examinations continued to show a neutophilic pleocytosis with raised protein and low glucose. Multiple investigations for malignancy and for bacterial, mycobacterial, fungal and spirochaetal infections were negative. Toxoplasma serology was positive for IgG but negative for IgM. CSF toxoplasma polymerise chain reaction (PCR) was negative. Magnetic resonance imaging of the brain showed meningeal contrast enhancement but no cerebral mass lesions. She was treated empirically for chronic meningitis with antibiotics, antituberculous therapy, amphotericin and steroids, but continued to deteriorate steadily and died nine months after onset of her first symptoms. In spite of the previously negative PCR for toxoplasmosis, the autopsy diagnosis was Toxoplasma gondii meningoencephalitis.

Discussion: The syndrome of chronic meningitis is a diagnostic challenge with a wide range of potential causes, often requiring empirical treatment. A predominantly neutrophilic CSF is relatively unusual. Although toxoplasmosis typically presents with an intracranial mass lesion in an immunocompromised host, there are rare reports of a more diffuse meningoencephalitic presentation almost invariably lymphocytic in nature. In this case, diagnostic difficulty was caused by the neutrophilic CSF, absence of cerebral mass lesions, falsely negative Toxoplasma PCR, and apparent immunocompetence of the patient. Toxoplasma should be added to the list of potentially treatable causes of chronic meningitis, both lymphocytic and neutrophilic, even in the apparently immunocompetent individual.

P607

Infectious myelitis: clinical, paraclinical and outcome profile

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Introduction: It is difficult to obtain a biological confirmation of an infectious acute myelitis.

Objectives: To define the clinical, paraclinical and outcome profile of infectious myelitis.

Patients and methods: This retrospective study included 153 subjects hospitalized in the department of neurology between 1993 and 2002 for treatment of a noncompressive acute myelopathy. Biological confirmation of recent infections was obtained in 12 patients (8 %).

Results: An infectious syndrome, previous to the neurological symptoms, was found in 67 % of the patients. The clinical symptoms were severe with loss of sensitivo-motor and sphincter functions and ascending spinal cord dysfunction (acute transverse myelopathy). Spinal cord MRI showed a transient extended T2 centromedullar hypersignal. CSF analysis showed hypercytosis, above 30/mm^3, and protein levels increase, in respectively 75 % and 58 % of the patients, without oligoclonal bands. Clinical outcome was good in all patients except one, however sphincter functions were late to recover.

Discussion: Our study shows a stereotypical clinical, paraclinical and outcome profile for infectious acute myelitis. These findings are significant for therapeutic discussion and prognosis at the initial phase of an acute myelopathy.

P608

Guillain-Barré syndrome and concurrent lymphocytic meningitis due to mumps infection

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Introduction: We present the first reported case of Guillain Barré syndrome (GBS) with concurrent meningitis in which mumps virus was cultured from the cerebrospinal fluid (CSF) and where the absence of parotitis posed an additional diagnostic challenge.

Case report: A 25 year old woman presented with poor balance and paraesthesiae of the extremities. For several days she had suffered from low grade fever and meningism. There had been no parotitis. She was pyrexial and photophobic, with neck stiffness. There was a left lower motor neuron facial palsy. Her gait was unsteady, she was unable to tandem walk but there was no limb weakness. Reflexes were depressed, plantar responses flexor. There was symmetrical distal sensory loss in the limbs.

CSF showed a lymphocytic pleocytosis with markedly raised protein and normal glucose concentrations. Immunoperoxidase staining revealed a predominantly B lymphocyte population, atypical for GBS. Gram stain, ZN stain and cryptococcal antigen were negative. Nerve conduction studies showed features of early GBS.

Treatment with antibiotics and intravenous immunoglobulin was initiated but over the following 48 hours her condition deteriorated. Her facial weakness became bilateral and she developed progressive limb weakness until bedbound. She became areflexic and developed dysautonomia. An echocardiogram showed septal hypokinesia. Mumps virus was cultured from the CSF. CSF and serum tests for alternative viral, tubercular, fungal and spirochaetal aetiologies proved negative. Within several days her condition began to improve and she was discharged approximately one month later, having made a full recovery.

Discussion: Before the advent of mass vaccination, neurological complications of mumps infection were common in Europe, the most frequent being a benign lymphocytic meningitis. Other extraparotid manifestations of mumps are well recognised, including a myocarditis in up to 15 %. Mumps meningitis may occur without clinically evident parotitis in up to 50 % of cases. GBS has been reported in conjunction with mumps as a postinfective inflammatory disorder, diagnosed by serum antibody titres. This is the first reported culture-proven active mumps meningitis associated with concurrent GBS. In view of the current vaccination controversy and subsequent fall in vaccination rates it is important to be aware of mumps as a potential cause of aseptic meningitis, or as in this case causing GBS with atypical CSF.

P609
Distal demyelinating polyneuritis due to Rickettsia conorii infection
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Background: Mediterranean spotted fever is a tick-borne disease caused by Rickettsia conorii. It is considered endemic in the Mediterranean region. Fever, rash, and the presence of a black eschar are the most prominent clinical features of this mostly benign infection. Neurological involvement manifests as encephalitis-like illness. Meningismus, headache, mental deterioration and occasionally coma are encountered in a minority of cases. Involvement of the peripheral nervous system is extremely rare. There are only few reports of isolated facial nerve palsies and Guillain-Barré syndromes.

Case report: A 76-year old man suddenly developed headache with tinnitus, vomiting and fever. Two days later he presented in the hospital with a complete right facial nerve palsy and severe abdominal pain. During the following days he remained afebrile, but he additionally developed hoarseness, severe difficulty in swallowing fluids and a progressive weakness of all four extremities. His clinical situation showed a slight progression and about a week later he was not able to walk or stand without assistance. He was then transferred to our department for further evaluation. On admission a complete right side Bell's palsy, hoarseness, dysphagia, symmetrical flaccid tetraparesis were documented. There was no sensory deficit. Repeated CSF examinations revealed normal protein levels with elevated cell counts (68–135 lymphocytes), excluding Guillain-Barré syndrome. Subsequent electromyograms revealed denervation only in the muscles innervated from the right facial nerve. Conduction studies revealed initially a significant reduction of the compound muscle (CMAP) and sensory action potentials (SNAP). An indirect immunofluorescent antibody test four weeks after symptom onset revealed eightfold-elevated IgM titres for Rickettsia conorii (1:80, negative = 1:10). The patient received orally Doxycycline (200 mg daily) for two weeks and showed a rapid clinical progression. CSF became normal and repeated conduction studies showed an impressive CMAP- and SNAP-restoration.

Conclusion: Based on the paucity of denervation and the rapid improvement of the amplitude of the CMAPs and SNAPs after treatment we assume a distal demyelinating sensorimotor polyneuritis, also affecting the facial nerve, as a highly uncommon neurological complication of an acute Rickettsia conorrii infection.

P610
Current outbreak of tetanus in intravenous drug users
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Tetanus is an acute, often fatal infection caused by the exotoxin from Clostridium tetani. Characteristically it produces generalized rigidity and spasms of voluntary muscle, ultimately with death being caused by respiratory paralysis. Tetanus is rare with only 175 cases reported to the Communicable Disease Surveillance Centre (CDSC) in the United Kingdom (UK) in the years 1984 to 2000. An at risk group are intravenous drug users (IDUs), who may contract tetanus using contaminated needles, drug paraphernalia or heroin. Interestingly, only 2 of the 175 cases between 1984–2000 were in (IDUs). In contrast in the United Sates (US) IDUs comprise 15–18 % of cases reported. Since July 2003 seven cases of tetanus in IDUs have been reported in the UK with one death. There is a wide national distibution to the cases reported, raising concerns that this is not an isolated outbreak. Therefore the potential exists for more cases to occur anywhere in the country. Among this recent outbreak is a 30 year old female IDU with tetanus was admitted in Exeter. The clinical management of this patient is described, as is diagnostic testing and prophylaxis of tetanus.

P611
The presence of IgM antibodies to beta-tubulin class III in the course of borreliosis (Lyme disease)
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In this study, we tried to asses the chance of detecting neuronal loss in patients with inflammations, such as the Lyme disease (LM), which is caused by the spirochete Borrelia burgdorferi. As borreliosis, accompanied by neurological symptoms, in some cases resembles multiple sclerosis with demyelination and neuronal loss, we tested for the presence of antibodies (IgG and IgM) to β-tubulin class III (βtIII) in the serum of 26 patients whose CSF contained either Borrelia or antibodies (IgG and IgM) against Borrelia. Here we employed an ELISA-test to detect serum antibodies against the C-terminal amino-acid sequence of βtIII, which is a cytoskeletal protein constituent found only in neurones. At the time of their collection, the sera of about 38 % (10/26) of the patients displayed a significantly increased titre of IgM antibodies as opposed to only about 8 % with an increased titre of IgG antibodies. As all patients tested manifested some neurological symptoms and no discernible difference appeared in the composition of these symptoms for patients with or without IgM antibodies against βtIII, the autoimmune response to βtIII seems to be asynchronous with the momentary neurological state. In conclusion, the presence of antibodies to βtIII in the serum of LM-patients documents the loss of neurones in the course of this inflammatory disease. The relatively low incidence of IgM and IgG antibodies in the serum may reflect the transient nature of the antibody presence in the circulatory system.

P612
A serial cerebrospinal fluid analysis in American trypanosomiasis
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Background: American Trypanosomiasis (Chagas' Disease) is caused by Trypanosoma cruzi. Meningoencephalitis has been described among immunocompromised individuals, mainly HIV-infected subjects, as a reactivation of acute disease.

Objective: To report a serial CSF analysis in a brazilian-infected patient, successfully treated with benznidazole.

Methods: CSF/serum paired samples were collected 5 times along the follow-up of the patient: the first three exams were obtained at the beginning of the disease and the last two, 30 and 60 days after introduction of benznidazole 7 mg/kg/day. Total CSF/serum IgA, IgG, IgM, and free light chains were measured in a BN-2 nephelometer (Dade-Behring). Chagas' serologic tests were performed with 3 different methodologies: ELISA, indirect hemagluttination (HAI), and indirect immunofluorescence (IFI). The trypanosoma-specific IgG antibody index (AI) was calculated using HAI-IgG assay.

Results: A 59-year-old heterosexual brazilian man, with asymptomatic chronic Chagas' disease was admitted to University Hospital with a 7-days evolution of mood and behavioral changes. Brain MRI scan disclosed diffuse white matter involvement. HIV infection was detected (serology and PCR); CD4 count: 224 cells/mm^3; HIV-viral load: 760 copies. Chagas' antibody response was identified in CSF and serum (IgG and IgM class). Reversion of T. cruzi seropositivity occurred after benznidazole treatment. IgG intrathecal synthesis and free light chain synthesis were demonstrated just after correction of CSF-blood dysfunction. No IgA or IgM intrathecal synthesis were shown. Pathological trypanosoma-AI (HAI-IgG) was determined in three CSF exams. Hemoculture identified T. cruzi after 70 days-observation, although not demonstrated in CSF direct visualization or blood smear.

Discussion: CSF analysis, in chagasic meningoencephalitis, may express mild pleocytosis, mild to moderate CSF-blood barrier dysfunction, no evidence of increased anaerobic glycolysis, absence of global humoral immune response, positive Chagas' antibody response and trypanosoma-specific intrathecal synthesis.

P613
Interaction between Neisseria meningitidis and human dendritic cells is strain-dependent and not mediated by major protein antigens of the bacterial surface
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N. meningitis infection depends on the ability of the bacteria to cross the epithelial barrier of the oropharynx. Within this barrier, dendritic cells (DC) are one of the first lines of defence, likely to play a major role in initiating an immune response. We have shown previously that phagocytosis of N. meningitidis by human DCs is efficient in unencapsulated strains. In contrast, expression of the capsule prevents adherence and phagocytosis of the bacteria. In this study, the function of major protein antigens of the bacterial outer membrane in DC-N. meningitidis interaction was examined for the hypervirulent clinical isolate MC58. In contrast to epithelial cells, the outer membrane proteins OpcA and OpaA did not mediate bacterial adhesion to the surface of DCs. In addition, expression of class I pili did not confer an adherent phenotype to unencapsulated N. meningitidis strains. Adherence of N. meningitidis to human dendritic cells could be partially inhibited by mannan and poly-I in some experiments, indicating

a possible role for the macrophage mannose and scavenger receptors in N. meningitidis recognition. However, the contribution of these receptors seemed to be highly variable for DCs of different donors. Furthermore, meningococci with different genetic backgrounds differed markedly with regard to their interaction with human DCs.

Although the nature of the physical interaction between human DCs and N. meningitidis is not clear, it will be of significant interest to determine bacterial and cellular factors contributing to recognition of N. meningitidis. Given the central role of DCs in antigen presentation and T-cell activation, the inter-strain differences could significantly influence activation of the immune system.

P614

Meningeal cryptococcosis in AIDS patients in Tunisia

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Objectives: To assess the meningeal cryptococcosis incidence in HIV patients,and to analyze the clinical aspects, the treatment and the outcome of patients in a developing country.

Methods: All adult patients records admitted to the department of infectious diseases of Rabta hospital between March 1991 and December 2002 and who were HIV-positive were reviewed retrospectively. To establish the cause of the disease and the immunologic status of the patients, clinical and laboratory investigations were performed. The classic India ink test from CSF smear, cultures from CSF and blood cultures were performed in all patients too.

Results: Among 346 hospitalized patients, 12 (3.47 %) had cryptococcal meningoencephalitis. There were 8 males and 4 females, aged 22–42 years (median age 32 years). Risk behaviour was homo/bisexual in 5 cases (41.7 %), IVDU in 4 cases (33.3 %) and heterosexuality in 3 cases (25 %). Cryptococcal meningitis was the first AIDS defining illness in 5 cases (41.7 %). All patients were HIV class C (average value of CD4 = 62 lymphocytes/mm^3) at the moment of cryptococcosis. Headache (100 %), vomiting (83.3 %), fever (75 %) and neck stiffeness (50 %) were the main symptoms. All patients were treated first with amphotericine B. 5 patients were switched to fluconazole: because of side effects in two, and for oral administration in the latter three. The overall mortality was 83.3 %. Only one patient receiving HAART is still alive with negative CSF cultures at 10 months from the onset of the illness.

Conclusion: Cryptococcal meningitis is the second opportunistic infection of central nervous system after toxoplasmosis in our experience. Because of poor prognosis,early diagnosis and treatment are of great importance in the management of this disease.

P615

Brucellosis incidence in subjects with headache in Eastern Turkey

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Objective: Brucellosis is common in areas where domestic animals harboring Brucella are raised, where adequate control measures are lacking and where the population has the custom of ingesting unpasteurized milk or its products. In this study, we investigated brucellosis incidence in patients with the complaint of headache. Our purpose was to determine the incidence of brucellosis in the etiology of headache in our country.

Methods: The study includes 503 patients (78 male and 425 female) who were admitted with chronic headache and 50 healthy subjects (15 male and 35 female). The ages of the patients and healthy subjects were between 12–63 years.

Results: Of 503 patients with headache 67 (13 %) patients (54 were females, 13 were males) had positive titters 1/80 or above. In healthy subjects the agglutination test was positive in 3 (%6) subjects; in all of them serum agglutination test was 1/80. In the patients group, headache was recovered in 39 (58 %) patients, but insisted in 11 patients (16 %) with specific antibacterial therapy. Seventeen (25 %) patients could not be followed up.

Conclusion: Brucellosis is still endemic in many parts of the world including the Mediterranean and Middle Eastern countries although its is disappearing in many developed countries We found that brucellosis was an important cause of headache in our region; therefore, we recommended that brucellosis should be considered in patients admitted with the complaint of headache.

P616

Meningitis and myelopathy following vestibular schwannoma surgery

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Introduction: We report the case of a patient who developed meningitis and irreversible myelopathy related to an iatrogenic dural defect.

Case report: Ten weeks after removal of a vestibular schwannoma, a 28 year old woman became septicaemic without obvious focus of infection. She was treated with empirical benzylpenicillin for several days and her symptoms resolved. Culture of blood and urine grew penicillin-sensitive Streptococcus oralis, and although there had been no pyuria she was discharged with a diagnosis of S. oralis urinary tract infection.

Three days later she developed a flaccid paraplegia with a thoracic sensory level, evolving over 24 hours and associated with thoracic back pain. She was apyrexial with no neck stiffness. Magnetic resonance imaging showed extensive arachnoiditis and an area of intrinsic high signal within the thoracic cord. Cerebrospinal fluid (CSF) showed a mixed pleocytosis, markedly raised protein and low glucose concentrations. Gram stain, ZN stain, cryptococcal antigen and multiple blood cultures were negative. An echocardiogram was normal. The patient reported that since the operation she had a trickle of clear fluid from the nostril, suggesting a postoperative dural leak. This was identified and repaired. Following antibiotic treatment her CSF normalised but her neurological state failed to improve and she remains paraplegic.

Discussion: CSF leak is a common complication of vestibular schwannoma surgery, with incidence rates of up to 21 %, and associated meningitis in up to 5.3 %. The oropharyngeal commensal S. oralis is a member of the viridans group of streptococci, which are an uncommon cause of meningitis, typically associated with pharyngeal pathology or neurosurgery. S. oralis is not, however, a known pathogen of the urinary tract.

This patient developed meningitis and myelopathy related to a post-surgical dural defect. Her septicaemia was misattributed to a urinary source when in fact it was meningeal in origin. Cord infarction and inflammation are both recognised in the context of bacterial meningitis, and seem to have a similarly poor prognosis. In this case irreversible myelopathy was the culminating feature of an unusual and unfortunate series of events. It illustrates an important lesson which can be generalised to other cases involving investigation of infection: finding an unusual organism in an unusual context should prompt careful thought as well as action.

P617

MRI findings in a case of listerial brain abscess

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Background: Listeria monocytogenes often causes meningitis or meningoencephalitis and rarely brain abscess.

AIM: To describe the unique MRI findings in a case of a listerial brain abscess successfully treated.

Case presentation: A 55-year old man, with a history of ulcerative colitis under corticosteroid treatment, presented with low-grade fever. During his hospitalization, he developed right-sided deafness, slurred speech and right-sided ataxia. Meningeal signs were absent. Brain MRI showed scattered, non-specific foci within the brainstem and the hemispheres. A diagnosis of CNS vasculitis was made. The patient received high dose of methylprednizolone intravenously and the symptoms subsided. Few days later, the patient was presented with left-sided paralysis and anesthesia. Brain MRI showed a multiloculated inhomogeneous lesion in the right parietal lobe with peripheral enhancement in a cylindrical linear pattern. There was also a significant amount of surrounding vasogenic edema and mass effect at the adjacent ventricular system. On Diffusion-Weighted Imaging, the lesion exhibited high signal due to restricted water diffusion, a finding consistent of a viscous content. A listerial infection was suspected, and the patient was treated with high dose ampicilline and gentamycin. The second day after admission he developed signs of increased intracranial pressure, for which he had an emergency craniectomy. Culture of aspirate confirmed the infection by L. monocytogenes. The patient continued the antibiotic treatment for three months with relative good recovery. However, MRI continued showing changes in the site of the abscess following resolution of the mass effect.

Conclusions: A case of L. monocytogenes infection with a lobar localization is presented. MRI findings including a unique cylindrical enhancement pattern with no evidence of meningeal involvement persisted besides the good recovery.

P618
Adjunctive cortisone in acute Herpes-simplex virus encephalitis: a pilot study
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Background: Herpes-simplex-Virus encephalitis (HSVE) still carries significant mortality and serious sequelae in survivors despite advances in treatment and critical care. The initiation of antiviral treatment on suspicion of encephalitis is important, but it is not enough to improve the long-term prognosis. The ability of a virus to modulate the immune response can have a pivotal effect on the disease course. Adjunctive treatment with cortisone, an anti-inflammatory and anti-edematous agent, could promote favourable effects as recently suggested in animal models and during the pre-acyclovir era.

Methods: We report four patients (1 man, 3 woman; mean age 64) with PCR-proven acute HSVE admitted in 2003 to the Department of Neurology at Heidelberg University, Germany. All were treated with the standard acyclovir regimen over 14 days, the therapy was started already on suspicion of HSVE. Furthermore, the therapy consisted of adjunctive cortisone (2 patients: 3×10 mg Dexamethasone over 4 days, 2 patients: Methylprednisolone).

Results: None of the four patients experienced adverse events that could be traced back to the adjunctive cortisone therapy. The recovery was not altered in terms of clinical deterioriation and patients could be discharged for rehabilitation of the residual neuropsychological impairment typical for HSVE.

Discussion: The outcome of viral encephalitis may triggered by the host immune response. We report a series of four HSVE patients who received a regimen of cortisone in addition to antiviral treatment. All patients recovered significantly in the clinical course. The adjunctive therapy did not alter the typical disease course and no severe adverse events were observed. Since animal studies suggest a beneficial long term effect of adjunctive cortisone, further studies are necessary to evaluate this effect in humans.

P619
Neurocryptoccocosis with mass effect simulating progressive multifocal leucoencephalopathy – Case report
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A 46 years old male patient, who had worked as a framer, was first admitted due to chronic headache. Cryptoccocal meningitis was diagnosed and he underwent treatment with Fluconazole and B Amphotericin. ELISA serologic testing for HIV was negative. Five months after discharge he was once again admitted due to neck pain, frontal headache, progressive visual deficit and weakness of the right lower limb and tremor on the right side. Fundoscopy showed signs of intracranial hypertension. A brain CAT scan disclosed several hypointense digitform lesions in both hemispheres, more evident on the left, predominantly involving white matter with mass effect. A new treatment course for neurocryptoccosis and measures to lower intracranial pressure were started. Whole blood count revealed a reduction in lymphocytes and a low CD4 count of 131 cells/mm^3. ELISA anti-HIV testing was again negative. Three months after this last admission, his visual deficit progressed and another CAT scan showed a diffuse hypointense white matter lesion, with great mass effect and ventricular compression. CSF mycological testing was negative, a third anti-HIV test was once again negative and he remained with 131 CD4 cells/mm^3. After two months he was once again admitted with simple partial motor seizures of the right upper and lower limbs, progressive right hemiparesis, facial myoclonus, holocranial headache and neck rigidity. CSF analysis disclosed a diminished glucose content with no further abnormalities. ELISA testing for cryptoccocus was positive and again HIV testing was negative with a CD4 count of 176 cells/mm^3. Extensive investigation for other causes of immunodeficiency was negative and he had no compromise of other organs. Brain MRI showed bilateral white matter lesion on the parieto-occipital regions, as well as right frontal, left fronto-parietal regions and the corpus callosum, suggestive of progressive multifocal leucoencephalopathy. After a new course of B Amphotericine the patient had an improvement of the motor deficit. A new brain MRI showed partial reduction of the lesions. A brain biopsy disclosed infection by cryptoccocus and had no histological signs suggestive of PML. Neurocryptoccocosis is a severe neurological disease with an elevated mortality, most of the time associated with immunosupression and resistant to treatment in a number of cases. Our patient had an atypical presentation, similar to that of a immunocompetent patient with PML.

General neurology

P620
Syringomyelia extending to the corona radiata
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Background and purpose: Frequently, the syringomyelia extends to the medulla oblongata, being then called syringobulbia. Exceptionally, the syrinx extends beyond the brainstem, being then called 'syringocephalia' or 'cerebral syrinx'. To our knowledge, only nine cases have been described in the literature. We report a case of syringocephalia with associated Chiari malformation in which there is radiological demonstration of the syrinx extending to the corona radiata through the pons, the midbrain, the basal ganglia and the internal capsule.

Methods: A 59-year-old woman was admitted with an acute progression of weakness of the lower and upper left limbs. She had a history of dystocic birth. She was well until the age of 35, when she experienced balance disturbance. A cranial tomography showed an arachnoid cerebellar cyst with hydrocephalus. Surgical treatment was performed. She remained asymptomatic until the age of 56, when she started suffering from a slow progressive left-side weakness. At the age of 59 she was admitted to hospital due to acute worsening of her left-side weakness, numbness in the right side of her face, double vision and slurred speech.

The patient had bilateral abducens nerve paralysis. Tactil sensation was disturbed in the right side of the face and the masticatory right muscles were weak. The weakness of the right-side face was evident. She had dysarthic speech and dysfagia, as well as tetraparesis, that was severe in her left limbs, and global hyperreflexia. Both plantar responses were extensor. All sensory modalities were impaired in her left limbs. No cerebellar signs were observed.

Results: Magnetic resonance imaging showed the scar of the surgery in the right cerebellar hemisphere, a Chiari Type I malformation and a continuous syrinx extending from the conus medullaris to the right corona radiata through the brainstem, the basal ganglia and the internal capsule. The lesion in the pons extended to the left side following the floor of the fourth ventricle which was considered the cause of bilateral abducens nerve palsies.

Conclusions: The syrinx in patients suffering from syringomyelia can extend to the pons, the midbrain and, exceptionally, the basal ganglia, the internal capsule or the corona radiata.

P621
Magnetic resonance imaging study: apparent diffusion coefficient characteristics in the ageing mouse brain
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Permitting visualization of dynamic and regionally varying tissue processes, novel magnetic resonance imaging (MRI) techniques such as diffusion-weighted imaging (DWI) play an advancing role in neuroimaging. Future indications of diffusion-weighted sequences are still on the way of being researched, and the effects of aging on diffusion are yet to be determined. In order to establish reference values for future experimental mouse studies we tested the hypothesis that absolute apparent diffusion coefficients (ADC) of the normal brain may change with age.

A total of 41 healthy mice (group 1: < 3 months, n = 6; group 2: 3 months, n = 12; group 3: 4–5 months, n = 12; group 4: 6–9 months, n = 6; group 5: > 9 months, n = 5) were examined by means of standard T2-weighted and diffusion-weighted imaging. For each animal average whole brain ADC calculations on a voxel-by-voxel basis on 3 coronal slices were performed and compared with the animals' age. The mean entire brain ADC of all animals (n = 41) was 0.731 (± 0.033) × 10^{-3} mm^2/s. Young mice had ADCs of 0.715 (± 0.016) × 10^{-3} mm^2/s, group 2 0.748 (± 0.023) × 10^{-3} mm^2/s, mice aged 4 to 5 months 0.736 (± 0.040) × 10^{-3} mm^2/s), group 4 0.696 (± 0.031) × 10^{-3} mm^2/s and animals older than 9 months 0.736 (± 0.020) × 10^{-3} mm^2/s. After proof of normality ANOVA and post hoc testing outlined a significant difference between groups 2 and 4, but no other significant changes between groups could be shown. Mean whole brain ADCs showed a trend towards lower values with aging, but linear regression analysis did not prove a significant correlation with age (p = 0.38).

In our study, we observed minimal non-significant diffusion changes of the whole mouse brain with advancing age by determination of ADCs. According to our data ADCs remained nearly constant during the aging process of the brain with a small but statistically non-significant trend towards decreased diffusion in older animals. Thus, longitudinal mouse studies can be performed without interfering age-related effects in the ex-

amined age-range. Our results may help by serving as reference diffusion MRI values for experimental studies to come.

P622
Intracranial arachnoid cysts as an incidental finding
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Objective: To study the distribution of intracranial arachnoid cysts in a healthy population.

Methods: Cranial MRI. The population of interest is constituted by male applicants for military flying. In the last four years, the German Air Force Institute of Aviation Medicine screened all applicants for military flying during the selection process by cranial MRI to rule out relevant intracranial abnormalities regardless of the findings of the physical examination.

Results: In this time period, about 1 ‰ (n = 34) of all applicants (all men, mean age 20.5 years) presented with a hitherto unknown intracranial arachnoid cyst. On MRI, the cysts were nonenhancing and followed CSF on all sequences. In 25/34 the cysts were localized in the temporal fossa, 13/25 on the left side (9/25 on the right temporal side, 3/25 on both temporal sides). 9/34 were frontal or multiple. Only three carriers of a temporal arachnoid cysts (2 left, 1 right side) had an abnormal EEG (intermittent generalized slowing, no focal slowing), the rest had normal findings (neurological history, neuropsychiatric examination, neuropsychological testing, EEG, VEP).

Conclusion: From a cross-sectional point of view, carriers of an intracranial arachnoid cyst are asymptomatic. Neurological investigation reveals no possible predictors for clinical deterioration in the future.

P623
Analysis of neurological activity in the emergency department of a university hospital in France
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Background: The Lille University Hospital has a continuous neurological activity 24h/24. The missions are (i) to ensure the continuous monitoring of patients of the neurological clinic (157 acute beds), (ii) to deal with the neurological emergencies occurring in other departments and (iii) to manage neurological patients admitted in the emergency department.

Objective: to analyze the neurological activity in the emergency department of the Lille University Hospital.

Methods: prospective collection over a 1-month period of the consecutive neurological interventions carried out in the emergency unit.

Results: 518 interventions were carried out (median: 17/d; range: 8–37). The most frequent reasons for calls were: abrupt neurological deficit (27 %), seizure (22 %), headache (17 %) and confusional state (10 %). The most frequent diagnoses were: stroke (28 %), epilepsy (22 %), migraine (7 %), psycho-somatic (5 %) and extra-neurological (4 %). The patients were directed towards the neurological clinic (51 %), treated as out patients (30 %), monitored for more than 24 h in the emergency department (6 %), admitted in neurosurgery or intensive care unit (4 %), admitted in other departments(5 %), refered to the local hospital (2 %), or decided to leave despite medical advise (2 %).

Conclusion: Neurology is an important activity in an emergency department and requires the implication of neurologists. One patient out of 4 can be treated as out patient when seen by a neurologist in emergency.

P624
Double trouble: association of facioscapulohumeral muscular dystrophy and adult form of acid maltase deficiency
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We report the unusual association of two distinct myopathies in a single family: adult acid maltase deficiency and Facioscapulohumeral muscular distrophy (FSHD). The 56 year-old proband, born from non-consanguineousparents, presented since the age of 30 with muscle pain, contractures after prolonged exercice, ptosis 'proximal leg weakness. CPK, AST and ALT were mildly elevated. Diagnosis of acid maltasedeficiency was made based on the clinical picture and the very low acid maltase activity on the muscle biopsy (0.05 mU/mg protein, control 0.55). At the age of 50 he progressively developed weakness of facial and shoulder muscles with an asymmetric involvement resulting in bilateral scapular winging, with sparing of the elevator scapulae and deltoid muscles. Abdominal muscles were also affected and Beevor's sign was present. These clinical feature are unusual in acid maltase deficiency and are evocative of FSHD. We therefore reconsider the initial diagnosis. To elucidate the molecular defect in the patient, we analysed both the Glucosidase alpha (acid maltase – GAA) gene and the chromosome 4q35 region involved in FSHD. The patient was a compound heterozygous for two common mutations in the GAA gene: deletion of exon 18 and a T > G transversion at position –13 of intron 1. The latter mutation is typically associated with the adult form of acid maltase. Southern blot analysis of chromosome 4q35 revealed a 28kb EcoRI/BnlI fragment compatible with the diagnosis of FSHD. His 50 year-old brother, presenting with similar clinical picture, had the same genetic defects. An asymptomatic 52 year-old brother was found negative for both GAA mutations and FSHD. Three daughters of the proband were found to harbor the FSHD mutation, two in association with the GAA intron 1 mutation, and one with the GAA exon 18 deletion. Another daughter carried only only the GAA intron 1 mutation. They are all asymptomatic. This is the first description of the association of FSH and adult acid maltase. The possibility of a "double trouble", even though these events are infrequent, should always be kept with patients with atypical clinical pictures. In this case the correct diagnosis of FSH is crucial for correct genetic counselling: acid maltase deficiency is an autosomal recessive disease and the recurrence risk in the offspring is low, FSH instead has an autosomal dominant pattern of inheritance, with a much higher recurrence risk, 50 %.

P625
Idiopathic hypertrophic pachymeningitis – a case report with cervical manifestation and without response to steroids
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Idiopathic hypertrophic pachymeningitis (IHP) is a rare disorder with diffuse involvement of the dura. It can be idiopathic or secondary to infections, vasculitus, carcinomatosis or inflammatory diseases. It usually affects cranial meninges, localisation at spinal or craniospinal level is less frequent.

We describe a 64 year old woman with IHP who was affected primarily by hypaesthesia of both hands 1998 (5 years before death). Both MRI and histopathological findings suggested an inflammatory disease, probabaly tuberculosis, due to a history of pulmonal tuberculosis in 1971.

In 2002 she was admitted to our hospital with progressive tetraparesis. CSF showed increased protein and oligoclonal bands. Neuroimaging revealed diffuse thickening of the cervical dura. A second meningeal biopsy showed dense fibrosis with inflammatory cell infiltration composed mainly of lymphocytes. The patient was submitted to extensive investigation without evidence of any underlying disease. Two surgical interventions only led to temporary and partial relief. Contrary to most published cases, our patient showed only short-term benefit from corticosteroids. Immunosuppressive therapy with cyclophosphamide could not alter the progression. The autopsy revealed diffuse thickening of the dura with massive compression of the spinal cord, especially at craniospinal level.

The clinical course of IHP with cervical manifestation can be relapsing remitting. MRI-findings and biopsy are usually key to diagnosis of this disorder. Therapy with steroids and laminectomy produce partial relief, but failed in our case.

P626
Functional transcranial doppler (fTCD): test-retest reliability of the method in determining hemispheric lateralisation
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Background & objective: Changes of the regional cerebral blood flow (rCBF) influence the small arteries and arterioles and are reflected as changes of flow velocity of the central artery in the corresponding territory. Transcranial doppler (TCD) assesses these changes and in this way can estimate indirectly the rCBF at a high temporal resolution. Special cognitive tasks perfomance with simultaneous recording of flow velocities consists the method of functional transcranial doppler (fTCD). The aim of the study was to estimate the reliability of the method on repeated measures.

Method: We re-examined a random sample of 20 healthy volunteers out of a total number of 60 persons who were previously examined with fTCD to determine hemispheric lateralization. TCD device with 2MHz probes

and simultaneous bilateral recording was used. During the perfomance of the cognitive tests, the flow velocities of the MCArteries were recorded simultaneously. Laterality indices (LI) were assessed by numerical value that was calculated based on the percentage change of the flow velocity of the one hemisphere to the other. LIs were estimated on the basis of the flow velocities recordings for each test separately(LI1–LI6).

Results & conclusions: Using the Wilcoxon Matched-Pairs Signed-Ranks test we compared the values between the first and the second recordings and no significant statistical difference was found ($p > 0.05$). The Bland-Altman technique for assessing agreement between two pairs of measurements showed 95–100 % repeatability coefficiency. According these results we concluded an excellent test retest reliability. The functional transcranial doppler consists an easy to use and non invasive method and in combination with its excellent reliability on repeated measures constitutes an important tool for the study of the cerebral functions during specific cognitive tasks.

P627

Hemifacial spasm and Egyptian art

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Hemifacial Spasm (HFS) is characterized by intermittent twitching of the muscles supplied by one facial nerve, initially described by Schultze in 1875.

Occasionally neurological diseases can be discovered in classic Art.

We describe the statue of an old man representing a Egyptian priest from late Ptolemaic empire (30–70 BC) with HFS (Egyptian Museum of Berlin, n° 10.972). The priest has clear asymmetry in the lower face with deviation of the corner of the mouth to the right suggesting a right hemifacial contracture, the upper face is symmetrical and frontal wrinkles can be seen on both sides. The left face is normal. This piece probably represents a man with a posparalitic HFS.

