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Short Communications

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Cerebrovascular diseases 1

SC 101

Sleep apnoea disorder is a vascular risk factor

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Sleep apnoea is defined as a cessation of sleep respiration lasting 10 seconds or longer. Hypopnoea is a 30% reduction in thoracoabdominal effort or flow of air and a 4% drop in oxygen saturation. Sleep apnoea disorder (SAD) usually occurs in overweight individuals who snore loudly, have a thick neck and abdominal obesity. The prevalence of SAD in the general population has been estimated at 4% in men and 2% in women. SAD is a risk factor for the development of systemic hypertension, in itself a major risk factor for myocardial infarction and stroke. Several major epidemiological studies have shown a dose-response relationship between the severity of SAD (as measured by the respiratory disorder index and the desaturation index) and the odds ratio for development of systemic hypertension. There is proof that successful correction of the SAD with CPAP applications lowers the mean blood pressure. Patients with moderate to severe SAD are also at risk for development of nocturnal cardiac arrhythmias that include sinus arrest, atrioventricular block, premature atrial or ventricular contractions, and atrial fibrillation. There is evidence that during the apnoea event there is a decrease in mean cerebral blood flow as measured by intracranial ultrasonography; this phenomenon may contribute to stroke. Following stroke, patients have a high prevalence of SAD that further increases the risk of secondary stroke and heightens mortality. In patients with advanced SAD, altered cerebral evoked potentials are not corrected with CPAP applications suggesting permanent cerebral structural damage.

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The prognostic significance of CT density changes in established cerebral infarcts

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Introduction CT density changes reflect the severity of ischaemic damage after stroke. However, the effect of time influences the visibility of infarcts. This prospective study analyses if the degree of CT hypodensity at 2 time intervals after stroke has a predictive value on the clinical outcome.
Method The study was restricted to 150 patients displaying an anterior circulation syndrome. All patients had CT scans without contrast enhancement on day 3 (±8h) and on day 10 (±8h) after stroke onset. The degree of hypodensity of the infarct was expressed in percentages comparing the Hounsfield's units, determined in the centre of the infarct area to the corresponding zone in the contralateral hemisphere. The modified Rankin scale subdivided the patients, according to their degree of disability at 3 months in R 0–1, R 2–3, R 4–5, R 6.
Result Patients R 4–5 and R 6 had the most severe impairment upon admission. The average density change on CT day 3 was not different between the 4 groups, but the hypodensity was significantly more pronounced on day 10, according to the severity of the disability. CT density increased between days 3 and 10 in R 0–1, was unchanged in R 2–3 and further decreased in R 4–5 and R 6.
Conclusion CT density of the infarct on day 10, but not on day 3, has a prognostic significance. Increase of CT density on day 10 is known as fogging effect and appears as a favourable prognostic factor.

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Pure lateral medullary infarction: clinical, MRI and angiographic correlation of 130 acute, consecutive patients

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Introduction Although there were a few attempts to make clinical-MRI correlation in patients with lateral medullary infarction (LMI), studies with a large number of patients are unavailable.
Method We analysed clinical features, MRI findings and angiogram results of 130 acute, consecutive patients with pure LMI. MRI identified lesions were classified rostro-caudally as rostral, middle and caudal, and dorso-ventrally as typical, ventral, large, lateral and dorsal. These results were correlated.
Results Patients with rostral MRI lesions more often had dysphagia and facial paresis ($p<0.01$, respectively), and less often had nausea/vomiting and headache ($p<0.05$, respectively) than those with caudal lesions. Typical, ventral, large, lateral and dorsal types were correlated with ipsilateral trigeminal, contralateral trigeminal, bilateral trigeminal, isolated limb/body and isolated trigeminal sensory patterns, respectively. Patients with large type lesions more often had dysphagia, hoarseness and dysarthria ($p<0.01$, respectively) while those with ventral type lesions less often had severe gait ataxia ($p<0.01$), than those with other type lesions. Angiogram showed vertebral artery disease in 67% and posterior inferior cerebellar artery disease in 10%. The presumed pathogenetic mechanisms included large vessel infarction in 49%, arterial dissection in 15%, small vessel infarction in 13%, cardiac embolism in 5%. Dissection more often occurred in patients with caudal (vs. rostral) lesions ($p<0.01$) while dorsal type infarcts (vs. other types) were more often related to cardiogenic embolism ($p<0.05$).
Conclusion We conclude that the three dimensional (rostro-caudal and dorso-ventral) classification helps us understand the clinical and partly, etiopathogenetical aspect of the heterogeneous LMI syndrome.

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Proton magnetic resonance spectroscopy (H1-MRS) of the frontal lobes in post-stroke depression

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Introduction Almost one half of stroke patients may suffer from depression. However the causes of these mood disturbances are still poorly understood. Research has implicated dysfunction of the frontal lobes in the pathophysiology of major depression. Our aim was to investigate the association between H1-MRS measures in the non-affected frontal lobes and depression, in the group of first-ever stroke patients.
Method 31 patients with a first ischemic stroke not involving the frontal lobes and 20 healthy subjects were included into the study. Single voxel H1-MRS was performed to measure N-acetylaspartate/ creatine (NAA)/Cr, glutamate+glutamine (Glx)/Cr, GABA/Cr, choline (Cho)/Cr and myoinositol (MyoI)/Cr ratios. Point resolved spectroscopy (PRESS) was used. Stroke patients were assessed between day 7 and day 12 after cerebrovascular accident. Diagnosis of depression was made according to the DSM-IV criteria, and its severity was assessed by Hamilton Depression Rating Scale (HDRS) and Geriatric Depression Scale (GDS).
Results 12 out of 31 patients (38%) were classified as depressed. Preliminary analysis has shown that patients with right-sided stroke and depression had higher GlxA/Cr ratio in the left hemisphere than healthy controls. No significant correlation was found between metabolite ratios and depression ratings.
Conclusion These findings indicate the possible role of excitotoxic amino acids in the pathogenesis of post-stroke depression and suggest the need for further research of interhemispheric differences.

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S-Cortisol reflects severity and mortality in acute stroke

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Introduction The adrenocorticoid stress-response in humans causes catabolism, increasing blood glucose, increasing heart rate, and possibly potentiate ischaemic damage to neurons. These effects could induce secondary brain damage in acute stroke.
Method This prospective study was based on single determination of s-cortisol in 172 patients included within 24 hours of stroke onset, 50% within 12 hours of stroke onset. All patients were admitted to hospital within 6 hours of stroke onset. We investigated the relations of s-cortisol to neurological deficit measured by Scandinavian Stroke Scale (SSS), lesion volume on CT-scan, blood glucose on admission, pulse rate, blood pressure, body temperature, deteriorating stroke, and outcome.
Results In a multivariate logistic regression analysis s-cortisol was independently related to death within 7 days of stroke onset, OR (odds ratio) Cortisol $_{+100\ nmol/l}$ 1.4 (CI 95% 1.1–1.8) as well as death within 3 months of stroke onset, OR cortisol $_{+100\ nmol/l}$ 1.3 (CI 95% 1.1–1.5). S-cortisol correlated to SSS ($r=-0.45$, $p<0.001$) as well as to body temperature ($r=0.27$, $p<0.001$), pulse rate ($r=0.26$, $p<0.001$), and lesion volume ($r=0.38$, $p<0.001$). S-cortisol was related to neurological deterioration.
Conclusion The adrenocorticoid stress-response appears to increase acute stroke mortality. S-cortisol was related to stroke severity and markers reflecting stroke severity.

SC 106

Soluble adhesion molecules (sICAM-1 and sVCAM-1) in acute ischemic stroke

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Introduction There has been increasing evidence that inflammatory-immunological reactions are involved in the pathogenesis of ischemic brain injury. An acute inflammatory response during and/or after an ischemic episode is followed by leukocyte infiltration and increased expression of adhesion molecules (AM) produced by interaction of activated endothelia and microglia. Soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) reflect further accumulation of inflammatory cells.
Method Serum (S) and cerebrospinal fluid (CSF) concentration of sICAM-1 and sVCAM-1 were determined, by commercially available kits, in patients (of both sexes; age range 65.7+–7.3) with transit ischemic attack TIA (n=15), reversible ischemic attack RIA (n=20), completed stroke CS (n=35) and controls (n=15). Samples were collected within 3–7 days after the cerebrovascular incidence. The diagnosis was established by history, clinical examination and cerebral CT and MRI scan. Control group was subjected to diagnostic radiculography and there was no evidence of cardiovascular malignant, inflammatory or autoimmune disease.
Results The concentration of sICAM-1 was significantly and progressively increased in both serum and CSF of patients with TIA ($S=p<0.05$; $CSF=p<0.01$), RIA ($S=p<0.001$; $CSF=p<0.01$) and CS ($S=p<0.001$; $CFS=p<0.001$). Also sVCAM-1 remarkably increased in serum and CSF of patients with TIA ($S=p<0.05$; $CSF=p<0.05$), RIA ($S=p<0.05$; $CSF=p<0.01$) and CS ($S=p<0.001$; $CFS=p<0.001$). The peak concentration of AM was observed during 3–4 days following ischemia. Maximal evaluation of AM was found in patients with most severe ischemic damage (CS).
Conclusion Ischemia induced up-regulation of sICAM-1 and sVCAM-1 represents secondary inflammation and one of the fundamental mechanisms responsible for neuron damage. Therapeutic benefit can be obtained by anti sICAM-1 antibody treatment.

Neuromuscular disorders
Motor neurone diseases

SC 107

Identification of a novel locus for autosomal dominant pure hereditary spastic paraplegia (SPG19)

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Introduction Hereditary spastic paraplegia (HSP) includes a heterogeneous group of neurodegenerative disorders characterized by progressive spasticity of the lower limbs. Clinically, HSP has been divided in pure and complicated forms. In pure HSP no other neurological features are present and slowly progressive spastic gait is usually associated with mild decrease of vibration sense and sphincter disturbances. The mode of inheritance may be autosomal dominant, autosomal recessive or X-linked. So far, seven loci responsible for autosomal dominant pure HSP (ADPHSP) have been mapped to chromosomes 14q (SPG3), 2p (SPG4), 15q (SPG6), 8q (SPG8), 12q (SPG10), 19q (SPG12) and 2q (SPG13). Two ADPHSP genes have been identified so far, the SPG4 gene (Spastin) and the SPG3 gene (Atlastin).
Method A large Italian family with 10 individuals affected by ADPHSP spanning three consecutive generations was evaluated. Linkage with all known ADPHSP loci was excluded. A genome wide search was then performed using 400 microsatellite markers covering all autosomes.
Results The phenotype in our family is characterized by adult onset (range: 36–55 years), a high incidence of urinary disturbances, mild muscle weakness and wasting, and benign course (only two patients were wheelchair-bound after 20 to 30 years of disease). Patients often complained of mild lower limbs paresthesias and diurnal fluctuations of spasticity. The genome-wide search allowed to map a novel ADPHSP locus (SPG19) to a 36 cM region on chromosome 9q.
Conclusion We have identified a novel ADPHSP locus; the phenotype is characterized by adult onset and slow, benign course of the disease.

SC 108

Homozygosity for short allele (SS) of heavy neurofilament subunit gene is associated with ALS and increased CuZnSOD activity in erythrocytes

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Introduction Mutations in the gene encoding heavy subunit of neurofilament (NFL-H) are rare cause of amyotrophic lateral sclerosis (ALS). Predisposing role of light subunit (NFL-L) and protective role of NFL-H in relation to ALS were suggested. We searched for allelic variances of NFL-H gene and SOD-1 mutations, measured SOD-1 activity in erythrocytes and malondyaldehyde (MDA) serum content in ALS patients.
Method Samples from 52 ALS patients without D90A SOD-1 mutations and 45 healthy donors were screened for NFL-H allelic variances (S/L) by PCR and double strand conformation polymorphism. SOD-1 activity in erythrocytes was measured by detection of auto-oxidation of 6-hydroxydophamine. MDA content was measured by spectrophotometry. Patients were assessed by the Norris ALS score each 6 months.
Results Homozygosity for short NFL-H allele S was registered with higher frequency in sporadic ALS group vs controls: 17/52 vs 3/45 (37.1% vs 6.7%; $\chi 2=9.97$; $p<0.005$). Neither correlation was found between allelic frequencies and age or site of the onset, nor with the type of disease progression. SS carriers had higher SOD-1 activity then controls (^735 vs ^689 U/ml HB, respectively; $p<0.03$), and higher then SL+LL carriers (^735 vs ^684 U/ml HB; px2=0.08) between whose SOD-1 activities no difference was found. No difference in MDA content was found between ALS patients with various NFL-H genotypes and controls.
Conclusion Further investigation is required to determine whether increased SOD-1 activity unrelated to oxidant stress in SS genotype carriers is ALS-specific.

SC 109

Congenital myasthenia: four Portuguese patients with two compound heterozygous mutations of the AchR epsilon subunit

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Introduction Congenital myasthenias are a group of genetic syndromes affecting neuromuscular transmission. Mutations have been found in several subunits of acetylcholine receptors (AchR). We present four cases from two non-consanguineous families with mutations for the epsilon subunit.
Cases reports In the first family, the older brother is 20 years old, had trouble sucking at birth, was weak and suffered of ophtalmoparesis since 4 years of age. In the younger brother, now 8 years old, ophtalmoparesis was noticed at 6 months and weakness aggravated by exercise at the age of 4 years. The others two patients are sisters. The older sister, now 16 years of age, had ophtalmoparesis since birth and later on weakness with easy fatigability. The younger sister, now 13 years old, had a similar clinical picture but more severe than her sister. Repetitive stimulation revealed a decremental response. They all improved with Mestinon treatment.
Results In the first two patients, two heteroallelic mutations of the AchR epsilon subunit gene (epsilon1293insG and epsilonG857T) were identified. Epsilon1293insG results in frame-shifting and premature termination of translation, epsilonG857T leads to an amino acid exchange of a conserved residue. In the other two patients two heteroallelic mutations of the AchR epsilon subunit gene (epsilon1293insG and epsilon 70insG) were identified. Both mutations are predicted to result in frame-shifting and premature termination of translation.
Conclusion The clinical diagnosis of congenital myasthenic syndromes is supported by neurophysiological investigations. Genetic studies allow for a correct classification of the syndrome and an adequate genetic counselling for families.

SC 110

Titin and ryanodine receptor epitopes are expressed in cortical thymoma along with co-stimulatory molecules

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Introduction Cortical type thymomas are associated with myasthenia gravis (MG) in 50% of the cases. MG is caused by antibodies against the acetylcholine receptors (AChR), but additional non-AChR muscle autoantibodies such as those against titin and ryanodine receptor (RyR) are found in up to 95% of MG patients with thymoma. Our objective was to elucidate the induction of non-AChR autoantibodies in thymoma-associated MG.
Method We studied cortical type thymomas from seven thymoma MG patients, and sera from six of them. Five normal thymuses were included as controls. All tissues were examined for

the occurrence of titin and RyR antigen epitopes and LFA3 and BB1 co-stimulatory molecules in immunofluorescence and immunohistochemistry. The co-expression of antigen epitopes and co-stimulatory molecules was examined.
Result Titin and RyR epitopes were co-expressed along with LFA3 and B7 (BB1) co-stimulatory molecules on thymoma antigen presenting cells in all thymomas. In normal thymus, the staining by anti-titin, anti-RyR, anti-LFA3, and anti-BB1 antibodies was weak and occurred exclusively in the medulla and perivascularly. 6/6 patients had titin antibodies, and 4/6 had RyR antibodies.
Conclusion Our results indicate a primary autosensitization against titin and RyR antigens inside the thymoma. In MG associated thymoma, the mechanisms involved in the initial autosensitization against titin and RyR are probably similar to those implicated in the autosensitization against AChR. In all cases there is an over-expression of muscle-like epitopes and co-stimulatory molecules indicating that the T-cell autoimmunization is actively promoted by the pathogenic microenvironment inside the thymoma.

SC 111

Cognitive and behavioural profiles of myotonic dystrophy patients correlate with regional cerebral blood flow reductions

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Introduction Multisystem involvement in the myotonic dystrophies is well-recognized but the characteristics of brain involvement in the adult onset myotonic dystrophies (DM1 and DM2/PROMM) are unclear. The aims of our study are to determine whether: (i) there is a typical cognitive and neuropsychiatric profile of patients with DM1 and DM2 and; (ii) this correlates with regional cerebral blood flow reductions (rCBF).
Method 20 patients with DM1 (CTG 500-700n; mean age 40 years ±6.7) and 20 patients with genetically confirmed DM2/PROMM (mean age 43 years ±4.2) were subjected to a battery of frontal lobe tests (Computerized Attentional Assessment TEA, Wisconsin Card Sorting Test, WCST; Stroop Test, ST; Trail Making Test A and B, TMT; Tower of London Test, TLT), neuropsychiatric assessment (SCID-II personality scale, self-administered anxiety/depression scales) and to brain SPECT scans.
Results Cognitive strategies and visual-spatial decisions (ST, TLT) were significantly impaired in patients with DM2/PROMM and DM1 ($p<0.001$). The neuropsychiatric assessment demonstrated that patients with DM2/PROMM and DM1 showed significant avoidant behavioural trait clustering ($p<0.05$). Brain SPECT scans demonstrated rCBF reductions in the frontal, and temporoparietal regions, in DM1 more than in DM2.
Conclusion Patients with DM1 and DM2/PROMM display a severe limitation in performing visual/spatial planning tasks and have pronounced avoidant behaviours. These data suggest there may be a specific cognitive and behavioural profile of patients with myotonic dystrophies which correlates with rCBF. The characteristics and the severity of brain involvement may be useful end-measures of therapeutic trials in these disorders.