Although several examples of HFS has been described prior to 1875 in arts, this is the oldest example of HFS in our knowledge.

Classical art still is a source of neurological information.

P628

Request for an electromyography study in a general hospital

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Objective: To analyse the source, the suspected aetiology, and the results of the electromyography (EMG) of those patients referred to our laboratory for an EMG evaluation.

Methods: Our EMG laboratory is sited in a general hospital. The hospital counts with all the medical specialities except paediatrics and all the surgical ones except vascular surgery and neurosurgery. During 18 consecutive months, we prospectively selected all the patients referred for an EMG evaluation to our laboratory. The examining physician (neurologist) did a neurological examination to all the patients before to do the EMG evaluation. We collected the speciality of the referring physicians, with their suspected diagnosis, the diagnosis from the neurologist and the result of the EMG test.

Results: One thousand and fifty-eight patients were evaluated during this period. There was 39 different suspected diagnosis with 29 different diagnosis after the EMG evaluation. Seven hundred and twenty-one patients were referred from traumatology (68 %), 183 from rheumatology (17 %) and 113 (10 %) from neurology. Four hundred and forty-one patients had a normal EMG evaluation. Sixty-four patients had an abnormal EMG with a different diagnosis from that suspected. In 451 patients the suspected diagnosis was carpal tunnel syndrome (CTS), that was confirmed in 257 cases (57 %). Lumbosacral radiculopathy ($n = 219$) was the second suspected diagnosis and was confirmed in 98 (45 %). The examining physician thought the test to be useful to confirm abnormality in the 75 % of patients, with a diagnostic concordance between the referring and the examining physician of 68 %. The EMG confirmed the referring suspected diagnosis in the 54 % of cases.

Conclusion: The more frequent suspected diagnostics in our EMG laboratory sited in a General Hospital were carpal tunnel syndrome and lumbosacral radiculopathy. Those were the more frequent diagnostics found after the test with a diagnostic concordance of 57 % and 45 %, respectively.

P629

A new uncommon case of late postpartum eclampsia without preeclampsia

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Introduction: Eclampsia typically involves seizure activity in conjuction with the classic preeclamptic signs: hypertension, proteinuria and edema. Most of the cases occur ante or intrapartum,whereas approximately 30 % take place postpartum, 50 % being within the first 48 hours following delivery. Late postpartum eclampsia (LPE) is considered when convulsions begin more than 48 hours but less than 4 weeks after delivery. LPE rarely combine an atypical clinical presentation with few or absent pre-eclamptic prodromi with an unusual timing which makes it a diagnostic challenge. We describe the clinical and neuroradiological course of one patient who presented LPE without preeclampsia.

Method: A 32-year-old woman (gravida two, para one) with history of migraine delivered a healthy girl in pregnancy week 41. She did not have clinical signs of preeclampsia, neither during pregnancy nor puerperium. She was on cabergoline following delivery to supress lactancy. On subsequent days she developed severe headache with photophobia, nausea and vomiting which did not respond to analgesia and corticosteroid therapy. On 7th day postpartum she presented three generalised tonic-clonic seizures. The neurologic examination revealed a bilateral papilledema and tendon reflexes were brisk although simetrical. CT-scan showed hypodensities in both hemispheres. Brain magnetic resonance T2 weighted and FLAIR imaging (MRI) revealed multiple hyperintensive bilateral and simmetric lesions on the grey-white matter junction in temporo-occipital, parietal and frontal lobes. Lumbar puncture showed a cerebral spinal fluid protein content of 920 mg/l with single cell.

Results: Anticonvulsive treatment with valproic acid was initiated. MRI-venogram and conventional angiography were normal. Patient rapidly improved over the following days and was discharged 7 days after admission persisting only bilateral papilledema. Patient never presented proteinuria, edema or hypertension. Treatment was discontinued after one week and patient remained asymptomatic. MRI performed 40 days after was normal.

Conclusion: Late postpartum eclampsia without the classical preeclamptic signs is a rarely noticed complication of pregnancy. Initial headache is the commonest clinical feature, according to the literature. Neither the unusual timing of presentation, nor the absence of classic signs of preeclampsia must rule out eclampsia as complication of pregnancy in these subjects.

P630

A familial case of Melkersson-Rosenthal syndrome

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Melkersson-Rosenthal syndrome (MRS) is usually characterised by triad of symptoms, i. e. chronic swelling of the lips, peripheral facial palsy that tends to relapse, and in some cases furrowed tongue (lingua plicata). Although most reported cases of MRS involve asymmetric enlargement of the lips, swelling of the intraoral, periocular, chin and cheek area may occur as well. Since the swelling is granulomatosus inflammation, histologically characterised by noncaseating giant cell granulomata and epithelial histiocytes, it may gradually becomes persistent and more manifest, leading to disfiguring facial synkinesis. The etiology of the disorder is unknown, however the possible association with some autoimmunologic and infectious diseases has been proposed. A familial cases of MRS were also reported, but most authors suggest a multifactorial origin including a genetic basis.

We present here the case of familial, possible inherited MRS. We treated the 28-year old woman who suffered from unilateral facial palsy with ipsilateral cheek oedema. She had had the first episode of facial palsy, and facial oedema at her age of 13 years, and now it was her 8th episode. Physical examination revealed swelling of the right intraoral area, the fissured tongue, and right-side peripheral facial palsy with some taste disturbances. Standard laboratory work-up revealed no inflammation features. Determination of Borrelia burgdorferi IgG and IgM serum antibodies using enzyme-linked immunosorbent assay in serum as well as in cerebrospinal fluid was negative. Brain imaging studies (CT, MRI) were also non-contributory, showing bilaterally the symmetric, normal facial nerves images. Oral administration of prednisone 1 mg/kg/day for 2 weeks, antibiotics, massages and electrical stimulation yielded significant, almost complete improvement of the facial palsy and cheek oedema. Careful analysis of the family history revealed that both brothers of patient had the

oligosymptomatic form of MRS. They had had unilateral facial palsy, one with transient course, currently without any symptoms and one with persistent sign of facial nerve impairment, but they neither developed swelling nor furrowed tongue and they were never treated. In conclusion, we report the familial case of incomplete form of MRS. It is also worthy to notify that until the origin of disease is still unknown, the steroids seem to be the most effective therapy.

P630A
Isolated dysfunction of the blood-cerebrospinal fluid (CSF) barrier: what are the clinical determinants?
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Objectives: An isolated dysfunction of the blood-CSF barrier is a frequent finding in routine CSF analysis. It is associated with an elevation of the albumin CSF/serum concentration quotient (Qalb) without any further pathological CSF findings. As there is a lack of research on determinants of blood-CSF barrier function, the clinical significance of an isolated barrier dysfunction frequently remains unclear.

We examined various neurological disorders associated with an isolated elevation of Qalb thereby detecting determinants of blood-CSF barrier dysfunction.

Methods: In 411 (134 female, 277 male, mean age 57.5 ± 17.8 years) out of 3873 patients receiving diagnostic lumbar puncture at the University Hospital of Ulm (Germany) an isolated dysfunction of the blood-CSF barrier was detected. Clinical data as well as MRI findings of these patients were analysed. Since the albumin quotient is strongly age-dependent, an individual upper reference range for Qalb was calculated according to the formula Qdiff = Qalb – Qalb* (Qalb* being the age-dependant maximum for Qalb).

Results: There was a significant difference regarding the frequency and extent of barrier dysfunction among the various diseases, with highest values for Qdiff found in Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP) and brain tumours. There was a significant correlation of Qdiff with both weight and body mass index (BMI). In patients with ischaemic stroke, barrier dysfunction was significantly higher in territorial ischaemic brain infarction than in lacunar infarction.

Conclusions: In a distinct subgroup of clinical entities like GBS or CIDP a barrier dysfunction occurred with a high frequency. Therefore, disease-related mechanisms affecting CSF turnover rate contributing to barrier dysfunction are assumed. Moreover, barrier function seems to be influenced by disease-independent determinants like weight and BMI.

Cerebrovascular disorders

P631
Laboratory findings in patients with epileptic seizures after stroke
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Purpose: The objective of this study was to identify laboratory markers that are associated with a first ever seizure, with early seizures and with the occurrence of recurrent epileptic seizures (epilepsy) after stroke.

Methods: A total of 2,906 patients (aged 18 to 98) with a recent hemorrhagic or ischemic stroke (including TIA) were prospectively enrolled at nine neurology departments over a period of 39 month (The Vienna Stroke Registry). Laboratory findings (blood chemistry and CBC at the time of admission and consecutive basal analyses) were related to patients with a first ever seizure, with early seizures and with recurrent seizures. Mean follow up was 20.4 months. Seizures occurring within 14 days after stroke were classified as early seizures. Vascular epilepsy was defined as recurrent unprovoked seizures. Patients with seizures before the stroke were excluded.

Results: The following laboratory findings were significantly ($p < 0.05$) associated with epileptic seizures: hypokaliaemia (first ever seizures [mean with/without seizures: 4, 0/4, 1 mmol/l]), leukocytosis (first ever seizures [mean: 11, 4/8, 7 G/l], early seizures [mean 12, 4/8, 9 G/l] and vascular epilepsy [mean: 10, 3/8, 9 G/l]) and hypocalcaemia (early seizures [mean 2, 3/2, 4 mmol/l]).

Conclusions: Our preliminary results suggest that hypokaliaemia, hypocalcaemia and a leukocytosis are associated with the occurrence of epileptic seizures after stroke.

P632
Axonal pathology in subarachnoid and intracerebral haemorrhage
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Background: Electrically active axons degenerate in the presence of nitric oxide (NO) in vitro. High CSF NO metabolites (nitrate, nitrite = NOx) concentrations have been observed in patients with hemorrhagic brain injury such as subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH). This study investigated the evidence for axonal injury in SAH and ICH and related this to CSF NO levels.

Methods: Neurofilament phosphoforms (NfH-SMI34, NfH-SMI35, NfH-SMI38 and NfH-SMI310) markers for axonal injury were measured by ELISA and NOx using a vanadium-based colometric assay in cerebrospinal fluid (CSF) from patients with SAH and ICH and from a group of controls. Injury severity was classified using the Glasgow Coma Scale and survival was used as the outcome measure.

Results: Compared to the control group a higher proportion of patients with SAH and ICH had elevated NfH-SMI34 levels from day 0 to day 6 ($p < 0.001$), elevated NfH-SMI35 levels from day 1 to 6 ($p < 0.001$) and elevated NfH-SMI310 levels at day 0, 1, 4, 6 ($p < 0.001$). The NOx levels were higher in the SAH and ICH patients than in the controls ($p < 0.05$) and distinguished the non-survivors from the survivors ($p < 0.05$). No direct correlation was found for Nox with any of the NfH phosphoforms.

Conclusion: This study provides evidence for primary and secondary axonal injury in patients with SAH and ICH, with non–survivors also having higher NOx levels. CSF NfH phosphoforms are a valuable surrogate marker for monitoring the development for secondary axonal degeneration in neurocritical care and guiding targeted neuroprotective strategies.

P633
Is it safe to stop vitamin treatment in ischaemic stroke patients with hyperhomocysteinaemia?
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Introduction: There is a lack of consensus on when to stop folic acid and vitamin B12 treatment after stroke occurrence in patients with hyperhomocysteinemia. Fasting hyperhomocysteinemia is considered an independent factor for ischemic stroke and treatment was associated with lower stroke recurrence. We studied consecutive ischemic stroke patients aged less than 65 years and looked for the results of specific treatment.

Methods: Both fasting and an abnormal methionine-loading test are used to measure homocysteine (Hcy) levels. We prospectively studied 162 consecutive ischemic stroke patients aged less then 65 years or of any age when all other etiologic investigation was negative. We measured fasting Hcy concentration by ELISA (FPIA) (n < 15 umol/L) and 4 hours after the load of 100 mg/Kg of oral methionine (n < 40 umol/L). We treated hyperhomocysteinemia patients with folic acid (5 mg/day), vitamin B6 (150 mg/day) and associated vitamin B12 if the Hcy levels were still elevated after 2 months treatment. Median age was 56 years (19–64) and 111 patients (68.1 %) were male.

Results: Hyperhomocysteinemia was present in 15 (9.25 %) of our 162 patients. Four patients had fasting Hcy levels above normal and eleven were only identified after methionine-loading test. All patients completed the first year of treatment and 14 controlled their Hcy levels. One patient never normalized his Hcy levels and is still on treatment without any recurrence. Only one hypertensive patient that decided to stop vitamin therapy had ischemic stroke recurrence.

Discussion: In our sample of patients aged less than 65 years 9 % had Hcy levels above normal. Correction of those levels was observed in all except one patient. Recurrence occurred in one patient that stopped vitamin therapy after one year. The risk of stopping therapy in patients with hyperhomocysteinemia must be taken in consideration.

P634
Stroke following snakebite by Bothrops Lanceolatus in Martinique: a report of three cases
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Snake bites are not rare in Martinique(20 to 30 cases per year). The only snake involved, specific to Martinique, is Bothrops Lanceolatus (BL) belonging to crotalidae family.

BL has haematotoxic venom by opposition to snakes producing neuro-

toxic venoms. BL's bite complication is lead to thrombotic events (30 %) such as stroke, pulmonary embolism, myocardial infarction, contrasting with rare haemorrhage (3 %) predominant in others snakes species.

We report three patients bitten by BL who developed cerebral infarction.

Specific therapy (purified monospecific F(ab') antivenom serum (Bothrofav)) was delayed in two cases because cutaneous signs ad pain induced by a small snake bite were minor.

The first patient was treated two days after the bite when she was aphasic and did not improve. The second one got a transient aphasia 24 hours after the snakebite and then developed extensive left hemispheric infarct despite treatment. The third patient presented with a left homonymous quadranopsy two hours after the bite. Very early administration of antivenom serum prevented progression of stroke.

Occurrence of stroke following BL's bite has been estimated to 11 %.

Thrombopenia is the hallmark of envenoming induced by platelet aggregating, local consumption or/and disseminated intravascular coagulopathy. Nevertheless, thrombotic complications can arise without thrombopenia and even without detectable disturbance in the coagulation cascade(45 %). Early anticoagulation and/or thrombolytic treatment did not show any efficacy in a martinican historical cohort of BL's bite. By contrast early infusion (with six hours) of specific antivenom serum is effective and safe (anaphylactic reaction in only 4 % because of a high degree of purification).

These three cases emphasize that specific antivenom is the treatment of choice of BL's bite and that it must be used very early without waiting for signs of more severe envenomation.

P635

Neuropsychological dysfunction associated to clinical syndrome and unique or multiple lacunar stroke

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Introduction: A number of investigations studied the causes and risk factors leading to lacunar infarcts but only few works investigated its neuropsychological correlates relative to their syndromic manifestations and neuroimaging characteristics.

Objective: To correlate lacunar infarct topography and the presence of isolated or multiple chronic infarcts with patterns of cognitive dysfunction relating clinic aspects with magnetic resonance parameters and neuropsychological assessment.

Methods: 20 consecutive patients diagnosed as preseting a ischaemic lacunar syndrome according to Miller Fisher, from the Neurology Service at the Sagrat Cor Hospital in Barcelona were included in the study. Structural magnetic resonance images were acquired from all cases and were assessed by means of an exhaustive neuropsychological battery. Patients were classified into two groups according whether the lacunar infarct observed on admission was isolated or it coexisted with chronic 'silent' infarcts.

Results: The following results were obtained: a) any syndrome group presenting increased or reduced severity of lacunar infarcts, b) similarly, clinical groups did not differ in the amount of white matter damage as reflected by the presence of leuko-araiosis. C) Significant differences were found on the Benton's Line Orientation Test ($F = 3.460$; $p < 0.04$) where patients with a disartria-clumsy hand syndrome exhibited better performance (mean = 16.8; SD = 1.1) as compared to patients with pure sensitive syndrome (mean = 15; SD = 0.7). D) Significant differences were found in category ($t = 2.23$; $p < 0.04$) and phonetic fluency ($t = 2.1$; $p < 0.05$) tests between patients presenting with a single lacunar infarct (category: mean = 17.62; SD = 6, phonetic: mean = 33.51; SD = 14) or additional chronic infarcts (category: mean = 11.75; SD = 5.54, phonetic: mean = 21.83; SD = 10.83) were compared. E) Leuko-araiosis was not related to cognitive performance among patients.

Conclusions: Present results indicate that the presence of multiple chronic lacunar infarcts, may result in increased neuropsychological dysfunction in patients diagnosed with a lacunar syndrome. Our findings additionally indicate that disartria-clumsy hand syndrome associates to a better visuoespatial function as compared to other clinical syndromes. Future studies should investigate whether patients exhibiting cognitive impairment caused by lacunar infarcts are at increased risk for developing dementia, particularly of a subcortical vascular type.

P636

Brain representation of picture naming and word retrieval based on neuropsychological language processing model in dyslexic and aphasic patients: fMRI study

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Goal:Compared with brain activation of normal controls, the brain activation pattern of an acquired dyslexic and aphasic patients were investigated by use of hierarchical neuropsychological assessment model and fMRI study with four tasks according to language processing

Method: 1) Subjects: Nine aphasic patients with Broca aphasia (five), Wernicke aphasia (two), anomic aphasia (two), and one acquired dyslexic patient participated in this study. In normal control group, we studied 9 healthy adults using four tasks. All subjects were right handed. 2) Paradigm and fMRI data acquisition: Functional image was performed using 4 tasks of block design (4 activation blocks, 5 control blocks per session); 1) picture naming, 2) picture-word matching, 3) word reading, 4) semantic categorization. The data acquisition was performed using an ISOL 3.0 T MR scanner with EPI sequence (TR/TE = 300/35 ms, 4 mm no gap, 20 slices, 64×64 matrix, FOV = 220 mm, Flip angle 80°). All data processing and statistical analysis were performed using SPM 99 and statistical significance level was $p < 0.01$.

Result: 1) dyslexic patient:The activation in right broca area was typical in picture naming, and basal temporal lobe, both prefrontal lobe, right temporoparietal area (picture-word matching), both inferior parietal, prefrontal area (semantic categorization), both anterior inferior frontal, prefrontal (reading) was represented. 2) aphasic patients: During picture naming, the activation of ipsilateral perilesional area was typical in Wernicke's and anomic aphasic patients, but in Broca's aphasic patients, the more strong activation of the contralateral Broca's area was produced. In the others tasks, the activations in aphasics were different from that of normal controls. 3) normal controls: In picture naming, the middle temporal, supramarginal, fusiform gyrus, and Broca area of left hemisphere was predominantly activated. In picture-word matching and semantic categorization, the activation in Broca's area and superior parietal lobule was typical and during reading task supramarginal and angular gyrus activation is more remarkable.

Conclusion: In dyslexic and aphasic patients, the brain activation pattern was different from that of normal person. There are evidences of reorganization of expressive language area into right Broca's homologue area. The right hemisphere and undamaged perilesional areas in the left hemisphere does play a role in some patients.

P637

Plasticity of language-related brain function after ischaemic stroke and changes in cerebral blood flow

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Background and purpose: In our prospective study we investigated the correlation between recovery of aphasia after ischemic stroke and changes in cerebral blood flow (CBF).

Methods: 34 aphasic patients were tested using BDAE (Boston Aphasia Test), scored with a maximum of 68 points, in days 7, 21 and at 3 month after stroke. All patients were right handed at Edimbourg manual laterality test. Patients were examined using cerebral computed tomography (CT) and single photon emission computed tomography (SPECT) in the first 3 weeks, but at least at 48 hours after stroke. SPECT was performed in one session, at rest and during verbal tasks, the patient being visually and phonically isolated. The verbal stimuli were phonemes, words, pseudowords, reversed speech, short phrases recorded at 12 seconds intervals on audio tape using a male voice. We compared the global lateralization index with the aphasia recovery coefficient and the results were statistically analyzed.

Results: A high coefficient for aphasia recovery was correlated with an improvement of CBF in border zones at the periphery of cerebral lesion, sometimes concomitantly with a hypo- perfusion of contralateral homologous areas.

At verbal task test we obtained an increase in CBF in affected left hemisphere especially at patients with severe aphasia.

A high coefficient for aphasia recovery (> 20 %) is associated to an improvement of perfusion in right hemisphere in patients with mild and medium aphasia and it is not correlated with initial aphasia score.

Discussions: The recovery of aphasia is correlated with restoration of

CBF at the language network in left hemisphere but a better recovery is associated however with an increase of perfusion in right hemisphere.

P638
Ripost study: perception of the profile of patient with arterial hypertension at neurovascular risk according French general practioners
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Objective: to describe perception, according to the French general practitioners (GPs), of the profile of patients at neurovascular risk.

Methods: Public opinion poll carried out in 2003 near 2,282 French GPs selected by drawing of lots.

Results: 36 % of GPs think of the risk as from 45 years and 36 % as from 55 years. After this age, 90.7 % of GPs consider that there is a threshold (150/90 mmHg) with beyond which this risk can be mentioned. 96 % of GPs aim at a value of arterial pressure (135/80 mmHg on average). 80 % of GPs choose the treatment according to the neurovascular risk by privileging the antagonists of angiotensin II then the inhibitors of the enzyme of conversion. Measurements of prevention considered are the treatment of the arterial hypertension (83.9 %), then the treatment of a cardiopathy (52.3 %), diabetes (48.1 %), hypercholesterolemy (39.4 %) and the stop of the tobacco (41.7 %).

Conclusion: The GPs know that the arterial hypertension is the major risk factor of stroke but by defining a value "threshold" of the blood pressure (150/90 mmHg) and of this fact by underestimating the neurovascular risk.

P639
Institutionalisation in stroke
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Objective: Several studies have shown strong association between some vascular risk factors (VRF) and functional outcome at discharge in patients with stroke. Our purpose is to analyse which of these factors may predict institutionalization.

Methods: Observational study from our stroke data bank (1994–2002). We identified patients with Brain Hemorrhage (BH) and Non Lacunar Stroke (NLS): Atherothrombotic stroke (AS), Cardioembolic stroke (CS) and Undetermined stroke (US), and analysed VRF: Hypertension, DM, Hypercholesterolemia, smoking, age, sex, peripheral vascular disease, coronary heart disease, atrial fibrillation and neurological status at admission, by means of the Canadian Stroke Scale (CSS) and functional status at discharge (modified Rankin Scale). Risk factors of institutionalization in stroke were analysed by multiple logistic regression analysis.

Results: 4263 stroke patients, 402 were BH (male 207/female 195; mean age 71.5 ± 12) and 1837 NLS (male 973/female 864; mean age 70.6 ± 11.6): AS 771 (34.4 %), CS 668 (29.8 %) US 398 (17.8 %). DM in US ($p < 0.05$); atrial fibrillation and hypertension ($p < 0.05$) in CS and US; CSS at admission, older age and female ($p < 0.0001$) in all groups were identified as predictive factors of Institutionalization. There were more institutionalization among BH than NLS ($p < 0.0001$).

Conclusions: Older age, female and low score in CSS were associated with higher average of institutionalization. Brain Hemorrhage is the subtype of stroke associated more frecuently with Institutionalization.

Poster session 5

Peripheral neuropathy

P640
Toxic polyneuropathies due to glue sniffing: clinical electrophysiological and nerve biopsy studies
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Objective: To report the clinical findings, electrophysiological, and nerve biopsy studies of 20 juvénile patients who had a toxic polyneuropathy due to glue sniffing.

Background: Progressive sensorimotor neuropathy developped after glue sniffing was described. The neurological picture consisted of a symmetrical progressive, ascending, mainly motor, polyneuropathy with muscle atrophy. Electrophysiological and nerve biopsy studies consisted in an axonal neuropathy with axonal degeneration and presence of giant axonal due to accumulation of neurofilaments on electron microscope. It is concluded that n-hexane inhalation produces a toxic effect with axonal changes.

Methods: Twenty patients admitted for a progressive sensorimotor neuropathy due to glue sniffing in the National Institute of Neurology were selected. All patients had clinical examination, electrophysiological and sural nerve biopsy studies on optic and electron microscope.

Results: The mean age at examination was at 17.5 ± 2.5 years (range: 12 to 23 years). The mean duration of the exposure to the toxic with prolonged inhalation of n-hexane (glue sniffing) was 2.3 ± 2.4 years (range: 4 months to 8 years). All patients developped weakness and paresthesia mainly in lower limbs at a mean duration of 4 months after inhaling the glue. All patients were men and had similar clinical features characterized by a symmetrical progressive, ascendly, sensorimotor polyneuropathy with pronounced amyotrophy and severe motor handicap leading to wheelchair bound in 9 patients (45 %). Electrophysiological studies showed axonal and mixed sensorimotor neuropathy predominantly in lower limbs. Nerve biopsy study showed an axonal neuropathy with axonal degeneration, and presence of giant axonal in 7 patients (35 %) with neurofilaments accumulation on electron microscope. Teased fibers analysis showed segmental demyelination with axonal degeneration. Muscle biopsy found a severe neurogenic atrophy with target fibres in 60 % of patients.

Conclusion: These findings seem to indicate the pathological process of axonal swellings and confirm the toxic mechanism with primary axonal changes due to the n-hexane inhalation associated sometimes to demyelination features.

P641
Loss of chaotic short-term variability on heart rate and blood pressure in autonomic neuropathy. A flat or inverted circadian pattern
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Autonomic failure (AF) induces disabling orthostatic symptoms. Short-term heart rate (HR) and blood pressure (BP) orthostatic patterns are well characterized in these patients but data with long term blood pressure and heart rate monitoring are lacking. The aim of this study was to access circadian HR and BP variation in AF patients.

We studied 8 patients with severe AF (9 with familial amyloidotic polyneuropathy TTRmet30+ and 1 with pure autonomic failure) Group A, and 2 control groups (8 assymptomatic patients TTRmet30+: Group B, and 16 normal aged matched controls: Group C). All groups underwent 24 HR and BP monitoring.

Twenty-four hours-SBP and 24h-DBP were similar in all groups (114.5 ± 10.6 and 73.2 ± 6.7; 123.0 ± 6.2 and 79.0 ± 9.5; 118.6 ± 10.1 and 71.4 ± 9.4 mmHg for groups A, B and C, respectively). BP dipping was attenuated or even inverted ($p < 0.01$) in AF patients (SBP and DBP differences between day and night: −1.6 ± 11.6 and 3.3 ± 6.3; 10.0 ± 1.0 and 11.7 ± 1.5; 15.6 ± 7.9 and 16.2 ± 5.8 mmHg; for groups A, B and C, respectively; $p < 0.01$).

Although mean 24 h HR were similar between patients and controls (80.9 ± 14.0; 87.0 ± 4.6; 80.7 ± 5.2 bpm for groups A, B and C, respectively), there were striking differences in heart rate variability among groups (max-min 24 h-HR difference: 46 ± 16; 89 ± 11 and 91 ± 9 bpm; pNN50: 0 ± 0; 6 ± 2 and 12 ± 6 %; SDRR: 68 ± 24; 128 ± 10; 148 ± 32 ms for groups A, B and C; $p < 0.01$).

There were significant differences between normal controls and assymptomatic TTRmet30+ controls in mean HR, diastolic blood pressure dipping and NN50; $p < 0.05$.

Autonomic failure can be suspected by simple twenty four hours blood pressure evaluation and by heart rate monitoring. Assymptomatic TTRmet30+ patients may show already some degree of autonomic impairment, namely concerning early vagal dysfunction.

P642
Diagnostic value of sulfatide-IgG-antibodies in immune-mediated neuropathies
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Objective: Some types of neuropathies are associated with elevated serum titers of anti glycolipid antibodies. Anti sulfatide IgM antibodies are asso-

ciated with sensory or sensomotoric neuropathies. However, less is know about anti-sufatide IgG antibody associated disorders.

Methods: In our laboratory 755 samples were screened for anti-glycolipid antibodies (GM1 IgG and IgM, GQ1b IgG and IgM, Sulfatide IgG and IgM). In 61 patients elevated titers of anti-sulfatide IgG antibodies were detected. Medical records of these patients were reviewed to obtain the clinical diagnoses and the electrophysilogical results.

Results: Clinical diagnosis was available in 49 patients. Ten patients had GBS, 2 had MFS, 3 had acute polyneuritis and 5 patients had CIDP. MMN was diagnosed in 6 patients (only 2 of whom had anti-GM1 IgM antibodies) and 12 patients had chronic PNP of unknown etiology (demyelinating, axonal, sensory or motor). Diabetic PNP and paraproteinemic PNP was present in one patient each and 9 patients had no neuropathy. Anti-sulfatide IgG titers did not differ significantly between groups. In most patients, no other anti-glycolipid antibodies were detected.

Conclusion: Elevated titers of anti-sulfatide antibodies are frequently associated with immune-mediated neuropathies possibly providing diagnostic help. In chronic PNP without detectable cause the presence of anti-sulfatide antibodies could indicate an immune-mediated disorder. These patients might benefit from immunosuppressive or immune-modulating therapies. However, eleveted titers of anti-sulfatide antibodies can not help to discriminate different immune-mediated neuropathies.

P643

Contribution of nerve biopsy to the diagnostic evaluation in neuropathy: a retrospective study on 40 consecutive patients

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Background and goals: to evaluate the diagnostic utility of nerve biopsy in patients with peripheral neuropathy (PNP) in a referral center.

Methods: we reviewed the charts of all patients from our neuromuscular clinic who underwent nerve biopsy from 11/2001 through 1/2004. Indication for biopsy was either disabling, painful, or progressive PNP of unknown etiology despite extensive diagnostic work up including EMG (electromyography and -neurography) and/or exclusion/suspicion of vasculitis or amyloidosis. Patient history, EMG, clinical, and histologic data were analysed. Depending on the progression of symptoms within 4 weeks, up to 3 months, or longer, disease was classified as acute, subacute, or chronic.

Results: 40 patients out of a total of 120 (21 women, 19 men, mean age 58 years, range from 4 to 84 years) were analysed. A combined nerve and muscle biopsy was performed in 36 patients (31 superficial peroneal nerve/peroneus brevis muscle, 3 superficial peroneal nerve/quadriceps femoris muscle, 2 sural nerve/peroneus brevis muscle). In 4 patients only nerve biopsy (2 suralis, 1 saphenus, 1 superficial peroneal nerve) was done. Disease was acute in 1, subacute in 14, and chronic in 25 cases. EMG classified the PNP as purely motor in 6, sensory in 2, sensorimotor in 26 patients; as axonal in 19, demyelinating in 3, mixed in 12 cases. In 6 patients EMG was normal, 3 of whom showed axonal damage in biopsy. Histology was axonal in 24, demyelinating in 2, and mixed in 13 patients. One biopsy was technically insufficient. In addition to previous extensive investigations, biopsy allowed final diagnosis in 15 patients (37.5 %). Vasculitis was diagnosed in 6, anti-MAG- and paraneoplastic neuropathy in 2 cases respectively. Etiology of 25 neuropathies (13 axonal, 2 demyelinating, 10 mixed) remained undetermined.

Conclusions: while classification of PNP can reliably be made by clinical and electrophysiological examination, biopsy allows final diagnosis in about 40 % of the cases which remain unclear despite extensive laboratory testing. A vasculitis was detected histologically in 25 % of our patients with axonal neuropathy.

P644

Chronic sensory ataxic neuropathy: a prospective study of 12 patients

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Background. Chronic sensory ataxic neuropathies are defined by occurrence of proprioceptive ataxia and areflexia. Etiologies are classified upon EMG patterns.

Objectives: 1) To define clinical, electromyographic and histological patterns of patients with chronic sensory ataxic neuropathy 2) to determine etiologies in a prospective study of consecutive patients.

Methods: This study was conducted in one universitary neurological centre since 1999 to 2003. Standard biochemical levels, protein immunoelectrophoresis, immuonological study, VIH, Lyme, EBV, VZ, hepatitis B and C serologies, gliadin antibodies and neuronal antibodies, antiganglioside antibodies studies (MAG, Anti-GM1, antidisialosyl antibodies (GD1a, GD1b 'GT1b 'GQ1b), accessory salivary biopsies were determined in all of the cases. CSF study was performed in 7 cases. EMG was performed in each patient. Results were classified upon patterns, ie demyelinating neuropathy, CIDP, axonal and mixed neuropathies. Absence of sensory potentials and normal EMG patterns lead to sensory ganglionopathy diagnosis. Proximal conduction block was searched in each case. Spine MRI was performed in 5 patients. In addition, extensive research of an underlying neoplasia was made in each patient. Sural nerve biopsies were performed in 4 cases.

Results: 12 patients (male: 7/female: 5), mean age: 57 yo (range 43–71 yo), were included in this study. Mean delay onset of the disease to the diagnosis was 7.5 years. Clinical symptoms consist of isolated ataxia in 5, ataxia and distal parethesias in 7. All of them have decrease of diapason perception in lower extremities and generalized areflexia. Biological studies revealed benign monoclonal gammopathy (MGUS) in 2 cases (IgM and IgG gammopathy) and polyclonal gammopathy in 1. EMG patterns consist of demyélinating neuropathy in 4 cases, including 2 CIDP, mixed neuropathy (axonal and demyelinating) in 1, axonal in 5 cases, sensory ganglionopathy in 1. EMG was normal in only 1 patient. Nerve biopies results confirm EMG patterns in all of the cases (axonal neuropathy (1 case), demyelinating (2 cases) and normal (1case)). sensory ataxic neuropathies consist of a heterogenous group of disorders. MGUS was found in 2 demyelinating neuropathies. Absence of etiology was found in the remaining patients. Type of neuropathy was distributed in demyelinating and axonal neuropathy. Sensory ganglionopathy was retained in only one case.

P645

Immunohistochemical analysis of cutaneous innervation as a tool in the diagnosis of small-fibre neuropathies

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Objective: To describe, quantitative and qualitatively, intraepidermal nerve fibers (IENF) and sweat gland innervation (SG) in patients with diabetic and idiopathic small fiber neuropathies.

Methods: 19 patients with clinical features of painful sensory neuropathy (8 diabetic and 11 idiopathic) and 10 normal subjects underwent skin biopsy at the lateral side of mildcalf (A) and the dorsum of the foot (B). Skin sections were immunohistochemically stained with antibody to protein gene product 9.5 (PGP 9.5), a ubiquitin C-terminal hydrolase universally present in nerve fibers, and antibody to collagen IV to visualize the epidermal basement membrane. Cutaneous innervation was evaluated by measuring epidermal nerve density (END), expressed as the number of IENF per milimetre of epidermal length (fibers/mm), and the proportion of sweat gland area innervated (%). We describe quantitative and qualitative differences with regard to normal subjects.

Results: END and proportion of sweat gland area innervated values of neuropathic patients were significantly reduced compared to values of normal subjects at both A and B sites: END-A ($4{,}516 \pm 1.21$ versus $21{,}792 \pm 1.16$ fibers/mm; $p < 0.001$); END-B ($6{,}607 \pm 1.95$ versus $24{,}318 \pm 1.05$ fibers/mm; $p < 0.001$); proportion SG-A ($5{,}330 \pm 1.15$ versus $20{,}295 \pm 0.74$ %; $p < 0.001$); proportion SG-B ($5{,}092 \pm 0.91$ versus $20{,}933 \pm 1.29$ %; $p < 0.001$). Qualitative differences were: 1) fragmented and irregular immunoreactivity of IENF; 2) swelling of INEF; 3) abrupt end of nerves from subepidermal plexus just below the basement membrane; 4) marked depletion with residual immunoreactivity in subepidermal nerve plexus.

Conclusions: Immunohistochemical analysis of cutaneous innervation is a useful tool in the diagnosis of small-fiber neuropathies. This method allows to establish a correct diagnosis and has particular use in idiopathic small fiber sensory neuropathy with normal routine electrodiagnostic studies.

P646

Haemodynamic, autonomic and neurohormonal behaviour in different orthostatic intolerance syndromes

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Several different orthostatic intolerance (OI) syndromes are described in literature. They all share symptoms like dizziness and orthostatic syncope, however the pathophysiology is somewhat different. Our goal was to study the autonomic, neurohormonal and hemodynamic profile in different patients with OI.

We studied in basal (SUP) and during the first ten minutes of head-up

tilt test (HUTT), eight patients with autonomic failure (Group A), eight patients with neurocardiogenic syncope (passive HUTT (+): group B) and 16 normal controls, aged matched (Group C).

Beat-by-beat BP and HR were continuously monitored and digitised at 500 Hz/channel. The baroreceptor alfa-index gain (vagal reflex: BRG), high frequency of RR variability (vagal tonus: HFRR) and low frequency of systolic pressure variability (sympathetic tone: LFSAP) were calculated. Cathecolamines were assayed by fluorimetric HPLC and plasma brain and atrial natriuretic peptides were also measured. Hemodynamic data were derived and calculated by the modelflow® method.

After tilting, stroke volume drops significantly more in Group A (difference between HUTT and SUP, −38 ± 21*, −23 ± 12 and −22 ± 7 mL for each group). Within the first ten minutes of HUTT there was also a huge drop in mean arterial presure in group A (difference between HUTT and SUP, −32 ± 23*, + 10 ± 04 and + 15 ± 7 mmHg).We observed very low levels of any parameter of neurohormonal and autonomic function in Group A, in basal and with values near zero in first minutes of HUTT. HR, LFSAP and ADR had a significant higher rise at HUTT in Group B compared with normal controls. A significant decrease of BRG was noted in group B, even several minutes before neurocardiogenic syncope developed. BNP did not change within the initial minutes of HUTT in any group. Adrenaline had a huge rise in group B (62.2 ± 32.6 pg/ml) compared with groups A (3.5 ± 3.2)and also group C (11.7 ± 6.5) after initial passive tilting.

Orthostatic intolerance syndromes share similar clinical symptoms but may show important hormonal, autonomic and hemodynamic differences already after the first minutes of passive orthostatism.

P647
Solitary plexiform neurofibroma presenting as purely motor axonal cervical plexopathy
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A 27 year old male presented with three years of progressive weakness and atrophy in his right arm. He did not have sensory complaints or pain but occasional proximal arm dysesthesias. Neurological examination showed severe right shoulder girdle atrophy and proximal limb weakness affecting muscles supplied by the fifth and sixth cervical roots. Strenght was normal distally in right arm and in the other limbs. Deep tendon reflexs were normal. Sensation was normal. Laboratory studies showed increased creatine kinase levels. Anti-GM1 IgM antibodies were not found. Electrodiagnostic studies were consistent with either focal motor neuronopathy or right brachial plexopathy involving the upper trunk. Nerve conduction studies did not show conduction blocks or slow conduction velocity. The CMAP amplitude of the right median nerve was normal. EMG showed chronic denervation and fibrillation potentials in paraspinal and arm muscles innervated by right C5–C6. MRI studies revealed a markedly increased signal intensity on T2-weighted images of the fifth and sixth right cervical roots and upper trunk of right plexus with contrast-enhanced T1-weighted images. A provisional diagnosis of motor axonal inflammatory plexopathy was made based on the purely motor focal deficit, increased creatine kinase levels and enhancing focal hypertrophic roots on MRI, as described in CIDP and MMN. The patient was treated with high dose IVIg 2 gr/Kg over four days with not improvment. Two months later a biopsy of enlarged cervical root revealed a plexiform neurofibroma. The patient did not have a family history or other typical abnormalities of neurofibromatosis (NF1), including cafè-au-lait spots, skin fold freakling, Lisch nodules in the iris and bone displasia. Solitary plexiform neurofibroma may occur in patients without other stigmata of NF1 and should be considered in the differential diagnosis of purely motor focal inflammatory radiculoplexopathy.

P648
POEMS syndrome without overt osteosclerotic myeloma improving with melphalan monotherapy
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POEMS syndrome is characterized by the simultaneous presence of neuropathy, organomegaly, endocrinopahy, monoclocal gammopathy and skin changes and by its frequent association with osteosclerotic myeloma. Patients with POEMS and osteosclerotic myeloma often improve after radiation therapy or surgical resection of solitary bone lesions while those with multiple lesions require a combination of chemotherapy and radiation. In patients without overt myeloma the combination of melphalan and steroids is sometime effective. A 58 years old man presented with two years of progressive limb sensory and motor impairment leading to progressive difficulty in walking. In the last year he also became impotent. Based on reduced conduction velocities in motor and sensory nerves and increased CSF proteins (118 mg/dl) with normal cells he had been treated with oral steroids with no improvement but with the onset of a severe manic episode. On admission in our Department six month later, he had asymmetrical distal and proximal leg weakness, reduced or absent deep tendon reflexes and reduced touch, vibratory and position sensations in the legs. He could only walk with bilateral support. He had bilateral oedema and cyanotic appearance of the legs. Sensory action potentials were absent in the median, ulnar and sural nerves while motor conduction velocities were reduced in the median (32 m/sec) and peroneal (19 m/sec) nerves where CMAP amplitudes are also reduced. Serum immunofixation showed the presence of an IgG lambda M-protein. Serum anti-GM1 IgM antibodies (1/10.240) and VEGF levels (3634 pg/ml) were markedly increased while total serum testosterone was reduced. Sural nerve biopsy showed a marked reduction of myelinated and unmyelinated fibres and abnormally enlarged endoneurial vessels. Bone marrow biopsy, skeletal scintigraphy and radiography were normal while liver and spleen were enlarged on abdominal echography. The patient was treated with 8 courses of melphalan (15 mg/die for 7 consecutive days every 6 weeks) without steroids. Starting form the fourth course the patient progressively became able to walk without support and to climb stairs. Seven month after therapy suspension his improvement remains stable. VEGF decreased to 784.4 pg/ml and anti-GM1 IgM to 1/640 while total serum testosterone normalised. The response to melphalan in this patient suggests that its association with steroids might not be always necessary in the treatment of POEMS without overt myeloma.

P649
Survivin in the pathogenesis of vasculitic neuropathy
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Survivin, the smallest inhibitor of apoptosis protein (IAP) identified so far, blocks the extrinsic and intrinsic pathway of apoptosis by binding to caspase-3 and -7. It could be detected in a variety of human cancers, where its expression correlates with resistance to radio- or chemotherapy and worse prognosis.

Since evidence is accumulating that survivin may also be involved in the pathogenesis of inflammatory diseases, we investigated the expression of this IAP in vasculitic neuropathy.

Immunohistochemistry using monoclonal anti-survivin antibodies was performed on tissue specimen of vasculitic neuropathy.

Upregulation of survivin could be detected in the cytosol of epineurial-perivascular infiltrating mononuclear cells.

The expression of survivin in inflammatory infiltrates of vasculitic neuropathy suggests this protein being a pivotal factor for the potential resistance to apoptotic stimuli of pathogenic T lymphocytes and perpetuation of the inflammatory process.

Our finding implies a role for survivin in the pathogenesis of vasculitic neuropathy and indicates it as an important target for immunotherapeutic approaches, e. g. by interferon beta or retinoic acid.

P650
Population pharmacokinetics of pregabalin: patients with chronic pain
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Aims of investigation: To describe the pharmacokinetics (PK) of pregabalin following single and multiple doses in chronic pain patients (CPP) and to identify concomitant medications that impact pregabalin's PK in these populations.

Methods: Data from 1202 pregabalin plasma-concentration observations in 974 subjects from 9 studies in adult patients with chronic pain were pooled with 4,381 observations from healthy volunteer and renal impaired patients (HV) and epilepsy patients (EP) to develop a population PK model. CPP model parameter estimates were then obtained using CPP data alone. The effects of concomitant oral antidiabetic agents, diuretics, and insulin on P disposition in CPP were also determined.

Results: Pregabalin PK were well described in CPP, HV, and EP by a one-compartment pregabalin PK model with first order absorption and a lag time. After inclusion of covariates, no significant differences in pregabalin disposition between CPP, EP, and HV were observed. Pregabalin's oral clearance (CL/F) in CPP increased proportionally with creatinine clearance (CLcr) from 0 up to 105 mL/min, above which pregabalin CL/F was independent of CLcr. Pregabalin volume of distribution (Vd/F) in CPP was

dependent on body weight and was approximately 19 % higher in females. Administration of pregabalin with food in CPP decreased the rate of drug absorption, but this is not expected to be clinically significant. The ratios of CL/F values of CPP taking concomitant medications, expressed as a percentage of CL/F for CPP not receiving the concomitant medication was 110 %, 93 %, and 102 % for oral antidiabetic agents, diuretics, and insulins respectively.

Conclusion: Pregabalin demonstrates linear PK in CPP. Pregabalin CL/F is related to CLcr, and this relationship is similar between CPP, HV, and EP. In patients with renal impairment, dosage adjustment based on CLcr is necessary. Pregabalin dosage adjustment in CPP is not required for concomitant administration of insulins, diuretics, or oral antidiabetic agents.

P651

Meralgia paresthesica: an unusual first manifestation of a retroperitoneal tumour

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Introduction: Meralgia paresthetica (MP) is a mononeuropathy of the lateral femoral cutaneous nerve (LFCN). It is normally caused by an entrapment of the LFCN at the anterior iliac spine often related with stretching injuries (obesity, pregnancy, ascites, tight garments, seat belts, etc). In a few cases compression of the nerve in the retroperitoneum or pelvic region has been reported as a cause of MP. We report a patient with MP as first and sole manifestation of a suprarenal tumour.

Material and methods: Physical examination, laboratory analysis, abdominal ultrasonography, abdominopelvic computed tomography (CT) and magnetic resonance (MR) were performed.

Results: A 54-year-old male patient presented with a 10-month history of paresthesia and dysesthesia at the anterolateral thigh of the right leg without other symptoms or signs. Laboratory data showed no abnormalities. Abdominal ultrasonography revealed a great mass situated in the right suprarenal gland (SG). It was confirmed by abdominopelvic CT and MRI. At laparotomy, an adrenalectomy was performed. Histopathologic examination of the tissues obtained found a solitary fibrous tumour of the right SG, $15 \times 7 \times 12$ cm in size.

Conclusion: Although the MP is normally caused by an entrapment of the LCFN at the anterior iliac spine, it is important do not forget that it can be secondary to other more serious ethyologies in pelvic and retroperitoneal regions.

We suggest that in all patients with MP to perform, at least, an abdominal ultrasonography to exclude an abdominopelvic mass.

P652

Acute painful sensory neuropathy as a presenting feature of Hodgkin's disease – a case report

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Background: Peripheral neuropathies have been reported in 0.1–2 % of lymphoma patients, least commonly in Hodgkin's disease (HD). Infiltration neuropathy in HD is extremely rare and has never been reported in distal nerves. Hodgkin's disease has been associated with subclinical peripheral nerve involvement, GBS syndrome, CIDP, acute dysautonomia, motor neuron disease and a subacute predominantly sensory neuropathy.

Case report: A 36 year-old man was admitted to our department having developed over a few days severe burning dysaesthesias of the lower limbs in a 'stocking' distribution. This resulted in great difficulty standing and walking due to pain. Examination revealed a pyrexia (37.5˚C), an antalgic gait, normal muscle power, mildly reduced tendon reflexes on the right side, symmetrically reduced lower limb vibration and position sense distally, symmetrically reduced lower limb pain and temperature sensation distally as well as severe distal lower limb allodynia and hyperpathia. Electrophysiological studies revealed a purely sensory axonal polyneuropathy with involvement of small unmyelinated fibres. Electromyography revealed no denervation up to a month following the onset of symptoms. CSF was acellular with a protein of 157 mg/dl. Modest autonomic nervous system involvement was present. Sural nerve biopsy was not performed. A thoracic CT demonstrated a soft-tissue mediastinal mass (5×3.5 cm). Surgical excision of the mass was performed and histological examination revealed nodular sclerosing Hodgkin's disease. Other possible causes of the neuropathy were excluded; the patient was treated symptomatically and referred to the oncologists.

Discussion: The presence of a subacute predominantly sensory neuropathy in patients with HD has been documented in the literature. However, no particular attention has been drawn to an acutely developing painful sensory neuropathy in these patients. Of the cases in the literature, only one possibly mirrors the mode of presentation in the present report. Hodgkin's disease should be included in the differential diagnosis of an acute painful sensory neuropathy.

P653

Recurrent Fisher's syndrome: its relationship with antiGQ1b antibodies and HLA

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Background: Recurrences of Fisher's syndrome, a disease associated with serum antiGQ1b antibodies, are rare and had been related with certain HLA alleles.

Objective: To report the case of a patient who suffered three bouts of Fisher's syndrome over 17 years.

Case report: An 80 year-old man was admitted in February 2000 because of the rapid onset of ataxia, ophthalmoparesis, dysphagia and dysarthria, a week after a flu-like illness. Intravenous high-dose immunoglobulins were administered for 10 days, improving progressively until he became asymptomatic two months after the onset, except for persistent generalized arreflexia. Cerebral magnetic resonance imaging showed some pontine hyperintense lesion in flair sequences. He had suffered Fisher's syndrome in January 1983 and again in February 1996. In the second period the clinical picture evolved to a Guillain-Barré syndrome, ending in a locked-in state. Both episodes were fully reversible. AntiGQ1b antibodies were demonstrated in the sera at the onset of the second and third periods, becoming negative in the recovery phase both these times. The patient was HLA-DRB1* 1501 and 1608.

Conclusion: Fisher's syndrome recurrences are associated with reappearance of antiGQ1b antibodies, which disappeared coinciding with the disappearance of symptoms. HLA-DRB1* 1501 and 1608 may be associated with Fisher's syndrome recurrences. The case of this patient supports the notion that Fisher's syndrome, Guillain-Barré syndrome and brainstem encephalitis may represent a nosological continuum.

P654

From mononeuritis multiplex to polyradiculoneuritis due to cytomegalovirus infection in a patient with AIDS presenting with Horner's syndrome

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We report here a patient with AIDS who complained of narrowing of the right eye fissure, right pupil miosis and paresthesias in both hands. Clinical exam showed a right Horner's sign, reduced sensation in the right thumb and left 5th finger and normal reflexes except for left bicipital arreflexia. Electromyographic (EMG) examination showed reduced sensory nerve action potentials (SNAPs) in the right ulnar nerve with no other signs of peripheral nerve involvement. Brain and cervical magnetic resonance imaging and thoracic computerized tomography were normal. Cerebrospinal fluid (CSF) showed normal protein content and absence of nucleated cells. A polymerase chain reaction (PCR) was requested to examine the presence of cytomegalovirus (CMV) or other type of infection. The CD4 cell count was 6/mm^3. Antiretroviral treatment was initiated at that moment. EMG was performed again 10 days later when he complained of reduced strength for abduction of his right shoulder. Data were similar to the previous exam, plus denervation signs in the right deltoid and brachioradialis, and left biceps and flexor digitorum communis muscles, and the diagnosis of multineuritis was suggested. The patient was re-examined when the PCR of the CSF was found positive for CMV and treatment with gancyclovir was started. At that time, the clinical situation of the patient had worsened, showing generalized weakness, distal paresthesias in limbs and dyspnea. He had absence of all tendon jerks except for the right biceps. The third EMG examination showed a delay in distal motor latency and in the F wave latency in many nerves of the upper and lower limbs. SNAPs were normal except for reduced amplitude in the right ulnar nerve. At that time the patient complied with the clinical and EMG criteria of polyradiculoneuritis. Three months later, clinical examination showed the persistence of the Horner's sign and focal asymmetric weakness in both upper limbs. Reflexes were present again. EMG examination showed again features of a multifocal neuropathy together with a mild delay of the F wave latency.

The conclusions from this study is that the patient had a mononeuritis multiplex manifested initially with a Horner's sign with progression to

polyradiculoneuritis probably due to meningeal CMV infection. This is an unusual presentation and progression of this entity, and enlarges the spectrum of the peripheral neurologic complications of CMV infection in AIDS patients.

Neuro-oncology

P655
Long-term evolution of anti-Hu antibody (Hu-ab) titres in patients with paraneoplastic neurological syndromes
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Background: The long-term outcome of Hu-ab titers in patients with PNS is not known.

Objective: To describe the evolution of Hu-ab titers in patients with PNS in relation to the neurological and oncological outcome.

Methods: We retrospectively selected 34 patients with. 1) at least two serum samples separated six or more months; 2) clinical information available to correlate with the titer evolution. Titers were determined by immunohistochemistry using serial dilutions of the serum. All samples from the same patient were analyzed in the same experiment without knowledge of clinical information. A change in the titer of at least two dilutions was used to define an increase o decrease in the Hu-ab titer.

Results: The Hu-ab titer did not change in 19 patients and decreased in 15. Median time between the basal and follow-up samples was 31 months in the group with unchanged Hu-ab titer and 34 in that with decreased titer. In the whole series, no correlation was observed between the decrease of Hu-ab titers and neurological outcome, tumor evolution, or type of treatment. However, there were three patients with a clear correlation between Hu-ab titers and neurological evolution. In two of them, the Hu-ab titers became negative when a complete response (CR) of the tumor was achieved and the PNS stabilized. The Hu-ab reappeared at the time of progression of the PNS. The third patient had a fourfold increase of the Hu-ab titers when the PNS progressed.There were five patients in whom Hu-ab became negative, all of them showed a stabilization of the PNS and the tumor was in CR in the three patients with cancer. However, 5 of the 12 patients in the series with tumor in CR and PNS stable did not have any drop in the Hu-ab titer. No tumor was found in 10 patients after a median follow-up of 48 months. Although the percentage of patients with decreased Hu-ab titers was similar compared with the group of patients with cancer, the actuarial median time to observe a decrease in Hu-ab titers was longer in patients without tumor (76 vs. 40 months, $p = 0.04$)

Conclusion: No correlation was observed between decrease of Hu-ab titers and neurological outcome, tumor evolution, or type of treatment. In 3 patients there was a clear correlation between Hu-ab titers and neurological evolution. In all 5 patients in whom Hu-ab became negative the PNS stabilized. Time between basal titer and decrease of Hu-ab titers was significatively longer in patients without tumor.

P656
Bilateral brachial plexopathy as presenting symptom of B cell lymphoma
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Tumor infiltration is one of the common causes of non-traumatic unilateral brachial plexopathy. However, cases of bilateral involvement in cancer patients are more associated with delayed radiation injury than to a mass effect.

We report a case of a 47-year-old woman who was referred to our hospital for evaluation of bilateral upper limb pain and paresis. On admission, she had brachial diplegia, depressed upper limbs reflexes, right facial and upper limb hypohidrosis, and bilaterally increased knee reflexes on physical examination.

Bilateral brachial plexopathy was confirmed by electromyography, and the cervical magnetic resonance imaging revealed bilateral supraclavicular and vertebral canal masses communicating through the intervertebral foramina. The spinal cord was also compressed by an epidural mass. Cervical ultrassonography revealed multiple lymphadenopathies. B cell lymphoma was diagnosed by fine-needle aspiration cytology of the supraclavicular mass.

The clinical investigation of bilateral brachial plexopathy should include the search of a bilateral tumor infiltration. To our best knowledge, there are no previous reports of a bilateral brachial plexopathy as a lymphoma clinical presentation.

P657
Lhermitte Duclos disease: a report of three cases
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To describe in 3 patients the characteristic MRI pattern of Lhermitte Duclos Disease (LDD – a rare cerebellar lesion featuring both malformation and benign neoplasm) and the associated pathology

Materials: There were 2 females and one male, ranging in age from 34 to 56 years. The first two patients shared similar clinical features (ataxia and headache) due to a cerebellar space occupying lesion. In both cases MRI showed a well defined right cerebellar mass in low signal on T1-weighted and high signal on T2-weighted pulse sequences with a peculiar striated pattern and no contrast enhancement, suggesting the diagnosis of LDD. Mass effect was present with supratentorial ventricular enlargment. The diagnosis of LDD was histologically confirmed with a thickened molecular layer with hypermyelination, abnormal granular layer and absence of normal Purkinje cells. In the remaining patient, who presented with generalized seizures, dysarthria and ataxia, MRI showed a small left cerebellar cortical dysplasia. In addition, an associated arterio-venous fistula and dermatologic lesions suggested the diagnosis of COWDEN disease (CD). This diagnosis was confirmed by the genetic screening (mutation of the PTEN gene)

Discussion: LDD is a rare condition of the cerebellum, associating a dysplasia and a benign tumour.

Age at presentation is mainly in the third and fourth decades. Usual signs include headache, ataxia, visual disturbances and papilledema. When cortical dysplasia is large, the MRI pattern is usually characteristic with a preserved cerebellar gyral pattern but enlarged folia. Despite the very slow growth of the lesion, surgical treatment is the rule since sudden deterioration and death have been described. Furthermore, tumours such as medulloblastoma can exceptionally mimic LDD.

LDD can be a manifestation of a Cowden disease, an uncommon autosomal dominant mucocutaneous condition and part of the group of phacomatoses. As previously hypothesized, LDD may reveal Cowden disease and should receive a complete screening since some associated lesions can turn into malignant tumours. Pathogenesis, associated pathologies and treatment will be discussed

P658
Gap Junction Communication of astrocytoma cells can be inhibited by Intracellular TNF alpha
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Background: Like astrocytes in the CNS, different astroglioma cells form a well coupled syncytium via gap junctional communication (GJC). Astrocytic gap junctions consist of connexin(Cx)43. Human astrocytomas of various malignancy are known to be resistent to regulatory effects of TNF alpha and other proinflammatory cytokines. TNF alpha and a majority of inflammatory cytokines inhibit GJC in astrocytes, but not in glioma cells. In order to elucidate the TNF alpha resistance, we evaluated the effect of intracellularly applied TNF alpha on GJC in the rat glioma clone F98.

Methods: We investigated GJC and membrane resting potential (MRP) of primary astrocyte/microglia cocultures and F98 glioma cells by Lucifer Yellow dye-transfer and patch clamp technique after previous incubation with TNF alpha (1000 U/ml), IL-1 beta (500 U/ml) and IFN gamma (100 U/ml) for two hours. Intracellular effect of TNF alpha (100 U/ml) was tested after 15 minutes. Expression of Cx43 and TNF alpha receptor 1 (TNFR1) was observed by immunocytochemistry and western blotting.

Results: Intracellular application of TNF alpha significantly reduced the number of coupled cells from 42.2 in control (Co) to 20.2 ($p = 0.016$, median). MRP was significantly increased from –32.0 mV to –15.8 mV ($p < 0.0001$). The intracellular effects of TNF alpha could be inhibited by staurosporine (8 ng/ml-1h) an inhibitor of protein kinase C: number of coupling cells increased up to 56 ($p < 0.001$) and repolarised to –32.1 mV ($p < 0.0001$). Control samples using cultures of primary astrocytes revealed an expected decrease of coupled cells from 48.5 (Co) to 6.4 in TNF alpha-treated astrocytes ($p < 0.0001$). A significant MRP-depolarisation from –72.5 mV (Co) to –46.8 mV was induced ($p = 0.0001$). IFN gamma and IL-1 beta both inhibited GJC and significantly decreased MRP in primary astrocytes [MRP: from –75, 9 mV (Co) to –52, 6 mV (IFN gamma,$p = 0$,

0007) and –49, 35 mV (IL-1 beta, p = 0, 0003), cell-coupling: from 42, 5 (Co) to 8 (IFN gamma, p = 0, 0051) and 3, 4 (IL-1 beta, p = 0, 0001)]. However neither IFN gamma nor IL-1 beta and TNF alpha affected coupling or MRP in glioma cells.

Conclusion: Our results suggested that TNF alpha resistance of gliomas with regard to GJC can be overcome by intracellular application of TNF alpha. A reasonable explanation of this effect is that either internalisation or retention of the TNFR1 in glioma cells is prevalent. Impaired GJC could indicate loss of integrity and constraint survival of glioma cells.

P659

Cancer diagnosis using body fluorodeoxyglucose-positron emission tomography (Fdg-Pet) in Patients with paraneoplastic neurological disorders (PND).

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Background: Patients with PND may benefit from early diagnosis and treatment of the underlying neoplasm, that is often at a limited stage and difficult to uncover by conventional techniques. Recent studies have demonstrated that total body FDG-PET is useful in identifying tumours not visible with other studies.

Objective: To report two patients with PND, in whom body FDG-PET demonstrated an occult neoplasm that eluded detection by other techniques.

Methods: Both patients were clinically evaluated. Studies searching for a neoplasm included physical examination, thoracic and abdomino-pelvic CT scans, mammograms, bronchoscopy, serological cancer markers and total body FDG-PET. Serum and CSF samples were evaluated for the presence of onconeuronal antibodies by immunohistochemistry and western blots of rat tissues. Antibodies to voltage gated calcium channels (VGCC) were evaluated by radioimmunoassay in case 2.

Case reports: Case1. An otherwise healthy 52-year old woman presented in April 2002 with a subacute pancerebellar syndrome and bilateral extensor plantar responses. CSF analysis was normal. Brain MRI showed severe cerebellar atrophy. Conventional studies searching for an occult cancer were negative, including mammograms. High titers of anti-Yo antibodies were present in serum and CSF. Body FDG-PET showed abnormal uptake in the right breast, whose pathological study evidenced invasive ductal adenocarcinoma. Despite of antineoplastic treatment, her neurological condition worsened and the patient died six months later. Case 2. A 57 year old man with smoking habit, presented in may 1999 with a Lambert Eaton myasthenic syndrome that associated symptoms of cerebellar degeneration. CSF and MRI studies were unrevealing. The serum of the patient had high titers of VGCC antibodies. Periodical conventional studies were negative for neoplastic disease. Two years after the onset of symptoms, a body FDG-PET showed abnormal uptake in the mediastinum that could not be biopsied. The patient was treated with chemotherapy for small cell lung cancer (SCLC) and the abnormal FDG-PET image resolved. The myasthenic syndrome improved, the cerebellar degeneration stabilized and the patient died 6 months later of tumor progression.

Conclusions: Body FDG-PET improves tumour detection in patients with PND when conventional studies are unrevealing. This technique may contribute to a better clinical management of patients suffering from PND.

P660

Paraneoplastic opsoclonus-myoclonus in a patient with epidermoid carcinoma of the lung

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Background: Paraneoplastic Opsoclonus-Myoclonus Syndrome (OMS) has first been reported in children with neuroblastoma. A few cases of OMS are associated with several tumours in adults, more frequently small-cell lung cancer (SCLC) and breast neoplasm in women.

Aims: To present the clinical features, outcome and immunological findings of a 53-year-old man with non-SCLC who developed OMS simultaneously to the diagnosis of a lung tumor.

Patient/Methods: The patient was admitted to our hospital after a six months history of toxic syndrome (anorexia, weigth loss) and respiratory symptoms. The week previous to admission he worsened and began to be drowsy, disoriented and unstable. After hospitalization he rapidly developed involuntary eye movements with chaotic saccades (opsoclonus) accompanied by truncal ataxia. He also began to present limb and facial myoclonus with progressive encephalopathy until death 12 days after admission. Cerebral CT, MRI, and CRF study were normal. Thoracic CT disclosed a left lung mass. Bronchoscopic biopsy confirmed and epidermoid carcinoma. Serum detection of antibodies to anti-Hu, anti-Ri, anti-Yo and anti-amfiphysine (Dr. F. Graus) was negative.

Results: The clinical presentation of OMS was recorded by video and will be presented as an illustrative example of this rare condition.

P661

High-grade oligodendroglioma: bone marrow metastasis and remission after chemotherapy

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High-grade (HG) oligodendroglioma is a rare primary brain tumor which rarely metastasises extraneurally because of the absence of a lymphatic system, the presence of the blood-brain barrier and poor survival. Oligodendroglioma may spread via the cerebrospinal fluid or after surgical innervention. Metastasis to bone marrow is extremely rare. We herein report a case of a 50 year-old man, with a long history of jacksonian fits, who was diagnosed to have a HG oligodendroglioma. At onset he was treated with radical resection and radiotherapy. Three years later, he was admitted to the Oncology Department for severe anemia. The peripheral blood smear showed the presence of large and immature cells. Both the bone marrow aspiration and the biopsy revealed a diffuse replacement by glioma cells. The patient was treated with CCNU, Epirubicin, Vincristine, Procarbazine achieving a complete remissin lasting two years. This unusual case suggests that bone marrow metastases can be successfully managed with chemotherapy. Moreover the long time to progression from the onset, the detection of bone marrow involvement and prolonged survival after chemotherapy are to be emphasized.

P662

Meningeal carcinomatosis in a patient with breast cancer

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Introduction: Meningeal carcinomatosis (MC) occurs in approximately 5 % of patients with breast cancer. MC usually occurs as a late complication of tumoral illness. Rarely, it represents the first clinical evidence of cancer.

The clinical presentation of MC includes manifestations of increased intracranial pressure, cranial nerve palsies, stroke-like syndromes, seizures and encephalopathy. Symptoms are often obscure and diagnosis can be difficult.

Case presentation: a 67-year old female presented with paraparesis, sensory disturbances in all limbs and sphincter dysfunction. Her symptoms were gradually worsening, reaching paraplegia in 5 months from onset. During the 4th month of disease course, as part of investigation, mammogram was performed, leading to bilateral partial mastectomy with removal of maxillary lymph nodes. Pathology revealed invasive lobar carcinoma with lymph node metastases. Chemotherapy was interrupted due to neurological deterioration of the patient. Neurological examination at admission showed paraplegia, absent tendon reflexes of the lower limbs, extensor plantar response at the right, decreased proprioception of all limbs. Investigation: Laboratory routine tests were normal. Paraneoplastic screen, immunologic screen and tumor markers were negative. Somatosensory evoked potentials showed complete bilateral block at the lower limbs.Cerebrospinal fluid (CSF) studies revealed cell count = 10/mm^3, glucose = 82 mg/dl and protein = 400 mg %. Isoelectric focusing (IEF) showed oligoclonal bands in CSF. CSF cytology revealed neoplastic cells. Initial magnetic resonance (MRI) of the spinal cord was normal, but gadolinium was not used at that time. A second MRI of brain and spinal cord, with a double dose gadolinium infusion, showed leptomeningeal enhancement at the full length of the spinal cord, infra- and supra-tentorialy and high signal of CSF at the basilar cisterns.

Conclusions: Our patient presented with a neurological syndrome caused by MC as the first manifestation of cancer. Therefore, MC should be included in the differential diagnosis of patients with subacute neurological symptoms. Meningeal contrast enhancement is a non-specific finding, because it can be seen with infections, trauma, subdural hematomas and even following lumbar puncture. CSF cytology is diagnostic. Repeated lumbar punctures may be required. Early diagnosis of MC may lead to effective therapy, which prolongs survival for a few months.

P663
Central nervous system malignant lymphomatosis: a clinicopathological report of 2 cases
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Intravascular lymphomatosis (IVL) is a rare type of lymphoma in which malignant lymphoid cells are found inside small blood vessels lumen of affected organs, which predominantly affects the central nervous system. We report on the clinicopathological findings in 2 patients with CNS malignant lymphomatosis (CNSML) in order to illustrate the various manifestations of this disease.

Patient 1, a 72-y-old w., had a 1 year history of fever and fatigue associated with anemia. Two months prior to admission, she had transient episodes of aphasia and headache. One month later, she developed walking difficulties and dysuria and became paraplegic within 2 weeks. Spinal cord MRI was normal. She subsequently developed progressive aphasia and episodes of myoclonia. Brain CT-scan showed asymmetrical non-enhancing, hypodensities of the supratentorial white matter. Her condition deteriorated uickly and she died from respiratory failure 3 days after admission in our service.

Patient 2, a 67y-old w., had a history of congenital rubella with sequellar blindness. One month before referral, she manifested vomiting, headache and loss of weight. Brain CT-scan was normal. She developed episodic confusion and progressive speech difficulty. A 2nd brain CT-scan showed multi-nodular contrast enhancements. Brain MRI showed extensive high signal areas in white matter with multi-nodular contrast enhancements. She then manifested epilepsy and encephalopathy and died from aspiration pneumonia within a few weeks. ESR was increased in both pts but LDH was normal. Serum immunofixation (SI) showed polyclonal IgA & IgM hyperglobulinemia in Pt 1, an IgMk monoclonal protein in Pt 2. Peripheral blood flow cytometry showed a small B cell (CD20+, CD5+) clonal expansion. CSF studies showed increased protid content in 2 pts.

Post-mortem studies showed macroscopically multiple mixed haemorrhagic ischemic lesions in brain parenchyma and ischemic lesion in cervical spinal cord in pt 1, but was normal in pt 2.

Microscopically, in pt. 1: there were multiple small necrotic ischemic lesions in brain parenchyma and necrotic and haemorrhagic lesion in cervical spinal cord, in association with multiple demyelinated areas in the brain and a single one in dorsal spinal cord. Lumen of cortical & meningeal vessels & spinal arteries was occluded by CD20+ tumoral lymphocytes.

In pt 2: Post mortem study showed diffuse invasion of brain parenchyma and Virschow spaces by CD20+ B cells, with intra & extravascular B lymphocytes infiltration of many small brain vessels.

Conclusion: Ischemic, haemorrhagic and demyelinating lesions occur in CNS malignant lymphomatosis as a result of occlusion of small blood vessels, alteration of vessel walls, and, presumably of demyelinating effect induced by malignant lymphocytes infiltrating the white matter.

P664
The treatment of adults with medulloblastoma: a chemo-radiotherapy study
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We analyzed the progression-free survival, overall survival, and toxicity in 27 consecutive adult medulloblastoma patients treated in our istitution from 1993 to 2003. Twenty-seven patients (5 female, 22 male) with a median age of 26 years (range, 19–55 years) were treated with surgery, radiotherapy and Cisplatin-etoposide adjuvant chemotherapy regimen. All tumors were infratentorial (17 in 4th ventricle and 10 in left or right hemisphere). Eighteen patients had gross total resection, 5 had subtotal resection (> 50 % removed), and 4 had partial resection (< 50 % removed), moreover 6 patients were shunted for hydrocephalus. Postoperatively, 2 patients had positive cytology and 3 had positive spinal MRI. All patients were treated with Cisplatin (40 mg/sqm day 1–3) and etoposide (120 mg/sqm days 1–3) combination. The treatment was stared during the first week after the surgery and repeated every 4 weeks up to a maximum of 3 cycles. The radiotherapy was started during the first month after surgery (36 Gy to craniospinal axis plus a boost of 18–20 Gy in posterior fossa). Seven of 27 patients relapsed, (4 at the primary site. 2 leptomeninges, 1 bone and brain). The estimated median relapse-free survival (Kaplan-Meier) was 61 months (95 % confidence interval, 0.97–0.104). Five patients dead at 26, 36, 44, 53 and 54 months from first diagnosis. Toxicity during the treatment was moderately severe, with only 17 of 27 patients able to complete all therapy. Hearing loss occurred in 6, neutropenia (< 500 µl) in 7, thrombocytopenia (< 50,000 µl) in 12, nephrotoxicity in 2. Ten patients have persistent nausea and vomiting. To know whether adding adjuvant chemotherapy to craniospinal radiation in adult therapy increases relapse-free and overall survival, we must draw a larger randomized controlled clinical trial.