SC 112

Do introduction of riluzole or PEG affect time to diagnosis and survival in ALS?

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Introduction To compare survival in ALS before and after introduction of Riluzole and PEG as therapeutic options.
Method All patients diagnosed as ALS during the periods 1985 to 1989 and 1995 to 1999 were registered. Patient files were reviewed and cases classified as bulbar or spinal ALS according to defined criteria. Survival was studied in relation to treatment, ALS type, age and initial progression of symptoms.
Results A total of 79 patients fulfilled the diagnostic criteria, 40 men and 39 women. Thirty-seven were from the first period, 42 from the last. Average annual incidence was 1.9 per 100,000. Thirty-three patients received Riluzole (78%) and 23 had PEG (55%), all from the last period studied. Median survival from onset was 39 months. Young age at onset and spinal cases compared to bulbar were favourable prognostic factors. There were no differences in survival between the two periods of the study. Riluzole or PEG did not affect survival. Selection of bulbar from spinal patients and cases with short or longer time from onset to diagnosis did not affect the results. The time from onset to diagnosis was similar in the two periods studied.
Conclusion In this retrospective study we failed to demonstrate any effect of Riluzole or PEG on survival or diagnostic approach in ALS.

Infections and AIDS

SC 113

Fluorescence Activated Cell Scanning (FACS-analysis) implemented into cerebrospinal fluid (CSF) routine diagnostics for discrimination of inflammatory and clonal pleocytosis: a series of neuroborreliosis with unusual clinical presentation

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Introduction FACS-analysis discriminates inflammatory and neoplastic pleocytosis in CSF. Several antigenic surface profiles are analysed via fluorochrome marked antibodies at the same run (1). CSF in neuroborreliosis may reveal large pleomorphic activated lymphocytes mimicking neoplastic lymphocytes. Production of specific antibodies may be delayed.
Method 3 patients (1M/2F) examined. Initial clinical presentation: paraparesis level TH8 (case 1), unilateral paresis of the rectus abdominal muscle (case 2, 3). CSF examination: Mor-

phology, cell count, proteins, FACS analysis, borrelia specific antibodies. FACS analysis demonstrated an elevated CD4/CD8 ratio in all patients. Patient 1 had a delayed antibody production, but was positive at a control puncture.

Results FACS analysis demonstrated an inflammatory pleocytosis in CSF also in 1 patient that had no specific antibodies in CSF at initial presentation. As results are available within 2 hours the examiner can wait and choose the further examinations on fresh native material accordingly.

Conclusion FACS analysis of CSF is a quick and reliable method for the discrimination between a clonal or inflammatory lymphocytic pleocytosis. Unnecessary examinations can be prevented, which helps to run a cost effective diagnostic pathway and patient management.

Literature

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SC 114

Changes in glycosylation and distribution of the prion protein in neurons correlate with a decrease in synaptophysin levels but are not caused by axonal transport impairment or loss of target neurons

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Introduction In prion diseases, the cellular prion protein (PrPc) undergoes a conformational change that results in the formation of the prion protein scrapie (PrPsc). In rodents, the majority of the retinal ganglion cells project to the superior colliculus offering an opportunity to study the propagation of the disease in a relatively simple neuronal pathway.

Method Injection of scrapie in the superior colliculus.

Results After injection of scrapie in the superior colliculus, we found that PrP, mainly protease sensitive PrP, and its non-glycosylated band accumulate first in the retina and then in the optic nerve following the course of the disease. We studied whether or not PrPc changes were caused by a general axonal transport impairment or removal of target neurons. PrP abnormalities were not associated to overall axonal transport impairment, as shown by metabolic pulse labelling studies. Moreover, PrPc did not occur concomitant with abnormal distribution of other proteins such as the amyloid precursor protein (APP), phosphorylated heavy neurofilament subunit and tubulin. Removal of target neurons by kainic acid lesion of the superior colliculus or blocking of the axonal transport by intraocular injection of colchicine did not induce alterations in the glycopattern of PrP in retinas, as observed in scrapie. However, abnormalities in PrPc distribution and glycosylation preceded a decrease of synaptophysin in retinas.

Conclusion Our results suggest that the glycosylation abnormalities of PrPc are not caused by an overall impairment of axonal transport or removal of target neurons but they precede synapse dysfunction in prion diseases.

SC 115

Kynurenic acid metabolism in different types of brain pathology in HIV-1 infected patients

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Introduction Recently we demonstrated elevated synthesis of the broad spectrum EAA receptor antagonist kynurenate in the brain of HIV-1 infected patients [1]. The present study was designed to examine the relationship between alteration of biosynthetic machinery kynurenate in respect to different types of pathologies in the brain found after HIV-1 infection [2].

Results Among 25 HIV-1 examined cases opportunistic infection (OPP) was the most frequent pathology (52%) followed by HIV-1 in brain than malignant lymphoma of brain (LY, 20%), infarction of brain (INF, 20%) and glial dystrophy GD (16%). Kynurenine aminotransferases I and II (KAT I and KAT II) catalyse the formation of kynurenate from L-kynurenine. Kynurenate was increased in frontal cortex in LY (392% of CO), HIV (253% of CO), and in cerebellum in GD (291% of CO; $p<0.05$). Significant increase of L-kynurenine in the cerebellum was found only in LY (333% of CO). KAT I activity increased in the frontal cortex and cerebellum in all subgroups except in cerebellum of INF. While KAT II increased in the frontal cortex of INF and OPP in cerebellum of INF and GD it was mildly reduced.

Conclusion Present data indicate that the various types of pathologies are accompanied by different patterns of changes of kynurenine metabolism. An increase of KAT I activity is probably due to astrocytosis and/or astroglia activation.

SC 116

Chronic herpes virus encephalitis (clinical picture and pathogenesis)

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Introduction Besides acute herpes virus encephalitis there are cases with gradual feverless beginning and continued progressive course of this disease. It is believed that herpes virus encephalitis can have latent infection reactivation in the CNS. However, the mechanisms of such types of encephalitis have not been investigated.

Method We observed 52 patients, mainly above 40 years of age, with chronic herpes virus encephalitis (CHVE). Diagnosis has been confirmed by isolation of herpes simplex virus (HSV) from the cerebrospinal fluid (CSF) of 3 patients, and by detection of HSV antigens with fluorescence antibodies and polymerase chain reaction in CSF and histological brain specimens.

Results Encephalitis with progressive dementia, epileptic and akineticorigid syndromes formed the general clinical picture. In some cases chronic relapsing meningocephalitis with protein-cell dissociation in CSF were registered. The lethality after 6 months–5 years reached 80%.

Histological studies of CNS (40 died) allowed to establish a productive type of a pathological process with proliferation of astrocytes and microglia cells, diffuse neurone prolapse, virus-

induced polymorphism of cell nuclei, predominantly of the type II, at the absence of necrotic foci.
Conclusion In experimental studies on the fibroblast tissue culture the ability of HSV to induce a formation of antiviral macromolecular complex that depresses viral cytolitic properties and has anti-apoptosis effect has been established. We suppose that such mechanism of the virus pathogenicity decrease causes the development of a chronic infection of the CNS. The prevalence of the nucleus type II changes is the marker of this process. Our data allow to consider the CHVE as clinical and pathogenetic variant of the CNS herpes virus infection.

SC 117

Brain stem infection is common in listeriosis. A retrospective study of adult listeriosis in Norway 1977–2000

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Introduction Infection by the bacterium Listeria monocytogenes occurs sporadically (0.2–1.5:100,000/yr) or in regular epidemics (1). In adults, listeriosis mainly occurs as sepsis or meningitis. A particularly serious syndrome; brain stem encephalitis with progressive brain stem deficits and coma, also occurs. The frequency of this syndrome has never been determined. A review from 1992 identified only 62 cases reported in world literature (2). We present a retrospective study of the frequency of brain stem infection in adult, non-pregnancy-related listeriosis.
Methods 247 cases of listeriosis were nominally reported in Norway in the period 1977–2000. 133 patients had definite adult listeriosis. The others were pregnancy-related, or data were un-available. We studied medical records, laboratory results and (in 5 cases) autopsy material. Brain stem infection was identified by clinical and/or histopathological criteria.
Results Although brain stem infection was not diagnosed in any of the patients during their illness, symptoms and signs of brain stem infection were recorded in 20 of the 133 adult listeriosis cases. Their clinical pictures varied widely. Moreover, autopsy demonstrated brain stem infection in some patients in which no neurological deficits had been recorded.
Conclusion Brain stem infection is frequently present in adult listeriosis. Neurological examination should therefore be performed on all listeriosis patients. Also, listeriosis should always be considered when brain stem deficits from an unknown cause are in progress.
Literature
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SC 118

The clinical features of tick-borne encephalitis (TBE) in Middle Urals

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Introduction TBE is a rural endemic infection of the Sverdlovsk region with an average morbidity rate of 21.7 per 100 thousand of population. In the 1990ies we observed a considerable increase in TBE morbidity and severity of CNS impairment.
Method Clinical syndromes of TBE have been analysed in 5788 patients from the database of the regional centre of tick diseases (1994–2001), as well as in 150 patients, admitted to the 1st Regional Hospital during 1994–1999.
Results Febrile form of TBE was shown to be prevalent in the clinical structure of the disease (62.2% of cases), whereas meningeal and focal forms were observed in 25.6 and 12.2% respectively. Among focal forms, we distinguished patients with multilevel CNS impairment in 68.8%. Lethality was 2%. Systemic inflammatory syndrome in 80.7% was performed by monophasic fever pattern (often 14 days and more), in 19.3% we observed byphasic fever pattern (prevailed when alimentary way of transmission had been present). Among encephalitic syndromes altered consciousness was observed to prevail. We registered also sensory-motor zone impairment with severe central hemipareses (in 81.8% of encephalitic forms), cerebellar dysfunction (in 18.2–33.3% of focal forms). Poliomyelitic syndrome revealed in simultaneous involvement of cervical and lumbar motor neurons of the spinal cord (in 48.1%), the "falling head" sign was observed in 62.9%. Polioencephalitic syndrome was characterized by severe bulbar lesion (in 87%) and oculomotor nerve impairment: III– in 43.5%, VI– in 32.6%.
Conclusion Clinical peculiarities of TBE in the Sverdlovsk region show a considerable variety and severity of acute period syndromes of the disease.

Peripheral nerve disorders
Spinal cord and root disorders
Neuro-otology

SC 119

Apolipoprotein E genotypes and outcome in Guillain-Barré Syndrome

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Introduction The cholesterol transport protein apolipoprotein E (apoE) is known to be involved in axonal regeneration. There is a biologically significant polymorphism in the human APOE gene with three common alleles e2, e3 and e4 encoding different protein isoforms. APOE genotype influences the susceptibility to and outcome after central nervous system disorders including head injury, Alzheimer's disease and subarachnoid haemorrhage. It may have similar effects in peripheral nervous system disorders such as neuropathy due to diabetes mellitus or HIV. We hypothesised that APOE genotype influences recovery from Guillain-Barré Syndrome (GBS).
Method 91 patients with GBS were recruited prospectively in the South East of England. Their disease was characterised clinically and electrophysiologically. Outcome at one year was

assessed according to a disability scale. DNA was stored and APOE genotypes determined.
Results The distribution of genotypes in GBS was similar to that of a control population. Poor outcome one year after GBS was not associated with any particular APOE genotype.
Conclusion APOE genotype does not appear to influence recovery from GBS in this population. This may be because recovery is not limited by transportation of cholesterol, or because apoE is not the only biologically significant cholesterol transport protein in GBS. Larger studies would be needed to detect small differences in outcome associated with particular APOE genotypes.

SC 120

Predictive factors for long-term outcome in patients treated conservatively or surgically for spondylotic cervical myelopathy

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Introduction The aim of this prospective randomised study with 3-year follow-up was to evaluate the power of the entry clinical, electrophysiological and imaging data to predict the outcome of conservative treatment or surgery in patients with spondylotic cervical myelopathy.
Method The study sample consisted of 66 patients, who were randomised for conservative (33 subjects) and surgical treatment (33 subjects). The clinical status and outcome were measured by mJOA score, timed 10-m walk test, subjective estimation by the patients themselves and the score of daily activities recorded by video and evaluated by two blinded observers. The cervical spine was investigated by MRI, CT and plain radiography and quantitative parameters evaluated to describe the pathological findings. The functional status of the cervical spinal cord was evaluated by EMG and evoked potential study.
Results The difference in entry parameters between patients treated conservatively with the favourable and unfavourable outcome was significant in: Pavlov's index, AP spinal cord diameter and duration of the disease, in patients treated surgically in initial mJOA score, timed 10-m walk and electrophysiological parameters (CMCT and CSCT).
Conclusion The positive therapeutic response to the conservative treatment appears to be expected in the patients with higher values of Pavlov's index (i.e. with larger congenital AP diameter) and associated imaging parameters of the spinal canal, with older age and longer duration of the disease. The positive responders to the surgical therapy initially have a lower mJOA score and slower walk.
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SC 121

Unifying follow-up concept for patients with lumbar spinal stenosis: a pilot study.

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Introduction The typical symptoms of lumbar spinal stenosis (LSS) include neurogenic claudication (NC), back and leg pain, permanent weakness, and mixed symptoms. Signs and symptoms (especially NC and pain) fluctuate during the follow-up period, but from a clinical point of view it would be useful to express this fluctuating course numerically. In this study we try to evaluate the correlation between frequency of NC during follow-up (the "NC load") and Oswestry disability index, pain score, and permanent motor and sensory deficit of the lower extremities.
Method The data from a group of 29 consecutive patients (mean age 54 years) with shallow lumbar spinal canal were evaluated. NC load (during follow-up period 1.5–2.5 years) was compared with mean Oswestry disability index, mean pain score, and mean score for the permanent deficit of lower extremities. Analyses were based on Mann-Whitney and Kruskal-Wallis test.
Results Positive correlation between all the above-mentioned scales and neurogenic claudication load was established (NC load vs. Oswestry questionnaire $p=0.021$, NC load vs. permanent deficit score $p=0.048$, NC load vs. pain score $p=0.009$). The result of patient development expressed as NC load was supported by high correlation with independent clinical judgement ($p=<0.001$)
Conclusion The NC load score reflects (expressed as a percentage) the presence of NC during follow-up and correlates with other clinical scales frequently used in assessment of patients with LSS. Therefore it could be a useful and reliable tool reflecting comprehensively the clinical development.
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SC 122

Can electrophysiological examination predict clinical development in patients with mild lumbar spinal stenosis?

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Introduction No information exists about the prognostic value of the initial electrophysiological examination with respect to clinical development in patients with mild lumbar spinal stenosis (LSS). The goal of this study is the assessment of electrophysiological examination as a predictor of the clinical status expressed as the "neurogenic claudication load score". This score (expressed as a percentage) was established to evaluate further clinical development of patients with LSS and reflects the presence of neurogenic claudication (NC) during follow-up. It also correlates with other clinical scales. Therefore it is a useful tool which reflects comprehensively the clinical development.
Method A group of 29 consecutive patients (age 54 (42–67)* years) with proven LSS was evaluated. The degree of LSS was mild: no paresis, Oswestry disability index 36.0% (16.0%–54.0%)*. Soleus H-reflex, tibial F-wave and MEP to the abductor hallucis muscle were examined initially. The observation period was 1.5–2.5 years. Comparative analyses were based on the Mann-Whitney and Kruskal-Wallis test.
Results The initial values for the chronodispersion of the tibial F-wave, latency and amplitude of soleus H-reflex indicate further development of the NC load (chronodispersion of tibial F-wave $p=0.021$, latency of soleus H-reflex $p=0.051$, amplitude of soleus H-reflex $p=0.018$).
Conclusion The electrophysiological examination of patients with mild LSS provides valuable information about further clinical development. Tibial F-wave and soleus H-reflex can predict development of NC, which is a typical symptom of LSS limiting walking and common daily activities.
*median (10%–90% quantiles)
Supported by IGA MH CR Grant No 5938-3

SC 123

Which is the treatment of choice for benign paroxysmal positional vertigo?

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Introduction Benign paroxysmal positional vertigo (BPPV) is a common cause of treatable peripheral vertigo. Neuro-otologists report on 70% to 90% of success after one single physical treatment. In almost all studies, additional measures such as head vibration, keeping the head patient upright for 48 hours after treatment, the use of neck collar, and repeating examination only after 72 hours have been recommended. The objective of this study was to evaluate effectiveness and possible side effects of repeated physical procedure to treat BPPV during one session.
Method Fifty consecutive BPPV patients were treated with repeated Epley manoeuvre during the same session with no additional measures (group I). Results were compared to those of 75 BPPV patients treated with a single manoeuvre only (group IIa; 50 patients) and a single manoeuvre followed by the use of a neck collar and keeping the head upright for 48 hours (group IIb; 25 patients). All patients were re-examined within a week.
Results 46 patients (92%) of group I; 40 patients (80%) of group IIa and 21 patients (84%) of group IIb were completely free of signs and symptoms when re-examined. Only one patient experienced vomiting during treatment. Transient nausea and dysequilibrium was frequently reported but well tolerated.
Conclusion Although all approaches were highly effective, repeated procedures during the same session seems to be superior and more convenient than a single manoeuvre. Additional measures are not necessary for successful treatment. No serious side effects were found or reported by patients.