Neuro-epidemiology

P665
Prevalence, clinical features and prognosis of the autosomal dominant spinocerebellar ataxias in Madrid-Area 5
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Introduction and objectives: The autosomal dominant spinocerebellar ataxias (ADCAs) constitute a group clinical, pathological and genetically heterogeneous. It still remains at least 20 % of ADCAs in which their genetic aetiology has not been possible to establish. We have studied the prevalence and cumulative incidence, and analysed the functional deterioration and survival of the ADCA in Madrid-Area 5.

Material and methods: During the years 1994–2003 we have carried out the follow-up of 128 patients, 14 years and older, remitted to the Department of Neurology ("adults") of the University Hospital "La Paz", with cerebellar ataxia of degenerative type. Thirty (30) of them reunited criteria of ADCA by anamnesis and/or genetic study: SCA 3/MJD 6, SCA 6 3, SCA 7 5, and other 16. All the patients were studied with the purpose of identifying both different phenotypes and genotypes. 16 cases were considered valuable for the study of prevalence. We analysed the functional deterioration and survival by means of the method of Kaplan-Meier. We have compared these last parameters with those corresponding to the other groups of Ataxias: autosomal recessive (ARCA), idiopathic late onset ("pure" ILOCA) cerebellar ataxias, ILOCA-plus and OPCA. The possible risk factors, which could influence in the functional deterioration and survival, were valued by means of Cox regression.

Results: Prevalence in the general population (681,046) of Madrid-Area 5: 2.34/100,000 inhabitants. In 53.3 % it was not possible to identify the genotype. The rhythm of progression of the functional deterioration and the survival don't differ significantly of other groups: ARCA, ILOCA and ILOCA-plus. A larger grade of clinical cerebellar affectation ($p < 0.01$) and a larger volume of the IV ventricle ($p < 0.05$) were associated with more acceleration to requiring aid to walk and wheel chair. The increment of volume of the IV ventricle was associated significantly to the reduction of the survival ($p < 0.02$).

Conclusions: The prevalence of ADCA in the population of our Area is higher than in previous studies, Northeast of Libya (Sridharan et al. 1985), Torino (Italy) (Brignolio et al. 1986), Cantabria (Spain) (Pole et al. 1991), Molise (Italy) (Filla et al. 1992) and Valley of Aosta (Italy) (Leone et al. 1995); however, it is similar to Holland (Van of Warrenburg, 2001). The distribution of mutations shows similarities and differences with other studies.

P666
Prevalence of vestibular vertigo in Germany: a population-based study
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Background: Dizziness and vertigo rank among the most common complaints in medicine.Thus far, the prevalence of vestibular vertigo has been studied only in selected patient groups but not in the general population.

Objective: To determine the prevalence of vestibular vertigo in the general adult population in Germany.

Methods: A computer-assisted telephone interview (CATI) survey was conducted with a representative sample of 4,869 men and women aged 18 years and older residing in Germany. The CATI identified 1,403 subjects with a history of moderate or severe dizziness or vertigo, 1,157 of whom were willing to participate in a detailed dizziness interview conducted via telephone by medical students thoroughly trained in a dizziness clinic. Diagnostic criteria for vestibular vertigo were rotational vertigo, positional vertigo, or recurrent dizziness with nausea and at least one additional feature (head motion intolerance, oscillopsia or imbalance). In a concurrent validation study, 61 patients were interviewed by telephone and independently examined in a specialised dizziness clinic by a neurologist trained

in neurotology. Vestibular vertigo was detected by telephone interview with a specificity of 94 % and a sensitivity of 88 %.

Results: From the original sample (n = 1,157) 1,003 interviews were completed (response rate 87 %). A history of vestibular vertigo was reported by 243 participants (178 women and 65 men), 89 % of whom had recurrent vestibular vertigo. The proportion of vestibular vertigo within the whole dizziness/vertigo group varied with age, increasing from 14 % (men 8 %, women 17 %) in the age group 18–39 years, to 28 % (24 %, 31 %) in the age group 40–59 years and 37 % (32 %, 41 %) in the age group ≥ 60 years. The estimated lifetime prevalence of vestibular vertigo in the general population in the three age groups was 7 %, 10 % and 16 % in women and 2 %, 5 % and 8 % in men.

Conclusions: Vestibular vertigo is a common health problem which increases with age and affects women twice as often as men.

P667

Prevalence and prognosis of multisystemic atrophy in Madrid-Area 5

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Introduction and objectives: We have studied the evolution of the symptoms and signs of the multiple system atrophy (MSA), their prevalence, diagnosis and the possible risk factors associated to the prognosis.

Material and methods: The incidence of MSA and of its types has been studied in Madrid-Area 5 during the period 1983–2003. The number of patients referred to the University Hospital "La Paz" that reunited criteria of MSA was of 37: type OPCA 11, type SND 21 and Shy-Drager Syndrome 5. The functional deterioration and the survival have been compared among MSA subgroups and with these of other groups: PSP, CBD, ILOCA and ILOCA-plus. We analysed the functional deterioration and survival by means of the method of Kaplan-Meier. The percentage of cases of ILOCA and ILOCA-plus that evolve toward MSA was calculated. The possible risk factors, which could influence in the functional deterioration and survival, were valued by means of Cox regression.

Results: Of 60 cases with sporadic cerebellar syndrome, 11 patients (18.3 %) evolved toward MSA. Prevalence in the general population of Madrid-Area-5: 1.46/100,000 inhabitants. Prevalence in the population of advanced age (> 50 years) of Madrid-Area 5: 4.7/100,000 inhabitants. Incidence in the general population of Madrid-Area-5: 0.28/100,000/year, (M/F: 0.11/0.17). Incidence in the population of advanced age of Madrid Area-5: 0.92/100,000/year, age > 50 years, (M/F: 0.35/0.57). 18.3 % of cases of ILOCA + ILOCA-plus evolved to MSA. Grade of dysautonomic affectation is a risk factor significantly associated with decrease of survival rate. Grade of parkinsonism is a risk factor significantly associated to functional deterioration. Time from the beginning up to the presentation of both the motor and dysautonomic symptoms seem to predict the functional deterioration and survival in MSA.

Conclusions: The prevalence of the MSA in Madrid-Area 5 is relatively similar to other studies: Faroe Islands (Wermuth et al. 1997), Low Aragon (Errea et al. 1999), Aquitaine (Tison et al. 2001), being much lower than in these performed in Italy (Chian et al. 1998) and London (Schrag et al. 1999).The incidence of the MSA in Madrid-Area 5 is relatively lower than the one obtained by other groups: Minnesota (Bower et al. 1997), London (Schrag et al. 1999). Some parameters were associated to functional deterioration and reduction of the survival.

P668

Prevalence, clinical features and prognosis of late-onset autosomal recessive cerebellar ataxias in Madrid – Area 5

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Objectives: Autosomal recessive cerebellar ataxias (ARCA) constitute a heterogeneous group of rare neurodegenerative diseases characterized by early-onset cerebellar ataxia associated with other neurological manifestations and ophthalmologic and systemic signs. Only a few diseases have been genetically characterized. Late onset ARCA (LOARCA) is the aim of the study.

Methods: 17 patients (12 men and 5 women) with LOARCA (more than 20 years onset) were studied (17.4 % of all late-onset ataxias). All of them were studied clinically, neurophisiologically, neuroradiologically and genetically.

Results: Prevalence LOARCA in Madrid-Area 5 is 2.49/100,000, with the following genotype distribution: FRDA 0.29/100,000, non-characterized genotype 2.20/100,000. It was only possible to identify the genotype in 11.8 %. The most common phenotype in the non-characterized genotype group was spastic ataxia (5 patients), followed by ataxia with ophtalmoparesy and corticospinal dysfunction, ataxia with optic neuropathy and corticospinal dysfunction, and familiar episodic ataxia (3 patients in each phenotype), and ataxia with neuropathy (1 patient). Protuberance atrophy was associated to an earlier need for walking assistance ($p < 0.03$).

Conclusions: Although phenotypes are heterogeneous, the clinical signs determine the diagnosis in FRDA patients. Phenotype analysis shows an overlap with other ataxia groups (ADA, ILOCA). Some factors seem to predict the functional deterioration in LOARCA.

P669

Health-related Quality of Life in Myasthenia Gravis: a community-based study

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Introduction: There is an acknowledged need for both generic and disease-specific quality of life measures in clinical trials of myasthenia gravis (MG). Two previous studies have looked at MG and health-related quality of life (HRQoL) amongst partly selected groups of patients in Italy and the USA. The Myasthenia Gravis Activities of Daily Living Score (MG-ADL) has been proposed as a disease-specific questionnaire suitable for use in clinical practice and trials.

Objectives: We have attempted to measure and assess the impact of increasing severity of disease status upon HRQoL in a large unselected community-based cohort of patients with MG in the UK. In order to look at the usefulness of the MG-ADL in this context we have assessed its relationship to HRQoL, and compared this with disease status as classified by both modified Osserman classification (MO), and the Myasthenia Gravis Foundation of America Clinical Classification (MGFA) criteria.

Methods: Patients were recruited from an ongoing community-based epidemiological study of all patients with MG in Greater Manchester, UK. They were interviewed using a structured questionnaire, complemented by review of the notes. HRQoL was measured using the Short Form-36 (SF-36), disease severity graded using the MO and MGFA classifications and also scored with MG-ADL. Data, stratified by MO, MGFA and MG-ADL was compared with age and sex-stratified population norms.

Results: Results from 140 patients have been analysed. As in previous studies, we found significant differences in HRQoL between patients with MG and an age-matched normal population. Increasing severity of myasthenia as measured by both MO and MGFA criteria was associated with significantly lower HRQoL, MGFA was more closely correlated with HRQoL than was MO. There was an inverse correlation between increasing MG-ADL scores and HRQoL, with a suggestion that of the three scores MG-ADL score relates most closely to HRQoL, particularly in ocular myasthenia.

Discussion: This is the largest study of HRQoL in MG yet performed, and being community-based minimises selection bias in MG severity. As expected, MG of increasing severity impacts increasingly negatively on HRQoL. The results support use of the MGFA in preference to MO criteria as a measurement of disease status. The MG-ADL correlates well with HRQoL, adding validity to its use as a relevant tool for clinical practice and in clinical trials.

P670

Knowledge of stroke in stroke and non-stroke patients

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Aim: Introduction of new methods to stroke treatment requires immediate action in acute stroke and that is why social knowledge concerning the disease is very important. We compared general knowledge of stroke in stroke and non-stroke patients.

Subjects: Subjects were 53 patients who experienced stroke (mean age: 63.3 ± 13.2; M/F = 29/24) and 74 non-stroke patients (mean age: 59.2 ± 12.6; M/F = 29/45) of Neurology Department of Lublin Medical University. Patients with cognitive and speech disorders were excluded from the study.

Methods: A standardised, structured interview, with close-ended questions was performed to assess patients knowledge concerning stroke risk factors, stroke warning signs and action needed when stroke signs occur.

Results: General knowledge of stroke risk factors among stroke and non-stroke patients does not differ significantly; only diabetes mellitus was underestimated as a strong stroke risk factor in a group of non-stroke

patients ($p < 0.05$). Prior stroke was not considered to be a stroke risk factor in stroke patients group ($p < 0.05$). 11.3 % of stroke patients and 14.8 % of non-stroke patients could not identify neither single cause of stroke nor an appropriate action needed when stroke warning signs occur. Only one in five investigated patients in both groups knew all warning signs of stroke.

Conclusions: Neurological patients' knowledge of stroke signs and risk factors is considerably poor and does not differ significantly in both investigated groups. Further public education is necessary to increase awareness of the warning signs and risk factors of stroke. It could improve early recognition, reduce time to treatment and reduce the risk of stroke.

P671

Space-time clustering of multiple sclerosis in Northern Sardinia

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Space-time cluster analysis is used to see whether cases occurring close in time also tend to occur close geographically, and is thus designed for disclosing disease epidemics and detecting infectious etiological agents.

Space-time clustering of multiple sclerosis (MS) in the prov. of Sassari, Sardinia, a high-risk area for MS, with prevalence rates of 150/100,000 and an increasing incidence trend in the past 3 decades, was investigated. Complete information on residence changes from birth to MS onset was recorded for 649/776 (84 %) cases included in the province MS registry, and who had had clinical onset between 1946 and 1999. The study area comprises 90 communes and 6 linguistic sub-areas, and is mostly populated by Sardinian natives. The total population in 2001 was 453,628.

Space-time clustering was determined by analysing contemporaneousness according to age classes. Time closeness interval for each pair was arbitrarily chosen at 1, 2 and 5 years. Two patients were considered close in space if they were living in the same community in one analysis and in the same linguistic sub-area in another analysis. Separate analyses were also performed for patients with onset < 30 and ≥ 30 years, respectively.

Significant space-time clustering was observed within age 3 for both time closeness intervals of 1 and 2 years. Space-time clustering up to 9 years of age was also observed when time closeness was of 5 years. The statistical model applied to linguistic areas, using a 2-year interval for closeness in time showed higher overall clustering as compared to that applied to communes, and especially for year 1, 2 and 3. In order to disclose whether a young vs. and older age at onset could be predominantly associated to space-time clustering in infancy, an analysis by age at onset was conducted which showed space-time clustering only for earlier onset.

Sardinians born within the same birth cohort had lived significantly closer to each other than would be expected before age 3. Space-time clustering in childhood indicates a lower age at clinical onset, as reported for other populations, such as Norwegians. Due to incidence even increase throughout the whole province, significant demographic variations were ruled out. These findings provide further evidence to the hypothesis of an etiological role of an infection acquired in genetically susceptible individuals during childhood, the putative age for MS acquisition, as already supported by migration studies.

P672

Prevalence of neurological diseases in a gypsy population in Northern Greece

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Introduction: Gypsies in Northern Greece live mostly in settlements near large cities. Although they are not travelers any more, there are still difficulties for medical access (absence of records, method of approach).

Aim: to study the health status and prevalence of neurological diseases in a Gipsy population living in a settlement in the outskirts of our city.

Method: we interviewed Gypsies settled in Echedoros Municipality, after consent of their council. 266 persons (141 females, 125 males) were divided in 3 groups, reflecting 3 consequent generations:

group A (male:female = 1:1, n = 52, mean age 56 years)
group B (male:female = 1:1.06, n = 155, mean age = 32 years)
group C (male:female = 1:1.45, n = 59, mean age = 8 years)

Gypsies agreed to be asked questions in the setting of their own homes, and with the whole family being present.

We recorded demographic data, everyday habits, medical history and current ailments.

Results: all participants were born in Northern Greece and were residing, for the last 4 years, in the aforementioned settlement.

In group A: established medical diagnoses were:

Stroke: 13.5 %, cardiovascular diseases: 11.5 %, hyperlipidemia: 7.6 %, hypertension: 7.6 %, diabetes melitus type 2: 5.7 %.

In group B: established medical diagnoses were:

Allergy: 9.6 %, depression: 7 %, headache: 5.8 %, cardiovascular diseases: 4.5 %, stroke: 4.5 %.

In this group, we also noticed: 61.5 % were smokers, 73 % were alcohol abusers, 80 % had more than 4 meat meals per week. 88.5 % were using no method of contraception and 61.5 % of the women had abortions (mean: 8 abortions/woman). No person in this group had a complete vaccination program.

In group C: all children had breast-feeding for longer than a year. 3.4 % had infantile paralysis and 3.2 % a history of allergy.

Conclusions: Stroke and cardiovascular disease prevalence was remarkably high in the relatively young population of groups A and B. This could be attributed to the habits and way of life of this community.

Absence of inherited/familial disorders, autoimmune, and degenerative diseases in our sample was remarkable. This could be a methodology drawback since there were no medical records. Universal breast-feeding and absence of autoimmune diseases is a matter worth looking into.

P673

Idiopathic cerebellar ataxia. Study with 49 patients

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Background: Idiopathic late onset cerebellar ataxia (ILOCA) represents an ample group of neurodegenerative disorders of heterogeneous neuropathology. We classified phenotipically patients with pure cerebellar syndrome (pure ILOCA) and patients with aditional no cerebellar symptoms (ILOCA-plus).

Our aim is to evaluate differences of pronostic and associated risk factors between both groups.

Material and Methods: From 1994 to 2003 we studied 49 patients, 22 pure ILOCA, 27 ILOCA-plus. Clinical, neurophisiological and neuroimagen studies were carried out on all them. We used the Kaplan-Meier method for comparision of survival between subgroups and Cox regression to evaluate risk factors.

Results: Prevalence of ILOCA in Area 5-Madrid is 6.65/100,000 inhabitants with the following distribution into genotype subgroups: 3.1/100,000 for ILOCA-plus and 3.4/100,000 for ILOCA-plus. Analysis of slow ocular pursuit demostrated a more disfavourable mean score in plusILOCA than pure ILOCA. We didn't find significant diferences with onset age, survival or functional deterioration between both groups. Patients with more cerebellar afectation associated a more marked acceleration in requiring help for walking and use of wheel-chair.

Conclusions: Prevalence of ILOCA in Area 5-Madrid is similar to other places as Val d'Aosta and superior to prevalence in Benghazi or Cantabria. The functional deterioration in patients with ILOCA was only associated significantly to the degree of cerebellar clinical afectation.

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The therapy of Morbus Parkinson with controlled-release Levodopa/Carbidopa (NACOM RETARD/Sinemet CR)

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Controlled-release (CR) levodopa/carbidopa (NACOM RETARD/Sinemet CR) is mostly administered in the evening for the avoidance of nocturnal akinesias in patients with idiopathic morbus parkinson. The objectives of these post-marketing surveillance studies, which included 635 patients with Parkinson's disease, was to assess the tolerability, safety and efficacy of CR-levodopa/carbidopa in the daytime therapy and at night during a 12-week period in study I and a 8-week period in study II.

Patients were switched from standard levodopa/carbidopa to CR-levodopa/carbidopa or received CR-levodopa/carbidopa in addition to her anti-parkinson medication. The change of medication was monitored closely in study II. In addition, study II included the rating of sleep items with the PDSS (290 patients) and in-depth case studies (43 patients).

In the post-marketing surveillance study I the daily dose of CR-levodopa/carbidopa was increased, in accordance with the prescribing information for health professionals, to 372 mg at endpoint. Under such treatment, significant improvements in akinesia, rigor, tremor, as well as a

reduction of dyskinesias and motor fluctuations could be observed. The drug was well tolerated, and only two patients experienced side-effects.

This open-label study demonstrated that a more efficacious improvement of symptoms can be achieved through the switch to CR-levodopa or titration of CR-levodopa, without serious, quality of life affecting, side-effects. In this short-term surveillance, an improvements of motor fluctuations and dyskinesias could also be reached.

Muscle disorders

P675

New mutation in thymidine kinase 2 gene associated with mitochondrial encephalomyopathy

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Mitochondrial DNA depletion syndrome (MDS) is an autosomal recessive mitochondrial disease characterized by a reduction in mitochondrial DNA copy number. The clinical presentation of MDS is diverse: in some patients only one organ is affected, whereas in others the disease is multisystemic.

The commonest clinical presentations include: 1) an infantile disease associated with hypotonia, severe muscle weakness, elevated serum creatin kinase (CK) and lactic acidemia, with early and late variants; 2) a progressive neonatal encephalopathy with hepatic failure and renal tubulopathy. The family history of patients with MDS is generally indicative of an autosomal recessive mode of inheritance. Affected tissues have markedly reduced mtDNA copy number which impairs the synthesis of respiratory chain complexes. In late 2001, mutations in two nuclear genes controlling the mitochondrial nucleotide pool have been reported in patients with MDS. Changes in the mitochondrial deoxyguanosine kinase were identified in patients with the hepatocerebral form, mutations in thymidine kinase 2 (TK2) in patients with isolated myopathy. The tissue selectivity of these disorders and especially the exclusive muscle involvement in TK2 mutations is unknown. We studied two children of non-consanguineous healthy parents displaying myopathy and severe psychomotor delay. A 5-year-old boy was born at term after an uneventful pregnancy, his early development was normal. At 2 years of age is presented with hypotonia, elevated serum CK and progressive severe psychomotor delay. A muscle biopsy showed ragged-red-fibers and activities of respiratory chain enzyme revealed a defect of complex I. The younger sister was normal until 2 years of age, when she had an acute respiratory infection and subsequently developed progressive gait impairment, muscle weakness, hypotonia and inability to stand. The muscle biopsy showed dystrophyc alterations and severe infiltration with connective tissue and fat, while respiratory chain enzyme were normal. Southern blot analysis of muscle mtDNA showed mtDNA depletion. Sequence analysis of the six exon of the TK2 gene showed a novel homozygous mutation: a C-T substitution at nucleotide 331 resulting in a alanine-to-valine change at residue 108 in the two affected children, while both parents were heterozygous for the mutation. The mutation changes an highly conserved aminoacid position within TK2 protein, and adds to the few mutations so far reported in MDS.

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Molecular and cellular distribution of mtDNA control region mutations in POLG1/PEO patients

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Somatic alterations affecting the mitochondrial DNA (mtDNA) have been observed in normal and pathological conditions. Autosomal dominant and recessive progressive external ophthalmoplegia (ad/arPEO) are neurodegenerative disorders caused by mutations in three different nuclear genes, namely ANT1, C10ORF2 and POLG1, and are associated with the presence of multiple mtDNA deletions in patients' tissues. We recently demonstrated that specific POLG1 mutations directly affect the integrity of the mtDNA by reducing the proof-reading exonuclease activity of the DNA Polymerase gamma, resulting in the accumulation of heteroplasmic levels of both randomly rare and recurrent point mutations in the skeletal muscle tissue from eight patients. Aims of the study were to define the distribution of mtDNA mutations at the cellular level and to unravel somatic mutational hot-spots. We analysed the mtDNA control region in biceps brachii skeletal muscle from five new well-characterised POLG1/PEO patients and therefore we could compare the mutation burdens in 8 age-matched healthy controls, 13 POLG1-positive and 6 POLG1-negative PEO patients; in addition, we investigated the relationship between the presence of mtDNA mutations and the cytochrome c oxidase (COX) phenotype in 16 individual muscle fibers from three POLG1-positive PEO patients. Within the control region, the mtDNA mutations found in the POLG1-PEO patients were not randomly distributed; in particular, the POLG/PEO patients accumulated mutations around the heavy-strand replication origin and the conserved sequence block I (spanning nucleotides 170–240) and specific hot-spots were easily identified (i. e. A183G, C186T and A214T). On the contrary, non-POLG1/PEO patients and healthy controls, characterised by significantly lower mutational burdens compared to POLG1 patients, showed a random distribution of the mutation pattern within the mtDNA control region analysed. At single-fiber level, we found no significant correlation between COX phenotype and the cumulative mutation loads; however, a trend toward an increased number of mtDNA molecules was observed in COX- fibers compared to COX + (51.1 % ± 21.4 vs 37.6 % ± 13.3; $p = 0.07$). Our findings provide new insights about the contribution of somatic mtDNA mutations in the molecular pathogenesis of POLG1-PEO "mtDNA multiple deletions" syndrome.

P677

Sleep apnoea does not simply attribute to respiratory failure in myotonic dystrophy: evaluation by somnography

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Sleep apnoea and hypopnoea have been reported in myotonic dystrophy (MD), but it is unclear whether those are simply attributable to respiratory impairment as well as respiratory muscle weakness. The aim of this study was to assess the correlation of the disrupted nocturnal sleep and awake respiratory function, and to deduce a mechanism of respiratory failure in MD. The study population comprised eighteen patients with MD and seventeen patients with other types of muscular dystrophy for a control group. Patients in the control group were chosen to represent a similar range of the results of routine spirometry examination, particularly the expected/observed forced vital capacity (%VC). Arterial blood gases were also examined early in the morning. Sleep apnoea and hypopnoea were evaluated in all patients using somnography (Sleep Tester LT-200, Fukuda Denshi Co., Japan). The number of apnoea and hyponoea during night (NA) was counted and types of apnoea were judged; the percentage of central type apnoea (%CSA) and obstructive apnoea (%OSA) among total apnoea. Transcutaneous recording of oxygen saturation during night were simultaneously performed. The mean nadir and minimal value of oxygen saturation were obtained. The apnoea index (AI) and the nocturnal hypoxia index (NHI) were calculated. The mean age of the MD group was significantly younger than that of the control group (42.9 ± 11.7 vs. 51.6 ± 12.8 years). There was no significant difference in the %VC between the two groups (63.0 ± 15.4 vs. 65.7 ± 23.4). The mean PaO2 in MD was significantly lower and the mean PaCO2 in MD was higher than those in the control (78.8 ± 13.2 vs. 94.1 ± 10.9 mmHg, 49.1 ± 3.9 vs. 40.3 ± 4.9 mmHg). The mean nadir (94.7 ± 1.6 vs. 96.9 ± 0.7 mm Hg) and minimal value (73.0 ± 15.9 vs. 85.6 ± 7.5 mm Hg) of oxygen saturation in MD were significantly lower than those in the control. The mean NHI in MD was significantly higher than that in the control (96.1 ± 45.3 vs. 36 ± 16.7). On the other hand, there were not significant differences in the NA, the %CSA, the %OSA, or the AI between the two groups. Moreover, all the parameters for apnoea did not correlate with the results of spirometry or arterial blood gases, although the AI correlated with the NHI or the %CSA in MD. Our results suggest that respiratory failure in MD is not simply owing to sleep apnoea or respiratory muscle weakness, but might be due to impaired chemosensitivity or ventiratory output.

P678

A novel homozygous missense mutation in the GNE gene of a patient with quadriceps-sparing hereditary inclusion body myopathy associated with muscle inflammation

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An adult-onset hereditary inclusion body myopathy (hIBM) with sparing of the quadriceps muscle was originally described in Iranian Jews and assigned to a locus on chromosome 9p12-p13. Recently, mutations of the UDP-N-acetylglucosamine-2-epimerase/N-acetyl-mannosamine kinase (GNE) gene were reported to cause hIBM and one type of distal myopathy

in a world-wide distribution. Importantly, the lack of muscle inflammation was used to distinguish hIBM from the sporadic form of inclusion body myopathy (sIBM). We report a case of a quadriceps-sparing myopathy in a non-Jewish, Iranian patient with a high degree of muscle inflammation. A novel homozygous G-to-A mutation (128933G > A) in exon 7 changing a valine to isoleucine (V367I) in the kinase domain of the GNE gene was found. We conclude that muscle inflammation is not sufficient to exclude the diagnosis of hIBM. Furthermore, the GNE gene was analyzed in more than 30 patients presenting with inclusion body myopathy.

P679

Mitochondrial intestinal pseudo-obstruction with neurogenic bladder syndrome with a point mutation at T8356C: a new mitochondrial disease

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A point mutation at T8356C is known as the locus of myoclonic epilepsy with ragged-red fibers. We report a patient with progressive external ophthalmoplegia, intestinal pseudo-obstruction, and neurogenic bladder. Ragged red fibers were observed in patient's muscle specimen. By electron microscopy, these fibers contained abnormally large and abnormally structured mitochondria. Genetic study in this patient showed a point mutation at T8356C. We suggest that this case is a new mitochondrial disorder rather than a new variant of mitochondrial neurogastrointestinal encephalomyopathy.

P680

Clinical and genetic study of myotonic dystrophy type 1 in Serbian population

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The aim of this study was to analyse clinical and genetic characteristics of DM1 in Serbian population.DNA was isolated from white blood cells using a standard phenol chloroform protocol.All subjects were studied by both polymerase chain reaction(PCR) and Southern Blot analyses. Between 1983 and 2002, 245 registered patients with DM were reviewed. Genetic study was performed in 36 % of patients.In 84 (95 %) patients (44 men and 40 women), we detected a CTG repeat expansion(DM1).One patient had no expansion of the repeat, inspite of the clinical diagnosis of DM and 3 patients suffered from proximal myotonic myopathy without CTG expansion (DM2/PROMM). The mean of the smallest CTG expansion (progenitor allele) was 193 ± 103 (from 63 to 508),the largest CTG expansion was 924 ± 393 (146–1659) and the mean of the average expansion was 460 ± 179 CTG repeats (101–764).The size of CTG repeats in male and female DM1 patients didn't differ significantly ($p > 0.05$). However, the mean of the smallest CTG expansion was lower in patients with paternal DM1 mutation inheritance than in those with maternal inheritance ($p < 0.05$). The number of CTG repeats was related with muscular disability and intelligence quotient ($p < 0.05$). We found a negative linear correlation of age at onset and average expansion size in DM1 patients whose progenitor allele is less than 239 repeats long. Our results favor the hypothesis of an existing threshold in the progenitor allele size beyond which the number of CTG repeats does not influence the age of onset. The presence and severity of cardiac abnormalities, respiratory insufficiency, cataracts, gastrointestinal and endocrinological disturbances was not related to the number of CTG repeats. This study suggests that mechanisms leading to systemic disorders may be different from those responsable for neuromuscular disturbances in DM1 patients.

P681

Language disorders in Duchenne's muscular dystrophy

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Background: Duchenne Muscular Dystrophy (DMD) is a fatal recessive x-linked muscular disease caused by the absence of dystrophin. Dystrophin isoforms are also expressed in the cerebral neocortex and in the cerebellum. Cognitive impairment is described in 1/3 of DMD patients, particularly in patients carrying deletions in the distal part of the gene. Difficulties in verbal skills and reading abilities are more frequently described in English speaking patients. According to the literature children with DMD show linguistic deficits already in the early phases of language development which mainly consist of poor expressive verbal abilities and deficits in short-term memory. These observations suggest that in some cases dystrophinopathy may be associated to language disorders. Preliminary results in our group of Italian speaking children showed deficit in Grammatical and Syntax Comprehension.

Aims of the study are: 1) to describe the language and reading ability in a group of italian DMD children, 2) to clarify the nature of the language and reading deficits.

Patients: 13 children with DMD (mean age 8.3 years; standard deviation 1.7) were diagnosed according to international standard criteria. Full Intelligence Quotient (assessed using Wechsler Intelligence Scale) was > 70.

Methods: Language and Reading abilities were determined through: "Test dello sviluppo Morfosintattico", Battery of standardized tests, Battery to evaluate Dyslexia and Dysortography and Tasks of correctness and rapidity. To exclude additional cognitive deficits we evaluated attention/executive functions domain and memory and learning domain thought a Developmental Neuropsychological Assessment (NEPSY particularly: Auditory attention and response set – Visual attention – List learning – Memory for names).

Results: 8 patients out of 13 showed deficit in Syntax Comprehension. 7 patients out of 13 manifested deficits in Grammatical Comprehension. No DMD patients (except one) presented disabilities in reading. Most of the patients showed mild attention and memory deficits.

Discussion: An early identification of the language and eventually attention/memory difficulties, would be important for an early treatment, to support DMD children in their learning course.

P682

Brain involvement in the limb girdle muscular dystrophies

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Background: Limb girdle muscular dystrophies (LGMD) are a genetically heterogeneous group of disorders, characterised clinically by predominant weakness of the pelvic and shoulder girdle musculature. The LGMD2 C-F are caused by primary mutations in four genes encoding the components of the dystrophin associated sarcoglycan (SG) complex; LGMD 2A is caused by mutation in gene encoding the calpain3.

The precise function of sarcoglycans is not completely understood. In the brain, bSG may be part of the dystroglycan (DG) complex, involved in the synapse formation. Calpains are a group of intracellular proteases. The ubiquitous calpain isoforms (1 and 2) are expressed in the CNS and are activated in necrotic and apoptotic conditions, as neurodegeneration. The so called "muscle-specific" calpain3, has been found in astrocyte -like cells in the corpus callosum and in the dentate gyrus.

The aim of the study is to find a possible association between intellectual level and the protein defect.

Patients and methods: According to a clinical assessment and immunohistochemistry, immunoblotting and/or molecular analysis on muscle biopsy: 5 patients were affected by sarcoglycanopathy and 6 patients by a deficit of calpain3. Total number of patients: 11; age range from 14 to 72 years. The intellectual level was assessed through the Wechsler Intelligent Scales.

Results: the comparison between the mean of Full Intelligence Quotient (FIQ) of the patients with sarcoglycanopathy (FIQ 85 ± 11) and the mean of the patients with a calpain3 deficiency (FIQ 111 ± 18) showed a higher intellectual level in second group. The results indicate also that the patients with sarcoglycanopathy show a significant discrepancy between Verbal Intelligence Quotient (VIQ) and Performance Intelligence Quotient (PIQ) (mean VIQ = 78; mean PIQ = 96).

Discussion: all patients showed FIQ > 70. Subjects with sarcoglycanopathy manifested a middle-low intelligent level and better ability in performance than in verbal tasks. On the contrary, the patients with deficit of calpain3 showed a middle-high intelligent level, without significant discrepancy between verbal-performance subtests. This study suggests for the first time a possible role of the dystrophin associated proteins in "non muscular" districts.

P683
Jordans's anomaly associated with myopathy: case report
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Jordans's anomaly consists in lipidic cytoplasmic inclusions in leukocytes and their precursors, originaly reported by Jordans in 1953 in two brothers, both of whom had myopathy. Ever since, 23 cases have been traced out from the literature, and the abnormality had been associated with congenital ichthyosis, lipide storage disease, fatty liver, cardiomyopathy, myopathy and neurosensory hearing loss, but some of the cases reported were asymptomatic. An autosomal dominant inheritance was observed by many authors, but the gene or its product are not yet understood, such as the biochemical basis of the abnormality. We describe a 53 years old woman, who at forty seven years of age presented with proximal weakness of the arms, with progressive involvement of the distal arms and pelvic girdle, over and above atrophy predominantly of the proximal muscles of the arms and dysphagy. Creatine kinase was elevated at 446 U/L (normal < 90 U/L). Peripheral blood smear showed prominent cytoplasmic vacuolation in most of neutrophils, and positive reaction with staining with May-Grünwald-Giemsa revealed three to ten round vacuoles in all her neutrophils; serum triglyceride, serum cholesterol and renal function was normal. Eletrophysiologic studies demonstrated myopathic signs and muscle biopsy made evident vacuoles in the muscle fibers, predominantly in type-1 fibers, with positive reaction to Oil Red O staining affirming their lipidic content. Jordans's anomaly in association with myopathy is a rare condition, mentioned in literature only by four authors until now.

P683A
Increased Bax/Bcl-2 ratio upregulates caspase-3 and increases apoptosis in thymus of patients with myasthenia gravis
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Background: The ratio of Bax (apoptosis promoter) to Bcl-2 (apoptosis inhibitor) has been characterized as the best regulator of apoptosis. This study investigates the possible relation of Bax/Bcl-2 ratio with apoptosis co-ordination enzyme, caspase-3, in thymus of patients with myasthenia gravis (MG).