SC 124

Neuro-otologic findings in a family with episodic ataxia type 2 (EA2) caused by a novel CACNA1A splice cite mutation

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Introduction Episodic ataxia type 2 (EA2) is a rare neurological disorder inherited as an autosomal dominant trait of the CACNA1A gene encoding the alpha1A-subunit of a calcium channel expressed mainly in the cerebellum. EA2 is characterized by episodes of nausea, vertigo, nystagmus, ataxia, and fatigue. Episodes are often triggered by exercise or emotional stress and relieved by acetatzolamide. Progressive cerebellar atrophy and ataxia often start later on. Interictal findings of nystagmus have been found localizing to the vestibulocerebellum.
Method We performed a neuro-otologic test pattern of static posturography, electronystagmography (ENG), audiometry and video-oculography (VOG) to an EA2-family (N=12) having a novel CACNA1A splice cite mutation (M.Kaunisto, unpublished data) and compared the results to a healthy control group.
Results The posturography and saccadic accuracy results of the EA2-family were significantly worse than those of the controls ($p<0.001$ for both). The VOG findings were mainly consistent with the previous oculomotor studies on EA2: spontaneous, gaze evoked and positional nystagmus were commonly seen. However, the oculomotor findings were heterogeneous; three patients had normal VOG. No hearing loss in audiometry or caloric weakness in ENG could be verified. Acetatzolamide corrected abnormal VOG-findings in one patient.
Conclusion Our results suggest that oculomotor and postural control disturbances are prevalent in EA2 caused by this CACNA1A mutation. The saccadic inaccuracy and nystagmus localize to the vestibulocerebellum, whereas the peripheral vestibular function as measured with caloric tests and audiometry seems to be intact.

Neurorehabilitation Neurotraumatology

SC 125

Guideline on mild traumatic brain injury: Report of an EFNS Task Force

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Introduction A Task Force on Mild Traumatic Brain Injury (MTBI) was set up under the auspices of the European Federation of Neurological Societies. A systematic search of the literature on existing classification systems, outcome data (CT abnormalities, need for neurosurgical intervention, mortality) and patient management was performed. It was our aim to propose an acceptable uniform nomenclature for and definition of MTBI; and to develop evidence based rules to guide initial management with respect to ancillary investigations, hospital admission, observation, and follow-up.
Results MTBI is defined as the consequence of blunt (non-penetrating) impact with sudden acceleration, deceleration, or rotation of the head with a Glasgow Coma Score of 13–15 on admission to hospital. If the duration of loss of consciousness is maximally 30 minutes and posttraumatic amnesia is less than 60 minutes, the outcome is considered good (mortality<1%) especially in the absence of risk factors. Risk factors are important and such factors should be included in a classification system to further assess the risk of immediate complications.
Conclusion The primary goal of initial management in MTBI is to identify the patients at risk of intracranial abnormalities and especially those that may need neurosurgical intervention. A clinical decision scheme (including head injury warning instructions and criteria for hospital admission) is proposed to facilitate patient management after MTBI.
Literature
Vos PE, Battistin L, Birbamer G, Gerstenbrand F, et al (2002). EFNS Guideline on Mild Traumatic Brain Injury. Report of an EFNS Task force. European Journal of Neurology; 9: 1–13.

SC 126

Guidelines for evaluation of mild traumatic brain injury in the acute care setting

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Summary Physicians evaluating mild traumatic brain injury (MTBI) and concussion in the acute care setting are faced with a number of challenges. Among these are: the need for neuro-imaging, parameters for return to athletic or regular activities and appropriate follow-up strategies. A number of consensus and evidence based guidelines have been published regarding strategies for imaging and return to activity. Practitioners have adopted guidelines for return to sports activities that use "Grades of Concussion" to determine the period of time required to avoid activities. The use of length of time with loss of consciousness often is the prime criterion for such grading. This can be challenged both in evidence and logic. Guidelines for neuro-imaging are also problematic. Most of the guidelines developed use studies with significant selection bias. In view of the difficulties for evidence-based medicine to provide definitive strategies, a number of logical strategies can be defended based on the facilities available and the proximity of neuro-imaging. Return to activity guidelines must be re-evaluated in light of the newer predictors of severity of injury and probability of sequelae.

SC 127

Life after brain injury determined by the model of rehabilitation

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The goals of rehabilitation are married to the basic beliefs regarding the value of human existence. A community of wellness needs to be established in order to enhance a patient's highest level of outcome. While many models for long-term rehabilitation have focused on the physical components, the long-term rehabilitation community must focus on executive functions, emotional relationships, structured support systems, and an enhanced quality of life. This long term living paradigm would empower the individuals to be a part of the community where they find meaningful work and supportive relationships. Since a loss of executive functioning impacts on a person's self determination, the ability to plan, as well as to sequence and initiate, it becomes a primary component of this environment. The very core of the individual's existence including intimacy, the ability to plan, to organize, to behave in a socially acceptable manner, meaningful work, being spiritual and being human must be addressed. The miracles of modern science have attempted to control nature, defy mortality, and, in the process, have created even greater disabilities in individuals with long term needs. Since science has not developed a brain prosthesis, or a "self transplant", a model of an environment that addresses the functional disabilities must be developed to return individuals to their previous level of functioning as much as possible. This presentation gives an overview of life after brain injury based on this conceptual model.

SC 128

Astroglial (S100b and GFAP) and neuronal (NSE) proteins in serum as markers of the primary and secondary brain damage traumatic brain injury

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Introduction Assessment of the damage after severe traumatic brain injury (STBI) remains difficult. We investigated if release of astroglial (GFAP, S100b) and neuronal (NSE) specific proteins in peripheral blood, indicates primary and secondary damage and predicts outcome after STBI.
Method 89 patients with an admission Glasgow Coma Score (GCS) [lt] 8) had serial blood samples taken that were analysed for S100b, GFAP and NSE. Clinical and demographic variables: GCS, papillary reactions, ISS, CT-findings, hypoxia, hypotension, ICP and CPP. Outcome was assessed with the Glasgow Outcome Scale (GOS) at 6 months.
Results Means ([plusminus] SEM): 63 men and 26 women were included: Age=36.47[plusminus]3.36, admission GCS=4.8[plusminus]1.7, ISS=31.03[plusminus]1.55 and initial serum parameters taken 6.6[plusminus] 11hrs after injury were S100b=7.4[plusminus]24, GFAP=7.8[plusminus]29 and NSE=25.5[plusminus]43. Serum levels were higher in patients with bad as compared with good outcome (GOS 4 or 5): S100b (13.3[plusminus]6.6 vs. 3.7[plusminus]0.9), GFAP (15.7[plusminus]8.6 vs. 2.1[plusminus]0.3) and NSE (38.1[plusminus]12.0 vs. 14.7[plusminus]1.2). A correlation between serum parameters and ISS and TCDB CT categories was found. S100b, NSE and GFAP were independent predictors of outcome when analysed with a multivariate logistic regression model and correlated with duration of coma, posttraumatic amnesia and secondary complications (raised ICP, decreased CPP).
Conclusion Serum NSE, GFAP and S100b levels indicate the severity of the primary damage after STBI, have prognostic significance and release patterns of these brain specific proteins reflect the occurrence of secondary complications and may be of assistance in monitoring the efficacy of therapy aimed at treating these complications.

SC 129

Post polio syndrome and other health problems among hospital admitted polio patients

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Introduction New loss of function and health problems among patients with previous polio are frequently reported and may have several causes.
Method All patients referred to the Department of Neurology, Haukeland University Hospital, Bergen, for 13 months during 2000–2001 with diagnosis late effects of polio were examined prospectively to identify their symptoms and loss of function. Eighty-five patients 47–91 years old with mean age 61 years were included.
Results The most common major complaints were pain (44%), muscular weakness (27%), and fatigue (16%). Muscular weakness occurred in lower limbs in 75%, in respiratory muscles in only 5%. Climbing stairs was impaired in 71% and outdoor walking in 64%. 17 patients (19%) reported no loss of function.

Post polio syndrome (PPS) was diagnosed in 26% of the patients. They had all increasing muscle weakness with new atrophy. Polio-related loss of function including cervical and lumbosacral radiculopathies, mononeuropathies and degenerative joint disease were found in an additional 53%. 11 patients (13%) had distinct non-polio-related disorders that caused new loss of function, including CNS-lesions and depression. The remaining 8% had a stable condition.
Conclusion The majority of polio patients who seek hospital experience a new loss of function due to polio-related disorders. A careful neurological examination is necessary to identify the correct diagnosis and treatment.

SC 130

Effect of spinal cord stimulation on severe spasticity in patients with traumatic spinal cord injury

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Introduction The purpose of this study was to evaluate the effect of spinal cord stimulation (SCS) on severe spasticity of the lower limbs in patients with traumatic spinal cord injury (SCI) under close scrutiny of the site and parameters of stimulation.
Method 10 SCI patients (4 women, 6 men) were included in the study. Levels of spasticity before and during stimulation were compared according to a clinical rating scale and by surface electrode polyelectromyography (pEMG) during passive flexion and extension of the knee, supplemented by a pendulum test with the stimulating device switched either on or off over an appropriate period.
Results Both the clinical and the experimental parameters clearly demonstrated that SCS, when correctly handled, is a highly effective approach to controlling spasticity in the spinal cord injury subjects. The success of this type of treatment hinges on four factors: (*i*) the epidural electrode must be located over the upper lumbar cord segment (L1, L2, L3); (*ii*) the train frequency of stimulation must be in the range of 50–100 Hz, the amplitude within 2–7 Volts and the stimulus width of 210 μsec; (*ii*) the stimulus parameters must be optimised by clinically assessing the effect of arbitrary combinations of the four contacts of the quadripolar electrode; (iv) amplitudes of stimulation must be adjusted to different body positions.
Conclusion Severe spasticity affecting the lower extremities of patients with chronic spinal cord injuries can be effectively suppressed via stimulation of the upper lumbar cord segment.

SC 130a

First experience with the "LOKOMAT" gait orthesis in post-acute brain-injured patients

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Patients with severe brain injury may develop seriously disabling movement disorders, which may be due to lesions of the corticospinal pathways as well as extrapyramidal dysfunction. Lengthy immobilisation also affects somatosensory afferents and body image. Therapeutic application of a mechanical gait orthesis is a new approach in the management of impaired motor control and postural instability in neurological patients. We present our first experience using the "LOKOMAT" in a patient with post-traumatic spastic quadriparesis with left predominance, who was examined prior to, during, and after a three-week training period. The Functional Ambulatory Categories (FAC) improved from 1 to 2. The Ashworth Score improved from 3 to 1 in triceps surae and from 2 to 1 in hamstring muscles on the more affected side. Notably, muscle strength improved on the less affected side in triceps surae (4 to 5), quadriceps (4 to 5), hamstrings (3 to 4) and gluteus maximus (3 to 4, according to Oxford Scale). The 10-meter walking time deteriorated temporarily from 7.09 to 8.12 minutes, but subsequently improved to 5.12 minutes. The same pattern occurred in the 6-minute walking test, with distances of 8.3, 7.3, and 10.5 meters, respectively. Functional evaluation using the Rivermead Visual Gait Assessment (RVGA) revealed similar results: 28, 31, and 16 points, respectively. The transient functional deterioration may be explained by the necessity to replace pathological locomotor patterns and to adapt to a new, more physiological motor programme. The overall improvement, as measured by various scales, underscores the efficacy of the "LOKOMAT" as a new and promising adjunct to neurorehabilitation.
Results of the evaluation of four additional brain-injured patients will be presentated.

Child neurology

SC 131

Effect of the immunosuppressant drug FK506 on neonatal cerebral mitochondrial activities and energy metabolism after transient intrauterine ischemia in rats

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Introduction The immunosuppressant drug FK506 reduced neocortical infarct size due to middle cerebral artery occlusion in adult animals. In the immature brain, the effect of this immunosuppressant during ischemia and reperfusion is, however, unclear. In the present study, mitochondrial respiratory activities and energy metabolism were measured in neonatal rat brains to evaluate the influence of transient intrauterine ischemia on the near-term foetus and to assess the effect of FK506 treatment.
Method Transient intrauterine ischemia was induced by 30 min of the right uterine artery occlusion at 17 days of gestation in Wistar rats. The vehicle or 1.0 mg·kg-1 of FK506 was administered after 1 h of re-circulation. All of the pups were delivered by caesarean section at 21 days of gestation and samples of cerebral cortical tissue were obtained from pups at 1 h after birth. The mitochondrial respiration was measured polarographically in homogenates. For the analysis of ATP, ADP, and AMP, neonatal brains were frozen in situ and fluorometric enzymatic techniques were used.
Results In the neonatal cortical tissue exposed to ischemia, mitochondrial respiratory activities and ATP concentrations decreased significantly to about 59% and 67% of those in normoxic controls, respectively. The deterioration of both mitochondrial respiratory activities and high-energy phosphates was prevented by FK506, given 1 h after the start of re-circulation.
Conclusion The results indicate that the transient intrauterine ischemia is accompanied by mitochondrial dysfunction and

cellular bioenergetics failure in the neonatal rat brain and suggest that treatment with FK506 prevents the deterioration, even when administered after the ischemic periods.

SC 132

Maternal treatment with dexamethasone advances mitochondrial maturation in the fetal rat brain

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Introduction When pre-term delivery is anticipated, antenatal therapy with glucocorticoids has been used for more than two decades in an attempt to reduce the frequency of neonatal complications, especially respiratory distress syndrome. In the present study the hypothesis was explored that prenatal therapy with the synthetic glucocorticoid hormone, dexamethasone, may affect mitochondrial oxidative metabolism and induce the changes in mitochondrial activity in fetal brain.
Method Mitochondrial respiratory activities were measured in fetal rat brain after administration of dexamethasone. Mitochondrial respiration was measured polarographically using homogenates of fetal cerebral cortical tissues on days 16 (n=8 with saline; n=8 with dexamethasone), 18 (n=8 with saline; n=8 with dexamethasone) and 20 (n=8 with saline; n=8 with dexamethasone) of gestation. Four doses of dexamethasone (0.1 mg·kg-1) or vehicle (saline) were given, with an interval of 12 hours, until 12 hours before each measurement.
Results In the vehicle treated animals, mitochondrial respiratory activities were increased significantly after day 18 of gestation. Dexamethasone treated animals showed a significant increase in mitochondrial activity at day 16 of gestation compared with those in vehicle treated animals.
Conclusion The results indicate that prenatal dexamethasone treatment contributes to the precocious maturation of mitochondrial activity in the fetal rat brain. Because acceleration in cerebral mitochondrial activities is required immediately after birth in order to maintain high-energy phosphate levels, the precocious maturation may be crucial for the successful outcome of the pre-term infant.

SC 133

L-2-hydroxyglutaric acidemia: clinico-pathological presentation

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Introduction L-2-Hydroxyglutaric acidemia is a recently described, rare, neurometabolic disease characterized by elevated concentrations of L-2 hydroxyglutaric acid in body fluids. Pathological studies of this disease are scarce with only two reports published, one of which referred to a neonate.
Case report A patient, diagnosed of L-2-hydroxyglutaric acidemia, presented since infancy progressive intellectual and language deterioration, gait abnormalities, and cerebellar signs. Epilepsy was well controlled with phenobarbital. At the age of 15 years, he was severely mentally retarded, with dysphasia, pseudobulbar signs, optic atrophy, strabismus, hypoacusis, spastic tetraparesis, and choreo-dystonia in upper limbs. Brain neuroimaging studies showed generalized atrophy, atrophy of the corpus callosum, and extensive white matter abnormalities. The patient died at the age of 16 years, after a spontaneous mesenteric thrombosis and massive gastrointestinal haemorrhage. Neuropathological examination showed a brain with a pseudomicrogyrical pattern. The cerebral cortex showed moderate neuronal loss, subpial gliosis, with spongiosis of the neuropil, and subcortical cavitations. Massive demyelination was present in the white matter, with cystic cavitations and abundant hyperplastic GFAP-positive astrocytes. The corpus callosum was relatively better preserved as were the anterior commisure, corticospinal tract and optic radiations. The cerebellum was atrophic, with granular cell loss. Abnormal storage material was not observed in neurons or glial cells.
Conclusion We present the clinical and neuropathological postmortem findings of a patient with L-2-hydroxyglutaric acidemia. The pathological findings include cortical gliosis, spongiosis and white matter massive demyelination with cystic cavitations. L-2-hydroxyglutaric acidemia is a type of spongiform leukoencephalopathy with cystic cavitations prominent in subcortical areas.

SC 134

Bilateral nodular diffuse heterotopia and Ehlers-Danlos syndrome: familial association.

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Introduction Periventricular heterotopias are clusters of neurons in the peri- or subventricular areas, secondary to abnormalities in neural proliferation or migration in the embryonic germinal zone. It may appear in children or adults with epilepsy, neurodevelopmental disorders, or as an incidental finding on imaging studies. The best-characterized syndrome is bilateral nodular diffuse heterotopia secondary to mutation in the filamin gene in the X q28 locus. This X-linked malformation usually presents in females, given its high lethality in males. The Ehlers-Danlos syndrome (EDS) includes a heterogeneous group of disorders of characterized by cutaneous hyperelasticity, articular hypermotility and tissue fragility. It is rare, with various subgroups, most with an unknown biochemical defect. Although bilateral nodular diffuse heterotopias in association with EDS have been reported in two case reports, familial associations of these two syndromes have not been described.
Method We describe a pedigree with 3 patients presenting bilateral nodular heterotopia, diagnosed by magnetic resonance imaging, and EDS type III. All were females. The pedigree showed an X-linked pattern of inheritance. A patient had a male abortion, and a male offspring died hours after birth with various malformations. Two patients were epileptic, and one presented a subarachnoid haemorrhage with negative angiography. One patient was asymptomatic.
Conclusion We present the clinical and radiological findings of a family with a bilateral diffuse nodular heterotopia and EDS type III. Matrix extracellular proteins involved in the pathogenesis of EDS may also affect neuroblast migration in its initial stages.

SC 135

Angelman Syndrome: further evidence of phenotypic evolution in adults

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Summary Angelman syndrome (AS) is a genetic disorder characterized by neurodevelopment delay with severe intellectual disability, speech absence, inappropriate laughter, sleep disturbances, movement disorders including tremor, gait ataxia, seizures with characteristic electroencephalographic pattern. Frequently associated features include postnatal microcephaly, macrostomia with wide-spaced teeth and tongue thrusting, prognathism, strabismus, hair skin and eyes hypopigmentation. Genetically AS results from the loss of function of maternally expressed genes clustered on chromosome 15 q11-q13 and subject to genomic imprinting. The most common defect give rise from a large maternal deletion while point mutations involving UBE3A, abnormalities in the imprinting process and paternal uniparetal disomy (UPD) have been reported in a minority of patients. The complete clinical picture is associated with maternal 15q11-13 deletion (contiguous genes syndrome) also involving P gene. The P gene is responsible for the hypopigmentation often present in these patients. We describe new ocular findings, retinochoroidal dystrophy (RCD), associated with optic disk paleness in two adult severely mental retarded patients with Angelman syndrome due to maternal 15q11-13 deletion. These ophthalmologic abnormalities are a further evidence of a phenotypic evolution in adult AS patients. Moreover they suggest that ophthalmologic examination may help in differential diagnosis of adult mentally retarded patients with overlapping clinical pictures. In addition, the problems related to progressive visual loss should be considered in management and prevention of long-term disability in AS patients.

SC 136

An analysis of 20.200 children / adolescents who sustained traumatic brain injuries in the USA

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Introduction This presentation will examine data collected by the National Paediatric Trauma Registry (NPTR) on 20,200 children/adolescents who sustained brain injuries from 1994 to present.

Method The data will be analysed for the following variables: gender, age, cause of injury, place and time of occurrence of the injury event, severity of the brain injury, and utilization of resources during the acute hospital stay. The National Paediatric Trauma Registry (NPTR) compiles information about many aspects of paediatric trauma. Data is compiled on children and adolescents age 0 to 19 years who are admitted to the hospital for acute injury. Functional status of children at the time of discharge is rated in nine functional domains: vision, hearing, speech, self-feeding, bathing, dressing, walking, cognition and behaviour. The performance of the child in these functional areas is rated by clinicians as being "age appropriate," "impaired," or "unable."

Results Among the children and adolescents in this sample, most children (63.6%) sustained multiple injuries to the head and other body regions; most injuries occurred between noon and midnight (67.7%); on the road (50%) or at home (32%). Nearly 90% of the injuries were non-intentional, with the most frequent causes being falls (30%), motor vehicle crash (32%), pedestrian injuries (15.9%), and bicycle injuries (10.3%). Among the children analysed, 6.1% died and 68.8% left the hospital without apparent functional limitation, 16% had one to three limitations, and 6.2% had four to none functional limitations.

Neuroepidemiology Neurogenetics

SC 137

Myoclonus-dystonia syndrome in a large Danish family caused by a mutation in the epsilon-sarcoglycan gene

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Introduction Myoclonus-dystonia syndrome (MDS) is an autosomal dominant disorder with incomplete penetrance characterized by myoclonus or dystonia or frequently a combination of both without other signs of neurological dysfunction. MDS is almost always alcohol responsive, in accordance with the earlier name: "inherited dystonia with lightning jerks responsive to alcohol". In 1999 MDS was linked to a 28cM region of chromosome 7q21-q31[(1.)] and in 2001 the gene was identified to be epsilon-sarcoglycan gene (SGCE)[(2.)]. Another locus for MDS was found on chromosome 11q in a large family [(3.)], but not yet verified. We report on two families who were independently referred with dystonia.

Method The two probands and twelve relatives were examined clinically and blood samples were collected. Linkage analysis was performed in one of the families with two affected children, before the gene was identified. The markers D7S515 and D7S492 were used. Sequence analyses of all eleven exons were done on DNA from the two probands, and of the relevant exon on DNA from all relatives.

Results 7 affected were found in three generations in the two families. The affected individuals differed phenotypically as they presented from very few myoclonic jerks to generalized dystonia. The linkage study showed lod score 0.3. A not earlier reported deletion (974delC or R325X) in exon 7 in SGCE was found in the two probands, the five affected relatives and in one non-affected proband.

Conclusion We have confirmed that mutation in SGCE can cause MDS. Six mutations in the SGCE causing MDS are now reported, including the here described.

SC 138

Reduction in size of the myotonic dystrophy trinucleotide repeat mutation during transmission

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Introduction Myotonic dystrophy type 1 (DM1) is a multisystemic disease caused by expansion of a CTG repeat, located in the 3-untranslated region of the DMPK gene. This locus appears to show most dramatic instability, with often very high levels of somatic mosaicism and large intergenerational differences. The size of DMPK expansion usually increases upon intergeneration transmission and underlies phenomena of genetic anticipation. However, the reduction (contraction) in size of the DM1 trinucleotide repeat mutation during transmission is relatively rare (exclusively in male transmission).
Method DNA was isolated from white blood cells of 10 DM1 parent-child pairs, using a standard phenol chloroform protocol. All subjects were studied by both polymerase chain reaction (PCR) and Southern blot analyses.
Results We analysed a CTG repeat expansion (progenitor allele) in 8 mother-child and 2 father-child pairs. In all cases of maternal transmission we found increased CTG repeat expansion in the children (from 63 to 123 CTG repeats in the mothers and 129 to 566 CTG repeats in the children). In one father-child pair we found increased CTG repeat expansion (from 126 to 313) but in the other paternal transmission we found reduction (contraction) in size of the CTG repeats (from 113 to 96).
Conclusion We analysed intergeneration transmission in 10 DM1 parent-child pairs and found only one intergegerational contraction in a case of father-child transmission. However, it is not clear whether this is a true contraction or just a reduction of CTG repeat expansion due to age-dependent somatic expansion.

SC 139

Genetic analysis of LMNA in patients with dilated cardiomyopathy and/or conduction defects.

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Introduction Dilated cardiomyopathy (DCM) is a common condition characterized by ventricular enlargement and systolic dysfunction. Mutations in the lamin A/C gene (LMNA), responsible for autosomal dominant and recessive Emery Dreifuss muscular dystrophy, have been associated with familial DCM with conduction system defects. The frequency and genotype-phenotype correlation of LMNA mutations in these conditions remain unknown. The objective of this study was to determine the frequency and clinical relevance of LMNA mutations in isolated DCM and/or conduction defects.
Methods 61 patients were divided into 3 subgroups: (1) pure DCM (28), (2) conduction defects/arrhythmias (19) and (3) combination of both (14). The patients were screened for LMNA mutations using polymerase chain reaction (PCR), denaturing high-performance liquid chromatography (DHPLC) and sequence analysis.
Results Two novel mutations were identified: the heterozygous missense mutation, R435C, was found in a male patient (JiR) suffering from DCM without rhythm disturbances. The second mutation, a heterozygous missense mutation (R343Q), was found in a male patient (NE5) suffering from conduction defects requiring pacemaker. Several relatives of NE5 were diagnosed serious rhythm disturbances and some died of sudden cardiac death. Two relatives had severe elbow contractures. The case appeared familial and the mutation segregated with disease phenotype.
Conclusion (1) Mutations in LMNA gene in cases of isolated DCM and/or conduction defects are rare (2/61) and their clinical relevance low; (2) DCM is genetically highly heterogeneous and is probably caused by rare mutations in many genes; (3) mutations in LMNA gene may rarely cause pure dilated cardiomyopathy without rhythm disturbances.
Supported by Telethon Italy and IGA MZCR NF 5919-3.

SC 140

Effect of the G-174C interleukin-6 promoter polymorphism on the outcome after cerebral infarction

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Introduction Increased interleukin-6 (IL-6) levels in plasma and cerebrospinal fluid of patients with cerebral ischemia (CI) are independent factors for early clinical worsening. The production of IL-6 is genetically controlled and gender-dependent.
Method To examine, whether the IL-6 G-174C polymorphism influence the clinical course of CI and if the influence is gender-dependent, we typed IL-6 genotypes (PCR-RFLP method) in 301 patients with CI, and in 80 control subjects.
Results The distribution of genotypes in patients population was: C/G (49.2%), G/G (27.9%), C/C (22.9%) (No significant difference has been noticed between male and female subjects) and in controls: C/G (55.5%), C/C 26.5%), G/G (18%). Compared to allele-C non-carriers, allele-C carriers (C+) showed significantly better functional outcome at discharge as measured using the Barthel Stroke Scale and Oxford Handicap Scale ($p=0.009$ and $p=0.03$, respectively). However, this observation was restricted to the male population. The influence of IL-6 genetic polymorphism on 30-days mortality rate was observed only in women population. The C/G genotype carriage was associated with the highest mortality rate (22.5%) as compared with C/C and G/G genotypes carriage (summarized fatality rate 10.6%), $p=0.07$. In univariate logistic regression analysis, the C/G genotype carriage in women was associated with 2.5 fold increased risk of death during 30-days period following stroke (OR=2.56, 95%CI 1.27-5.18, $p=0.009$).
Conclusion Results of our study suggest that genetic variation at the IL-6 locus in Polish stroke patients population is a genetic factor that influence the clinical course of the disease with differences in its significance in male and female populations.

SC 141

Angiotensin converting enzyme ACE gene polymorphism is as a risk factor for ischemic stroke due to large or small vessels disease.

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Introduction The aim of this study was to assess the significance of ACE gene deletion/insertion (D/I) polymorphism in patients with large vessel disease as compared to other stroke etiologies.
Method We genotyped 167 ischaemic stroke patients (mean age: 68.5±13.1 years, 52% female) and 51 healthy controls matched for age and sex. Stroke aetiology was classified according to TOAST criteria.
Results There was not significant difference in the ACE genotype distribution of all stroke patients and controls (D/D-23, 9%, D/I-47, 4%, I/I-28, 7% vs. D/D-23, 5%, D/I-52, 9%, I/I 23.5%). The genotype distribution of 74 patients with large vessel disease (D/D-18.9%, D/I-52.7%, I/I-28.4.%) was not different from patients with other determined stroke etiologies, small vessel disease and cardioembolic stroke (n=76): (D/D-28.9%, D/I-42.2%, I/I-28.9%) and patients with undetermined or rare aetiology (n=17): (D/D-23.5%, D/I-47.1%, I/I-29.4%), p=n.s.
Conclusion We did not observe an association between ACE gene deletion/insertion (D/I) polymorphism in patients with the diagnosis of stroke due to large or small vessels disease.

SC 142

Self-reported stress and risk of stroke

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Introduction The objective of this study was to examine the association between self-reported stress and risk of stroke.
Method 12,574 participants in the Copenhagen City Heart Study were followed-up from 1981–83 until 31. 12. 97 for new first-time ever stroke (FES) events. The WHO stroke definition was used. Participants were asked about their stress level; light, moderate, or high, and about how often they were stressed: never/hardly ever, monthly, weekly, or daily. In Cox regression analyses, using age as time axis, adjustment was done for: gender, smoking; education; physical activity; body mass index; systolic blood pressure; alcohol intake; diabetes mellitus; forced expiratory volume in one second; and myocardial infarction. Fatal strokes were defined as events where the patient died within 28 days from stroke onset.
Results 929 subjects developed a FES (456 women 49.1%) and 473 men (50.9%). Of these 207 (22.3%) were fatal. In analyses of all strokes and non-fatal strokes there were no significant associations between self-reported stress and risk of stroke. In analyses of fatal stroke a high level of stress, and weekly experience of stress were associated with an increased risk of FES, relative risk=1.88 (95% CI: 1.10–3.19), and 1.48 (95% CI: 1.00–2.21), respectively.
Conclusion The present study indicates that a high level of self-reported stress and weekly experience of stress are associated with an increased risk of fatal stroke.

Monday, October 28

Movement disorders 1

SC 201

Slower progression of Parkinson's disease in patients treated with ropinirole compared with L-dopa: REAL-PET – a randomised controlled 18F-dopa PET study

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Introduction A 2-year, double-blind, multicentre study was conducted to compare rates of loss of putamen dopamine terminal function in patients with early PD treated with ropinirole or L-dopa.
Methods The primary endpoint was change in putamen ^{18}F-dopa uptake (Ki) measured using positron emission tomography. Data were transformed into standard stereotactic space and analysed with a standard region-of-interest template and statistical parametric mapping. Dyskinesias were defined as a score of at least 1 on item 32 of the Unified PD Rating Scale or their report as an adverse event.
Results 93 patients were randomised to each group; 73% of the ropinirole and 74% of the L-dopa group completed the study. Loss of putamen Ki was significantly less with ropinirole (–13%) than L-dopa (–20%; p=0.022). Nigral dopamine storage deteriorated with L-dopa but not ropinirole. The mean treatment difference at baseline was greater for the more affected side (9.4 [95%CI 2.4–16.4]) compared with the less affected side (4.3 [95%CI 1.9–10.5]). Fewer patients in the ropinirole group developed dyskinesias compared with the L-dopa group (3/92 and 23/91 of patients, respectively; p=0.0002). Within the L-dopa group there was no significant difference in median loss of putamen Ki for patients with dyskinesias (–23.3%, n=19) compared with those without (–18.5%, n=40; p=0.52).
Conclusion The loss of dopamine terminal storage capacity (a measure of disease progression) was 30% slower in patients with early PD taking ropinirole compared with those taking L-dopa. Additionally, use of L-dopa was associated with a 10-fold higher incidence of dyskinesias.

SC 202

Pramipexole versus Levodopa in the CALM-PD CIT study: Effects on Parkinson's disease progression assessed by dopamine transporter imaging

Parkinson Study Group
Presented by Kenneth Marek
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Introduction Dopamine transporter imaging with [123I]b-CIT was used to compare the nigrostriatal dopaminergic degeneration after initial treatment with pramipexole or levodopa in early PD.
Methods Patients (N=82) in the CALM-PD study (JAMA 2000; 284:1931–1938), underwent 4 scans during a 46-month period. Participants were recruited at 17 centres in North America. The primary outcome variable was the percent change

from baseline in striatal [123I]b-CIT uptake after 46 months evaluation. Clinical severity of PD was assessed using the "defined off" UPDRS.

Results In the study cohort sequential SPECT imaging showed a decline in [123I]b-CIT striatal uptake from baseline of 10.3±9.8% at 22 months (n=78), 15.3±12.8% at 34 months (n=71) and 20.7±14.4% at 46 months (n=65). Comparison of the treatment groups demonstrated that the percent loss in striatal [123I]b-CIT uptake from baseline was significantly reduced in the group initially treated with pramipexole compared to the group initially treated with levodopa: 7.1±9.0% vs. 13.5±9.6% at 22 months p=0.004; 10.9±11.8% vs. 19.6±12.4% at 34 months, p=0.009; and 16.0±13.3% vs. 25.5±14.1% at 46 months, p=0.01. The percent loss from baseline in striatal [123I]b-CIT uptake was correlated with the change from baseline in UPDRS at the 46 month evaluation, r=–0.40, p=0.001.

Conclusion Patients treated initially with pramipexole demonstrated a relative reduction in percent loss from baseline of striatal [123I]b-CIT uptake of approximately 40% compared to those treated initially with levodopa during a 46-month evaluation. These imaging data highlight the need to further compare imaging and clinical endpoints of PD progression in long-term studies.

SC 203

Cancelled

SC 204

Clinical impact of performing SPECT imaging with the dopamine transporter imaging agent 123 I-ioflupane (DaTSCAN™) in patients with a clinically uncertain diagnosis of Parkinsonian syndromes

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Introduction SPECT with DaTSCAN™ has been reported to be useful in the differential diagnosis of PS. This study was conducted to assess the impact of DaTSCAN™ both upon the neurologist's diagnostic confidence of PS and clinical management of patients with clinically uncertain PS.