Design: The study included 38 patients (16 M/22 F-median age 36 yr) with MG, who underwent thymectomy for treatment. Pathology of thymus showed: hyperplasia-19, atrophy-8, thymoma-9, thymic carcinoma-2. Clinical staging (Osserman classification) included: stage I-3, IIA-19, IIB-13, III-3. Normal embryonic thymic tissues were used as controls. Paraffin sections were subjected to a) immunohistochemistry in order to detect I) bax and bcl-2 protein distribution, II) caspase-3 protein expression and III) Ki67 antigen presence (cell proliferation marker), b) in-situ hybridization (bax and bcl-2 mRNA production) and c) TUNEL-stain (detection of cells undergoing apoptosis). Staining results (% positive cells) were correlated with clinicopathologic parameters. Bax to bcl-2 mRNA/protein ratio was determined for each sample by dividing %bax (+) cells by % bcl-2 (+) cells.

Results: In MG instances, Bax mRNA was significantly increased and Bcl-2 mRNA decreased towards advanced disease stages (290 % and –72 % in MG stage 3). Similar results were recorded for Bax and Bcl-2 protein (310 % and –28 % in MG stage 3). The ratios of Bax/Bcl-2 mRNA and protein increased significantly towards advanced MG stages. These ratios were correlated with up-regulated caspase-3 expression ($r = 0.782$ and 0.583, $p < 0.01$), apoptosis ($r = 0.591$ and 0.358, $p < 0.01$ and $p < 0.05$) and cell proliferation ($r = 0.650$, $p < 0.01$ mRNA only).

Conclusions: In thymus of patients with MG who underwent thymectomy, Bax/Bcl-2 ratio may upregulate caspase-3 activation and modulate apoptosis associated with progress of the disease. These results may have prognostic and therapeutic implications in the long-term management of patients with MG.

Multiple sclerosis

P684
Gene expression analysis indicates distinct immune pattern in relapsing remitting (RR) and primary progressive (PP) MS disease type
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Background: Relapsing-remitting (RR) multiple sclerosis (MS) and primary progressive (PP) MS show different pathology. Comparing single immune factors in the peripheral blood between PPMS and RRMS no consistent differences have been found.

Objective: This study aimed to identify different expression pattern of immune genes by using Gene Expression Array analysis as general approach.

Methods: Gene Expression Array analysis was performed using pooled RNA derived from peripheral blood mononuclear cells (PBMC) of patients with RRMS ($n = 9$) and PPMS ($n = 9$) in the early disease phase who had not received any immunomodulatory or -suppressive treatment. Human Cytokine Expression Array (R) (R & D Systems) containing more than 800 immune relevant genes e. g. cytokines, chemokines, growth factors, apoptosis-related genes and their receptors as well as signal transduction molecules using P33-labeled gene specific primers was performed. Signal intensities of expressed genes were quantified by phosphoimaging and compared for inter-group differences. Genes exceeding at least two fold differences in expression intensity were selected and further analysed using TaqMan® Assays-on-Demand Products® (Applied Biosystems) for semi-quantitative specific mRNA measurement in individual MS patients.

Results: By help of Gene Expression Array analysis more than 60 immune-related genes differentially expressed in RR-MS and PP-MS could be identified. In a second step, several candidate genes were further analysed individually on the mRNA level in MS patients of both cohorts. In line with array results, we found increased expression of the co-stimulatory molecule CTLA-4 ($p = 0.03$) and chemokine-receptor CXCR2 ($p < 0.0001$) in RRMS patients, while the death domain containing protein TRADD involved in tumor necrosis factor receptor (TNFR) superfamily signalling was elevated in PPMS patients ($p = 0.0001$).

Conclusion: Gene Expression Array analysis may help as screening approach in pooled patient samples of MS to identify differentially expressed genes. These preliminary results further support the hypothesis that PPMS and RRMS may differ in relation to the underlying pathogenic process as indicated by different expression of immune-related genes.

P685
Neutralising antibodies have a higher affinity to interferon-beta than non-neutralising antibodies
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Background: Patients with multiple sclerosis (MS) receiving recombinant interferon-beta (IFN-beta) may develop binding antibodies (BAB) against IFN-beta during treatment. With respect to biological activities two types of BAB can be distinguished, neutralizing (NAB) and non-neutralizing antibodies (NNAB). Patients with NAB have greater BAB titers than patients without NAB, suggesting that the quantity of antibodies against IFN-beta is correlated with neutralization of IFN-beta. However, the correlation between NAB and BAB is weak and there is evidence that IFN-beta neutralization also depends on qualitative components, like different immunoglobulin subtypes of NAB and NNAB or different binding patterns to IFN-beta epitopes.

Objective: To determine whether there is a difference of binding affinity to IFN-beta between NAB and NNAB.

Methods: Thirty-eight serum samples with BAB of 27 MS patients receiving IFN-beta-1a or IFN-beta-1b were included in this study. Of these, twenty-one samples were NAB-positive and seventeen were NAB-negative.

The relative affinity values (RAV) of IFN-beta antibodies were determined using an affinity assay as described (J Neuroimmunol 1996; 66:85–93). The determination of RAV in this ELISA is based upon disrupting interactions between antibody and antigen using increasing concentrations of a chaotropic agent (sodium isothiocyanate).

Results: RAVs were significantly higher in NAB-positive (266.6 ± 5.884) than in NAB-negative (223.8 ± 15.96) serum samples. The amount of antibodies as measured by optical density did not differ between both groups (0.9803 ± 0.035 vs. 0.9771 ± 0.033). No significant correlation was observed between RAV and BAB or NAB titers.

Conclusions: After exclusion of confounding factors these results indi-

cate that NAB have a higher affinity to IFN-beta than NNAB. This goes in line with earlier results that neutralization of IFN-beta do not only depend on the quantity but also on the quality of antibodies.

P686
The persistence of neutralizing antibodies to interferon (IFN) beta over 6 years of treatment in MS patients is dependent on titre and IFN beta product
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Background: Neutralizing antibodies (NAbs) have been shown to reduce the clinical efficacy of interferon (IFN) beta products in patients with MS. However, there are conflicting reports regarding how long NAbs persist to the different IFN beta products.

Objective: To determine the persistence of NAbs to IFN beta-1b and intramuscular (IM) IFN beta-1a (phase III product) in multiple sclerosis (MS) patients who switched treatment to IM IFN beta-1a (commercial product) in the open-label, safety-extension of the pivotal phase III trial of IM IFN beta-1a (Avonex).

Methods: A total of 382 patients were enrolled in the open-label, safety-extension study of the pivotal phase III trial of IM IFN beta-1a. Of these, 218 patients had participated in the pivotal phase III study (103 received placebo and 115 received IM IFN beta-1a [phase III product]) and 164 patients did not participate in the pivotal phase III trial (140 who were previously exposed to IFN beta-1b therapy and 24 who were naive to IFN beta treatment). At the start of the open-label extension study, all patients were switched to IM IFN beta-1a (commercial product) 30 mcg once weekly, with no washout period. NAbs were measured every 6 months. Serum levels of NAbs were measured using a two-step enzyme-linked immunosorbent assay (ELISA)/antiviral cytopathic effect (CPE) assay.

Results: Forty-nine patients were positive (titer ≥ 5) for NAbs (NAb+) to IFN beta-1b and 11 patients were NAb+ to IM IFN beta-1a (phase III product) at the start of the safety-extension study. Of patients who were NAb+ to IFN beta-1b and became NAb-, the median time to become NAb- was approximately 6 months. Of patients who were NAb+ to IM IFN beta-1a (phase III product) and became NAb–, the median time to become NAb– was approximately 3 years. Ten of the 49 patients who were NAb + to IFN beta-1b had NAb titers ≥ 100; of these 10 patients, 5 (50 %) remained NAb+ at the end of 6 years. Six of the 11 patients who were NAb+ to IM IFN beta-1a (phase III product) had NAb titers ≥ 100; of these 6 patients, 5 (83 %) remained NAb+ at the end of 6 years.

Conclusion: These data suggest that the persistence of NAbs over the long term are dependent on NAb titer and IFN beta product.

P687
A novel fMRI assessment of cognitive function in multiple sclerosis
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Cognitive decline is found in 30 to 50 % of patients with multiple sclerosis (MS). The heterogeneous pattern of cognitive involvement is notoriously difficult to quantify, and conventional magnetic resonance (MR-) scanning shows only a very modest correlation with the patient's cognitive status. Functional neuroimaging (fMRI) has been of limited use for the assessment of cognitive deficits in MS. This is due to the fact that recent and current cognitive fMRI studies are focusing on paradigms that try to isolate single cognitive processes which may be sensitive for cognitive impairment but do not always account for the overall cognitive status in a single MS patient. We developed an fMRI-paradigm suitable to study the "global" cognitive status of MS-patients.

The task addresses: visual search, working memory and mental arithmetic. The paradigm takes about 30 minutes to perform within the scanner. Participants included 10 individuals diagnosed with definite relapsing-remitting MS with an Extended Disability Status Scale- (EDSS-) range from 0 to 4 points, and 10 healthy controls matched for age and education. Task: In any given run, specific target items (e. g. blue triangles) are defined. The subjects has to (a) determine the number of target items in a display, (b) keep this number in working memory, (c) signal by button press, whether the next display has fewer or more target items, (d) add up the number of target items for the entire run.

Brain activations in control subjects included areas known to be involved in visual attention, working memory, and motor preparation. The activations in the MS-group were more broadly distributed.

The global stimulation paradigm revealed more widespread activation in the group of the MS-patients compared to controls, indicative of cortical reorganisation similar to the one seen in deafferentiation.

In it's current implementation the "global stimulation paradigm" is suitable for MS patients with mild to moderate symptoms and may provide a first step towards a new method of examining cognitive functioning of MS-Patients.

P688
Individual risk profile for multiple sclerosis patients – usefulness for clinical decision making
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Background: The Sylvia Lawry Centre for MS Research (www.slcmsr.org) is an international research Centre which has collected a large set of data from clinical trials and academic research centres – containing detailed information about the evolution of the disease of more than 14,000 patients, overall more than 75,000 patient years.

Aim: The Centre aims at developing methods which will help to bring better treatment options to MS patients earlier than now by using innovative combinations of mathematics, computer science and medicine.

Idea: One important way to use the Centre's database is to make it available to health care professionals via the internet by developing tailor-made "online analystical processing" tools. This can help e. g. physicians and their patients to make evidence based decisions about when to start with which treatment.

Status: A prototype of an OLAP-tool using SAS/INTRNET was developed in close co-operation with the medical experts associated with the Centre using data from placebo patients from clinical trials. Users can choose the most important variables, which influence the future course of the disease. Examples are the number of relapses in the last 1–2 years, duration of the disease, age at onset, the actual level of disability measured by EDSS and the disease course – either relapsing remitting, secondary progressive, primary progresive or CIS. Once a selection has been made the user can see via internet how the disease evolved in untreated patients in the database with matching characteristics. At the moment we are collecting information about the usefulness of this tool for clinical decision making. The inclusion of information about MRI baseline variables and from treated patients is planned for the future.

Acknowledgement: The SLC would like to thank all its data donors. A complete list can be found at www.slcmsr.org/en/partners. We thank Prof. G. Edan for his suggestions.

P689
GLANCE: A double-blind, randomised, placebo-controlled, parallel-group safety study of natalizumab (Antegren) in combination with glatiramer acetate (Copaxone) in subjects with relapsing-remitting multiple sclerosis
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Background: Natalizumab is a humanized monoclonal antibody with specificity for alpha-4 integrin (VLA-4). Binding of this adhesion molecule on the surface of activated lymphocytes interferes with cell trafficking across the blood-brain barrier. A preliminary study of 6 monthly intravenous infusions of natalizumab in relapsing multiple sclerosis (MS) demonstrated significant reduction in the frequency of clinical relapses and gadolinium-enhancing MRI lesions. Pivotal trials of natalizumab therapy alone and in combination with interferon beta-1a are in progress. However, there are no data about the combination of natalizumab and glatiramer acetate (GA).

Objectives: The primary objective is to determine whether adding natalizumab to the standard regimen of GA, when compared to placebo, is safe. The secondary objectives include evaluation of tolerability and the pharmacokinetics of natalizumab in the presence of GA.

Methods: The trial is a double-blind, randomized, placebo-controlled, parallel-group design of 110 subjects with relapsing-remitting MS. Subjects receive 300 mg of natalizumab or placebo, by IV infusion, every 4 weeks in addition to 20 mg of GA by daily SC injection, for up to 20 weeks. Inclusion criteria are a definite diagnosis of MS (by McDonald criteria); age between 18 and 55 years; baseline EDSS between 0.0 and 5.0; treatment with GA for at least the 12 months prior to randomization; at least 1 relapse during the 12 months prior to randomization. The primary endpoint is the number of new active lesions determined on 6 monthly cranial MRI scans compared to the baseline scan. MRI measures include Gd-enhancing, T2,

and T1 lesions. Clinical safety assessments include EDSS, relapses, and adverse events. Pharmacokinetic parameters include: Tmax, Cmax, AUC(0-last), Cl, AUC(0-infinity), Cmin, Ctrough. Samples for alpha 4-integrin saturation and antibodies against natalizumab are being collected.

Results: To date, 110 subjects (83 % female; mean age 41 ± 8 years) have been randomized. At entry, the median time since diagnosis was 5 years; median EDSS was 2.5; 65 % had only 1 relapse in the year prior; and the mean number of enhancing MRI lesions at baseline was 0.6 ± 1.5 (range 0 to 11, median 0). The final number of completed or withdrawn subjects will be presented.

Conclusions: This is the first study designed to evaluate natalizumab and GA combination therapy in MS. It will generate important safety, tolerability, and pharmacokinetics data.

P690

A novel network of human B cell effector cytokines is disregulated in multiple sclerosis

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There is growing interest in the fundamental roles that B cells may play in regulating immune responses. Emerging animal studies point to an important contribution of B cell effector cytokines to immune-modulation. We report that the profile of human B cell cytokine production is context dependent, being critically influenced by the balance of signals through the B cell receptor and CD40. B cells appropriately stimulated by sequential B cell receptor and CD40 stimulation proliferate and secrete tumour necrosis factor-a (TNFa) and lymphotoxin (LT) which contribute to germinal center reaction and thereby amplify the ongoing immune response. In contrast, CD40 stimulation alone – a mimic of a B cell receiving bystander T cell help in the absence of specific antigen recognition – induces negligible pro-inflammatory cytokines ($n = 15$; $p < 0.0002$) but significant production of IL-10 ($n = 15$; $p < 0.004$) that serves to suppress inappropriate immune responses. We further observed that this novel network of reciprocal regulation of B cell effector cytokines, is abnormal in patients with relapsing remitting multiple sclerosis where B cells maintain their capacity to produce the proinflammatory cytokines TNFa and LT ($n = 8$; $p = 0.46$ compared to normals), but have a significantly diminished capacity to produce IL-10 ($n = 8$; $p < 0.02$). In summary, we ascribe active roles for human B cells in appropriately promoting or suppressing local immune responses in the normal state, and suggest that dysregulation of this B cell response profile is associated with the human autoimmune disease multiple sclerosis.

P691

Role of amyloid protein precursor in multiple sclerosis

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Introduction and objectives: There are many evidences about primary and early axonal injury in Multiple Sclerosis (MS). Using anti amyloid protein precursor (APP) antibody, the density of APP-positive axons in the margin of MS lesions is high showing axonal damage. We propose analyze presence of APP in cerebrospinal fluid (CSF) of MS patients.

Patients and methods: Retrospective study in CSF of MS patients in three consecutive years (2000–2002) to measure APP (ELISA method). We selected CSF controls of patients with no autoimmune or inflammatory disorders. We analyzed correlation with CSF parameters (IgG, Tourtellote and Reiber index, oligoclonal bands, and cell count) and clinical parameters at moment of lumbar puncture (LP) (age, type of MS, EDSS score, number of relapses, and time of evolution).

Results: We obtained 69 cases and 33 matched controls. There were no significant APP differences in two groups. In cases group there were no differences in APP levels and age, EDSS score, time of evolution, number of relapses, cell count and IgG index. We found a significant correlation in APP levels and Tourtellote an Reiber index (p 0.001, r –0.42 and p 0.001, r –0.39 respectively), and positive oligoclonal bands (p 0.046). There was no difference attending type of MS or moment of LP (relapse/no relapse and first/following relapse).

Conclusions: APP is not a diagnosis or prognosis marker in MS. There was a negative correlation in CSF immunological parameters with APP levels. Probably it shows two inmunopatogenic patterns of axonal injury (primary and demyelinating related) in early MS patients.

P692

Diffusion tensor variables and brain atrophy to predict clinical severity in multiple sclerosis patients

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Background: Clinico-radiologic correlation is usually weak in multiple sclerosis (MS) patients, which limits the usefulness of neuroimaging markers to monitor disease progression. This study aimed to assess the predictive value of various global and tissue-specific diffusion tensor variables and the brain parenchyma fraction (BPF) for two clinical severity scores.

Methods: Histogram-analysis was performed from mean diffusivity (MD) and fractional anisotropy (FA) maps of brain parenchyma, gray and white matter (GM, WM) in 45 patients with MS (35 relapsing-remitting, 10 secondary progressive) and 23 age- and gender matched healthy controls. Partial correlation and multiple regression analysis was performed against the expanded disability scale and the multiple sclerosis functional composite score (MSFC) for variables distinctly abnormal in MS.

Results: MS patients differed significantly from controls in most global and tissue-specific MD and FA histogram-metrics. Variance of global MD showed one of the largest effect sizes and was most strongly correlated with MSFC (partial correlation coefficient, controlled for age and gender: –0.74). Correlations with MSFC generally exceeded those with EDSS. Atrophy (BPF) was strongly correlated with the majority of diffusion quantities, moderately with clinical scores and accounted for about 16 % of the explained variance between MSFC and variance of global MD. Step-wise multiple regression analysis, however, showed no additive predictive power of BPF or FA-variables over variance of global MD.

Discussion: Variance of mean diffusivity histograms was the best predictor of clinical severity scores in this study sample of relapsing-remitting and secondary progressive MS patients. About 50 % of the variance of MSFC, a recommended integrated clinical outcome measure, was explained by this variable alone, and the model could not be improved by adding a brain atrophy measure or other MD or FA-metrics. Tissue heterogeneity may thus be a valuable neuroimaging marker to monitor disease progression in multiple sclerosis.

P693

Deep grey matter atrophy in patients with multiple sclerosis revealed by voxel based morphometry

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Background: in recent years changes in the grey matter of patients with multiple sclerosis (MS) gained increasingly attention. Atrophy of the cortical grey matter is well documented whereas little is known about changes of the deep grey matter. We applied the method of voxel-based morphometry to assess changes in the deep grey matter.

Method: we studied 26 individuals having a definite diagnosis of MS. 18 patients had a relapsing remitting course of the disease (RR-MS), 8 patients a secondary progressive course (SP-MS). 22 healthy persons with similar demographic parameters served as control population. We obtained 3d-T1 weighted images. The scans were normalized to a study-template and segmented using SPM99. A T-test was performed to detect areas with reduced grey matter volume (threshold t-score > 3). Group comparisons as well as single subject comparisons were performed. Flair-images were used to segment T2-lesions using the a semi-automated contour technique (DispImage-software, London).

Results: Group comparisons (study-population versus controls) showed a highly significant loss of deep grey matter in MS patients with the strongest effect located in the area of the putamen. Single subject comparisons for further characterization of patients with atrophy of atrophy in the basal ganglia revealed 14 of the 26 patients with highly significant circumscribed volume changes in the putamen. This patient group had significantly longer disease duration ($p < 0.05$) and a higher T2 lesion load ($p < 0.05$). Moreover a significant cortical atrophy ($p < 0.05$). In contrast there was no significant difference in the white matter volume between the groups. The disease type and disability had no significant effects on the distribution of the deep grey matter atrophy. Conclusion: Atrophy of the deep grey matter may take place concomitantly with changes of the cortical grey matter but seems to occur independently of the atrophy of the white matter.

P694

A computerised Stroop test may be useful for the evaluation of cognitive impairment in multiple sclerosis

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Objectives: The Stroop test is usually utilized for the neuropsychological assessment of frontal lobe functions, which are frequently involved in Multiple Sclerosis (MS). The aim of our study was to assess the usefulness of a computerized version of the Stroop test as an easy-to-do measure for the evaluation of cognitive impairment in patients with Multiple Sclerosis (MS).

Methods: Fourty patients with progressive MS (age 45.5 ± 11.4; 16 Primary Progressive – PP, 24 Secondary Progressive – SP; mean Expanded Disability Status Scale (EDSS) 4.9 + 1.4) and to 40 normal control subjects (age 49.6 ± 15.6) underwent a computerized version of the Stroop test. Colour names in a congruent or incongruent colour were randomly presented on a computer screen. Subjects had to respond by pressing a mouse button according to simple, go-no go and choice reaction times (RT) tasks. Patients also underwent the the paper version of the Stroop color/word interference test, and the Rao's brief repeatable battery of neuropsychological tests (BRB-N) assessing verbal and spatial memory, sustained attention, information processing speed, and verbal fluency.

Results: According to a failure on more than 2 tests at the BRB-N, we identified 21 cognitively impaired patients (7 PP, 14 SP), whose EDSS was not significantly different from the unimpaired MS patients. Cognitively impaired patients showed significantly delayed RTs in all tasks, with a greater extent in the go-no go and choice tasks, and committed more errors in the go-no go and choice tasks compared both with unimpaired MS patients and with normal subjects ($p < 0.04$; Student's t-test). No significant differences were found comparing unimpaired MS patients and normal subjects or between PP and SP MS patients. Finally, no significant difference at the computerized Stroop test was found between MS patients who failed in the paper Stroop color/word interference test (5 SP, 2PP) who were equally distributed among the cognitively impaired and unimpaired groups, as assessed by the BRB-N.

Conclusions: Our finding of abnormal performance in the computerized Stroop test in patients impaired at the BRB-N suggest the possible usefulness of this method in the assessment of cognitive function in MS patients. The discrepancy in our findings between results at the computerized and the paper versions of the Stroop test suggests that these versions may involve different aspects of cognitive processing.

P695

Epilepsy in multiple sclerosis

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Introduction: Epilepsy and multiple sclerosis (MS) are frequent neurological disorders. Seizures are more frequent in MS than in the general population. Partial epilepsies with focal seizures often with atypical symptoms with or without secondary generalization are the usual pattern. A spectrum of paroxysmal symptoms can also be observed, which may be confused with epileptic seizures.

Aim: We studied patients with definite MS, who had seizures or epileptiform phenomena. Our aim was to investigate possible correlations of MS and epilepsy.

Patients-methods: 15 patients were studied (10 female, 5 male, mean age = 39.2 years, range = 20–58 years). There was a total of 21 EEGs in 15 patients. Emphasis was given to the following MRI features: atrophy, cortical and subcortical lesions and corpus calosum involvement. Form, disease duration, Kurzke scale at EEG time, treatment for MS were also recorded.

Results: Our 15 patients had focal motor seizures (1 patient), focal motor seizures with secondary generalization (3 patients), generalized tonic-clonic status epilepticus (1 patient), isolated auras (3), tonic spasms (2), paroxysmal paraesthesia (2), paroxysmal dysarthria (1), paroxysmal akinesia with altered perception (2).

EEG findings were: normal EEG (8/15), focal or both focal and diffuse theta and/or delta activity (6/15) and focal paroxysmal discharges (1 patient).

All MRIs had abnormal findings: atrophy (10/15), subcortical (12/15) and cortical (3/15) lesions and corpus calosum involvement (8 patients).

9 patients had relapsing-remitting (RR) MS with a mean Kurzke scale of 3, disease duration of 9 years and mean age 38.6 years. 6 patients had secondary- progressive MS (mean Kurzke = 7, disease duration = 18 years, mean age 42.6 years).

Patients with normal EEGs had epileptiform manifestations (7/8) mostly.

There were 3 patients with a seizure as the initial manifestation of MS, and all 3 had RR MS.

Conclusions: EEG was helpful in distinguishing epileptiform manifestations from true seizures. Repeated recordings may be necessary.

The 3 patients that had seizures at MS onset had all abnormal EEG and RR MS. This could imply that seizures could be pathogeneticaly related to relapses.

Larger studies are needed for definite conclusions to be drawn.

P696

Mitoxantrone: who to treat with which dosage and schedule?

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Background: The report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (TTAS-AAN) (Neurology 2003, 61:1332–1338) suggests to use mitoxantrone (MX) in rapidly deteriorating multiple sclerosis (MS) patients only. Relapsing-remitting (RR-MS) patients should be treated when experiencing frequent relapses with concomitant magnetic resonance imaging (MRI) activity, secondary progressive (SP-MS) patients only if deteriorating faster than expected (0.5 EDSS score/year). Gonsette, in a review article (J Neurol Sci 2003, 206:203–208) also suggests that indications should be refined, reserving MX to rapidly deteriorating patients refractory to current therapies.

Patients and methods: We report our experience with 29 consecutive patients (18 females) treated since 2001. There were 12 RR-MS, 14 SP-MS, and 3 rapidly progressing primary progressive relapsing (PR)-MS. Mean EDSS score was 4.5 ± 1.11 at –24, 5.12 ± 1.17 at T0 in RR-MS and 5.64 ± 1.48 at –24 and 6.62 ± 1.33 at T0 in SP-MS. Patients were treated initially with the FDA approved scheme (12 mg/sqm every 3 months). We subsequently decided, due to unsatisfactory early response, to modify the scheme to obtain earlier efficacy, especially in frequently relapsing patients: 8 mg/sqm once a month (mo) for 3 times, then 12 mg/sqm every 3 mo. for 8 extra times, from mo 5 on (cumulative dose = 120 mg/sqm). Methylprednisolone (MP, 1 g at every infusion of MX) was added to the scheme both to reduce nausea and neutropenia and to increase efficacy in most patients.

Results: 6 patients developed neutropenia (< 500 cells/cmm) and had to be treated with growth factors, subsequently reducing to 75 % (9 mg/sqm) the dosage of MX between mo 9 and 24. One RR-MS patient after dosage reduction had a severe relapse, we therefore decided to modify the dosing regimen as follows: 8 mg/sqm every mo for 3 mo, then 8 mg/sqm every 2 mo until mo 24 (14 courses, 112 mg/sqm cumulative dose). 8 patients (1 RR, 5 SP, 2 PR) did not show any efficacy during treatment. None of them had an active MR scan nor an increase in lesion load before treatment, despite rapid deterioration but the RR and 1 SP.

Conclusion: We believe that our experience, although on a small group of patients and in an open observational study, reinforces what suggested by Gonsette and the report of the TTAS-AAN. Further controlled studies are needed to perfection treatment regimens and choose the right candidates to treatment with MX.

P697

White matter tract injury and the multiple sclerosis functional composite score

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Background: MR measures of lesion load correlate weakly with clinical severity in multiple sclerosis (MS) patients, but may be enhanced by using diffusion tensor imaging (DTI) and MS functional composite score (MSFC). Voxel-based (VB) regression analysis based on lesion probability maps was shown to be useful to explore the functional importance of lesion location.

Goal: We combined the VB approach with the advantages offered by MSFC and DTI to study the interrelation between injured white matter (WM) tracts and functional impairment.

Methods: 36 MS patients (28 relapsing-remitting, 8 secondary progressive, 38.6 ± 9.3 years of age) underwent MSFC and DTI assessment (spin echo EPI, TR/TE = 4200/120 ms, 6 non-collinear directions [n = 3], b = 888 mm²/s and 2 b0-images, 24 slices, 1.875 × 1.875 × 3 mm, 1 mm gap). After brain extraction, affine and non-affine normalization of T2-weighted b0-images was done onto a standard T2-template using SPM99. Then the deformation field was used to transform FA maps that were subsequently smoothed (Gaussian 8 mm kernel). Regression analysis was performed for

EDSS, MSFC and subscores (timed 25 foot walk, 9 hole pegboard test [9HPT], paced serial addition test [PASAT]) using a cutoff of FA > 0.1 and age and gender as covariates. Maps were thresholded at an exploratory $p < 0.005$ (uncorrected) and at $p < 0.05$ corrected for multiple testing using the false detection rate.

Results: At the corrected level MSFC revealed substantially more areas of significant (positive) interrelation than EDSS (negative) with only partial overlap. The 9HPT was the only subscore revealing correlated FA clusters at the corrected level. The cluster pattern was largely symmetric for EDSS, but asymmetric for MSFC and 9HPT with an extended left frontal cluster including the arcuate fascicle. This region was not interrelated with EDSS even at the exploratory threshold, but was correlated with the PASAT subscore that also revealed clusters in the corpus callosum and right occipitoparietal WM.

Discussion: This preliminary study demonstrates that VB-FA analysis is well suited to probe for regions, which predominantly affect clinical and cognitive impairment in MS. A higher sensitivity compared with lesion probability maps can be assumed due to the known sensitivity to extralesional ultrastructural damage. Thus FA changes are in part related to Wallerian degeneration, which enhances the group-averaged detectability of affected pathways.

P698

Characterisation of CSF B cells and plasma cells in MS and infectious CNS diseases

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Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) with an as yet unknown aetiology. Although intrathecal IgG synthesis is a key feature of disease, little is known about B cells and plasma cells in the CSF of MS patients. Therefore, we compared the phenotype and kinetics of B cells and plasma cells in the CSF and blood of patients with MS and acute infectious CNS diseases. We performed serial 4-color flow cytometry of CSF and blood cells and nephelometry for immunoglobulins and albumin in patients with MS and acute spirochetal or viral meningitis.

Plasma cells and B cells were detected in the CSF of most patients with MS and acute infectious CNS diseases. CSF B cell and plasma cell numbers were independent from the distribution of these cells in the peripheral blood. CSF B cells expressed mostly an antigen-experienced memory phenotype (CD19++, CD27+). Plasma cells in CSF were characterized by the expression of CD138++, CD19+, HLA-DR++ und CD27++. In contrast to CSF, most B cells in blood were naive. Furthermore, plasma cells were only rarely observed.

Serial CSF analyses of patients with infectious diseases disclosed that plasma cells were only seen during the acute phase of infection and disappeared within few weeks when the disease-causing antigen was removed, whereas B cells were observed in CSF even months after remission of infection. In MS patients, however, plasma cells were observed at various time points during the course of disease with little change over time, accompanied by a stable intrathecal IgG synthesis.

Overall, our findings disclose a significant accumulation of B cells and plasma cells in CSF of patients with acute infection of the CNS and patients with multiple sclerosis. The continued intrathecal IgG-synthesis and the persistence of plasma cells in CSF of MS patients suggest an ongoing humoral immune response against antigens produced in the CNS.

P699

Dissecting the T-cell repertoire in CSF and blood suggests a dominant role of CD8+ T-cells in the pathogenesis of MS

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Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) characterized by inflammation, demyelination, and axonal damage. The immune system plays a central role in the disease process, although major target antigens are still largely unknown. Recent studies have been addressing the repertoire of T- and B cells demonstrating clonotypic accumulation of T cells and antigen matured B cells in the CNS of MS patients.

In this study, we systematically analysed the repertoire of T cells in the CSF and blood of patients with multiple sclerosis. We found clonotypic accumulation of T cells in the CSF of all 10 patients studied. Dissecting the entire T cell repertoire in CSF and blood of 2 patients at two time points revealed that clonal accumulation is much more frequently observed among CD8+ than CD4+ T cells. CSF clonotypes were not prevalent in the blood and blood clonotypes not found in the CSF. CD8+ T cell clonotypes persisted in the CSF although new clonotypes were recruited to the CSF during the course of disease.

Our study demonstrates a dissociation of the CSF and blood repertoire with the dominance of persistent CD8+ clonotypes in the CSF of MS patients. These data further support an important role of CD8+ T cells in the pathogenesis of disease.

P700

Neuropsychiatric symptomatology in multiple sclerosis

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Background and purpose: Dealing with neuropsychiatric symptoms in multiple sclerosis (MS) is part of clinical day life with MS patients. These symptoms do not appear in neurological examination but may have relevance in patient care. We looked for prevalence of neuropsychiatric symptomatology in our MS patients.

Materials and Methods: We observed 25 MS patients (16 women), at least 6 months after the clinical diagnosis. Age ranged between 23 and 50 years, with median of 38. The median scholarship was 4 years. We used a semi-structured questionnaire and the SCL-90 scale as a screening tool to search for psychopathological symptoms. Using items such as somatization, obsessive/compulsive, interpersonal relations, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, eating disorders, sleep disorders, thoughts of death and guilty feelings. All patients were classified according to the EDSS scale and had at least one MRI. In this prospective and descriptive study was used the statistical programme SPSS 10.0 for Windows.

Results: Age of diagnosis varied between 16 and 44, with median of 34. EDSS mean was 4. Exclusively medullar demyelinating lesions were observed in 5 patients. Psychopharmacology was prescribed to 17 patients. From 25 MS patients, obsessive-compulsive symptomatology was significantly present in 18 (72 %) patients. Depressive symptomatology was observed in 15 (60 %) patients, paranoid ideation symptomatology in 7 (28 %), eating disorder symptoms in 15 (60 %) and 23 (92 %) patients presented sleeping disorders symptoms. Significantly death thoughts were observed in 10 (40 %) patients and significantly guilty feelings in 3 (12 %).

Discussion: The symptomatology observed in our MS patients includes obsessive/compulsive, depressive, paranoid ideation, eating and sleep disorders. Dealing with these symptoms, seems to be helpful in MS. A multi factorial approach might be an important step to a better and integrative care to these patients.

P701

Effect of exercise on fatigue level for multiple sclerosis patients

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Background: Fatigue is a prevalent symtom for Multiple Sclerosis (MS) patients. There is a difference between normal and MS patients for the symptoms of the fatigue. It can be seen with time getting on during the day, after minimal activity or feeling the fatigue continuously. Also, it can be seen, with loss of function with maximal effort. It can be increase with the increase of body temperature, drugs, intense activity, insomnia, spasticity, weakness and emotional stress. The aims of the study; is to investigate the alteration of the fatigue symptom with the exercises which prevents for the MS patients.

Methods: Thirty MS patients were included in this study. (23 F, 7 M). The mean of age were 40.23 ± 10.68 years. Expanded Disability Status Scale (EDSS) were 2–6.5 and they were stable. They participated in the exercise programs including flexibility, strengthening, balance, coordination, relaxation, ambulation, respiration three times weekly for 12 weeks. They were evaluated with Fatigue Severity Scale (FSS) before and after program. The score of the evaluation is between 1–7 points, for 9 different condition. Exercise programme evaluated for the effect of fatigue level, and the differences were identified. Data were analysed by SPSS Statistics Package, by means of paired samples t test.

Results: The value of FSS before exercises is 42.29 ± 7.01 and 32.28 ± 6.99 after exercises. There is a %22.36 difference. The results of FSS decreased after exercise and there is a statistically higher significance. ($p < 0.001$).

Conclusions: Regarding evaluations results, fatigue level will improve with exercises. Exercise programmes prepared specially for MS patients, applying with rest intervals; it can be decreasing fatique level and independence level may be increasing.