Methods A prospective, open clinical trial was conducted in 15 European hospitals. DaTSCAN™ SPECT was performed on 118 patients with clinically uncertain PS. Images were visually classified as normal (symmetric intense tracer uptake in striatum) or abnormal (asymmetric or bilaterally decreased putamen or whole striatal uptake). The level of confidence of the neurologist in the diagnosis of PS (not confident at all=0%, completely confident=100%), and the patients' planned management were recorded before and after knowledge of the DaTSCAN™ image.

Results DaTSCAN™ imaging had an impact on diagnosis (either more confident with or a change in their initial diagnosis) in 109/118 patients. After imaging with DaTSCAN™ the neurologists became more confident with their initial diagnosis in 56 of these 109 and the initial diagnostic suspicion was changed from "PS" to "other than PS" or from "other than PS" to "PS" in the remaining 53. After imaging, planned clinical management was changed in 72% of patients. Changes involved therapy in 64.3% of cases, including either initiation or discontinuation.

Conclusion Visual assessment of SPECT with DaTSCAN™ increases the neurologist's confidence in the diagnosis of patients who present with uncertain PS and can lead to changes in the initial diagnosis as well as in the clinical management of these patients.

SC 205

Service use and costs of Parkinson's Plus syndromes

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Multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) are diseases that result in increasing disability and eventual death. MSA and PSP are likely to entail the use of a wide number of healthcare and social services and it is also probable that patients will require substantial support from family members. Therefore, the economic costs associated with PSP and MSA may be high, but no known health economic studies have previously been reported. This paper will present service use information and economic costs for around 800 patients with PSP or MSA in France, Germany and the UK from the NNIPPS (Neuroprotection and Natural History in Parkinson Plus Syndromes). Use of a wide range of formal services and informal care will be measured over a six-month period and costs will be calculated using an established method. Whilst the average costs of PSP and MSA will be of interest, it will be more informative to identify factors that are predictive of variations in cost. Therefore a multiple regression model will be presented with the dependent variable being service costs and patient and illness characteristics used as potential predictor variables. Such a model could be of use to those planning services for this patient group.

SC 206

Olfactory function distinguishes vascular parkinsonism from Parkinson's disease

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Introduction Olfaction is markedly reduced in Parkinson's disease (PD), irrespective of disease duration and treatment. We evaluated olfactory function in patients with a clinical diagnosis of vascular parkinsonism (VP).

Method The 40-odour University of Pennsylvania Smell Identification Test (UPSIT) was used. VP was diagnosed according to criteria proposed by Winikates&Jankovic 1. MRI inclusion criteria were modified based on findings by Zijlmans 2, requiring either bilateral white matter lesions or basal ganglia lesions. Significant cognitive impairment was an exclusion criterion. Each VP patient was matched for age, sex and smoking status with two normal controls and two PD patients.

Results Thirteen VP patients were tested (7 men, 6 women). Mean age was 73.5 years (range: 65-88). Mean UPSIT scores were: VP: 25.5 [SD 4.8]; PD: 16.1 [5.9]; normal controls: 27.5 [4.5]. The mean difference between VP and PD was 9.34 (95% CI 5.7, 13.0; $p<0.0001$); mean difference between VP and normal controls: –2.0 (95% CI –5.6, 1.4; $p=0.23$).
Conclusion Olfactory function was found to be significantly better in patients fulfilling clinical criteria for VP than in PD. Testing olfaction may help to differentiate between these two causes of parkinsonism.
Literature
1) Winikates J, Jankovic J (1999). Clinical correlates of vascular parkinsonism. Arch Neurol; 56:98–102.
2) Zijlmans JCM, Thijssen HOM, Vogels OJM, Kremer HPH, Poels PJE, Schoonderwaldt HC, et al (1995). MRI in patients with suspected vascular parkinsonism. Neurology; 45:2183–2188.

Multiple sclerosis

SC 207

Consensus guidelines for standardized MRI assessment of multiple sclerosis (MS)

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Introduction The objective of this study was to develop consensus guidelines for MRI standardized diagnostic protocols, and indications for follow up, in multiple sclerosis (MS). MRI is usually done as part of the diagnostic workup for MS. There are no guidelines for the use of MRI in practice. Standardized MRI protocols would help maximize the value of individual scans, as well as allow systematic data collection for clinical and comparison studies.
Method An expert consensus meeting on "MRI Protocols for the Diagnosis and Follow Up of MS", sponsored by the Consortium of MS Centres (CMSC) was convened November 3–4, 2001 in Vancouver. Participants included MS neurologists and radiologists from North America, Europe, and New Zealand, with representation from the American Academy of Neurology, American Society of Neuroradiology, and Radiological Society of North America.
Results Preliminary results propose ten MRI guidelines. The guidelines suggest a standardized MRI protocol to image brain and spinal cord, with specified required and optional features. Images would be obtained on a 1 Tesla or higher machine, using a slice thickness of £ 3mm (£ 1.5mm for 3D sequences), without gaps. Scan orientation would be on the subcallosal line using 3 planes, and a localizer if available. Routine follow up MRI's in practice are not recommended, until standardization has been validated. A prototype radiology report is suggested using standardized and consistent common language, describing such features as lesion number, location, size, shape, and character. A copy of the MRI should be retained permanently for future comparison.
Conclusions Consensus guidelines are available for review on the CMSC website for discussion and comment.

SC 208

Nitric oxide metabolites correlate with Gd-enhanced MRI activity in patients with multiple sclerosis

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Introduction Increased levels of the nitric oxide metabolites, nitrate and nitrite (NOx), were found in MS patients. This study aimed to investigate the relation of CSF and serum NOx to the disease progression and MRI markers of the disease activity.
Methods 33 MS patients [16 relapsing-remitting (RR) and 17 secondary progressive (SP) MS] and 15 control subjects were enrolled in the study. Total CSF and serum NOx was measured using a vanadium-based assay. MRI assessment included the number and volume of Gd-enhancing lesions, T1-hypointense and T2-hyperintense lesions. The clinical status of patients was assessed using the EDSS.
Results NOx was significantly raised in CSF (10.0±5.1μM vs. 6.3±2.2mM, $p=0.001$) but not in serum (42.4±11.1μM vs. 36.8±15.7μM, $p=0.1$) of MS patients compared to controls. We found significantly higher CSF NOx level in MS patients with EDSS<=4.0 compared to patients with more advanced disability (EDSS>4.0) (11.7±5.7μM vs. 7.8±3.0μM, $p=0.018$). The CSF/serum NOx index correlated with the volume of cerebral Gd-enhancing lesions ($R=0.41$; $p=0.014$). In the subset of patients with Gd-enhancing MRI lesions ($n=11$), representing acute inflammatory activity, a stronger correlation between the volume of Gd-enhancement and both CSF NOx ($R=0.74$; $p=0.01$) and the CSF/serum NOx index ($R=0.78$; $p=0.007$) was found. There was no correlation between the CSF and serum levels of NOx.
Conclusion CSF NOx levels, an indicator of intrathecal NO production, were increased in mildly disabled MS patients and correlated with acute inflammatory disease activity as measured by Gd-enhanced MRI.

SC 209

Functional cortical changes in patients with multiple sclerosis (MS) and non-specific conventional MRI scans of the brain

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Method Using functional magnetic resonance imaging (fMRI), we assessed the patterns of brain activations associated with simple motor tasks in 12 right-handed patients with clinically definite multiple sclerosis (MS) and non-specific T2-weighted abnormalities on conventional MRI scans of the brain and compared them with those from 12 sex- and age-matched right-handed healthy controls. Also investigated were the extent to which the fMRI changes correlated with normal-appearing white matter and grey matter (GM) pathology, measured using diffusion tensor MRI.
Results When performing the simple motor task with the dominant hand, MS patients had more significant activations of the ipsilateral supplementary motor area (SMA), the ipsilateral

superior frontal sulcus, the contralateral superior temporal gyrus, and the thalamus than controls. On the contrary, healthy subjects showed more significant activations of the medial part of the contralateral parieto-occipital fissure and the ipsilateral primary sensori-motor cortex (SMC) than patients with MS. In patients with MS, the relative activation of the ipsilateral SMA was correlated with the peak height ($r=-0.88$, $p<0.001$) and position ($r=0.87$, $p<0.001$) of the GM mean diffusivity histogram.

Conclusion This study shows that cortical reorganization occurs over a rather distributed sensorimotor network even in patients with MS and non-specific abnormalities on conventional brain MRI scans. This suggests that, in patients with MS, an increased recruitment of movement-associated cortical network can be elicited by the presence of normal appearing brain tissue pathology, which is independent of macroscopic T2-weighted abnormalities.

SC 210

Evidence of more extensive tissue damage in MS patients with APOE-ε4: two-year MRI follow-up shows higher proportion of lesions evolving to "black holes"

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Introduction The APOEe4-allele (e4) has been associated with clinical worsening in multiple sclerosis (MS) and more pronounced tissue damage on MRI and ^{1}H-MRS. We attempted to consolidate this assumption by using serial MRI of the brain to follow the evolution of "black holes", a putative marker of matrix destruction and axonal loss.

Methods 99 individuals with clinically definite relapsing-remitting MS (age 35.3+/–9.5yrs, disease duration 6.6+/–7.2yrs, Expanded Disability Status Scale 1.5+/–1.2) underwent genotyping and clinical examination. T_2- and T_1-weighted axial MRI of the brain (1.5 T, TR/TE=2500/30 and 90; 600/15) for semi-automated lesion segmentation was performed at baseline and after 2.7+/–1.1 yrs. "Black holes" were defined as T_1-lesions with signal intensity between cortical grey matter and cerebrospinal fluid.

Results At baseline, T_2- and T_1-lesion loads (LL) were non-significantly higher in patients with e4 (n=23; T_2-LL: 11.8±11.4; T_1-LL:1.2±2.3ccm) than in those without e4 (n=76; T_2-LL:8.9±9.5; T_1-LL:0.7±1.8ccm), despite a shorter disease duration (4.2±5.2 vs. non-e4:7.4±7.6 yrs, p=0.06) and the absence of significant differences in clinical variables between groups. During follow-up, T_2-LL significantly enlarged in patients without e4 (10.6±11.0ccm; p=0.001), whereas it remained unchanged in e4-carriers (11.3±11.7ccm). In contrast, T_1-LL significantly increased in the e4-subgroup (1.7±2.7 vs. non-e4:0.8±1.5ccm, p=0.039). Moreover, the proportion of "black-holes" [(T_1LL/T_2LL)x100] increased significantly from 5.5±7.7% to 12.4±13.9% (p=0.005) in e4-patients whereas it did not change significantly in non-e4 patients (baseline:5.0±7.9%, follow-up:5.7±7.3%, p=0.37).

Conclusion The observed higher proportion of MRI brain lesions that develops into black holes in MS patients with e4 provides further support for a more aggressive disease course in e4 carriers.

SC 211

A combined fMRI-TMS study on the effects of 3,4-diaminopyridine on brain motor function in multiple sclerosis

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Introduction 3,4-diaminopyridine (3,4-DAP), a potassium channel blocker, improves motor function in Multiple Sclerosis (MS). Both axonal and synaptic mechanisms have been postulated. We evaluated the effect of a single dose of 3,4 DAP on motor function in MS by combining fMRI, transcranial magnetic stimulation (TMS), and quantitative EMG.

Method We conducted a double-blind, crossover, placebo-controlled study in 7 women (mean ±SD age 38.9±9.9 years; median, range EDSS 2.0, 1.0–2.5) with relapsing-remitting MS. Each patient underwent fMRI in two separate occasions (under 3,4-DAP and under placebo) while performing a sequential thumb to index finger opposition task with the right hand. fMRI data were analysed using SPM99. After each fMRI study, paired transcranial magnetic pulses were delivered in a conditioning-test design with stimuli given at 3 and 10 ms inter-stimulus intervals (Kujirai et al, 1993) to test cortical excitability. EMG at maximum voluntary contraction for 120 s was also performed.

Results At fMRI the extent of activation in motor related areas was greater under 3,4-DAP than under placebo. In particular, a significantly higher activation was observed in the contralateral premotor area and in the contralateral primary motor area ($p\leq0.05$, paired t-test).

At neurophysiological evaluation 3,4-DAP produced a significant increase in cortical excitability both by reducing intracortical inhibition and by enhancing intracortical facilitation. Left central conduction time did not change.

Conclusion Our data suggest that 3,4-DAP modulates brain motor activity in MS by increasing the extent of cortical activated areas. This effect is probably due to an increased activity of excitatory synapses.

SC 212

Intense immunosuppression followed by autologous stem cell transplantation in severe multiple sclerosis

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Introduction Autologous haematopoietic Stem Cell Transplantation (ASCT) could be a new alternative therapeutic approach for severe cases of MS unresponsive to conventional therapies. Phase I studies have already been carried out, suggesting a possible clinical benefit but also showing a high mortality risk.

Method In Italy a phase II study has been organized, aiming to obtain information on the effect of ASCT on Magnetic Resonance Imaging (MRI) and other laboratory tests. 16 cases of secondary progressive multiple sclerosis (MS) patients, with EDSS between 5 and 6.5, unresponsive to traditional therapies, with MRI enhancing activity were treated with Cyclophosphamide 4grxm^2 followed by BEAM (BCNU, Cytosine-Arabinoside, Etoposide, Melphalan) conditioning regimen and rabbit ATG for T depletion in vivo. Patients were then submitted to monthly MRI, neurophysiological tests, quality of life evaluation, CSF examination (in 3 cases only).

Results In all patients we observed a complete abrogation of MRI enhancing activity which is sustained with time. The median follow up is now 24 months (range 5–42 months). Oligoclonal bands at immunoblotting were still found in the CSF after therapy. Quality of life improved. Clinically 14 cases remained stable or slightly improved while 2 cases resumed worsening after 9 and 36 months, respectively.
Conclusion These studies demonstrate that ASCT has a profound and sustained effect on MRI gadolinium enhancing activity. The clinical efficacy has to be demonstrated in a phase III study, comparing ASCT to standard immunosuppressive therapy.

Neuro-oncology

SC 213

Identification of DNA and amino acid metabolism in human gliomas by PET

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Introduction The objective of our study was to non-invasively compare DNA metabolism and amino-acid uptake in patients with gliomas by positron emission tomography (PET).
Method 7 patients (57.3±12.6 years) with astrocytoma WHO grade II (n=2), astrocytoma WHO grade III (n=1) and glioblastoma (n=4) were studied by multi-tracer PET on consecutive days. The DNA-, protein- and glucose-metabolism was determined by means of 3'-deoxy-3'-[18F]fluoro-L-thymidine (FLT), L- [methyl-11C]methionine (MET) and 2-[18F]fluoro-2-deoxy-D-glucose (FDG) PET after intravenous administration of [18F]FLT (251.6±114.7 MBq; range: 111–370 MBq), [11C]MET (720 MBq) and [18F]FDG (370 MBq), respectively. Moreover, high-resolution magnetic resonance imaging (MRI) was performed to allow co-registration of anatomical and metabolic data.
Results In all patients, [18F]FLT- and [11C]MET-PET images demonstrated a similar extent of tumour activity. Relative thymidine uptake (defined by [18F]FLT accumulation within the tumour in relation to a contralateral control region) was greater than relative methionine uptake. Maximal relative [18F]FLT uptake ratios ranged from 4.6±1.9 (astrocytoma grade II) to 12.7±1.9 (glioblastoma) and maximal relative [11C]MET uptake ratios ranged from 2.7±1.4 to 4.2±1.1, respectively. Moreover, one patient with glioblastoma demonstrated focal [18F]FLT uptake at the border of the tumour where relatively low methionine uptake was observed as possible indication for actively proliferating tumour tissue visualized by [18F]FLT-PET.
Conclusion [18F]FLT is a promising tracer to study tumour proliferation especially in areas with high [18F]FDG background, such as the brain. Relative [18F]FLT uptake within gliomas is greater than relative [11C]MET uptake indicating the possible role of [18F]FLT in improved diagnosis of critical tumour areas such as the glioma border and of low grade gliomas.

SC 214

In vitro model to assess neurotoxicity induced by anticancer chemotherapeutic agents

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Introduction Most chemotherapeutic agents have some deleterious side effects on normal host tissues. Also 5-Fluorouracil (5-FU) carries a risk of central nervous system toxicity such as leukoencephalopathy. We examined the ability of 5-FU exposure to kill cultured mouse cortical neurons and glia.
Method Mixed neuron/glial, astrocytic, and mixed oligodendrocyte/astrocyte cultures were exposed to 5-FU for 24 hours. Neuron and astrocyte damage was assessed by LDH assay and oligodendrocyte death was assessed by counting the number of viable galactocerebroside-positive (Gal-C(+)) cells per 100× field.
Results Neurons and astrocytes exposed to 10, 30, 100 and 300 μM 5-FU produced no changes in morphology and level of LDH. But mixed oligodendrocyte/astrocyte cultures exposed to 10, 30, and 100 μM 5-FU developed concentration-dependent oligodendrocyte death. Most oligodendrocytes were damaged by 100 μM 5-FU, but there was little damage on astrocytes.
Conclusion These findings suggest that oligodendrocytes are selectively vulnerable to 5-FU, and neurons and astrocytes were relatively resistant to 5-FU. Present observations raise the possibility that leukoencephalopathy associated with 5-FU may be caused by the drug-induced death of oligodendrocyte.

SC 215

Molecular imaging in the development of efficient gene therapy of human glioma

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Introduction The objective of our study was to non-invasively evaluate the safety and efficiency of vector delivery and gene transduction after gene therapy of patients with recurrent glioblastoma by positron emission tomography (PET) and magnetic resonance imaging (MRI).
Method 8 patients (age: 49–67) received a stereotactically guided Gd-DTPA infusion with subsequent MRI and intratumoral convection-enhanced-delivery (CED; max. flow: 0.6 ml/h, volume 30–60 ml) of a liposome-gene-complex (LGC; DAC-Chol/DOPE [w:w; 30:70]) transducing herpes simplex virus type 1 thymidine kinase (HSV-1-TK). Thereafter, PET was performed after injection of [124I]-2'-fluoro-2'-deoxy-1-ß-D-arabinofuranosyl-5-iodo-uracil ([124I]FIAU), a specific marker substrate for HSV-1-TK. Ganciclovir (GCV) treatment (2 x 5 mg/kg; 14 days) was started four days after LGC-infusion. Treatment response was recorded by MRI, [18F]-2'-fluoro-2'-deoxy-D-glucose (FDG) and L-[methyl-11C]-methionine (MET) PET.
Results Infusion of LGC was tolerated well. In 1/8 patient specific [124I]FIAU-accumulation was observed as indication for HSV-1-TK expression in co-registration to signs of necrosis after GCV treatment (FDG-/MET-PET). In 4/8 patients [18F]FDG- and [11C]MET-uptake was focally decreased in

areas co-registering to the distribution volume of Gd-DTPA. One patient showed transient reduction of the methionine positive tumour-volume by 50%. All patients developed tumour relapses outside areas with reduced tracer activity.
Conclusion Intratumoral CED of LGC is safe and leads to focal alterations of tumour activity. However, overall therapeutic efficacy is low indicating that more efficient vectors have to be engineered. Non-invasive imaging of vector distribution and vector-mediated gene expression by PET and MRI shall contribute to the development of standardized gene therapy protocols and improve efficiency and safety of vector applications in humans.

SC 216

ACNU+VM 26 as an alternative to PCV in chemotherapy of oligodendroglioma.

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Objective This study looks for a possibly better and less toxic regimen than PCV chemotherapy for recurrent oligodendroglioma.
Methods 12 patients (8 oligodendrogl., 3 oligoastroz., 1 radiological/clinical diagnosis only) with progressive contrast enhancing tumors in MRI/CCT received 2–7 cycles ACNU/VM 26 chemotherapy. ACNU dose: 90–100 mg/qm, VM 26 dose: 60–72 mg/qm. 2 of the oligodendrogliomas were newly diagnosed, the 10 others were recurrences. 9 of these were chemo-naive, 1 patient had received radiotherapy+PCV, 2 others had had adjuvant radiotherapy. Response was evaluated by McDonald's criteria based on CCT or MRI.
Results All patients clinically responded to ACNU/VM 26 with improvement in seizure frequency, focal signs and symptoms of intracranial hypertension, often already after application of one single cycle of chemotherapy. According to imaging criteria there were 3 (25%) complete and 3 (25%) partial responses, 6 (50%) had stable disease, no primary progression.The average time to tumor progression was 15.6 months (oligodendroglioma 16,8 months, oligoastrozytoma 12 months). The median time was 15 months. 5 patients (41.7%) had no tumor relapse up to now. 2 patients died after 12 and 41 months because of tumor progression. The follow-up was 5 to 48 months, in average 23 months. Side effects were minor with nearly exclusively hematological toxicity of moderate degree not requiring supportive therapy.
Conclusion ACNU/VM 26 chemotherapy in oligodendroglioma and oligoastrozytoma is a highly effective alternative with considerably less toxicity than what is reported for the PCV-regimen.

SC 217

Survival and prognostic factors of patients with brain glioma in Estonia

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Introduction 667 patients were diagnosed with brain glioma in Estonia between 1986 and 1996. The aim of the study was to find out survival and prognostic factors comparing our results with other surveys.
Method To maximize case ascertainment we obtained material from hospital records, the Estonian Cancer Registry and the Estonian State Statistical Office. All cases were histologically confirmed. Survival analyses was carried out on 590 patients, cases discovered at autopsy, lost to follow-up and diagnosed with another were excluded. Survival rates at 1 and 5 years and median survival were estimated.
Results Median survival was the best in low-grade (G1 and G2) astrocytomas (54.2 months), very poor in anaplastic astocytomas and glioblastomas (8.3 and 6.2 months, respectively). Patients with glioblastoma and anaplastic astrocytoma had the worst long-term outcome (5-year survival 8.6 and 15.8%, respectively). Approximately half of the low-grade astrocytomas patients (49.8%) survived beyond 5 years. 54% of patients were only operated on, 34% received additional radiation, 7% of patients additional radiation and chemotherapy. In multivariate analysis the best prognosis had low-grade astrocytoma ($p<0.0001$) and oligodendroglioma ($p<0.05$) patients of younger age, better clinical condition (Karnofsky score more than 60). There were no significant differences in patients who underwent surgery or received additional chemotherapy or radiation.
Conclusion The outcome of malignant gliomas is somewhat worse compared to other studies. We suggest the cause of such tendency is the shortcomings of neuro-oncology system in Estonia.

SC 218

A home care programme (HCP) for patients with advanced primitive brain tumours (APBT): the model of the Udine health district (HD)

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Introduction This paper reviews the model and 1 year activity data regarding a HCP for APBT patients in a HD with a territorial medical oncology service (MOS) integrated in a palliative care network.
Method The MOS providing specialist advice (Oncologist-Palliativist, OP), support for the general practitioner (GP) and oncological nurses providing pain and infusional therapy, feed tube, clinical follow-up during home-chemotherapy (e.g. with temozolomide) and laboratory examination. 24 hour-continuous-care by nursing and physicians in order to maintain at home e.g. patients with endocranial hypertension and dying ones. Emergency consultation trough a 24 hours telephone service is available. The home care service is completely free for the patient. The OP provides this service upon request from the GP for outpatient or from the hospital doctor for inpatients, which are seen at the hospital.
Results From Jan 01 to Dec 01, 11 APBT patients (accounted for 4.6% of advanced cancer subjects supported at home); median age 62 yrs (range 40–74) 9 with glioblastoma multiform, 2 anaplastic astrocytoma. Average care duration 89 days. Prevalent symptoms: confusional state, asthenia, incontinence, oral candidiasis and anorexia. 6 patients (55%) had pain; 1 (9%) was tube fed. Admission to hospital during the 2 weeks before death 2 (18%); dead at home 5 (63%); 4 alive. The patients required 17 medical visits; 1512 nurse interventions, 88 physiotherapeutic interventions.
Conclusion The HCP can allow continuous care in APBT patients improving their Quality of Life (monitored with Therapy Impact Questionnaire), decreasing days of hospitalisation and resulting in cost saving for the Health Service.

Cerebrovascular diseases 2

SC 219

Risk of stroke in Type 1 diabetic subjects in Finland

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Introduction Type 1 Diabetes Mellitus (T1DM) is associated with increased mortality from stroke. The impact of the late complications of T1DM on the risk of subarachnoid haemorrhage (SAH), intracerebral haemorrhage (ICH) and ischaemic stroke (IS) is insufficiently known.
Method We prospectively analysed the incidence of stroke by several variables, including attained age (up to 50 years old) at the end of follow-up (lasting up to 28 years), and duration of diabetes in all 5166 subjects participating in the Finnish T1DM register (diagnosed T1DM before the age of 18 years). We also studied whether the presence of diabetic nephropathy (DN) increased the risk of SAH, ICH and IS.
Results There were 118 patients with diagnose of stroke during the follow-up. The relative risk for T1DM patients with DN compared with patients without DN was 4.7 and 9.1 for SAH and ICH, respectively. In addition, we observed a 6-fold increase in the risk of IS, similar in men and women. The cumulative incidence of IS by the age of 50 was 14% in T1DM subject with DN, and only 2% in subjects without DN, irrespective of gender.
Conclusion Childhood-onset of T1DM increases the risk of all stroke subtypes already at young age, in both men and women. The increased risk strongly depends on the presence of DN.

SC 220

Stroke incidence and 30-day case-fatality in Tbilisi: an interim data analysis of the first population-based study in Georgia

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Introduction Until recently no population-based study of stroke incidence has been conducted in Georgia. We aimed to determine incidence and short-term case-fatality rates of a first-ever stroke using data of the ongoing prospective Swiss-Georgian population-based project on stroke epidemiology.
Method We identified all first-ever strokes from November 2000 to March 2002 in a defined population of 54 320 residents in the Nadzaladevi district of Tbilisi using immediate notification system and standard diagnostic criteria. Crude average annual incidence rates for each stroke subtype and 30-day case-fatality were calculated.
Results The average annual incidence rate for all strokes was estimated as 157 per 100 000 residents. Regarding stroke subtypes, the incidence rate was 86 per 100 000 residents for ischemic stroke (IS), 60 per 100 000 for hemorrhagic stroke (HS) and 15 per 100 000 for subarachnoidal haemorrhage (SAH). Fifty-three percent of stroke victims were women. One-month case-fatality rates were 16%, 47% and 40% for IS, HS and SAH, respectively.
Conclusion Stroke incidence rate in Georgia is comparable to that reported in developed countries, but significantly lower than in most countries in transition of Eastern Europe and former Soviet Union. Furthermore, IS incidence is among the lowest ever reported. On the other hand, there is rather high frequency of HS among all stroke types. Mortality at 30 days is also much higher for HS than for IS. Geographical and lifestyle variations may serve as a cause of such difference between Georgia and other countries with similar to Georgia's socio-economic and public health status.

SC 221

Predictors of post stroke epilepsy, the Copenhagen stroke study

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Introduction Post stroke epilepsy (PSE) is a frequent finding reported in 3-5%. In this study we sought to find predictors of PSE.
Method In this community-based study, we prospectively and consecutively investigated 1197 patients with acute stroke. Patients were followed for 7 years. We defined PSE as epileptic seizures with onset after stroke and requiring prophylactic anti-epileptic treatment. PSE was related to clinical factors (age, gender, onset stroke severity, lesion size on CT scans, stroke subtype, and risk factor profile) in univariate analyses. Independent predictors of PSE were identified through multiple logistic regression analyses.
Results Overall 38 patients (3.2%) developed PSE. PSE was significantly related to younger age at stroke onset (66 years vs. 75 years, $p<0.001$), ICH (21% vs. 7%, $p=0.007$), larger lesions (50 mm vs. 39 mm, $p=0.03$), and AF at stroke onset (3% vs. 19%, $p=0.009$). In a multiple regression model for the dependent variable PSE, independent predictors were younger age (OR 1.7 per 10 years; 95% CI 1.3 to 2.1), onset stroke severity (1.3 per 10 points decrease; 95% CI 1.0 to 1.6), lesion size (OR 1.2 per 10 mm enlargement; 95% CI 1.0 to 1.3), and ICH (OR 3.3; 95% CI 1.3 to 8.6).
Conclusion Post stroke epilepsy occurs in approximately 3% of all stroke patients within seven years after stroke. Factors such as age, ICH, lesion size, and onset stroke severity are predictors of PSE. The risk of PSE appears to be highest among younger stroke patients who have severe haemorrhagic strokes.

SC 222

Time from symptom onset to arrival in the stroke unit: analysis of 1.090 consecutive patients

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Introduction The timing of arrival of patients to a Stroke Unit (SU) and the factors that may delay their admission are relevant issues in order to obtain an optimal management of acute stroke. The objectives of our study were to record timing from clinical onset to admission to our SU and to identify the reasons for delay.

Method We prospectively examined acute stroke patients consecutively admitted to SU of Perugia (Italy) in the period between January 1st 2000 and March 31st 2002. Demographic and stroke characteristics, aetiology and time from symptom onset to the arrival in SU were recorded.
Results 38% of 1,090 patients admitted to SU arrived within 3 hours and 64% within 6 hours. In the remaining patients (36%) the underestimation of symptoms was the cause of delay in 56.5% of the cases. More hemorrhagic stroke patients than ischemic stroke patients arrived within 3 hours ($p<0.02$). 80.1% of the patients who arrived within 6 hours presented a Rankin score ^{3} 3 in comparison with 60.7% of the patients who arrived after 6 hours ($p<0.001$). Considering TOAST and OCPS criteria, there are significant differences between stroke subtypes; TACI subtypes arrived earlier ($p<0.001$) probably because of the severe clinical presentation.
Conclusion 64% of 1,090 consecutive stroke patients admitted to SU arrived within 6 hours; the main reason for delay was underestimation of symptoms. Patients with hemorrhagic strokes arrived earlier. The severity of deficit seems to be the main reason for earlier arrive to the SU.

SC 223

Systemic thrombolysis in acute stroke patients: survival, residual disability and complications. The Austrian Stroke Registry for Acute Stroke Units

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Introduction The aim of this study was to assess the outcome of thrombolysed stroke patients on Austrian stroke units for the years 1999 and 2000.
Method The Austrian Stroke Registry for Acute Stroke Units was designed to prospectively monitor the quality of performance. Among others, data on systemic thrombolysis were analysed.
Results 94 of 2313 patients (4.1%) received thrombolysis. Mean age was 66.7 years (med 70, STD 13.6). On admission, 11 patients had a mild stroke (NIHSS 0–7; 11.7%), 38 patients had a moderate stroke (NIHSS 8–14; 40.4%), and 45 patients had a severe stroke (NIHSS>14; 47.9%). Mean NIHSS was 14.7. Complications on the stroke unit were recurrent stroke in 6.4%, brain oedema in 10.6%, extracerebral bleeding in 3.2%, clinically relevant intracerebral bleeding in 7.4% (17 missing), and 9 patients (11.8%) died on the stroke unit. At 3 months follow-up modified Rankin Scale (mRS) was assessed in 59 patients (62.8%). Disability was none (mRS 0–1) in 20 patients (33.9%), mild to moderate (mRS 2–3) in 10 patients (17%), severe (mRS 4–5) in 15 patients (25.4%), 14 of 73 patients with available data had died (23.7%).
Conclusion Systemic thrombolysis was performed on 4.1% of patients treated in Austrian stroke units in the period 1999–2000. The results compare with other national surveys.

SC 224

Percutaneous left atrial appendage transcatheter occlusion (PLAATO) to prevent stroke in patients with atrial fibrillation - first human experience

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Introduction Anticoagulant therapy is effective in reducing stroke in patients with atrial fibrillation. However, it has a narrow therapeutic range and is contraindicated in many. The left atrial appendage is the source of thrombi in >90%. Obliteration of the appendage may prevent cardioembolic complications. We report the 1st human experience with percutaneous left atrial appendage transcatheter occlusion (PLAATO).
Method PLAATO was attempted in 31 patients (66–74 years) with atrial fibrillation, additional stroke risk factors, and contraindication to coumadin. The PLAATO™ device consists of a self-expanding cage covered with ePTFE delivered through a 12Fr transseptal sheath specially designed to access the left atrial appendage. Animal studies have shown efficacy at sealing the appendage with complete encapsulation and endothelialization by 1–3 months. Angiography and transoesophageal echo is used to determine the device diameter.
Results Implantation of the device was successful in all patients, in one of them during a second attempt. Hemopericardium during the procedure occurred in 2 patients, pericardiocentesis was performed without sequelae. No other complications occurred. Devices with diameters between 18 and 32 mm were implanted. Transesophageal echocardiography showed the device well seated. Follow up x-rays and echocardiograms revealed stable implants.
Conclusions Transcatheter closure of the left atrial appendage is feasible. This novel technology may offer an option for patients with atrial fibrillation who are not candidates for anticoagulation. Further clinical trials are needed to show the long-term safety and efficacy in reducing stroke.

Ageing and dementia 1

SC 225

Platelet amyloid precursor protein forms for the early identification of Alzheimer's disease among mild cognitive impairment (MCI) patients

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Introduction Patients affected by sporadic Alzheimer's disease (AD) show a significant alteration of amyloid precursor protein (APP) forms in platelets when compared both with non-Alzheimer's disease demented patients and age-matched controls. The objective of our study was to evaluate platelet APP forms' ratio (APPr) in early-stage AD and in MCI and its potential as a biomarker for the early identification of AD.
Method A community population-based sample of patients was admitted to 4 AD centres for investigation of cognitive disturbances. 60 patients with mild AD (mAD), 40 subjects with mild cognitive impairment (MCI), and 25 age-matched controls (CON) were included. APPr was evaluated by Western Blot analysis in platelet homogenate. All patients performed a neuropsychological evaluation and neuroimaging study (CT). In a subset of AD and MCI patients, SPECT was also administered
Results Compared to CON (mean ± SD = 0.93 ± 0.3), mean APPr was decreased in mAD (mean ± SD = 0.45 ± 0.26, $p<.0001$). With regard to the MCI group, a significant decrease in APPr was found compared with CON (mean ± SD = 0.60 ± 0.33, $p<.0001$). Fixing a cut-off score of 0.6, sensitivity was 88.6% (31 of 35) for mAD while specificity was 88% (22 of 25) for CON. Among MCI, 23 of 40 individuals displayed APPr values below the cut-off.
Conclusion Alteration of APP metabolism is an early event in AD and the measurement of platelets' APPr may be useful for the identification of pre-clinical AD in MCI subjects.