P702
Comparing different methods for the replacement of missing values in longitudinal magnetic resonance imaging datasets
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Background: In longitudinal multiple sclerosis (MS) trials, techniques for replacing missing values are used without thorough validation. In most studies the method of choice (if at all explicitely mentioned) was "last observation carried forward". The use of imputation methods provides larger datasets for sample size calculations, which can make these more exact and reliable. All analyses presented here are based on the placebo data form the pooled dataset of the Sylvia Lawry Centre for Multiple Sclerosis Research (SLCMSR) located in Munich, that currently includes data of 19,000 patients, 75,000 patient-years and with 27 MS trials that include magnetic resonance imaging (MRI) data.

Methods: Different methods for imputation have been compared. For that, missing values were generated at random in a complete dataset of 67 patients observed monthly for a period of 6 months. Each observation of each patient had the same probability to be chosen. The deleted values were replaced by 10 different methods and compared with the original data using the mean squared error and other measures of goodness of fit. As a next step, a group of 35 patients, each with one missing observation was examined for the proposal of being "missing at random" (i. e. missing independently of the value itself and of the value of any covariate).

Results: Imputing the mean of the neighbouring observations of a missing value was found to be the most valuable method. The values of the 35 patients mentioned above seem to be "missing completely at random", in the way Simonoff (1988) and Toutenburg (1998) have indicated. For that reason these observations could be merged with the 67 complete patients to a larger dataset of 102 patients with up to one missing observation per patient.

Conclusion: Future sample size calculations (Sormani et al. 2001) can be based on larger datasets with replacement done by the indicated method and even higher numbers due to the expansion of the SLCMSR database. It could also be thought of using this method for the replacement of missing values in clinical trials to enlargen the placebo group conform to the specific study protocol.

References

1. Simonoff J (1988) Technometrics, Vol. 30, No. 2:205–214
2. Sormani MP, et al. (2001) JNNP 70:494–499
3. Toutenburg H (1998) Quality Engineering. Prentice and Hall, Munich

P703
FTY720: a novel immunomodulator under clinical investigation in multiple sclerosis
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FTY720 is a sphingosine-1 phosphate receptor (S1P) agonist. Upon in vivo phosphorylation, it engages G protein-coupled receptors S1P1,3–5 and induces a reversible redistribution of T and B cells from the blood and spleen to peripheral lymph nodes. Subsequently FTY720 prevents the migration of lymphocytes from secondary lymphoid organs to target tissues. Based on convincing efficacy in preclinical models of allograft rejection, an advanced clinical development program in renal allograft recipients is ongoing. FTY720 also is active in autoimmune disease models, including experimental autoimmune encephalomyelitis (EAE). Two week oral therapy with < 0.3 mg/kg completely prevents EAE onset in Lewis rats when dosing starts on day of immunization. In a therapeutic regimen FTY720 rapidly suppresses established disease in DA rats immunized with syngeneic neuroantigen, providing sustained protection after drug cessation compared to chronic symptoms in vehicle-treated animals.

An international, multicenter, double-blind study is conducted to evaluate efficacy, safety and tolerability in relapsing-remitting and secondary-progressive multiple sclerosis patients. The effect of two different doses of FTY720 on the total number of gadolinium (gd)-enhancing lesions in monthly MRI scans will be compared to placebo during a 6 month treatment period. Secondary endpoints include relapse rate, the Multiple Sclerosis Functional Composite (MFSC) and the Expanded Disability Status Scale (EDSS) as well as quality of life and neuropsychological tests. Until spring 2004 a total of 240 patients will be randomized at 30 participating clinical centers in 11 countries. Patients receive once daily oral doses of 1.25 mg or 5 mg FTY720 or placebo.

FTY720 indicates potential to become one of the first orally administered immunomodulators with disease-modifying activity for multiple sclerosis patients.

Motor neuron disease

P704
Seroconversion to the GM1 antigen in patients with amyotrophic lateral sclerosis
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Objectives: To report on patients with motor neuron disease (MND) who developed antibodies against GM1 antigen during the course of their disease and following disease onset.

Background: Serum monoclonal IgM abs directed against gangliosides, such as GM1 and GD1b are occasionally present in patients with MND and motor neuropathies. Their role in disease pathogenesis is unknown, but in some of these patients, immuno-modulating therapies led to clinical improvement.

Materials and Methods: We retrospectively studied all files of amyotrophic lateral sclerosis (ALS) patients hospitalized in our institute within the years 1989 to 2003 for the presence of examinations of anti GM1 abs. Anti-GM1 antibodies were measured by ELISA.

Results: Three patients who had initial negative anti-GM1 abs and a positive follow up study were identified. Two patients died after one year follow-up. Only one patient was treated with plasmapharesis, with no apparent impact upon disease course.

Discussion: These three anecdotal cases raise several questions that only a prospective study might enable to examine their significance and eventually pave the way to more active immuno-modulating therapy in ALS: i) what is the incidence of anti-GM1 seroconversion in ALS patients? ii) Do these antibodies contribute to the damage to the nervous system? iii) Are they present at levels below detection at disease onset and therefore might cause the disease or whether are they the outcome of motor neuron damage with exposure of autoantigen to the immune system? iv) Are there additional antigens eliciting an immune response during ALS course?

P705
Disease stage related evaluation of Tau protein concentration in cerebrospinal fluid from patients with amyotrophic lateral sclerosis
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Background and Goal: The disease course of amyotrophic lateral sclerosis (ALS) is heterogenous, and at clinical onset it may be difficult to predict. A biological marker reflecting the neurodegenerative process would be of major relevance. Total tau protein (tau) in cerebrospinal fluid (CSF) is an established surrogate marker for neuronal damage of the central nervous system. So far its relevance has not been evaluated neither in patients with definite nor with suspected ALS.

Methods und Results: Total tau was studied in CSF samples from 84 patients (sporadic definite/probable ALS: n = 46; possible ALS: n = 8; only lower motoneuron (LMN) signs: n = 30). In definite/probable ALS, tau was found to be increased in 54 % of the patients (up to 5-fold of age-related upper normal values). If plotted against disease duration, tau concentrations were highest at early disease stages. In patients with a disease duration of less than 12 months mean tau levels were 280 ng/L for patients under 60 years and 456 ng/L for those above 60 years of age (reference ranges: 74–196 ng/L [< 60 y]; 87–291 ng/L [> 60 y]). In contrast, mean tau levels were normal in CSF of patients with a disease duration more than 3 years. In patients with isolated LMN signs, tau levels were elevated in 66 % up to 3.5-fold of upper reference values. In 13 cases of the LMN group the clinical diagnosis was re-evaluated after 24 months. The diagnosis was then converted in 12 patients into 4 possible, 6 probable, and 2 definite ALS cases based on additional clinical signs of upper motoneurons. Interestingly, 11 out of these patients with changed diagnosis have had elevated CSF tau levels initially (< 60 y: mean tau 241 ng/L; > 60 y: 514 ng/L).

Conclusions: 1. Tau protein is elevated in CSF of ALS patients especially in early stages of the disease. Considering the individually different disease courses our data suggest tau concentration changes related to disease stage. The dynamic of tau concentration may reflect the activity of the neuronal degeneration in regions adjacent to the CSF compartment. 2. In pa-

tients with clinical isolated LMN signs the determination of CSF tau may be relevant for the early detection of any subclinical involvement of upper motoneurons. Further prospective analysis will reveal whether tau levels at early stages of the disease are of prognostic and, in cases of suspected ALS, of diagnostic relevance.

P706
Impaired spontaneous autonomic neural control of heart rate in amyotrophic lateral sclerosis: new evidence
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Although autonomic disturbances are not considered to be a frequent clinical feature in patients affected by Amyotrophic Laterals Sclerosis (ALS), several studies revealed subtle abnormalities in the autonomic function of ALS patients. Data on this issue are not unequivocal and mostly based on traditional laboratory methods. To further examine the autonomic neural regulation of the cardiovascular system in ALS patients through modern techniques based on computer analysis of spontaneous blood pressure (BP) and pulse interval (PI, reciprocal of heart rate) variability.

Patients and Methods: 12 non-respirator-dependent ALS patients (mean age 47.1±10.6), BP (Finapres device), ECG and respiratory activity (Respitrace, inductance method) were continuously recorded for 30 min in supine position and for 15 min while standing. None had other diseases or took medications interfering with the autonomic functions. 7age-matched control subjects (mean age 46.4±11.0) underwent the same experimental protocol. In each subject, separately for supine and upright posture, we computed mean Systolic (S) BP and PI values, their standard deviation (SD) as an index of overall variability, and their spectral powers in the low and High frequency regions. Sensitivity of arterial baroreflex control of PI (BRS) was assessed as the slope of the regression line fitting SBP and PI values included in sequences of 3 or more consecutive heart beats characterised by either progressive increases (+PI/+SBP) or by progressive reductions (–PI/–SBP) in SBP and PI.

Results: ALS patients had similar SBP but lower PI than controls both in supine and standing position. Overall PI variability and PI LF spectral powers were similar between groups in supine position, but lower in ALS while standing. BRS (for –PI/–SBP sequences) was impaired in ALS vs controls both while supine and standing.

Conclusions: Our study provides for the first time evidence of an alteration in the spontaneous autonomic regulation of the heart in ALS patients, consisting in reduced parasympathetic and enhanced sympathetic tone (lower PI) and by a reduced reflex modulation of heart rate(lower PI SD and LF powers in upright position and blunted BRS for baroreceptor deactivation). The diagnostic, prognostic, and therapeutic implications of these findings deserve to be addressed in future studies.

P707
Marked down-regulation of metabotropic glutamate receptor 2 (mGluR2) mRNA in peripheral blood cells of Amyotrophic Lateral Sclerosis (ALS) patients
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A long line of evidence suggests that glutamate excitotoxicity plays an important role in the pathogenesis of sporadic ALS. Although excitotoxic neuronal death mainly involves ionotropic glutamate receptors, mGluRs appear also to be implicated in the selective vulnerability of motor neurons that characterizes the disease. Abnormal expression patterns for specific mGluR subtypes, have been reported in spinal motor neurons of ALS patients. Our group has demonstrated that peripheral blood cells under normal conditions, express several mGluR subtypes. In the present study we investigated the expression patterns of mGluR mRNA in peripheral blood cells of sporadic ALS patients.

Whole blood from 6 patients meeting the El Escorial criteria for clinically definite ALS and 30 control individuals with other neurological disorders were enrolled in the study. The expression of the mGluR subtype gene products was investigated by PCR, using specific primers for mGluR1, 2, 3 and 8. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA expression was used as reference.

Peripheral blood cells from control subjects were found to express mRNA of mGluR1a, mGluR2, mGluR3 and mGluR8 subtypes. The levels of their expression were normalized to the expression levels of GAPDH by densitometry and were found to be 0.56249, 0.88089, 0.97339 and 0.38753 respectively. Interestingly in all 6 patients with ALS, the levels of mGluR2 mRNA were below the detection limits of our method, suggesting a dramatic decrease in the expression of this receptor subtype in these patients. Expression of all other subtypes of mGluR was similar to controls.

Our results suggest that mGluR2 of blood cells are dramatically down-regulated in sporadic ALS. Given that the low expression of these receptors has been also found in spinal ventral horn neurons of ALS patients, peripheral blood may constitute a reliable marker of the glutamatergic dysfunction that characterizes this disorder.

P708
Decreasing amyotrophic lateral sclerosis mortality: results from 1990 through 2003
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Objective: International epidemiological studies on amyotrophic lateral sclerosis (ALS) show constant incidence and prevalence rates varying from 0.2 to 3.9 and from 0.8 to 8.5/100,000 respectively. Mean reported duration of ALS ranges from 20 to 42 months, with neither survival nor time to diagnosis being changing significantly over time. Accurate information on ALS mortality and survival are useful to the patients and their families, and may help the physicians in the management of the disease.

Materials and methods: Using data from our local ALS Register, we conducted a retrospective and prospective study of all ALS cases diagnosed in the province of Modena over a fourteen year period (from 1990 through 2003) to evaluate the effectiveness of a multidisciplinary clinic (active from 1999) on ALS survival. Results: During the period considered, 201 residents (98 men, 103 women) entered the study. The average annual incidence was 2.1/100,000, with a peak in the age class of 75 to 79 years. Mean prevalence rate was 4.5/100,000, and mean mortality rate was 1.7/100,000. The prevalence rates increased from 2.17 in 1989 to 7.2 in 2003, whereas mortality showed a decrease during the last years of the study to a minimum rate of 0.7/100,000 in 2003. ALS mean duration progressively increased from 17.38 months in 1990, through the years, with a maximum of 52.38 months in 2001. Seven out of 201 patients (3.48 %) underwent to invasive ventilation and 25 (12.44 %) to percutaneous endoscopic gastrostomy (PEG).

Discussion: The increase in ALS prevalence and the decreased ALS mortality are explained by the longer course of disease. The increase in survival can be ascribed to the improvement in the patients care and to effective treatment of dysphagia, malnutrition (PEG), and respiratory failure. The data suggest that this management will enhance survival, particularly among bulbar patients. The great increase in ALS prevalence and survival underlines the impact of multidisciplinary management for MND diseases.

P709
Executive dysfunction in Amyotrophic Lateral Sclerosis (ALS) and Primary Lateral sclerosis (PLS): evidence from computerised Stroop test
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Objective: Amyotrophic Lateral Sclerosis (ALS) was initially considered to be restricted to motor neurons. Over the last years, subtle cognitive deficits have been noted in non-demented patients with ALS, namely milder cognitive dysfunction is reported to be as high as 35 % of patients particularly related to frontal executive functions. In Primary Lateral sclerosis (PLS) the studies concerning cognitive functions are scarce. The Stroop Test is widely used to assess frontal cognitive processes, such as selective attention and flexibility.The aim of this study was to investigate the involvement of executive functions in ALS and PLS using computerised measures of performance at the Stroop test.

Methods: Thirty-eight right-handed patients with ALS (mean age 57.5 ± 20 yrs), 13 patients with PLS (mean age 52 + 12 yrs) and 30 normal subjects (mean age 53 + 14 yrs) participated in the study. Stroop test reaction times (RTs) were evaluated using simple, choice and Go-No Go paradigms using a computerised system.

Results: ALS patients had slower RTs and made more errors in all tasks compared to normal subjects ($p < 0.03$) while in PLS patients only significant slowing of the reaction times in all tasks ($p < 0.04$) was observed.

Conclusions: Our findings using a computerized Stroop test confirm the involvement of frontal lobe function in ALS and suggest the need for future validation studies correlating clinical and neuropsychological features. The subtle abnormalities found in SLP suggest that this function is relatively spared in these patients.

P710
Brachial amyotrophic diplegia: a case with a long-term follow-up
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Background: Brachial amyotrophic diplegia (BAD) is a recently described syndrome characterized by severe bilateral amyotrophy and weakness confined in upper limbs for extended periods of time. In the original description of this rare syndrome (Katz et al. 1999), 10 patients were reported with a disease duration ranging from 3 to 11 years.

Objective: To describe a case of BAD syndrome with a disease duration of 23 years. The results of various investigations, including transcranial magnetic stimulation (TMS), are presented.

Case report: The patient is a 55-year old man who presented with bilateral upper extremity weakness. His symptoms had insidiously begun 23 years ago and had slowly progressed ever since. The weakness was initially localized in the proximal right upper limb but gradually spread distally as well as to the left upper extremity. On examination, cranial nerves were normal. There was profound weakness in his upper extremities, particularly in the proximal parts of them and significantly more severe in the right than the left. Both upper limbs were atrophic and tendon reflexes were absent in the right upper extremity and mildly reduced in the left. An EMG study showed evidence of a chronic and active neurogenic lesion primarily involving the upper extremity muscles representing C5-T1 myotomes. However, some milder findings, such as fasciculations were noted in thoracic paraspinals as well as in the lower extremities. Extensive laboratory studies including an MRI of the cervical spine, anti-GM1 and anti-asialo-GM1 antibodies, B-Hexosaminidase and DNA testing for mutations in survival motor neuron gene and for Kennedy's disease were normal. Finally, a TMS study revealed reduced corticomotor threshold in FDI muscles (32 ± 0.7 % vs 41.7 ± 8 % in controls, Welch's corrected t-test, $p < 0.001$) and severely reduced MEP amplitudes. All other TMS parameters in upper and lower limbs were normal.

Conclusion: The present case, notable for a disease duration of 23 years, confirms the benign prognosis of BAD syndrome. Although subclinical involvement of thoracic and lower limb motor neurons was revealed by EMG, clinically the disease was confined in the upper extremities. TMS failed to detect involvement of the pyramidal tracts but revealed reduced MEP amplitudes and corticomotor thresholds in both upper limbs. The possible pathogenetic mechanisms of this latter phenomenon are discussed.

P711
The contribution of the pharyngoesophageal pressure profile to the evaluation of dysphagia in Amyotrophic Lateral Sclerosis (ALS)
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Introduction: The incidence of dysphagia in amyotrophic lateral sclerosis (ALS) is estimated at 76 %, and most patients develop some oropharyngeal symptoms during the course of their illness. Dysphagia results in sub-optimal caloric and fluid intake, and may complicate declining respiratory function. Pharyngoesophageal spasm is thought to play a role in dysphagia, though historically the procedure of cricopharyngeal myotomy has been successful in a minority of cases only.

Objectives: To assess the contribution of upper esophageal pressures in the role of dysphagia in our ALS patients, and to compare standard techniques of dyspahgia assessment with the invasive technique of esophageal manometry.

Methods: 25 patients who fulfilled the criteria for definitive or probable ALS were prospectively followed over 3 years, and underwent serial assessment of dyspahgia using both videofluroscopy (VFES) and fibreoptic endoscopic evaluation of swallow (FEES). Upper (UES) and lower esophageal sphincter (LES) pressures were assessed using a Miu Scientific compressor, infuser and a 6 port esophageal catheter. Dysphagia was rated according to the dyspahgia outcome severity scale (DOSS) and the Penetration Aspiration Scale (PAS).

Results: Both the techniques of VFES and FEES, and the modes of assessment using DOSS and PAS showed good intra- and inter-rater reliability. Patients who demonstrated evidence of pharyngoesophageal spasm scored poorly on the PAS and DOSS scales. Normal/low pressures were however observed in patients with predominantly bulbar ALS, but who also demonstrated severe dysphagia on the DOSS and PAS scales.

Conclusions: Though useful as an indicator of those patients at risk of pharyngoesophageal spasm, esophageal manometry is an invasive procedure. Standard techniques of swallow assessment are generally better tolerated, and have proved accurate in determining those patients with significantly functional dysphagia

P712
Muscle hypertrophy in a postpolio syndrome
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Introduction Muscle hypertrophy is a rare finding in neurogenic damage, where muscle atrophy seems to be the rule. It has been occasionally reported in nerve injuries, polineurophaties, radiculopathies and postpolio syndrome. Complex repetitive discharges could play a role in muscle hypertrophy development. This hypothesis has been studied in cramps and fasciculations syndrome and in acquired neuromyotonia.

Case report: A 31 year-old woman suffered from cramps both at rest and with physical activity, and a progressive enlargement of the right calf over the last 2 years. A diagnoses of an acute poliomyelitis was done when she was 18 months old. Despite mild residual lower extremity atrophy, the patient was able to walk and run properly. Physical examination showed an asymmetrical enlargement of the right calf, 2 cm larger than the left one. Fasciculations were observed on the right hamstring, quadriceps and deltoid muscles. Weakness on her right leg was diminished. Tendon reflexes were abolished in lower limbs and the plantar responses were flexor. The complementary exams showed normal CK levels and ECO-Doppler test. An MRI demonstrated a homogeneous increase of the muscle bulk in the right calf, with normal fat. EMG revealed a reduced number of motor units under maximal voluntary effort. There were fibrillation potentials and fasciculations without myotonic discharges. Muscle biopsy showed chronic denervation and some slight change suggestive acute denervation. No pseudohypertrophy was found. Over the next eight years, the patient developed palmar hyperhidrosis, generalized fatigue, myalgia and mild weakness on her right arm, with progressive disability.

Discussion: Our patient has a post-polio syndrome: gradual weakness, muscle fatigue, myalgias and joint pain, 28 years after neurological and functional stability from an acute poliomyelitis. She developed hypertrophy on a previously atrophic muscle confirmed by biopsy and EMG studies. Interestingly, palmar hyperhidrosis has never been described previously in a postpolio syndrome. The exclusion of neuromyotonic discharges on EMG, lumbosacral radiculophaties on MRI, and pseudohyperthrophy on muscle biopsy, suggests the probably relationship between muscle hypertrophy and recurrent cramps and fasciculations. Hypertrophy would be the result of an overuse syndrome resulting in dysfunction of surviving motor units or may be secondary to the hyperactivity itself.

Immunology

P713
The features of myasthenia gravis with anti-MuSK antibodies
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The circulating antibodies to acetylcholine receptor (AChR) are found in up to 80 % of patients with myasthenia gravis (MG). The remaining 20 % of patients do not have these antibodies (seronegative myasthenia gravis; SNMG). Recent studies have shown that 40 %–50 % of patients with generalized SNMG have antibodies to muscle specific tyrosine kinase (MuSK).

We have assayed anti-MuSK antibodies in 25 patients with SNMG, 9 males and 16 females. In 9 SNMG patients (36 %), all of them females, anti-MuSK antibodies were positive. The age of onset of MuSK positive SNMG ranged from 23 to 50 years (mean 34.8), with 66.7 % of patients presenting under 40 years of age. Initial symptoms were ocular in three, bulbar in four, and generalized in the remaining two patients. At the peak of the disease, according to the Ossermans' classification, 8 patients had IIB and one patient with otherwise borderline titer of anti-MuSK antiobodies had IIA form of the disease. No patient had pure ocular MG. The severe atrophy of oropharingeal and facial muscles developed in 2 patients in the chronic phase of the disease. In two patients there was associated systemic lupus erythematosus (SLE). Decremental response on repetitive nerve stimulation (n.facialis-m.nasalis and/or n.axillaris-m.deltoideus) was registered in 5 patients (55.5 %), while SFEMG was positive in all of them. The effect of neostigmine or edrophonium was negative in 3 patients. Four patients (44.4 %) showed hypersensitive response to usual average daily doses of

pyridostigmine (180–240 mg) developing cholinergic overdose muscle signs. Thymectomy was performed in 7 patients. Thymus pathology revealed normal or atrophic thymus gland in 5, and thymic hyperplasia in 2 patients. In addition to thymectomy all patients were treated by early and aggressive immunosuppressive therapy. At the end of the follow-up period three of them achieved remission, one significantly improved, two had unchanged condition and one patient died. The remaining two nonthymectomized patients presented significant improvement. During the course of the disease four patients developed severe deterioration with respiratory insuficiency, three of them responding to plasma exchange.

Our results indicate that presence of anti-MuSK autoantibodies identifies a subtype of SNMG. Measurement of these antibodies will substantially aid diagnosis and clinical management.

P714

Diagnostic value of anti-GM1 ganglioside serology and validation of the INCAT-ELISA

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Background: Serum antibodies against GM1 ganglioside have been reported in a variety of neuropathies and other neurological and inflammatory diseases. The frequency of these antibodies in these diseases varies considerably, partly based on the ELISA methods used. For this reason a standardized ELISA was developed by the European Inflammatory Neuropathy Cause and Treatment (INCAT) group (HJ Willison, Eur. J. Neur. 1999). The clinical relevance of anti-GM1 antibodies in these diseases however has not been determined.

Aim of the study: Validation of the INCAT anti-GM1 ELISA using large groups of patients with different forms of neuropathy, other diseases and healthy controls.

Methods: Serum anti-GM1 IgM and IgG antibodies were determined by ELISA according to the INCAT protocol. We extensively studied the exact variation between wells, plates, assays and technicians. The frequencies of these antibodies were assessed in patients with Guillain-Barré syndrome (GBS), chronic demyelinating inflammatory polyneuropathy (CIDP), multifocal motor neuropathy (MMN), paraprotein polyneuropathy (PP-PNP), other forms of inflammatory polyneuropathy (I-PNP), non-inflammatory polyneuropathy (NI-PNP), motor neuron disease (MND), multiple sclerosis (MS), other forms of autoimmune diseases (AID) and healthy controls.

Results: The INCAT ELISA was highly reproducible over time. Frequencies of anti-GM1 antibodies found were 97 (21 %) of 462 patients with GBS, 2 (5 %) of 41 CIDP, 5 (50 %) of 10 MMN, 3 (3 %) of 100 PP-PNP, 6 (14 %) of 43 I-PNP, 2 (3 %) of 72 NI-PNP, 7 (9 %) of 78 MND, 0 (0 %) of 20 MS, 2 (2 %) of 133 AID and 3 (2 %) of 124 healthy controls. IgG anti-GM1 reactivity was found in 59 (13 %) GBS patients, one (2 %) I-PNP patient and one (1 %) NI-PNP patient whereas no IgG anti-GM1 antibodies were detected in CIDP, MMN, MND, PP-PNP, MS, AID and healthy controls. Anti-GM1 IgM antibodies were less specific for diagnostic subgroups. IgM anti-GM1 reactivity was found in 64 (14 %) patients with GBS, 5 (11 %) I-PNP, 2 (3 %) NI-PNP and in 3 (2 %) healthy controls. Further studies are currently being done in an extended group of neurological diseases.

Conclusion: This study shows that the INCAT-ELISA has a good reproducibility and that the presence of anti-GM1 IgG antibodies is almost specific for inflammatory neuropathies. Anti-GM1 IgM antibodies, however, are found ambiguously and are therefore of limited diagnostic value.

P715

TNF G-308A gene polymorphism and outcome in different subtypes of ischaemic stroke

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Background: TNF (tumor necrosis factor) is a proinflammatory cytokine that has been implicated in the course of ischemic stroke (IS). In most experimental and clinical investigations deleterious role of TNF in IS has been demonstrated. Results of some studies suggest the protective action of TNF during IS. It has been suggested that the incidence of lacunar stroke could result partially from genetically determined increased sensitivity to vascular damage resulted from inflammatory processes. So – it could be supposed that enhanced inflammation (associated with increased production of TNF) in those patients could also be associated with worse stroke prognosis. A high interindividual variation of TNF levels has been observed in humans and led to the classification of "high", "intermediate" and "low" responder phenotypes. It has been demonstrated that G-308A substitution in the promoter region of the TNF gene has a direct effect on TNF gene regulation and may be responsible for the association of TNFA with "high secretor" TNF phenotype.

AIM: To examine, whether the TNF G-308A polymorphism is associated with the clinical course of different subtypes of ischemic stroke (IS).

Methods: TNF genotypes were investigated by PCR-RFLP (polymerase chain reaction-restriction fragments length polymorphism) method in 199 patients with IS.

Results: Distribution of genotypes in a whole IS patients population was: G/G (70.99 %), G/A (27.10 %), A/A (1.9 %). The carriage of genotype G/A was associated with significantly better neurological and functional outcome measured using the Scandinavian Stroke Scale (SSS), Barthel Stroke Scale (BSS) and Rankin Scale (RS) at entry (SSS, $p = 0.04$; BSS, $p = 0.03$) and at discharge (BSS, $p = 0.04$; RS, $p = 0.02$) as compared with G/G genotype carriage. Similar tendency was observed in patients with large artery disease, cardioembolic stroke and stroke of unknown etiology. In patients with lacunar stroke reverse relationship was noticed: the carriage of G/A genotype was associated with worse neurological and functional outcome.

Conclusions: Results of our study suggest that genetic variation at the TNF locus in Polish stroke patients population is a genetic factor that influences the clinical course of the disease. An association between different TNF genotypes and functional and neurological deficits is different in patients with lacunar stroke as compared with the rest of stroke subtypes.

P716

Autoimmune agrypnia is due to autoantibody against GABAB receptor

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We have described the clinical feature of a woman 55 years old with several relapsing-remitting episodes of agrypnia and continuous 9–11 Hz activity pattern in prolonged EEG recording, dysautonomic symptoms and nocturnal respiratory failure. Plasma exchange and high-doses of corticosteroid treatment induced a remission of clinical symptoms and recovery of REM and NREM sleep. Immunohistochemestry showed, after incubation with patient's serum and CSF, an intense immunoreactivity over brainstem, hippocampus and cerebellum granular layer. Using Western Blotting analysis, purified patient IgG recognized a protein of approximately 108 KDa on mouse cerebellum, cortex and brainstem. Immunohistochemical analysis of patient purified IgG showed a binding on GABAergic synapse-rich neuronal cells. In particular the distribution of immunoreactivity was similar to that of GABAB receptor1, as evidenced by immunoperoxidase staining using anti GABABR1 antibody. Preincubation of mouse cerebellum sections with patient's purified IgG completely abolished the staining obtained with the anti-GABAB R1 antibody. To confirm the specificity of the immunoreactivity of patient purified IgG with GABABR1, we incubated living CHO cells expressing human GABABR1, with patient and healthy control purified antibody and with goat polyclonal anti-GABABR1 antibody. A similar reactivity was shown by CHO incubated with patient purified IgG and with antiGABABR1 antibody, but was absent on CHO incubated with healthy subject purified IgG. To evaluate the pathogenicity of the antibodies present in the serum of our patient, her purified IgG, at different concentration, was injected into the cisterna magna of C57BL/6 mice, pre-implanted with two EEG electrodes. We observed, 12–20 hours after injection, a severe respiratory failure followed by death in the mice injected with high dose, a severe ataxia followed by breathing depression in mice injected with middle dose, and a progressive truncal ataxia in mice injected with low dose. These symptoms disappeared completely after 12 hours. The EEG analysis showed a strong reduction of delta EEG activity that started after 1 hour of IgG injection and persisted along 12–14 hours. The mice injected with IgG from healthy subject did not show any neurological symptom. Some mice was sacrificed at the peak of the symptoms and immunohistochemical analysis of the brain showed human IgG binding. Our study demonstrated that anti-GABABR1 antibody causes Autoimmune Agrypnia.

P717

Sex- and age-dependent differences in IL6 gene expression profile in murine model of Parkinson's disease

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Although the cause of Parkinson's disease (PD) remains unknown, there is increasing interest in the participation of neuroinflammation in nigrostriatal degeneration. The gender and advanced age are the important risks

factor for PD. The men developing PD about two times more than women. The reason for a sex bias in PD is unclear, but it is very likely that may relate to several factors that could include female sex hormone-related differences in immune response to neurodegenerative processes. One mechanism by which this sex hormone could modulated the immune reaction is regulation of the inflammatory molecules expression, such as cytokines. IL6 has been suggest to play a key role in regulating neuronal survival in the injured nigrostriatal system.

We investigated the possible sex- and age-related differences in the expression of IL6 gene in murine model of PD induced by 1-methyl-4-phenyl-1,2,3,6 tetrahydropiridine (MPTP). The level of IL6 mRNA was measured by RT-PCR in the striatum of male and female C57BL/6 mice (3 and 12 months old) after 6 h; 1, 3, 7, 14, 21 days post MPTP intoxication.

Administration of MPTP caused a marked increase of IL6 mRNA in striatum of young and aged male and female mice. In young male mice the IL6 mRNA increased at 1-day time point. After 7 days we still observed the elevated expression of IL-6 in young male mice. In aged male we noticed the gradually increased of IL6 gene expression from 3 day up to 14 days with the peak at the 7day after MPTP intoxication. In both young and aged female mice we observed the increased in IL6 gene expression at 1 day after MPTP injection. After 7 days the expression IL6 mRNA peaked in this time point and was continued at the increase level between 7 and 14 day post intoxication in young and aged female mice. We noticed that the increase in IL6 mRNA was higher in both aged male and female than in young male and female mice. Although the difference in IL6 gene expression between young and aged female was higher than observed in male mice.

We show evidence suggesting a gender skewing in the IL6 gene expression profile in striatum by MPTP intoxication. These observations suggest that the sex hormone may be responsible, in part, for the alter production of IL6 in female and male mice. Future research will define more clearly the influence of the sex hormones on neuroimmune processes observed in this disease and the role of inflammatory cytokines in gender differences in PD.

P718

Interferon beta reverts the effects of interferon gamma on endogenous catecholamines produced by blood mononuclear cells from multiple sclerosis patients

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Background: Endogenous catecholamines (CA) are synthesized by peripheral blood mononuclear cells (PBMCs) through tyrosine hydroxylase (TH)-dependent pathways and may play a role in the regulation of PHA-induced apoptosis. PBMCs from multiple sclerosis (MS) patients show altered content and production of CA and impaired expression of TH, possibly depending upon disease activity. Although several evidences point to a proapoptotic effect of IFN-beta, its mechanisms of action in MS remain obscure.

Aims: We assessed the effects of IFN-beta and IFN-gamma on endogenous CA production, TH expression and susceptibility to activation-induced apoptosis in PBMCs from 20 relapsing-remitting MS patients undergoing IFN-beta treatment, in comparison with 20 matched healthy subjects.

Methods: CA were measured in PHA-stimulated PBMCs by HPLC-ED and TH mRNA was assayed by RT-PCR. Annexin-V expression was evaluated by flow cytometry on PBMCs as a marker of apoptosis. Patients were observed at baseline and longitudinally during IFN-beta treatment.

Results: Both CA and TH mRNA increased in PBMCs during IFN-beta treatment. At opposite with healthy subjects, the percentage of apoptotic PBMCs did not decrease in MS patients after Dopamine stimulation. This finding was confirmed by experiments of pharmacological modulation with a selective inhibitor of TH (the limiting enzyme in CA synthesis).

In both healthy subjects and untreated MS patients, CA production was increased by IFN-beta and decreased by IFN-gamma, which also inhibited TH mRNA. IFN-beta partially reverted the effects of IFN-gamma. In treated patients, however, the ability of IFN-gamma to inhibit CA production was progressively reduced and the ability of IFN-beta added in vitro to antagonize IFN-gamma was consistently increased as treatment progressed. In healthy subjects, pharmacological inhibition of CA production significantly reduced apoptosis. This effect did not occur in MS patients, neither at baseline nor after 3 months of treatment.

Comment: IFN-beta and IFN-gamma seem to play opposite effects on endogenous CA production in PBMCs. Results from IFN-beta-treated MS patients suggest that such effects may be relevant even in the clinical setting. Further studies are warranted to assess possible differences in IFN modulation of CA production between responders and non-responders to treatment. The lack of a pharmacological modulation on endogenous CA on apoptosis in MS needs deeper careful assessment.

P719

Formation of antibodies against β-tubulin class III as a consequence of brain trauma

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The presence of antibodies against cytoskeletal proteins in serum, which indicate neuronal loss, have been frequently reported in patients suffering from neurodegenerative diseases such as Parkinson's disease, ALS or multiple sclerosis. However, the uncertainty concerning the onset and progression of these conditions has so far not allowed to gain much insight into the dynamics of an autoimmune response to cytoskeletal proteins of degraded neurones in the circulatory system. To remedy this state of affairs, we investigated the onset and the subsequent time course of an autoimmune response in 14 patients who had suffered brain trauma from various accidents and undergone MRI- or CT-investigations. Repeatedly, we measured the titre of IgG and IgM antibodies to β-tubulin class III (βtIII) in serum with ELISA microplates coated with an octapeptide whose amino-acid sequence matched the C-terminal sequence of βtIII. A transient autoimmune reaction to βtIII in the form of IgG antibodies appeared in 10 patients out of 14 within three weeks of a brain trauma. In a matter of days, the raised antibody titre returned to the baseline. Identifying a comparable response in the form of IgM antibodies was, however, more difficult. We detected IgM antibodies in the sera of only three patients. This unexpectedly low rate may reflect their short-lived nature and the somewhat lengthy periods (days rather than hours) between successive blood sampling. In conclusion, this study reports a trauma-related formation of antibodies to cytoskeletal proteins for the first time. We believe that the time-course pattern of the IgG titre can provide useful information for therapy and prognosis of patients after brain trauma.