SC 226

Glucocorticoids regulate pro-inflammatory cytokines phenotype in patients with Alzheimer's disease

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Introduction Pro-inflammatory phenotype can play a role in pathogenesis of Alzheimer's disease (AD). We used whole blood assay to determine the release of tumour necrosis factor (TNF alpha), interleukin-10 (IL-10) and interleukin-12 (IL-12) in AD patients and to establish how dexamethasone (DEX) regulates these cytokines synthesis.
Method 16 patients with probable AD and 11 control subjects were included. Cytokine level was measured using ELISA method, after 24 h of whole blood stimulation with LPS (10 ng/ml) or LPS and DEX (1 micromol/L) in 37 degrees Centigrade, 5% CO2.
Results Cytokine levels before whole blood stimulation, after stimulation with LPS and after treatment with LPS and DEX didn't differ significantly in AD patients as compared to control group. AD patients had higher TNF/IL-10 ratio before (159.3+/–450.2 vs 20.3+/–8.7, $p=0.01$) and after stimulation with LPS (513.4+/–1694.7 pg/ml vs 47.5+/–11.6, $p=0.03$) than control group. After incubation with LPS and DEX, TNF/IL-10 ratio was higher in AD patients than in control group, but that difference was not statistical significant (80.0+/–267.1 vs 9.2+/–3.7, $p=0.21$). In addition DEX inhibited significantly stronger TNF production in AD patients (5.9-times vs 4.4-times, $p=0.01$). Since IL-12 release was similar in both groups, this cytokine is probable not responsible for increased interferon gamma synthesis described previously in AD patients.
Conclusion Pro-inflammatory phenotype defined as TNF alpha/IL-10 ratio can be counter-balanced in AD patients by glucocorticoids, which shift cytokines production towards anti-inflammatory molecules.

SC 227

Neurotoxicity of antipsychotic drugs in Alzheimer's disease

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Introduction Tissue transglutaminase (tTG), a protein-cross-linking enzyme, which is involved in apoptosis, could be a biochemical marker for cell damage or apoptosis in neurodegenerative diseases. Although a pronounced increase in tTG activity or protein was found in post-mortem Alzheimer's disease (AD) brains, tTG protein expression was not measured in vivo so far.
Method TTG was examined in the cerebrospinal fluid obtained from 51 patients with dementing disorders (33 patients with AD and 18 patients with vascular dementia (VaD)), and compared to those from 33 patients without neuropsychological deficit. 21 controls and 10 Alzheimer patients were under neuroleptic medication in the last 24 hours before lumbar puncture.
Results We found a significant difference ($p<0.01$) between the AD and the other two groups (7.58 pg/ml vs 2.95 pg/ml). VaD and controls did not differ (2.93pg/ml vs 2.99 pg/ml). A highly significant influence of neuroleptics in the AD group (12.62pg/ml vs 5.39pg/ml) and the non-AD group (5.72pg/ml vs 1.04pg/ml) was revealed.
Conclusion Our results show that tTG is leaked out of the brain into the CSF. We could demonstrate acute neuronal cell death in vivo in AD patients. We furthermore could document acute neurotoxicity of neuroleptics, especially in AD patients. We conclude that tTG may serve as a biochemical marker for acute cell death to assess the efficacy of possible new anti-apoptotic drugs. We furthermore suggest that neuroleptics should be strictly limited in AD patients.

SC 228

Donepezil treatment benefits caregivers of patients with moderate to severe Alzheimer's disease (AD)

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Introduction This analysis investigated whether treatment benefits with donepezil in patients with moderate to severe AD are associated with measurable benefits to caregivers.
Method 290 patients with moderate to severe AD (standardized MMSE score 5–17) were randomised to receive either donepezil or placebo for 24 weeks. Caregivers were evaluated for their levels of stress with a modified, 20-item Caregiver Stress Scale (CSS). Time spent helping patients with both basic and instrumental ADLs was recorded using modifications of the Physical Self-Maintenance Scale (PSMS+) and Instrumental Activities of Daily Living Scale (IADL+).
Results Caregivers of donepezil-treated patients (n=141) did not differ significantly from caregivers of placebo-treated patients (n=146) with respect to age, gender, education, relationship to patient, or duration as caregiver. Similarly, at baseline, the mean total scores on the CSS did not differ significantly between the caregiver groups of donepezil- and placebo-treated patients. 87% of donepezil- and 88% of placebo-treated patients were community-dwelling at baseline. At week 24 (LOCF),

CSS total scores remained close to baseline for caregivers of the donepezil group (mean change=0.08±0.83), in contrast to a decline from baseline of 1.98±0.79 for caregivers of the placebo group. Caregivers of donepezil-treated patients reported spending less time assisting with both instrumental and basic ADLs during the study than did caregivers of patients receiving placebo (total treatment difference at week 24 LOCF=63.8 minutes/day).
Conclusion In this study, treatment benefits with donepezil in patients with moderate to severe AD were associated with measurable benefits in levels of caregiver stress and time spent care-giving.

SC 229

Donepezil slows functional deterioration in patients with vascular dementia

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Introduction Cholinesterase inhibitor therapy may have functional benefits in patients with vascular dementia (VaD). The objective of our study was the Evaluation of the functional and cognitive efficacy of donepezil in patients with probable or possible VaD.
Method This paper reports a combined analysis of two large-scale, randomised, double-blind, placebo-controlled, 24-week, parallel-group studies with identical protocols (Studies 307 and 308). A diagnosis of probable or possible VaD according to NINDS-AIREN criteria was required for inclusion; patients with a prior diagnosis of Alzheimer's disease were excluded. Patients were randomised to receive placebo, donepezil 5 mg/day or donepezil 10 mg/day (5 mg/day for first 28 days). Functional efficacy was assessed by the ADFACS. Results are reported for intent-to-treat observed cases.
Results Overall, 1219 patients were enrolled (392 placebo, 406 donepezil 5 mg/day, 421 donepezil 10 mg/day); 73% had probable VaD and 27% had possible VaD. At Week 24, both donepezil-treated groups showed significant improvements in cognitive function compared with placebo (ADAS-cog LS mean change from baseline score effect size: donepezil 5 mg/day, –1.79, $P<0.001$, n=317; donepezil 10 mg/day, –2.28, $P<0.001$, n=298). Donepezil-treated patients showed significant benefits over placebo-treated patients in their ability to perform activities of daily living (ADFACS mean change from baseline score treatment difference at Week 24: donepezil 5 mg/day, –1.014, $P=0.02$, n=306; donepezil 10 mg/day, –1.010, $P=0.02$, n=297).
Conclusion Significant benefits of donepezil compared with placebo treatment were observed on measures of cognition and function, indicating that donepezil may have an important role in the management of these symptoms in patients with probable or possible VaD.

SC 230

NNT data of galantamine for patients with "advanced moderate" Alzheimer's disease

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Introduction Galantamine (Reminyl®) is beneficial in patients with mild-to-moderate Alzheimer's disease (AD), also in those who are in the more advanced stage of the disease. In order to emphasise the efficacy in this last group, a number needed to treat (NNT) analysis was performed on the pooled data of patients with "advanced moderate" AD from three large-scale Phase III studies of 5–6 months duration.
Method Of the 705 patients that received galantamine 24 mg, 178 patients with baseline AD Assessment Scale-cognitive subscale (ADAS-cog) scores of >30 and 86 patients with baseline Mini-Mental State Evaluation (MMSE) scores of ≤14 were used in the NNT analysis. Patients were assessed for treatment responses compared with matched placebo groups (n=183 and 101, respectively). The NNT analysis was performed on responder data for improvements of ≥0, ≥4 and ≥7 points on ADAS-cog and "improved or unchanged" Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-plus).
Results In patients with baseline ADAS-cog scores of >30 the NNT is 3 for ADAS-cog improvement of ≥0 points, 4 for ADAS-cog improvements of ≥4 and ≥7 points and 5 for CIBIC-plus "improved or unchanged". In patients with baseline MMSE scores of ≤14 the NNT is 3 for ADAS-cog improvements of ≥0 and ≥4 points, 5 for ADAS-cog improvement of ≥7 points and 4 for CIBIC-plus "improved or unchanged".
Conclusion These consistently small NNT data for cognitive and global outcome in both subgroups strengthen the conclusion that galantamine treatment is very efficient in "advanced moderate" AD patients.

Autonomic nervous system
Clinical neurophysiology
Critical care

SC 231

Sildenafil has no negative effects on the autonomic cardiovascular modulation during exercise

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Introduction There is controversy whether Sildenafil (Viagra) enhances sympathetic activity during stress and increases cardiovascular risk (Phillips et al.: Circulation 2000;102:3068-73). In this study, we determined effects of Sildenafil on autonomic cardiovascular modulation at rest and during exercise.
Method In 40 healthy volunteers (16 women; 27.9±5.4 years), we monitored heart rate (HR), radial artery blood pressure (BP), respiratory frequency (RF) [Respitrace™], end-tidal carbon dioxide (CO2) and transcutaneous oxygen saturation (SatO2) [Colin Pilot™], during 10 min rest and ergometric exercise at 50, 100, 150 and 200 W (3 min each) (test 1). After 24 hours, the participants repeated the test 45 minutes after intake of 100mg Sildenafil or placebo (test 2). At rest and during exercise, we determined mean values and spectral powers of the signals in the low (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.5 Hz) ranges reflecting sympathetic and vagal influences on HR and BP oscillation.
Results HR, BP, RF and LF powers of HR and BP increased while HR-HF powers decreased with increasing exercise ($p<0.05$), SatO2 remained unchanged, CO2 increased slightly. Results of tests 1 and 2 and of the Sildenafil and placebo group did not differ, apart from lower BP values in the Sildenafil group at rest and at 150 and 200-Watt challenge.

Conclusion Sildenafil has no negative effects on autonomic cardiovascular modulation at rest or during physical challenge. The lower BP after Sildenafil suggests some protective cardiovascular effects.
Acknowledgement: The study was supported by an unrestricted grant from Pfizer Inc. USA.

SC 232

A systematic analysis of dose related local anhidrotic effects of botulinum toxin type B injections as measured by sudometry

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Introduction Until now, no systematic data are available on the effect of botulinum toxin type B (BoNT/B, Neurobloc®; Elan) on sweating. The objective of our study was to analyse dose dependency of BoNT/B-derived suppression of sweat gland activity.
Method Employing a standardised scheme (four injections in a 2 cm^2 area), different doses of BoNT/B (2-1000 U in a 1 mL saline solution) were injected subcutaneously in 15 healthy volunteers. Sweat tests were performed before, 3 weeks and 3 months after BoNT/B injections. Sweating was visualised by staining with iodine starch, and quantified by capacitance hygrometry after carbachol iontophoresis, the quantitative sudomotor axon reflex test (QSART).
Results Iodine starch staining indicated a threshold dose of 15 U leading to visible anhidrotic skin spots (>5 cm^2) after 3 weeks in all subjects. This was maintained for 3 months with doses of 62.5 U or higher, although the size of the anhidrotic skin area decreased over time ($p=0.001$) indicating partial recovery at the edges. After 3 weeks, QSART was significantly reduced (>90%) and completely suppressed by doses of 32.25 U or more. Both methods indicated that the suppression of sweating by BoNT/B is dose dependent.
Conclusion Our findings suggest that the effectiveness of BoNT/B can be quantified by testing sudomotor function. For the first time threshold doses for the suppression of sweating have been defined for BoNT/B. Compared with the equivalent motor endplate blocking dose previously reported by our group for BoNT/A1, BoNT/B seems to be more effective in inhibiting sweat production.

SC 233

Postural blood pressure and catecholamine responses in uremic type 1 diabetic patients prior to and after kidney and pancreas transplantation

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Introduction Orthostatic hypotension caused by autonomic neuropathy (DAN) is frequent in uremic diabetic patients. The study aim was the assessment of postural blood pressure (BP) and catecholamine (CA) responses in Type 1 diabetic (DM1) patients before and after kidney/pancreas transplantation (KPT).
Method 12 DM1 patients (mean age 44±12 years, 6 patients dialysed, creatinine 380±151mmol/l in 6) were examined before and 10±4 months after KPT with long-term normoglycemia. 10 healthy subjects were used as controls (C). DAN was tested by heart rate (HR) variability during deep breathing (inspiration-expiration (I-E) HR, abnormal <10/min). Systolic(s), diastolic (d) BP, plasma norepinephrine (NE) and epinephrine (E) levels were measured in supine position and at min 5 after standing up. BP was determined by cuff sphygmomanometry, CA levels by HPLC with fluorimetric detection. Two-sample Mann-Whitney and Wilcoxon paired tests were used for inter- and intra-group comparisons.
Results DAN was present in all DM1 patients (I-E: 3.4±2.5 /min). After standing up, sBP (min5 vs.0: 131±22 vs.155± 16 mmHg, $p=0.002$) and dBP (86±14 vs.92±12 mmHg, $p=0.03$) decreased in DM1 group, but not in C. However, similar CA responses occurred in both groups with NE increases (min5 vs.0: 2.5±0.8 vs.1.7±0.5, $p=0.02$ and 2.3±0.9 vs.1.4± 0.4 nmol/l, $p=0.006$, for DM1 and C) and no E changes. BP and CA responses did not change in the DM1group after KPT.
Conclusion Despite the presence of DAN and decreases in BP, no difference in postural CA responses in comparison with C was found in uremic DM1 patients. After a successful KPT, no significant change in postural BP and CA responses occurred.
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SC 234

Effect of acetyl-l-carnitine on painful HIV-related neuropathy

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Introduction Acetyl-L-Carnitine (ALC) is a safe and well-tolerated drug in the treatment of peripheral neuropathy in HIV infected patients. ALC efficacy is mainly focused on the modulation of TNF-alpha expression. Moreover, HIV infected patients present with reduced blood levels of endogenous acetylcarnitine. So ALC supplement may represents a valid therapeutic option. Peripheral nervous system is frequently involved during HIV infection and distal sensitive polyneuropathy appears in up to 30% of AIDS patients. Aetiology is still unknown. One of the pathogenetic hypotheses is the role of proinflammatory cytokines (TNF-alpha) in causing neuropathic pain.
Method 20 HIV- positive patients with neuropathic pain and EMG-evidence of axonal alterations were enrolled; we excluded patients with mini-mental test score less than 24, acute cytomegalovirus infection, chronic demyelinating neuropathies. All patients were treated with ALC at the dose of 1 gram 3 times daily for 4 weeks. A visual analogue scale (VAS) was used to evaluate characteristics of patient's pain before, during, and after treatment. Electromyographic and neurographic assessment was performed before and after treatment. To evaluate changes in VAS score we used non-parametric Friedman's test (F). Wilcoxon's test (W) was performed to timing the appearance of pain improvement and to evaluate neurophysiological data.
Results The changes in VAS score were statistically significant during ALC treatment (mean score: before 6.7±2.1 – after treatment 5.0±2.1) ($F=P<0.001$). Therapeutical effect appeared during the first ($W=P<0.03$) and the fourth ($W=P<0.05$) week of treatment.
Analysis of neurophysiological data showed a statistically significant improvement of peroneal nerve motor parameters: reduced motor distal latency ($W=P<0.02$), increased amplitude of compound motor action potential at distal ($W=P<0.02$) and proximal ($W=P<0.05$) site of stimulation.
Conclusion Our data show the efficacy of ALC in the treatment of neuropathic pain, confirming previous results (Scarpini E. et al., 1997). Moreover, the analgesic effects appear during the

first week of treatment according with pre-clinical data in different experimental models of pain (Ghilardini C. et al., 2002, submitted). Among mechanisms for ALC efficacy in those patients there is a neurotrophic effect as evidenced from patch-skin biopsy evaluation (Haart A. M. et al., 2002, submitted).