P720

Chronic regional pain syndrome is associated with autoantibodies against autonomic nervous system structures

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Complex regional pain syndrome (CRPS) is a disorder including pain, vasomotor and trophic dysregulation as well as motor impairment; it follows often trauma or operation. Although a disturbance of the sympathetic nervous system has been described, the etiology of the syndrome is unclear. Using immunohistochemistry and Western Blot we tested the sera of 23 CRPS patients for the occurence of autoantibodies against autonomic nervous system structures. Using immunohistochemistry on gut nervous system and sympathetic ganglia, we found autoantibodies in 12 out of 23 patients. Eight patients showed IgG binding to gut nervous system and symapthetic ganglia, three patients had only sympathetic ganglia antibodies and one patient was exclusively positive on gut nervous system. Moreover 5 out of 23 patients had surface binding on dissociated sympathetic neurones, but not on a fibroblast control cell line in flow cytometry. We could not detect autonomic nervous system autoantibodies in 20 healthy controls or 20 patients with non-inflammatory neuropathies. We hypothesize that CRPS may result from an autoimmune process against the sympathetic nervous system.

P721

Association of intravenous immunoglobulins and corticosteroids may lead to thrombotic events

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Background: Intravenous immunoglobulins (IVIg) and corticosteroids, widely used in autoimmune disorders and neurologic diseases, are considered safe.

Goal: To aware about the potential risk of thrombotic events following IVIg combined with corticosteroids.

Method: 2 patients who experienced thrombotic events after such a therapy are reported.

Result: A 62 year-old woman was suffering from haemophagocytic

lymphohistiocytosis of unknown origin. Since IVIg (20 g/day for 3 days) were ineffective to improve her condition, oral route corticosteroids (1 mg/kg/day) was started. On the 5th day, she experienced left hemiplegia due to right cerebral infarction. Although she had vascular risk factors, we did not find out any atheromatous degeneration, neither cardiac dysfunction. A 38-year-old woman suffering from secondary progressive multiple sclerosis unresponsive to immunosuppresive drugs, was admitted for her 6th course of IVIg (45 g/day for 2 days). Since her condition recently worsened, we proposed to combine methylprednisolone (500 mg/day for 2 days), on each morning of the scheduled once a day 45 g IVIg. A left iliofemoral thrombosis occurred six days after the completion of this therapy. Although she was still ambulatory, weakness was more pronounced on her left lower limb. She also had an inflammatory syndrome which may have supported thrombosis.

Temporal association between thromboembolic events in these 2 cases and administered treatment suggest IVIg and/or corticosteroids to have promote a procoagulant condition, which in association with other risk factors, led to clinical features. Thrombotic events are rare, but have already been described following IVIg, such as stroke, myocardial infarction, deep vein thrombosis or pulmonary embolism. Several mechanisms have been suggested: rising platelet count, altered levels of clotting factors, contamination of IVIg by factor XI, antiphospholipid antibodies, or hyperviscosity. Corticosteroids have also been suspected in procoagulant state thanks to platelet activation, thrombus deposition, vasoconstriction, decrease of antiaggregant factors, inhibition of fibrinolysis.

Conclusion: Although IVIg and corticosteroids are widely used and usually safe, physicians should be aware of the potential thromboembolic risk of their association. IVIg and/or corticosteroids should promote a procoagulant state, which in association with other risk factors should lead to arterial or venous thrombotic events.

P722

A 45-year history of acquired neuromyotonia

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Background: The syndrome of acquired peripheral nerve hyperexcitability (PNH), or neuromyotonia, is characterised by spontaneous and persistent muscle fibre activity. This results in cramps, muscle stiffness and continuous rippling fasciculations or myokymia. Autoimmune PNH is associated with antibodies to voltage-gated potassium channels (VGKC) and evidence exists that the antibodies are pathogenic. Autoimmune PNH may occur in isolation, be associated with other autoimmune conditions or be a paraneoplastic phenomenon. Here we report a case of isolated autoimmune neuromyotonia in a patient with a long history of cramps and stiffness and two clear-cut exacerbations separated by 40 years.

Methods: We performed a detailed history and clinical examination. Anti-VGKC, acetylcholine receptor (AChR) and glutamic acid decarboxylase (GAD) antibodies were assayed and a full screen for other autoimmune conditions was performed. Nerve conduction studies and needle electromyography (EMG) were performed. Cerebrospinal fluid examination, magnetic resonance imaging of brain and spinal cord and computed tomography of chest were normal.

Results: A 66-year-old man gave a long history of a painful right lower limb. His symptoms began at the age of 21 with the development of painful spasms in the right foot over the course of a few days. His condition then remained static for over 40 years although pain and stiffness persisted in his right foot. At 64 years, his condition began to slowly deteriorate. He developed progressive cramps and spasms in both lower and upper limbs. Clinical examination revealed a stiff, painful right lower limb with a flexion contracture. In addition, there was stiffness of the left lower limb. He was severely debilitated and required crutches to mobilize. Continuous undulating movements were observed in the muscles of upper and lower limbs (see video). Anti-VGKC antibodies were positive (titre > 600) and EMG was consistent with neuromyotonia. An extensive autoimmune and paraneoplastic screen was negative. His symptoms improved with the use of anti-spasticity agents and carbamazepine.

Conclusions: This is, to our knowledge, one of the longest reported histories of symptomatic acquired PNH. The occurrence of two exacerbations separated by a 40-year period is unusual and may suggest the presence of a precipitating factor for antibody formation such as an infectious agent or other external event.

P723

Mechanisms of action of intravenous immunoglobulins in patients with relapsing-remitting multiple sclerosis

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Intravenous immunoglobulins (IVIG) have been used successfully in the treatment of patients with inflammatory diseases of the central nervous system including multiple sclerosis (MS). Recent studies suggested a modulation of T-cell responses is involved in the immunomodulatory activity of IVIG in MS. To further explain the significance of T cells, we studied gene expression profiles of peripheral T cells in patients with relapsing-remitting MS (RRMS). We asked the question whether IVIG alters the gene expression profile in peripheral T cells of RRMS patients with exacerbation. Furthermore, we wanted to know whether certain gene expression profiles correlate with the clinical outcome.

Patients to be included in the study had to meet the following criteria: clinically or laboratory-defined RRMS, Expanded Disability Status Scale between 0.5 and 5.5 and age between 18 and 55 years. All 10 patients received a 5-day course of 0.4 g/kg body weight Endobulin S/D (Baxter AG) per day.

Blood samples were taken immediately before the first dose of IVIG as well as 24 hours and 3 weeks after the last dose. Peripheral blood mononuclear cells (PBMC) were prepared within 60 minutes after blood sampling. T cells were positively selected from PBMC at 4°C using a mixture of non-stimulating anti-CD4 and anti-CD8 Dynabeads. T cells were immediately transferred into TRIzol and stored at –20°C until preparation of RNA samples. Five micrograms of total RNA were in vitro transcribed, labelled and hybridized to the Human U133 A Genechip (Affymetrix).

Data obtained from the processing of chips were analyzed with GCOS-Software (Affymetrix). All information about genes that showed either a ≥ 2-fold induction or a ≤ 2-fold reduction in expression levels in at least 50 % of all patients was imported to a clustering program for the identification of gene families that were modified in expression levels. So far, we have identified two groups of genes that are differentially regulated upon treatment with IVIG. One group of genes is up to 8-fold up-regulated 24 hours after the last dose and returns to base-line expression levels by 3 weeks after the last dose. The other group of genes is up to 8-fold down-regulated at 24 hours after the last dose and returns to base-line expression levels by 3 weeks after the last dose. The up and down regulation of expression levels of the genes of interest is currently being confirmed by Real Time PCR.

P724

Acute disseminated encephalomyelitis associated with Campylobacter jejuni infection and ganglioside antibodies GM 1 IgG

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Campylobacter jejuni infection has been related to the axonal forms of the Guillain-Barré syndrome associated with the presence of antiganglioside antibodies GM 1 IgG. Campylobacter jejuni infection has been also associated with Miller-Fisher syndrome and Bickerstaff encephalitis with the presence of antibodies GQ1b.

We present a patient who developed a clinical picture consisting of perineal and perianal loss of sensation, distended bladder, brisk deep tendon reflexes and neck stiffness a few days after suffering a flu-like syndrome. A lumbar puncture disclosed a clear cerebrospinal fluid with lymphomononuclear pleocytosis, and normal glucose and protein values. Lumbosacral magnetic resonance (MR) revealed a hyperintense lesion in the conus medullaris in the T2 images, which was enhanced in the T1 weighted images with gadolinium. Two days later the patient showed diplopia due to right VI cranial nerve palsy, oscillopsia due to vertical upbeat nystagmus, rotational vertigo, central type facial palsy, weakness in upper extremities and sensory loss with low thoracic level. Cranial and cervicodorsal MR showed hyperintense lesions in the dorsal pons and the dorsal spinal cord. A diagnosis of disseminated encephalomyelitis was done. A few days later, the patient showed achilleal and patellar hyporeflexia. An electromyogram disclosed sharp positive waves in muscles depending of lumbosacral roots but nerve conductions studies, including F and H waves, were normal. Bacteriological analyses were negative except for Campylobacter jejuni growing in a stool sample. Immunological studies were negative except for antiganglioside GM1 IgG antibodies (1/13.203, ELISA-INCAT-Biomed).The patient improved after six plasma exchange sessions and was discharged a month later with residual bladder symptoms which have endured after more than one year follow-up.

This case is clinically fully compatible with an acute disseminated en-

cephalomyelitis. The late development of lower limbs hyporreflexia suggested a concomitant peripheral nerve involvement but conduction studies ruled out a demyelinating neuropathy. This case enhances the clinical spectrum of Campylobacter jejuni infection and is the first case described of acute disseminated encephalomyelitis associated with Campylobacter jejuni infection and antiganglioside antibodies GM1 IgG.

P725
A case of subacute parasympathetic failure
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A 36-year old Italian woman was admitted for subacute presentation of bilateral unreactive mydriasis. Five days before admission she presented a mild flu-like disease treated with acetaminophen. Her clinical and pharmacological history was otherwise insignificant. In the first days after admission the generalised fatigue worsened, and xerostomia, xerophtalmia, anhydrosis, abdominal pain, partial urinary and bowel retention also appeared. Laboratory screening for botulism, porphyrias, auto-antibodies, circulating immune complexes, rheumatoid factor and cryoglobulins yielded normal results; C3 complement fraction was 88 mg/dL (normal, 90–180), and total IgE level was 293 kU/L (normal, below 100). Cerebrospinal fluid (CSF) analysis performed 2 months from onset only showed markedly elevated protein level (294 mg/dL) and no oligoclonal IgG bands by isoelectrofocusing. EMG showed normal sensory and motor conduction velocities and F-wave responses; the sympathetic skin response (SSR) showed non-specific abnormalities. Diagnostic tests for Sjögren's syndrome gave inconclusive results; a salivary gland biopsy did not show lymphocyte infiltrates. The conjunctival instillation of 2% pilocarpine induced transient bilateral miosis of few hours duration. A short trial of intravenous immunoglobulins was followed by a mild recovery of pupillary reactivity to light. At 6 months since the onset of symptoms the patient's sicca syndrome and the visual disturbances further improved, and she was able to restart a near-normal daily and working activity.

Literature reports indicate a symptom cohort similar to that observed by us in association to connective tissue disease and in particular with Sjögren's syndrome. Acute or subacute dysautonomic neuropathy as a cause of this condition has been proposed. While some data (SSR findings, elevated CSF protein) seem to sustain the neuropathic origin of the disturbance, the clinical appearance and the absence of any other sign of peripheral nervous system involvement (for example, sensory involvement)agree only partially with this hypothesis. Antimuscarinic receptor antibodies have been identified in primary Sjögren's syndrome; recent literature reports strongly point in favour of their role in determining the sicca symptoms in this disease.

P726
Susac's syndrome and the role of infectious agents. A case report
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A female patient, 33 years old was admitted to Neurology department complaining of recurrent hearing loss, headaches and visual disturbances. Her history begins 3 years before admission, when she had reduction of visual acuity of the left eye, lasted for 20 days and remitted after the administration of corticosteroids. 7 months before admission she had an attack of abnormal hearing of the left ear, bilateral retroocular pain and low grade fever. She was treated with corticosteroids and the symptoms improved gradually. One month later she readmitted for right ear hearing loss and she was given corticosteroids.

On recent clinical examination there were no signs from cranial nerves, pyramidal tracts and cerebellum, or any sensory deficits. A recent brain MRI scan revealed four small (less than 1 cm), supratentorial lesions in the subcortical white matter, non-enhanced after intravenous gadolinium. The lesions were not typical of Multiple Sclerosis and could be interpreted as possibly ischaemic. A brain MRI angiography was normal.

A complete blood test investigation for coagulation, serology and immunology was held. Serum IgG antibodies for HSV I, HSV II and EBV were found in quite remarkable titers. All other blood/serum investigation was normal.

The audiogram was abnormal with left vestibular-cochlear impairment. The CSF examination showed 20 cells and band of oligoclonal antibodies.

Fundoscopy examination of retina showed no specific findings. The visual evoked potentials (VEP) were marginally abnormal during the visual symptoms. After a 6-month period free of symptoms, when the patient was treated with intravenous immunoglobulin, a new VEP examination was within normal range and CSF examination showed no oligoclonal antibodies.

Discussion: Our patient had the triad of symptoms: headache, recurrent hearing loss and visual disturbances that are compatible with the Susac's syndrome, a rare situation often misdiagnosed for MS. There was evidence of microangiopathy of the brain. We have to consider of the possibility of the coexistence of several factors in the pathogenesis of Susac's syndrome and among them the role of infectious agents. Herpes simplex and Epstein-Barr viruses can trigger several immune reactions resulting in small vessels vasculitis causing microinfarcts in the brain inner ear and the retina.

P727
Functional metabotropic glutamate receptors are expressed on human T-lymphocytes
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Several neurotransmitters and neuropeptides are known to regulate immune functions through specific activation of their cognate receptors on human T-lymphocytes. Glutamate, the major excitatory neurotransmitter in the mammalian central nervous system has been found to affect T-lymphocyte proliferation, while conditions of abnormal glutamatergic neurotransmission such as AIDS and hepatic encephalopathy are associated with impaired immune responses. Here we report that individual members of group I, II, and III metabotropic glutamate receptors (mGluR) are expressed and functionally active on human T-lymphocytes.

Mononuclear cells were isolated from the peripheral blood of 10 healthy consenting individuals through ficoll gradient centrifugation and monocytes were depleted by adhesion. The expression of the mGluR subtype gene products in the remaining T-lymphocyte population was investigated by the use of reverse transcriptase polymerase chain reaction (RT-PCR). Whole-cell patch-clamp recordings were performed on single T-lymphocytes to assess the functional consequences of mGluR activation.

Semi-quantitative RT-PCR analysis on freshly isolated T-lymphocytes revealed the presence of mGLUR1a, mGLUR2, mGLUR3, and mGLUR8 mRNA transcripts. The levels of their expression compared to the glyceraldehyde 3-phosphate dehydrogenase house-keeping gene were 0.56249, 0.88089, 0.97339 and 0.38753 respectively. Application of the non-selective mGluR agonist trans-(1S-3R)-ACPD during whole-cell recordings, modulated the electrophysiological properties of Kv 1.3 potassium channels, i. e. the predominant channel type of human T-lymphocytes. Use of agonists that are specific for each mGluR group, showed that activation of group I receptors up-regulates active Kv 1.3 channels, while group II receptors suppress channel activity by increasing steady state inactivation.

Our results provide the first evidence that metabotropic glutamate receptors are present on human T-lymphocytes. Additionally we directly show that activation of these receptors can directly regulate T-lymphocyte functions through Kv 1.3 channel modulation, given that these channels play a key role in T-lymphocyte activation and proliferation.

Genetics

P728
Ataxia with oculomotor apraxia type 1 (AOA1) in southern Italy
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Ataxia with oculomotor apraxia type 1 (AOA1) is an autosomal recessive disorder characterized by early onset, cerebellar ataxia, oculomotor apraxia, and peripheral neuropathy sometimes associated with extrapyramidal signs and mental impaiment. The causative gene (APTX) spans seven exons and encodes for a protein called aprataxin probably involved in DNA-repair. It is the most frequent cause of autosomal recessive ataxia in Japan and second to Friedreich ataxia in Portugal.

Twenty-eight index cases were recruited from a series of 85 cerebellar ataxia patients from southern Italy with degenerative and progressive ataxias. The inclusion criteria were: sporadic or autosomal recessive progressive ataxia, clinical (decreased or absent ankle reflexes and decreased vibration sense) or neurophysiological signs of peripheral neuropathy and negative molecular test for Friedreich ataxia. The coding sequence of APTX gene was analyzed by denaturing high performance liquid chromatography (DHPLC). Direct sequencing was performed in patients with a DHPLC mutated profile.

We identified three patients with mutations in the APTX gene. The first showed a typical phenotype including early onset oculomotor apraxia and choreic movements getting worse during the course of the disease. He was a compound heterozygote for A198V and P206L, the latter being the second most frequent Japanese mutation. The second one had onset at 28, hypoalbuminemia, hypercholesterolemia and no oculomotor apraxia. The homozygous missense mutation P206L was found in this subject.

The third patient had onset at 25 years, oculomotor apraxia, limb fasciculation, increased CK serum levels. He had a milder course of the disease with no wheelchair use after sixteen years of disease.

A new homozygous missense mutation 603T - > A, which result in the substitution of glutammine for histidine at amino acid residue 201 (H201Q) was identified. MRI showed marked cerebellar atrophy in all patients.

In conclusion: 1) We describe a new mutation, which seems to be associate with a milder and atypical phenotype. The substitution of histidine with arginine at codon 201 has been already described suggesting a hot spot of mutations. 2) A Japanese mutation (P206L) has been identified in two Caucasian patients for the first time. 3) Late onset in two of our patient suggests that AOA1 should be considered in patients with onset not only before 25 years old.

P729

A new DDP1 gene mutation in a family with X-linked deafness-dystonia syndrome

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Background: Deafness-dystonia syndrome (DDS) is a rare X-linked recessive neurodegenerative disorder, characterised by early-onset progressive neurosensorial hearing loss and progressive dystonia. Cortical blindness, spasticity and psychiatric symptoms are often present. It is caused by mutations in the DDP1/TIMM8a gene, which encodes a protein involved in mitochondrial intermembrane transport. Up to now, seven mutations have been described in the coding region.

Objectives: To search for mutations in the DDP1 gene in a family with two members affected with DDS.

Patients and methods: Patient 1 is a 30-year-old man with generalised dystonia of focal onset at the age of 11, and bilateral deafness diagnosed at the age of 4. He presented generalised dystonia, postural tremor and instability. He poorly responded to multiple pharmacologic and surgical treatments. Patient 2 is a 29-year old man, cousin of patient 1, who presented with a milder dystonia and myoclonus at the age of 20, hypoacusia and behavioural disorders.

Causes of secondary dystonia were ruled out. A genetic analysis was performed in both patients and other members of the family. Mutational screening in the DDP1 gene was performed through PCR amplification of the two exons and DNA direct sequencing, as previously described.

Results: An intronic mutation was found in both patients, consisting of a C to A change in the position –23 in reference to the first nucleotide of exon 2. The mutation was present in both patients and their respective unaffected mothers. It was absent in healthy males of the family as well as in 90 healthy controls screened through HinFI restriction analysis.

Conclusion: Intronic DDP1 mutations can also cause X-linked DDS. The presence of the mutation in the affected subjects and its absence in non-affected supports a pathogenic role of this mutation. Intronic mutations can cause protein dysfunction due to abnormal RNA splicing, but further studies are needed to clarify the role of intronic mutations in this disorder.

P730

Chorea triggered by hyperglycaemia in a maternally inherited diabetes and deafness (MIDD) patient with the A3243G mutation of mitochondrial DNA and basal ganglia calcification

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Background and significance: The A3243G mutation of mitochondrial DNA is associated with a variety of neurological syndromes including MELAS and is also known to be the cause of maternally inherited diabetes and deafness (MIDD). The neuroradiological abnormalities associated with MIDD such as intracerebral calcification and diffuse atrophy have been increasingly recognized but the neurological manifestation has rarely been mentioned in MIDD. Here we present a case of MIDD with the A3243G mutation of mitochondrial DNA who manifested chorea concurrent with hyperglycemia.

Case: A 28 year old female patient presented with sudden onset choreiform movements of her left arm and face. She had not taken neuroleptics and had suffered from poor hearing and diabetes mellitus (DM) from her early twenties. Her 60 year old mother was also diagnosed with DM at 40 years of age and complained of hearing impairment from 51 years of age. They were short of stature and had had no seizures, migraine-like headaches, or stroke-like episodes. Brain MRI showed symmetrical calcifications of bilateral basal ganglia and an A to G transition at nucleotide position 3243 of the mitochondrial DNA purified from leukocytes was identified. Blood levels of lactate, calcium, and parathyroid hormone were all normal. Muscle biopsy was negative for mitochondrial myopathy in the patient. The patient had an elevated serum glucose level (481 mg/dl) on admission and correction of hyperglycemia with insulin therapy markedly diminished the involuntary movements within a few days. But the chorea was not completely abolished and persisted to the time of last follow-up, 6 months later.

Conclusion: We report a case of MIDD with the A3243G mutation of mitochondrial DNA who manifested chorea associated with hyperglycemia. Considering brain imaging and clinical course, subclinical dysfunction of basal ganglia combined with hyperglycemia may play a role in development of chorea in this patient.

P731

Interleukin 1 receptor antagonist gene polymorphism and cerebral haemorrhagic events in patients with traumatic brain injury

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Head trauma can induce various haemorrhagic events that determine patient's clinical presentation and outcome. Experimental studies have shown that interleukin-1 receptor antagonist (IL-1ra) is important in counteracting the locally injurious effects of interleukin-1beta in endothelial cells and containing and healing mechanical induced lesions within the vessel wall. Allele 2 of a VNTR polymorphism in intron 2 of the IL-1ra gene was associated with decreased production of icIL-1ra1 (intracellular isoform of IL-1ra) in endothelial cells and enhanced sIL-1ra protein (secreted isoform)

We report a prospective clinical study designed to test possible association between IL-1ra gene polymorphism and various cerebral haemorrhagic events after traumatic brain injury.

We studied a series of patients (females = 23 [15, 2 %]) admitted after head injury to a neurosurgical unit (n = 151; mean age ± SD = 38.0 ± 20.14). After neurological assessment of the severity of the initial injury computed tomography scanning was performed. Magnetic resonance imaging was carried out in selected cases where neurological status was not in concert with CT findings. Patients were stratified as having or not haemorrhagic contusions, haemorrhagic diffuse axonal injury, subarachnoid haemorrhage, sub-epidural haematoma, intracerebral, intraventricular haemorrhage and any hemorrhagic event when counting all subclasses together. IL-1ra genotypes were determined from blood samples by standard PCR/RFLP method. Allele and genotype frequencies were compared by ÷2 test.

The population was in H-W equilibrium. There was a statistically significant difference between allele 2 carriers and non-carriers in the occurrence of brain contusions ($p = 0.02$), subarachnoid haemorrhage ($p = 0.008$) whilst this did not happen in patients with other type of haemmorhagic events. The frequency of allele 2 carriers in patients with any hemorrhagic event was 49.6 % compared to 17.6 % in those without ($p = 0.001$).

Our data show for the first time a genetic association of IL-1RN*2 allele with post-traumatic haemorrhagic events. The differences between haemorrhagic subclasses may reflect diverse pathogenetic mechanisms. The brain haemorrhage after trauma may be the result of structural susceptibility of the vessel wall due to decreased endothelial icIL-1ra1 seen in allele 2 carriers. Further studies are needed to confirm this association and investigate possible pathogenetic mechanisms.

P732

ARSACS also in Spain: a new mutation

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Objective: To perform a clinical and genetic study of a Spanish family with spastic ataxia.

Background: A form of early onset autosomal recessive spastic ataxia

has been described with high prevalence in the Charlevoix-Saguenay area in Quebec (ARSACS). Features include ataxia, dysarthria, spasticity, nystagmus, retinal striation and absence of peripheral nerve sensory potentials. The gene responsible for ARSACS maps to chromosome 13q11. SACS gene encodes the sacsin protein and presents only one gigantic exon. Recently, one Tunisian and two Turkish families have been linked to ARSACS locus and mutation in SACS gene have been found in Italian, Tunisian and Japanese families.

Materials and methods: The family include two patients and two healthy sibs born from consanguineous parents. Neurological examination, neuroimaging, neurophysiological studies and linkage analysis to ARSACS locus were performed on the two patients. Since data from linkage analysis were consistent with linkage to ARSACS locus, screening for mutations in SACS gene was conducted.

Results: The two patients presented a progressive spastic ataxia since infancy. Gait is still possible with support. Dysarthria, gaze evoked nystagmus, atrophy of intrinsic foot and hand muscles, brisk reflexes in the lower limbs with bilateral ankle clonus were present. No patients showed cognitive impairment or sphincter dysfunction. Neurophysiological studies revealed axonal sensorimotor neuropathy and severe involvement of somatosensory evoked potentials. Brain MRI showed cerebellar atrophy. Sequencing of SACS gene revealed the presence of a novel homozygous missense mutation C7848T. The mutation resulted in the substitution of arginine for cysteine at amino acid residue 2556.

Conclusions: We report a new mutation in the SACS gene in a family with a typical phenotype. This is the first mutation detected in a Spanish family confirming the worldwide presence of this disease and the existence of several different mutations. The phenotype, similar to that of the previously described ARSACS patients, confirm a uniform clinical presentation of the disease.

P733

A novel mutation in the paraplegin gene in a family with autosomal recessive HSP

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Hereditary spastic paraplegias (HSPs) are neurodegenerative disorders characterized by slowly progressive weakness and spasticity of the lower limbs. The occurrence of additional features allows the differentiation in pure (pHSP) and complicated (cHSP) forms. 23 different loci have been associated with different forms of HSP but only ten genes have ben identified so far. Paraplegin, a nuclear encoded mitochondrial metalloprotease, is mutated in one form of autosomal recessive HSP named SPG7. Mutations in the paraplegin gene have thus far been reported only in four families. Here we describe a new family with HSP, carrying a novel mutation in SPG7 gene.

Methods:The patient is an Italian 66-year-old woman born from non consanguineous parents.

One sister and one brother, both albin, and the daughter of the proband, were evaluated. One sister died at the age of 69 yrs because of a melanoma. Mutation analysis was performed on SPG7 gene by direct sequencing.

Results: The proband started complaining of lower limb weakness at the age of 41 years. Over the next 12 years her mobility deteriorated with increasing stiffness. She can actually walk for less than 100 mts with an anterior trolley. The neurological examination shows mild bilateral ptosis, wasting of the small muscles of the hands, thinning of the tibialis anterior and intrinsic muscles of the feet. Muscle strength is reduced bilaterally in the hip flexors, knee flexors and ankle dorsiflexors. Knee jerks are bilaterally brisk, the ankle jerks were absent. Mild cerebellar signs are evident. IQ is borderline.

Histochemical studies on a muscle biopsy showed numerous ragged red fibers (RRF) while respiratory chain (RC) enzyme activities on muscle homogenate were normal

The brother, 70 years old, underwent lobectomy because of a lung tumor. His neurological examination shows only brisk ankles reflexes and mild tibialis anterior muscle weakness.

The sister, 68 years old, overweight, does not show any neurological sign.

The young daughter, 25 years old, refers muscle fatigue.

Mutation analysis performed on SPG7 gene reveals a new non-sense mutation within the second exon of the gene, in the proband and in the mildly affected brother.

Conclusions: This study expands the mutational spectrum of paraplegin gene. The newly identified mutation is associated with focal signs of mitochondrial dysfunction in the proband's skeletal muscle tissue, though generalised RC defects were not observed by enzymatic analysis.

P734

Generation of transmitochondrial cybrids from myoblasts: a simplified method without prior enucleation

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Background: Transmitochondrial cybrids are a valuable tool for studying pathogenic mitochondrial DNA (mtDNA) mutations. In 1989, King and Attardi described the repopulation of cells devoid of mtDNA, termed rho0 cells, with exogenous mitochondria from mechanically enucleated cells. Enucleation of the mtDNA donor cells as well as auxotrophy of rho0 cells for uridine and pyruvate and their resistance to 5-bromo-2'deoxyuridine (BrdU) assure that only transmitochondrial cybrids survive the following selection process. This technique has been adapted and optimized for various cell types; it may in future chemical enucleation replace the tedious process of mechanical enucleation. For myoblast cultures, however, enucleation may be unnecessary, because or their specific requirement of trophic factors in the medium.

Material and Methods: Rho0 cells were obtained from an osteosarcoma cell line (143B.TK-) by long-term growth in ethidium bromide and were fused with clonal myoblast cultures carrying mtDNA mutations. Selection medium lacked uridine and was supplemented with BrdU. Western blots were probed with a monoclonal mouse anti-human desmin and a fibroblast-specific antibody. Polymorphic microsatellite markers were used to identify the nuclear background. Heteroplasmy of the mtDNA mutation was quantified by restriction fragment length polymorphism (RFLP) analysis.

Results: Several cybrid clones were obtained, which exhibited the nuclear background specific to the recipient rho0 cells. Western blots excluded expression of myoblast- and fibroblast-specific proteins. RFLP analysis showed comparable heteroplasmy of mtDNA in cybrids and myoblasts.

Discussion: Pure cultures of functional transmitochondrial cybrids can be obtained by fusion of myoblasts and rho0 cells without prior enucleation. The cybrid cell-lines show the nuclear fingerprint of the recipient rho0 cell-lines and clones harbor the mutational heteroplasmy of the donor myoblasts. Donor myoblasts are removed from the culture, because they require supplementation of growth factors in the medium. BrdU treatment positively selects clones with the pure nuclear rho0 background because of their thymidine-kinase deficiency and therefore hybrids with both nuclei will decay. Rho0 cells without mtDNA complementation are negatively selected because of the auxotrophy for pyrimidines. In conclusion, this is a simplified method for generating transmitochondrial cybrids from myoblasts.

P735

A novel missense mutation of doublecortin in a Korean patient with subcortical band heterotopia

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The neuronal migration disorders – X-linked lissencephaly syndrome (XLIS) and subcortical band heterotopia (SBH), also called "double cortex" – have been linked to missense, nonsense, aberrant splicing, deletion, and insertion mutations in doublecortin (DCX) in families and sporadic cases. Most DCX mutations identified to date are located in two evolutionarily conserved domains. We performed mutation analysis of DCX in two Korean patients with SBH. The SBH patients had mild to moderate developmental delays, drug-resistant generalized seizures, and diffuse thick SBH upon brain MRI. Sequence analysis of the DCX coding region in Patient I revealed a c.386 C > T change in exon 3. The sequence variation results in a serine to leucine amino acid change at position 129 (S129L), which has not been found in other family members of Patient I or in a large panel of 120 control chromosomes. We report here a novel c.386 C > T mutation of DCX that is responsible for SBH.

P736

European integrated project on spinocerebellar ataxias (EUROSCA): pathogenesis, genetics, animal models and therapy

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Twenty two European groups from 9 countries with an excellent reputation of clinical, clinical-genetic and basic research on spinocerebellar

ataxias (SCA) have jointly formed an "Integrated project" to define the pathogenesis and to develop a treatment for patients suffering from this rare neurodegenerative diseases. This project has started January 2004 and will run till December 2008. EUROSCA is co-financed by the European Commission. To reach the above described goal, an international standard on the clinical evaluation in form of a "Core Assessment Program for Interventional Therapies of SCA" (CAPIT-SCA) will be developed based on clinical rating scales, structural imaging, and electrophysiology. The generation of the world largest collection of information on SCA, the European SCA Registry (EUROSCA-R), will ensure standardized data acquisition. This powerful tool will facilitate continuous recruitment of SCA patients throughout Europe for linkage analysis, identification of novel ataxia genes and natural history studies. The potential to include all larger European SCA families into linkage analysis will lead to the identification of new SCA loci and to the cloning of novel ataxia genes, respectively. Genotype-phenotype correlations will follow. Subsequently, for the first time such a combined effort will offer a systematic large-scale search for genetic modifier factors in SCA allowing a better comprehension of factors accounting for wide clinical variability with application for prognosis and to identify new potential targets (modifier genes). EUROSCA will also implement strong research projects to generate and characterize cellular and transgenic models, which will allow a more defined study of the pathogenesis and will serve as a tool for first therapeutic studies. Nine European research groups will be supported by five core facilities such as transgenic Drosophila work, Expression-Chip-Technology, Proteomics, yeast two hybrid technology, and monoclonal antibodies. Training programs will complement research efforts and clinical work. Information available at www.eurosca.org

General neurology

P737

Evaluation of clinical features and alterations of cortical excitability and motor pathways function in patients with spinocerebellar ataxias type 1 and type 2 in Poland

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Spinocerebellar ataxias type 1 (SCA1) and type 2 (SCA2) are neurodegenerative disorders of autosomal dominant inheritance caused by the expansion of CAG triplets. They are clinically manifested by gait and limbs ataxia, dysarthria, saccade slowing, sensory and motor axonal neuropathy and pyramidal signs.

Aim: Evaluation of differences in clinical features, motor cortex excitability, functional state of motor pathways and the atrophy of cerebellar and cervical spinal cord in magnetic resonance imaging (MRI) for the verification of SCA1 and SCA2 phenotypes in patients molecularly confirmed.

Severity of clinical status was assessed in 31 patients with SCA1 and 20 cases with SCA2 by the modified International Co-operative Ataxia Rating Scale. Transcranial magnetic stimulation (TMS) was used to assess cortical excitability threshold (CET), central motor conduction time (CMCT), and the amplitude of motor evoked potentials (MEPs) from hypothenar and extensor digitorum brevis. Electrical stimulation of ulnar and peroneal nerves was conducted for F wave estimation. MRI was performed to measure the atrophy of brain, cerebellum and cervical spinal cord. Age of patients with SCA1 (mean 43.7 ± 10.2) and SCA2 (mean 41.4 ± 14.1), and the duration of the disease 7.6 ± 3.8 and 9.2 ± 7.7 were not statistically different. The number of CAG repeats ranged: in SCA1 from 40 to 65, in SCA2 from 37 to 52 and correlated inversely with the age of the disease onset: r = –0.73, and r = –0.82. Ataxia Rating Scale was similar in both groups of patients and significantly correlated with the duration of the disease. Pyramidal signs were more frequent in the SCA1 group, while in 80 % of SCA2 patients the decreased muscle tone and reflexes were revealed. CET was elevated mainly in SCA1 patients (55 %) for upper and lower limbs, accompanied by MEPs amplitude decrease. In SCA2 group CET was increased only for the lower limbs (25 %). CMCT compared with controls was significantly prolonged in all tested SCA1 cases but two. In contrast, in SCA2 CMCT was prolonged only in 20 % of cases. MRI revealed more evident cerebellar and brain stem atrophy in 87 % SCA2 patients, while the shrinkage of cervical spinal cord in 65 % of SCA1 patients was observed.

The results provide further evidence for the involvement of the motor cortex and corticospinal tracts in SCA1 patients, and documented the phenotypic differences with SCA2.

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P738

Experimental allergic encephalomyelitis facilitates recovery following spinal cord injury

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Passive immunization with T-cells against Central Nervous System (CNS) – associated myelin antigens has recently been found to offer neuroprotection following CNS trauma, leading to the concept of protective autoimmunity. However, limited research exists about whether actively induced CNS autoimmunity may offer any similar benefit. In this study, the kinetics and the effect of endogenously anti-myelin activated T-cells that invade CNS following spinal cord injury (SCI), were investigated. Experimental Allergic Encephalomyelitis (EAE) was actively induced in Lewis rats following immunization with Myelin Basic Protein (MBP). In vivo BrdU incorporation from activated T-cells was used as a marker. BrdU was injected on days 5.6,7 post-induction (DPI) at all EAE induced animals. On DPI 8, a hemi-compressive injury was induced by a transient extradural application of an aneurysm clip at the T8 spinal level. Control animals were sham operated. In a group of naive animals, BrdU was injected for 3 consecutive days and SCI was induced on the next day. According to this protocol, the pure percentage of invaded T-cells that are attributed to EAE or SCI could be evaluated. The animals were clinically evaluated during the following 4, 6, 8, 13 and 30 days. Cryostat spinal cord sections were stained for Hematoxylin-eosin, Nissl, Bielschowsky and BrdU immunohistochemistry. SCI resulted in spastic paralysis of one hind limb, ipsilateral to the trauma in all but sham injured animals. Recovery from SCI was significantly better in EAE animals. Activated mononuclear cells were selectively accumulated at the side of the injury, whereas in animals with EAE only, perivascular infiltrations were randomly distributed throughout the spinal cord. Axonal loss was less in the EAE group following SCI. Sham operated animals presented neither cell infiltration nor any neurodege-nerative process. Our findings indicate that actively induced autoimmunity against CNS myelin antigens may protect spinal cord pathways from mechanical injury. A neuroprotective, additional to the neurodestructive role of the inflammatory process whithin the CNS, may be attributed to the secretion of neuronal growth factors from the inflammatory cells and/or to the immunoregulatory role that some of these cells may have.

P739

Clinical and MRI aspects of post-irradiation lumbosacral radiculopathy

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Progressive flaccid paraparesia (PFP) is an unusual complication of lumbosacral irradiation for testicular cancer, lymphoma or vertebral metastases.

Aim of the study is to report the clinical characteristics and lumbosacral plexus and spine MRI findings in 5 pts who developed PFP after irradiation for cancer.

These pts have been treated for Hodgkin's disease (n = 4), plasmacytoma (n = 1). The median interval between therapy and referral was 144 mo. (7–204). The median duration of the symptoms at referral was 24 mo. (3–72). Irradiation was para-aortic (3), of lumbar spine (1), Y inverted (1), (4,000–4,250 cGy). Mean follow-up ranged from 1–4 y.

MRI was performed with a Magnetom Siemens 1.5 Tesla, studying 1) the lumbo-sacral plexus with coronal and axial T1 spin echo and T2 short time inversion recovery weighted images & coronal T1 after gadolinium and fat suppression (n = 4), 2) the lumbar spine with sagittal T1 and T2 weighted images and axial & sagittal T1 after gadolinium (n = 5).

Results: Inaugural manifestation was pain (3), or weakness in lower limbs (LL) (2). All patients complained of walking difficulty. On examination, there was a predominantly motor loss in L4-L5 (2), L5-S1 (1), L5 (2) territories which was asymmetrical. Sensory loss was unilateral and limited to stocking (2), or radicular (1) hypesthesia and reduction of vibration in the foot (4/5). Reflexes were diminished in both legs. None had sphincterian disorders. Electrophysiological studies showed motor axonal loss involving L4 L5 S1 roots territories with moderate asymmetry. All patients had a subtle (reduction of SNAP's amplitude < 30 %) and asymmetrical sensory loss, sensory conduction velocity suggested demyelination in 1. These data are in favour a diffuse predominantly asymmetric radicular lesion with possible plexus involvement. CSF protid content was increased in 4/5 without cells. On MRI, the bone marrow had a fat signal secondary

to irradiation. MRI of the lumbo-sacral plexus shows no abnormalities. MRI of the lumbar spine showed an abnormal enhancement of the anterior spinal nerve roots in 3 pts in the clinically affected territories. Neuropathy worsened progressively in all cases, so on last follow-up, 1 pt became wheelchair bound, 1 needed 2 crutches for walking, 2 one cane, 1 had steppage.

Conclusions: Post-irradiation radiculopathy are severe and disabling neuropathy; MRI of lumbosacral roots could be helpful to vizualize the damaged neural structures.

P740

Paraparesis of undetermined aetiology: a study of 24 patients

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Background: paraparesis is a frequently devastating symptom, dominating in a variety of neurologic diseases, such as multiple sclerosis (MS), motor neuron disease (MND), spastic hereditary paraplegia, tropical spastic paraparesis, infectious myelopathies and collagonosis. There are however cases that remain undiagnosed, despite detailed investigation, and severely affect the patients' quality of life.

Patients and methods: we reviewed 24 inpatients during 1998–2003, diagnosed with paraparesis of undetermined aetiology. Diagnostic work-up included neuroimaging, electrophysiology studies, routine blood tests, immunologic screens, serology for infectious factors (including HTLV-1), paraneoplastic screen, thyroid gland function. History included family history of neurologic disease and travels.

Results: 24 patients (8 males, 16 females, mean age = 47.7) were studied.

OCBs were positive in 10 patients and negative in 14 patients.

We further devided the patients to group 1 [subacute onset, stable course] and group 2 (insidious onset, progressive course]. The main differences between the two groups were:

Group 1:
OCB(+) = 2/11
Number of cells in lumbar puncture > 6 = 6/11
Intramedular lesion in spinal MRI = 7/11
Mean levels for B12, folate and HC
CSF B12 = 112.6 pg/ml, S B12 = 164 pg/ml
CSF folate = 15 ng/ml, S folate = 5.3 ng/ml
CSF HC = 0.37 umol/L, S HC = 12.7 umol/L
Group 2:
OCB (+) = 8/13
Number of cells in lumbar puncture > 6 = 1/13
Intramedular lesion in spinal MRI = 2/13
Mean levels for B12, folate and HC
CSF B12 = 149.6 pg/ml, S B12 = 502 pg/ml
CSF folate = 13 ng/ml, S folate = 4.65 ng/ml
CSF HC = 0.3 umol/L, S HC = 11.1 umpl/L

Investigation was negative for HTLV-1 and Borrelia in all patients. There were not significant differences between the two groups concerning the rest of the clinical and laboratory parameters we studied.

Conclusions: The combination of low cell number in CSF, presence of OCB (+), absence of intra-medullary lesion in MRI and normal B12 levels in serum and CSF might predict progressive course in paraparesis of undetermined aetiology. Furthermore, this combination might be compatible with autoimmune or degenerative pathogenesis.

P741

Idiopathic intracranial hypertension: a 10-year review of 28 patients

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Introduction: Idiopathic Intracranial Hypertension (IIH) is characterized by: elevated intracranial pressure, with normal CSF composition (no evidence of pleocytosis, cellular atypia or hypoglycorrhachia); symptoms and signs may only reflect those of generalized intracranial hypertension (headache, nausea, vomiting, transient obscurations of vision, papilledema), with no localizing neurological signs otherwise, with the single exception being VI nerve paresis; and normal imagiological study.

Methods: The authors did a retrospective study of the patients admitted (n = 47) in our Department, (coming from emergency department), during a period of 10 years, with the initial diagnosis of IIH. In the analysis of the patients we study several parameters: definitive diagnosis of IIH, demographic characteristics, disease evolution, and therapeutics.

Results: In the group of patients with IIH, 24 had isolated headache (n = 24) or in association with transient obscurations of vision (n = 10); diplopia (n = 6); and vomiting (n = 2). 4 (14 %) patients presented VI nerve palsy. Management: 27 patients had medical treatment with weight loss, diuretic, carbonic anhydrase inhibitors and corticosteroids therapy. In only 1 patient was necessary chirurgical therapy (lumboperitoneal shunt). Outcome was poor in 5 patients (18 %), with refractory headaches and progressive alteration of vision.

Conclusion: Present results can suggest that: (1) the diagnosis of IIH is not linear, even with the possibility of use CT in the emergency department (2) the outcome was good in the most of our cases, but a careful follow-up may help preventing a devastating visual loss and a refractory clinical picture.

P742

Haemangioblastomata of the cauda equina presenting as a Froin syndrome with papilloedema

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Froin syndrome is defined by a massive increase of proteins in the cerebrospinal fluid (CSF). A papilloedema can be associated. Classically, Froin syndrome was reported in Guillain-Barré syndrome and in spinal tumor. We report the observation of a haemangioblastomata of the cauda equina revealed by a Froin syndrome with papilloedema.

Case report: a 58 year old woman had complained for 4 years about a blurred vision. The ophthalmologic exam showed a bilateral papilloedema. Cerebral MRI showed a dilation of the optic nerves sheaths. Lumbar puncture confirmed an intracranial hypertension (high level pressure: 350 mm water) with a massive increase of proteins (1,000 mg/dl) in CSF without suspect cells. Spinal MRI found a tumor richly vascularized in the cauda equina which was operated. Histopathologic examination concluded to a haemangioblastomata. Six months after surgical removal of the tumor, patient's visual symptoms disappeared.

A massive increase of protein in CSF is regularly reported in spinal expansive process (Kobayashi M. et al. Acta Neurochir 1996; 138:480–1). Associated intracranial hypertension cause visual symptoms (papilloedema) and unusually headaches. Physiopathology of this intracranial hypertension in Froin syndrome is poorly understood. Hyperviscosity of the CSF and disorders of CSF hydraulics are considered.The classical localization of haemangioblastomata is the posterior cerebral fossa, particularly in Von Hippel Lindau disease. A spinal localization, particularly in the cauda equina is exceptional. The spinal tumors most frequently responsible for papilloedema are meningioma and neurinoma. Astrocytoma, ependymoma, paraganglioma and oligodendroglioma are rarely reported.

Conclusion: the high level of protein in CSF may be the cause of bilateral papilloedema due to intracranial hypertension. In patients with bilateral papilloedema without intracranial etiology, a spinal MRI must be applied to the search for a spinal tumor.

P743

Lorenzo's oil treatment in X-linked adrenoleukodystrophy (X-ALD)

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X-ALD is an inherited metabolic disorder that mainly affects the nervous system, adrenal cortex and testis. The principle biochemical abnormality is the accumulation of very long chain fatty acids (VLCFA) due to the impaired capacity to degrade these substances. The deficient gene has been mapped to Xq28.

Clinical manifestations range from a childhood cerebral form which leads to severe disability and often death before ten years of age, to mild forms (Adrenomyeloneuropathy, AMN) involving the spinal cord and peripheral nerves, some of which are compatible with survival to high ages. While the adrenal insufficiency responds readily to replacement therapy the treatment of nervous system involvement represents an unsolved challenge. Bone marrow therapy appears to be of benefit but only when applied in early stages of the cerebral disease. Dietary therapy in combination with oral administration of glycerol trierucate (GTE) and glycerol trioleate (GTO) (referred to as Lorenzo's Oil) is effective to lower elevated VLCFA levels in peripheral blood and tissues. The clinical effect of Lorenzo's Oil has been difficult to evaluate because of the great variability of the natural history of X-ALD and its relative rarity. No randomized studies have been performed, and only small patient series with a variety of phenotypes are published up to now.

We will present data from 47 patients with the pure AMN phenotype, treated with GTO/GTE over a mean period of 6.7 yrs. The clinical course as well as the progression of MRI abnormalities was significantly slowed under treatment. 48 % remained completely stable, 84 % were clinically better than expected based on their own natural history data.

From our data we conclude that GTO/GTE treatment is beneficial in non-inflammatory variants of X-ALD. We hypothesize that normalization of the biochemical defect may also prevent neurodegeneration, axonal damage, and the possible conversion from pure AMN without inflammation to inflammatory demyelinating disease that occurs in up to 20 % of the AMN patients in later stages. In this context the treatment may also at least partially preventive in previously asymptomatic patients.

Cerebrovascular disorders

P744

Role of previous treatment with statins in ischaemic stroke outcome: differences among aetiological subtypes

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Background: A recent study suggests that previous treatment with statins could be associated with better outcome in ischaemic stroke. Our goal is to evaluate the possible influence of previous treatment with statins in ischaemic stroke outcome.

Methods: Observational and sequential study from Stroke Unit Data Bank (1998–2002). Patients with lacunar (LI) and non lacunar infarction (NLI) (ethiological subtype: Atherothrombotic infarction (AI), cardioembolic infarction (CI) and undetermined origin (UO)) were included. Patients were classified in two groups (with/without previous treatment with statins). Outcome was evaluated by means of modified Rankin Scale (mRS) at discharge (poor outcome: mRS 3–6). Statistic tests: Chi square, ANOVA, multivariate logistic regression analysis.

Results: 2,231 patients with stroke, 1,512 had ischaemic stroke (985 NLI, 527 LI; age 70.5 ± 11.8); (38.3 %) AI, (38.8 %) CI and (22.9 %) UO. 5.5 % (83) were treated with statins. Previous treatment with statins were associated with a better outcome at discharge in LI ($p = 0.020$) and NLI ($p = 0.004$), mainly in AI ($p = 0.003$), in univariate analyses. Previous treatment with statins was an independent predictor of outcome in NLI $p = 0.003$; OR = 2.841 (CI 95 %: 1.414–5.707) in a multivariate logistic regression model.

Conclusions: Previous treatment with statins is beneficial in ischaemic stroke outcome patients and is an independent prognosis factor in non-lacunar infarction.

P745

The verbally asked single Yale question compared with its written form as screening tool for post-stroke depression

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Background: We set out to study whether the single Yale question for screening for post-stroke depression performs well when verbally asked compared with the written form.

Methods: In two different studies, which were carried out in the General University Hospital of Patras, Greece, the single Yale question (do you feel sad or depressed during the last two weeks?) has been administered in consecutive patients one-year after an acute stroke, in written, as well as in verbal form. In the first study, 170 post-stroke patients (mean age 66.4 (±11.4), females 41 %) returned a postal questionnaire, which was filled in either by the patient alone or by the patient with the help of a carer, containing among other scales the Yale question and Zung's Self rating Depression scale (SDS). In the second study, 170 post-stroke patients (mean age 65.2 (±10.8), females 39 %) were examined at the outpatient clinic, and the Yale question and the Montgomery Asberg Depression Rating Scale (MADRS) were administered separately by investigators blind to the results of each other.

Results: The single Yale question compared with the SDS in the postal survey, and with MADRS in the face to face interview, performed equally well in both written and verbal forms (Sensitivity 84 % (95 %CI 77–90 %) vs 79 % (95 %CI 70–86 %), Specificity 85 % (95 %CI 73–93 %) vs 89 % (95 %CI 80–95 %), Positive predictive value 94 % (95 %CI 87–97 %) vs 92 % (95 %CI 85–96 %), Negative predictive value 68 % (95 %CI 56–79 %) vs 73 % (95 %CI 62–81 %), Likelihood ratio-positive test 5.79 (2.91–11.53) vs 7.43 (3.66–15.08), Likelihood ratio-negative test 0.18 (95 %CI 0.12–0.28) vs 0.24 (95 %CI 0.16–0.35), respectively). The prevalence of depression in this population was considerably higher (61–72 %) than that expected in a general population, and this explains the better post-test probabilities.

Conclusion: A single question administered either verbally or in written form, seems to be effective in screening for depression in a post-stroke population, i. e. a group of patients with higher prevalence of depression.

P746

Evaluation of different side-effects of ultrasound-enhanced thrombolysis

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Background: Recanalization of cerebral arteries by enzymatic fibrinolysis can be accelerated by simultaneous ultrasound (US) insonation. In the range of 100 KHz-2 MHz we found 170 KHz as most potent insonation frequency to dissolve clots in an in-vitro study. In this study we investigated presumed side-effects of the 170 KHz US insonation: A, heating effect, B, endothelial cell necrosis and C, influence of mitochondrial membrane transport.

Method: 20 cadaver brains were insonated by US of 170 KHz with 0.1, 0.5 and 1 W/cm^2 energy for 60 minutes through the temporal window and the temperature was monitored simultaneously at 1, 2 and 3 cm depths from temporal bone in the brain parenchyma.

Human cultured brain microvessel endothelial cells were insonated for 1 hour by 170 KHz 150 mW/cm^2 US. Insonation-related cell necrosis was assessed by propidium-iodide stain.

Changes of mitochondrial membrane transport were studied by JC-1 stain, a sensitive indicator of ion-pump activity, and a consecutive spectrophotometric evaluation.

Results: Brain temperature increased by 0.71 ± 0.14, 0.35 ± 0.12 and 0.29 ± 0.12 degree C at 1, 2 and 3 cm depths respectively with 1 W/cm^2, and 0.44 ± 0.11, 0.25 ± 0.12 and 0.21 ± 0.11 C with 0.5 W/cm^2 energy, the differences were significant for all depths ($p < 0.05$); no heating effect was detected with the energy of 0.1 W/cm^2.

No significant increase in the number of necrotic cells during insonation was observed. Activity of mitochondrial membrane transport increased significantly during insonation (2.11 ± 0.19 vs. 1.64 ± 0.33, $p < 0.005$).

Conclusion: While biologically active, the 170 KHz US insonation with 0.1–1 W/cm^2 energy seems to be safe: neither substantial heating effect nor endothelial cell necrosis occured during the 1-hour insonation.

P747

No high-intensity transient signal (HITS) could be detected during ultrasound-enhanced fibrinolysis: an in vitro study

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Background: Low-frequency ultrasound (US) has been shown to enhance enzymatic fibrinolysis. As fibrinolysis is the only definitive treatment of acute ischemic stroke to date, enhancing its power by US may have substantial clinical impact. However, embolization during this treatment is a major concern. We investigated the efficacy of the method by clot weight reduction and D-dimer measurments and on the other hand, the safety by high-intensity transient signal (HITS) detection and post-treatment microscopic evaluation of the clots.

Method: 120 minutes old red thrombi were merged into circulating saline in a small container. 65 thrombi were added Actylase (1.4 mg/100 ml), 65 were additionally insonated by a 170 KHz, 1.2 W/cm^2 energy US beam, 16 were exposed only to US insonation and 14 controls were placed only in saline for a 1 hour period. Baseline and post-treatment clot weights were measured and weight-reduction computed and compared among groups. D-dimers, the indicators of fibrinolytic activity were measured semi-quantitatively. Specimens were frozen, embedded and analyzed by microscope. 20 thrombi were placed into an arteficial circulatory system and HITS were monitorized by transcranial Doppler during rTPA plus US insonation combined treatment.

Results: US alone did not cause significant weight reduction compared to controls. Weight reduction was highly significant both in the TPA-only and TPA plus US groups ($p < 0.005$), but in the latter group weight-reduction was significantly higher (16.7 CI (95) 3.5 vs. 13.7 CI (95) 3.9 microgram; $p < 0.05$). D-dimer concentrations in the control, the US, the TPA and the TPA plus US groups were 0, 0.4–0.8, 0.8–1.6 and 0.8–1.6 ng/ml respectively. Microscopic evaluation showed scattered, irregular surface of thrombi exposed to US plus TPA in contrast to specimens in the TPA-only group. HITS were not detected at all during the 1 hour treatment.

Conclusion: Low-frequency US insonation enhances fibrinolysis as shown by significant weight reduction and D-dimer production. US increases the surface of thrombi as large noumber of superficial incisions develop, without fragmentation of the whole thrombus. In harmony, no HITS could be detected during treatment suggesting that no major particles break away from the clots, indicating a good safety profile.

P748

Val64Ile polymorphism in the chemokine receptor 2 gene showed no strong association with carotid artery intima-media thickness in asymptomatic young men

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Background: Chemokines play an important role in inflammation. Chemokine receptor 2 (CCR2) is supposed to hold a key role in the pathogenesis of atherosclerosis and other syndromes characterized by chronic inflammation. Carotid artery intima-media thickness (IMT) is a widely accepted marker for the extend of early atherosclerotic changes. The aim of this study was to asses the relationship between IMT and the Val64Ile polymorphism of the CCR2 candidate gene which has been associated with cardiovascular disease before.

Methods: High resolution ultrasound in B-mode of the carotid arteries was performed in 546 healthy young German males (mean age 44 ± 8 yrs). Both carotid arteries of each subject were scanned in multiple planes in a standardized fashion to locate maximum thickness of the common carotid artery (CCA) and its bifurcation. Maximum and mean IMT measurements of both sides were obtained. The investigator was blinded for the person?s genotype. All subjects were genotyped for the Val/Ile polymorphism at position 64 in the CCR2 gene by PCR and TaqMan.

Results: Genotype distribution of the polymorphism was in Hardy-Weinberg equilibrium (VV n = 422 (77 %), VI n = 119 (22 %), II n = 5 (1 %), Chi-square = 0.67, df 2, p > 0.05). V-allele frequency was 0.88 corresponding to an I-allele frequency of 0.12. Mean CCA IMT [mm] was 0.70±0.12, mean IMTmax [mm] was 0.91±0.50. There was no strong association between genotypes of the CCR2 candidate gene and IMT. A slight trend to higher IMT with the I-allele – which, however, did not reach statistical significance – could be detected.

IMTmax [mm] for VV = 0.89±0.47, VI = 0.97±0.58, II = 1.20±0.61; ANOVA p = 0.14.

IMTmean [mm] for VV = 0.70±0.12, VI = 0.70±0.11, II = 0.82±0.17; ANOVA p = 0.07.

Wild type allele (n = 442) vs rare allele (n = 124) t-test p = 0.14 for IMTmax (0.89±0.47 vs 0.97±0.58) and p = 0.53 for IMTmean (0.70±0.12 vs.71±.11).

Only IMTmax of a small subgroup of smokers over 45 years (n = 71) was significantly associated with the rare allele of CCR2 (0.95±0.41 for VV vs 1.31±0.61 for VI and II genotypes; t-test p = 0.04).

Conclusion: Chemokine receptor 2 gene polymorphism showed no strong association with early carotid atherosclerosis. However, further studies including larger numbers and older subjects are still necessary.

P749

Dynamic perfusion CT in the assessment of acute ischaemic stroke patients

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Purpose: To evaluate Perfusion CT (PCT) capability of predicting brain infarction.

Materials and methods: First-pass double-section PCT was performed in 57 patients with acute hemispheric stroke, within 6 hours from onset of symptoms, after noncontrast CT (NCT). Four parametric maps were calculated: Time-to-peak (TTP), relative Mean Transit Time (rMTT), relative Cerebral Blood Volume (rCBV) and relative Cerebral Blood Flow (rCBF). Ischemic core was defined as the lesion area identified on CBF maps while TTP maps identified the sum of penumbra and core. Regions-of-interest were drawn in core, penumbra and contralateral hemisphere, obtaining relative indices. Twenty-three patients were treated with intraarterial thrombolysis. PCT maps were compared with follow-up CT at 21 days. Neurological status was assessed at admission and on day 90.

Results: PCT showed higher sensitivity than NCT in detecting early ischemia (97 % vs 62 %).

In 23 patients with thrombolysis corresponding hypoperfusion in the 4 maps (absent penumbra) was found in 4 (17 %) and after a successful thrombolysis the infarct size matched PCT (100 %). In 15 (65 %) patients with TTP/CBF mismatch (penumbra) after a successful thrombolysis there was no infarct growth (0 %) with neurological improvement in all patients (in 7 patients mRS). In 4 (17 %) thrombolyzed patients, with no recanalization and TTP/CBF mismatch, the infarct grew to penumbra (100 %).

In 34 untreated patients hypoperfusion in the 4 maps was found in 13 (38 %) and the infarct size matched PCT, while in 21 (62 %) patients TTP/CBF mismatched and in 7 the infarct grew to penumbra (33 %).

Perfusion parameters differed significantly in core and penumbra (DTTP 13.57 ± 7.55 vs 3.13 ± 2.80, rCBF 0.37 ± 0.28 vs 0.74 ± 0.20) (p < 0.01).

Conclusions: Perfusion CT can differentiate reversible from irreversible brain ischemia. A multiparametric assessment of perfusion deficits can predict size and location of cerebral infarction, representing a valuable tool for selecting patients who can benefit from intraarterial thrombolysis.

P750

Decompressive hemicraniectomy in malignant cerebral infarct

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Background: Malignant cerebral infarct occurs in up to 10 % of all stroke patients and is characterized by a mortality rate of up to 80 %. Decompressive surgery is an alternative therapy when medical therapy failed.

Objective: The aim of this study is to analyze the clinical data, time to surgery after stroke and immediate and one year outcome after decompressive hemicraniectomy.

Methods: The methods used included retrospective analysis of 6 patients admitted in the National Institute of Neurology of Tunis with the diagnosis of massive stroke infarct and who were treated by decompressive surgery. Initial clinical presentation was assessed by the modified Rankin Scale (m. R. S.), Barthel Index (B. I.), Glasgow Coma Scale (G. C. S.), and the Scandinavian Stroke Scale (S. S.S). C.T scan was done, at least twice, in 5 patients, and brain MRI was done in one patient. All survival patients were clinically and neuroradiologically assessed immediately (24 to 48 hours), three months and one year after decompressive surgery.

Results: Two women and four men were included in this study. The mean age was 37 years (19 to 46 years). All patients had complete middle cerebral artery infarct involving the dominant hemisphere in 2 patients. Signs of temporal herniation were noted in all patients. The G. C. S. varied between 9/15 and 11/15. The mean time between stroke and decompressive surgery was about 35 hours. Hemicraniectomy with accompanying duroplasty was done for all patients. A good outcome was favorable for 3 patients who were nearly independent after one year follow up. One death was recorded immediately after surgery, and one other death secondary to a non-neurological cause. The sixth patient was severely disabled.

Conclusion: Our study confirms the lifesaving nature of hemicraniectomy in severe cerebral infarct. Early decompressive surgery in patients who were deteriorating clinically may represent an alternative therapy especially in younger patients for a better outcome.

P751

Post stroke depression: who, where and why?

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Background and purpose: Studies observed more then half of the patients developing post stroke depression (PSD). Stroke location, lateralization, cognitive impairment, age and gender seemed to be important variables in stroke depression. The correlation between these variables and PSD although widely studied is still controversial. We studied the relation between these variables and PSD.

Materials and Methods: We interviewed 140 first ever ischemic stroke patients (55 women), 2 to 6 months after stroke. Age ranged between 19 and 87 years, with median of 64. The median scholarship was 4 years. We used the Hamilton 21-D scale for depression and the MMSE (adapted for our population) for cognitive impairment. We excluded patients with more than 6 months after stroke, with comprehensive aphasia and previous history of depression. We considered the Oxfordshire classification for ischemic stroke location. In this consecutive, descriptive and co relational study we used the statistical programme SPSS 10.0 for Windows and Qui-square and the C-Pearson.

Results: From 140 ischemic stroke patients, 88 (63 %) fullfiling criteria for depression, 49 (35 %) were men. Left stroke was present in 76 (54 %) patients. Age was significantly associated with depression (p = 0.025). From 114 patients with anterior location, depression was observed in 78. Nevertheless, having an anterior lesion was not significantly associated with depression (c = 0.243; p = 0.004). From 75 patients with lacunar infarct, 51 were depressed and no relation was observed between the occurrence of lacunar infarct and PSD. Cognitive impairment was observed in 29 patients and 16 of them were depressed. From 93 patients that were not on antidepressive medication, 51 fulfilled depression criteria (c = 0.227;

p = 0.006). No relation was observed between stroke lateralization, time of evolution or scholarship and PSD.

Discussion: In the studied group, 63 % presented PSD (35 % men), having 81 % an anterior lesion. It was not observed any relation between PSD and the other studied variables. Correlations between PSD and stroke variables might contribute to a better understanding of this controversial issue.

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Treatment of cardioembolic stroke with intravenous unfractionated heparin: is there still a role?

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Background: Cardiembolic stroke (CES) is prone to early recurrence. Acute antithrombotic treatment with heparin is used empirically to prevent recurrent stroke, although beneficial offset has not been documented.

Objective: To report our experience with intravenous heparin in acute therapy of CES.

Design: Retrospective observational study.

Materials and Methods: We searched the charts of all the patients with cerebrovascular disease admitted to the Neurology Department over a 6 year period (1/9/1997–1/9/2003). The TOAST classification was utilized to select those with cardiembolic stroke. The National Institute of Health Stroke Scale (NIHSS) and the modified Rankin scale (mRS) on admission and discharge were estimated from available records.

After obtaining brain CT, treatment with continuous intravenous infusion of unfractionated heparin was initiated. The starting infusion rate was 1000 U/hr and the dose was adjusted according to activated Partial Thromboplastin Time (target: 50–70sec) checked every 8 hours.

Results: Of 1194 patients with ischaemic stroke seen over the period 1/9/1997–1/9/2003, 352 patients (29.5 %) had cardiembolic stroke. The mean age of patients with CES was 76.7 years old (F: 51.7 %). Mortality was 11.9 % for all stroke patients and 17.9 % (63/352) for those with CES. Non valvular atrial fibrillation was the commonest cause. 57 patients (16.2 %) were taking oral anticoagulation. This was continued with dosage adjustment to achieve INR 2.5–3.5.188 (53.4 %) patients received IV heparin and 72 (20.5 %) were treated with antiplatelet agents. After adjusting to stroke severity (mRS > 3, NIHSS > 11) 41/168 (24.4 %) patients treated with heparin and 13/53 (24.5 %) on acenocoumarol had a favorable outcome (mRS < 3 on discharge). In comparison, 7/71 (9.86 %, p < 0.01) treated with antiplatelets had a favorable outcome. Deterioration plus mortality in the three groups was 15.9 %, 15.8 %, 38.9 % respectively.

Conclusions: Favorable outcome was obtained in 24.4 % of CES patients treated with continuous infusion of intravenous unfractionated heparin but only in 9.86 % of those treated with antiplatelets. Further prospective randomized studies are warranted in order to elucidate the role of intravenous unfractionated heparin in cerebrovascular disases.

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Papillary fibroelastomas as an unusual cause of cardioembolic strokes

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Introduction: Cardiac papillary fibroelastomas (CPF) are benign tumors of the heart and affect primarily the cardiac valves. These tumors are responsible for embolic accidents that clinicaly manifest as neurological and cardiovascular symptoms.

Purpose: Provide literature with three new cases, and explain differential diagnosis with other intraventricular mases especialy those we had had experience with.

Methods: Retrospective review of all patients admitted at the Neurology Department and Ecocardiographic casual discoveries, from 1 January 2001 to 31 dec 2003. Three patients presented CPF.

Results: Two males and one female. Age range between 45–69 years. CPF were located on aortic (1 case) and mitral (2 cases) valves. Case 1 presented Occipital stroke; Case 2, MCA srtoke; and 3 case, had no neurological stroke history and was asymptomatic. Surgical removal was practice in the first symptomatic case, with no reports of new stroke events. Case 2, died due to cardigenic shock secundary to heart anterior infarction and no surgery was practice because of intercurrent pathology. Third case was treated with anticoagulant therapy and continue asymptomatic.

Discussion:Independently of size and histologic aspect, CPF justify surgical removal due to their high potential of systemic embolism. The anticoagulant therapy in very old people and asymptomatic patients may be an alternative solution. Some thrombus may appear as CPF and are only diagnosed after removal.

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Admission characteristics, intensity of care and outcome of ischaemic strokes in a general hospital, Nikea, Greece

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Background: located in the western suburbs of Athens, the general hospital of Nikea has a current catchment area of more than 500,000, both Greeks and immigrants of mainly low socio-economic state. Admission characteristics of patients arriving with an acute ischemic stroke in our hospital, treatment and outcome are analyzed.

Methods: Consecutive patients admitted with acute ischemic brain attack were included. Characteristics of these patients, treatment received and case fatality were recorded.

Results: From the catchment area 111 patients with an acute ischemic stroke were admitted during a three month period. Mean age was 71.9 years, men were 9.39 years younger than women (66.4 vs 75.9, p < 0.001). Mean NIH stroke score at admission was 7. Almost 40 % of the patients were admitted within 3 hours of symptoms onset, while 13.6 % were admitted more than 24 hours later. The majority (68.2 %) used the ambulance service to come to the hospital. Computed Tomography brain scan was performed at 53.4 % at the emergency room and to the rest during the first few days of hospital stay. Urinary catheterization was performed to 46.9 %. During hospital stay elevated body temperature was measured in 32.4 % of patients and antibiotics were administered to all of them. Aspirin was administered to 87 % of patients. Mean length of stay was 7.8 days, with no difference between men and women. Hospital case fatality was 7.2 %.

Discussion: Sociodemographic characteristics of patients with an acute ischemic stroke in our hospital are similar to those reported in the most western countries. A significant percentage comes to the hospital within the three hour period that is required for applying thrombolytic treatment, but this technique is not yet available in our hospital.

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Venous angiomas associated to cavernomas

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Introduction: Venous angiomas also known developmental venous anomalies (DVA) are the most common cerebral vascular anomaly in the central nervous system and represent 50 % of all vascular malformations. They are a frequent incidental autopsy finding 0.25 %; with a low risk hemorrhage 0.22 % year. DVA are associated with cavernous malformation in about 8 % to 30 % of patient's series. In this case the risk hemorrage is more important and it would be recommended surgical approach.

DVA of the brain stem or of the cerebellum are exceptional, and linked to cavernoma are very rare; but in this location are more symptomatic these malformations.

Patients: We report five patients with DVA associated to a cavernoma. The DVA is located at infratentorial area, two in the brainstem and the others in cerebellum. The symptoms were bleeding in everyone with mass effect in two. One died, four presented rebleeding in 5 year follow-up period. All patients had magnetic resonance images that demonstrated DVA and cavernoma. Neither of them had been operated.

Discussion: The DVA have been considered a benign vascular malformation, but in these patients their course was very bad. In all patients was associated to a cavernoma and the symptomatic presentation was bleeding of posterior fossa, except in one with Wallenberg's syndrom three days prior to haemorrhage. It's suggested that elevated venous pressure in a venous angioma, due to restrictive disease in the venous angioma or thrombosis, leads to ectatic dilated microvasculature and formation of a endothelial sinusoidal structure, and enlarge to form a cavernoma. This theory would favor the possibility that some cavernous malformations are acquired lesions when they are associated a venous angioma, therefore they have a different natural history to solitary cavernoma. Both lesions are shown in magnetic ressonance imaging, the T2 images and enhanced T1 weighted images are useful to see DVA, while the gradient-echo shows the cavernoma.

Conclusions: The venous angiomas or DVA rarely produce symptoms, but sometimes and specially when they are associated to a cavernoma have a high risk of bleeding. When they are placed in the posterior fossa increases their complications. This association must would be considered candidate to surgical appoach of the cavernoma, with preservation of coexisting DVA since could cause venous infarct. The enhanced T1 weighted images and contrast CT scans have probed to be superior in the visualization of DVA.

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