SC 235

Intraoperative recording of local field potentials for assisting localisation of the targets for deep brain stimulation

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Introduction Deep brain stimulation (DBS) is an effective treatment for many movement disorders. To improve accuracy of anatomically localising the target beyond using fused CT and MRI images, and to avoid the long operating times that are needed for single unit recording, we recorded focal field potentials (FPs) during electrode implantation.
Method In 32 consecutive cases of electrode implantation (12 advanced Parkinson's disease; 3 multiple sclerosis; 2 essential tremor; 1 post-traumatic tremor; 2 myoclonic dystonia; 4 generalised dystonia and 5 chronic central pain), FPs were recorded via the DBS electrodes from targets including the subthalamic nucleus, the ventral thalamus, the zona inserta, the medial pallidum and the periventricular grey, respectively.
Results Oscillatory activity of various frequencies could be detected as local FPs in movement disorders and in pathogenic pain. Functional localisation of a target could be achieved according to the graded changes in FPs recorded via different electrode contacts corresponding to their positions relative to the target. During tremor and rhythmic myoclonus, the oscillatory activity was coherent with the EMG bursts in the frequency range of the symptoms. The function-anatomy correlation of the selected target could be revealed by superimposing recordings on fused images of the post-op CT onto the pre-op MRI.
Conclusion FP recording was helpful for improving the accuracy of image-guided localisation of the targets for DBS. Our results suggest that FP recording offer a useful alternative to microelectrode recording.
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SC 236

Risk factors for critical illness polyneuromyopathy

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Introduction The aetiology and mechanisms of neuromuscular involvement in critically ill patients are not completely understood. Numerous clinical, laboratory, and pharmacological variables have been reported as significantly associated with the development of critical illness polyneuromyopathy (CIPM).
Method We performed a prospective one-month observational clinical and electrophysiological study aimed at the identification of the risk factors for CIPM. The detection of CIPM was based primarily on electrophysiological criteria. 79 critically ill patients (median age 59, 33 women, 46 men) were enrolled into the study and 48 completed the 28-day follow-up.
Results Electrophysiological signs of CIPM were detected in 27 critically ill patients. The development of CIPM was significantly associated with the presence and duration of systemic inflammatory response syndrome (SIRS) and the severity of multiple organ failure (MOF) expressed as the sequential organ failure assessment score (SOFA). The mean 28-day total SOFA score reflecting the cumulative severity of MOF during the first month shows the closest correlation with CIPM development. The respiratory and central nervous systems were the only two systems whose failure displayed independent significant association with CIPM. A multivariate logistic model utilising these variables was able to correctly predict the development of CIPM at the end of the first month in about 85% of our cases.
Conclusion The presence and duration of SIRS and the cumulative severity of multiple, respiratory and neurological failures are associated with increased risk for the development of CIPM. These variables could be used for prediction of CIPM development.
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Neurology and art
History of neurology

SC 237

The original contribution of arts and theatre to the understanding of Alzheimer Disease

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Music, painting, sculpture, poetry and theatre are part of man's cultural DNA. In this expression of imagination and intellect he has found many cultural answers and explanations to some of the basic questions of life. Art is an essential component in any social and human context. The work of art (in this case theatre) is the expression of a visual event which aims to lead the user to a state of identification, that is empathy or involvement, purely through a mental process. The piece "A come non so" presented here is a monologue written and performed by Carlo Pontesilli. The piece shows the characteristic aspect of Alzheimer's disease from the first to the last stage: amnesia, aphasia, agnosia, and apraxia, as well as the different behaviour patterns and relations with the outside world of the patient, while the degenerative process gains ground. It tells the story of Carlo Pontercoli, gerontologist and specialist in cardiovascular and mental illnesses. He lives with his mother, who is affected by the disease and already reaching the very end of here life. Dr. Pontercoli is writing a report on "The elderly ad sexuality" for an important national congress on Alzheimer disease. While he is writing it, the doctor presents the initial signs of the disease that killed his mother not so long before. Pontercoli is also going to die because of the illness, and is going to go through all the phases of the disease, facing behaviour and language disorders, losing mental and intellectual faculties. The monologue aims to be a new contribution to the whole understanding of the problems concerning Alzheimer's disease through their observation and visual communication of the problems.

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SC 238

Neurology in Thomas Mann's novels

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Thomas Mann (1875–1955) is one of the most interesting authors of the 20th century. Although his own health was excellent (he even survived a lung-cancer), most of his novels contain medical subjects. I will try to give an overview of the neurological topics presented his novels.
Firstly "Buddenbrooks" (1901) – the novel that provided him with the Nobel prize in 1929; he is telling the story of degeneration of a family by disease over four generations: by a lot of neurological cases, from "too short nerves", migraine, tremors and a terrible death by cerebral typhus. The main topic in "Der Zauberberg" (1924) is the inside life of tuberculosis as lived in a sanatorium – with many psychoneurological complications. In the gigantic four-volume novel: "Joseph und seine Brüder" (1933–43) we meet a lot of neurological conditions, as they were experienced in biblical times. Shorter novels such as "Der Tod in Venedig" (1912) tell us about cholera, neurological complications and death.
Thomas Mann tries to give a sort of "philosophy of disease" – most convincing in the short novel: "Goethe und Tolstoy" (1921) – and above all in: "Doktor Faustus" (1947). This book is a must for every neurologist/every human for its deep wisdom of our human condition and for its description of various neurological conditions from hereditary migraine to epilepsy. And above all it is a sort of "bible of syphilitogy". What was the Devil in old German tradition (from 1587) and transformed by Goethe in "Faust I and II" – is transformed by Thomas Mann to be a syphilitic tragedy.
My aim is to show most of the neurological implications in Thomas Mann's work, their importance – and to express my admiration: where did he get his medical knowledge from?

SC 239a

Neuro-expressionism, Egon Schiele and Arthur Schüller

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The term "expressionism" is used to describe any art that raises subjective feelings above objective observations. Affected by the anxieties of accelerated social change, expressionist artists employed violent exaggerations and distortions of form and colour.
Austrian expressionist artist Egon Leo Adolf Schiele, born June 12, 1890, died October 31, 1918, was at odds with art critics and society for most of his brief life. Even more than Gustav Klimt, Schiele made eroticism, in a dystonic way with stronger linear effects and harsher outlines, one of his major themes. Schiele's narcissism, exhibitionism and persecution-mania can all be found united in the poster "St. Sebastian", such as spasms of facial muscles in "Selbstbildnis mit Hand und der Wange".
Arthur Schüller, the father of neuroradiology, was born in the north of Vienna and began his medical career in the field of neuropsychiatry.
In 1905 his first book " The skull base on the radiogram" was published and expressionism developed almost simultaneously in different countries. It was a comprehensive description of normal and pathologic anatomy as well as of many special radioprojections, like Schiele's linear effects, of the skull base.
Later on Francis Bacon's work maintains a sense of strict control, even precision. His use of Schüller's views from the book "Positioning in Radiography" give a further quasi-documentary atmosphere. Bacon is in accord with expressionism in his painful abrasions and distortions of faces evoking an agonized picture.
Among these artists who have tried to represent the inwardness of the body, Schüller holds a high place, along with Schiele and Bacon. Does neurology express art?

SC 239b

Neuro-expressionism, Otto Klemperer and Martha Graham

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Otto Klemperer (1885-1973) was born in Poland. First as revolutionary groundbreaker, later as champion of the classics from Bach to Mahler, amassed a recording legacy of masterworks perhaps unmatched by any other conductor, unequalled in their vision, depth, and power. After 1918 he emerged as one of the leading German conductors of his generation. His sympathy for and authoritative performances of an unusually wide range of contemporary music, as well as a less overtly emotional interpretation of the classics made him appear an expression of the "new age". At the age of 48, Klemperer immigrated to the United States and conducted the Los Angeles Philharmonic. In 1939 he underwent an operation for a brain tumour and his health and stability were gravely undermined. Later on, he was named principal conductor of the Philharmonic Orchestra of London. His performances were distinguished by a power and intensity in spite of having suffered further accidents and illnesses.
Martha Graham (1894–1991) was a major figure in the American modern dance. By 1930 she was beginning to identify a new system of movement and new principles of choreography, a method of breathing and impulse control she called "contraction and release". Her work was focused on emotional themes such as her famous solo "Lamentation". The narrative of the dance uses only a pure, abstract movement vocabulary to bring its story to life. At the age of 94 she suffered a stroke with aphasia. Her good recovery was clearly illustrated in her piece "Night Chant". Does neurology express art?

SC 240

Tremor in painters: the movement disorder of Max Svabinsky

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Max Svabinsky (1873–1962), one of the most illustrious Czech graphic artists of the 20th century, suffered from hand tremor that substantially marked his handwriting. The aim of the present study was to ascertain the kind of his tremor and to deter-

mine how it influenced Svabinsky's production. We studied Svabinsky's personal correspondence, graphic artefacts, and newsreel films preserved in the archives.
Chronological analysis of Svabinsky's handwriting and signature shows a progressive deterioration since the 1930s, with angular and uneven script. After 1950, the writing is considerably altered, with scattered characters and coarse lines. The listing of Svabinsky's art works demonstrates a definite change in graphic techniques, since 1944 moving to chalk lithography that is less sensitive than other techniques to uneven hand movements and shaking. Newsreel shots show significant action tremor of hands, however it scarcely interferes with Svabinsky's drawing. Svabinsky never sought medical care for tremor. He was cognitively intact and artistically active until his last days.
Based on typical symptoms including action tremor of hands, preserved cognitive and creative faculties and longevity, we believe that Max Svabinsky suffered from essential tremor. Despite its high prevalence, few cases of essential tremor were reported in artists (1). Curiously enough, different brain mechanisms might be involved in handwriting and drawing. We hypothesise that tremor may more interfere with automatic action of handwriting than with volitionally controlled drawing.

Literature

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SC 241

Jan Evangelista Purkinje (1787–1896), Founder of modern neurophysiology and mediator between two countries

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Purkinje, born in Libochowitz (Bohemia), aroused interest with his thesis submitted to the University of Prague, entitled "Knowledge of Visual Impressions from a Subjective Point of View"– based on Goethe's "Theory of Chromatics". In 1823 he was called to Breslau but returned to Prague in 1849. He founded Institutes of Physiology at both universities.
Purkinje established basic scientific knowledge – but not only in the fields of physiology and microscopic anatomy. He improved the techniques applied in microscopy and also made contributions to cell research in general; the term protoplasma was coined by him. Most important were his achievements in neurology and neurophysiology. He described cells and various structures of nerves, but mainly he was the first to discover cells in the CNS which were later named Purkinje cells located in the cerebellum. He published several studies about vertigo and about experimentally induced lesions in the brain to facilitate neurological diagnosis. He also performed self-experiments to test substances acting on the nervous system and revealed previously unknown interactions between brain function and localisation, explaining waking state, sleep and dream. Purkinje (in Czech: Jan E. Purkyně) presented his lectures in Prague both in German and Czech yet he was not only concerned with the Czech language as an instrument of scientific communication but has also made important contributions to improving mutual understanding between the Czech- and German-speaking population in Bohemia and Moravia. His tireless and fruitful efforts resulted in the founding of the Czech Karls-Universität in Prague.

SC 242

Neurology – myth and reality

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Since the age of enlightenment the sovereignty of reason had always claimed to be scientifically pure, but the objectivity claimed by this science is not entirely free from subjectivity. These subjective aspects may be traced not only to empirical art and literature, called realism and naturalism, and not only to socio-economic theories that claim to be scientific, but also to fields which by nature must be scientific and devoid of subjectivity. This brief summary sets out to trace the string of illusions in describing maladies. The descriptions of those illnesses have been proven to be developed by myth and fancy-like spermatorrhea to maladies. Their subjective origin is highly suspicious, but yet many neurologists use them like TOS. It must be noted however that emergence of these diagnoses as mixture of objectivity and subjectivity at any given time has had its particular economy and often served as needed.
The spectrum of these neurological diagnoses are from spermatorrhea – a strange diagnosis very popular at the beginning of 20th century today not well known – to a diagnosis like TO – a very weakened concept but yet living to RSD – a very loose concept of symptoms and signs – to other diagnoses such as pronator teres syndrome with an apparently strong basis but doubtful in the view of some well-known electrodiagnostic specialists.
In this paper I will review the evolution of these concepts in literature and the current situation of them with objective viewpoints.

Tuesday, October 29

Epilepsy

SC 301

MR-volumetry of subcortical structures in temporal and extratemporal epilepsy

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Introduction Animal and human data suggest a crucial role for subcortical structures in the modulation of seizure activity, mostly as seizure-suppressing relays. There is, however, little knowledge about the actual size of implicated subcortical structures in epilepsy patients.
Method Using high-resolution MRI, we measured the volumes of subcortical nuclei, such as the thalamus, caudate nucleus, putamen and pallidum, in both hemispheres of 27 patients with temporal lobe epilepsy (TLE) and 31 patients with extratemporal lobe epilepsy (ETLE). ETLE patients were further subdivided in patients with a left and right anterior, left and right posterior focus. 16 volunteers served as controls.
Results Compared to the control group, TLE patients showed significantly smaller striatal and thalamic volumes, predominantly on the ipsilateral side ($p<.01$). In contrast, ETLE patients as a whole did not differ from the control group. However,

ETLE subgroups (with respect to focus localization) differed with respect to thalamic volumes.
Conclusion Volumetric measurements of subcortical nuclei revealed significant atrophy of distinct subcortical nuclei in the TLE group, but not in the ETLE group. Our findings suggest that TLE and ETLE represent different entities also on the subcortical level. Differences of the focus localization in the ETLE group were reflected in different sizes of thalamic nuclei. A distinct pattern of subcortical atrophy is of particular interest with respect to development of alternative treatments.

SC 302

Low-frequency rTMS in patients with cortical dysplasia

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Introduction Epilepsy is associated with cortical hyperexcitability. Low frequency repetitive TMS (rTMS) can decrease cortical excitability. Recently data have been provided about the potential therapeutic role of rTMS in intractable epilepsy (Tergau et al., 1999). The aim of this study was to investigate the effects of focal low-frequency rTMS in refractory epilepsy due to cortical dysplasia.
Method We treated 4 patients (1 M, 3 F mean age 29.5±2.6, range 27–33 years) with refractory seizures due to cortical dysplasia (2 with single and 2 with multiple foci) at EEG and NMR imaging. 8 rTMS sessions were given biweekly for 4 weeks. Each session consisted of one train of 100 pulses at 0.5 Hz at 90% of motor threshold over the area of cortical dysplasia in the 2 patients with a single focus and over the vertex in the other 2.The number of seizures during the month before stimulation (time I) were compared by repeated measures ANOVA with that of the month during (time II) and after stimulation (time III).
Results rTMS significantly reduced the number and severity of seizures in patients with a single dysplasic focus (main effect of time: $F(2.3)=21.50$; $p<0.01$). The improvement concerned predominantly the disappearance of secondary generalization and was still persistent one month after the end of the treatment: (time I vs II, time I vs III: $p<0.001$ at post-hoc).
Conclusion Our results show that a long-lasting depression of cortical dysplasic area may temporarily improve intractable epilepsy.

SC 303

The antiepileptic drug levetiracetam reverses the inhibition by negative allosteric modulators of neuronal GABA- and glycine-gated currents

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Introduction In this study in vitro and in vivo approaches were combined in order to investigate if the antiepileptic mechanism(s) of action of levetiracetam (LEV; Keppra®) may involve modulation of inhibitory neurotransmission.
Method GABA- and glycine-gated currents were studied in vitro using whole-cell patch-clamp techniques applied on cultured hippocampal, cerebellar granule and spinal neurons. Protection against clonic convulsions was assessed in vivo in sound susceptible mice. The effect of LEV was compared with the AEDs carbamazepine (CBZ), phenytoin (PHT), valproate (VPA), clonazepam (CZP), phenobarbital (PB) and ethosuximide (ESM).
Results LEV contrasted the reference AEDs by an absence of any direct effect on glycine-gated currents. At high concentrations, beyond therapeutic relevance, it induced a small reduction in the peak amplitude and a prolongation of the decay phase of GABA-gated currents. A similar action on GABA-elicited currents was observed with the reference AEDs, except ESM. These minor direct effects contrasted with a potent ability of LEV (EC50=1–10:M) to reverse the inhibitory effects of the negative allosteric modulators zinc and b-carbolines on both $GABA_A$ and glycine receptor-mediated responses. This pharmacological profile was not mimicked – or only partially – by the reference AEDs. Likewise, co-administration of β-carbolines, but not flumazenil, abolished the seizure protection afforded by LEV (17 mg/kg, i.p.).
Conclusion The results of the present study suggest that a novel ability to oppose the action of negative modulators on the two main inhibitory ionotropic receptors may be of relevance for the antiepileptic mechanism(s) of action of LEV.

SC 304

Acute treatment of experimental status epilepticus with levetiracetam reduces chronic spontaneous recurrent seizures

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Introduction Levetiracetam (LEV) is very effective in the acute treatment of experimental status epilepticus (SE). We report its efficacy in reducing the long-term consequences of SE in an animal model of self-sustaining SE.
Method SE was induced by perforant path stimulation (PPS) for 30 mins in awake animals then LEV was injected iv. Seizures and spikes were recorded for 24 hours during SE, ≥ one week 1–2 months later, and analysed using Harmonie software.
Results I.v. administration of LEV 10 mins after PPS attenuated SSSE, reducing cumulative seizure time from control 606±57 to 22±96, 18±5 and 9±2 mins for LEV 200, 500, 1000 mg/kg respectively ($p<0.05$). At 40 mins, LEV reduced serum neuron-specific enolase (NSE), (26.8±3U to 8.2±2.1U) similar to controls (5.4±0.4U), suggesting a marked reduction in seizure-induced neuronal death. All control rats developed recurrent spontaneous seizures (SRS) 28±2 days after SE. Seizure frequency remained stable over the next 50 days (dl: 6±1; d10 8±1; d30 7±1; d50 7±1). LEV 200 mg/kg treated rats had SRS 31±1 days after SE, seizure frequency was only 1 (d1) or 0.5/day (d10, 30, 50). After LEV 1000 mg/kg, SRS were absent (50% rats) or infrequent.
Conclusion These results suggest acute treatment of experimental SE with LEV to reduce both incidence and severity of its chronic consequences.
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SC 305

Tolerability of levetiracetam in a population of older patients with cognitive and anxiety disorders

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Introduction The purpose of our study was to review the tolerability of levetiracetam (LEV) in a population of older patients (≥65 years) diagnosed with a cognitive or anxiety disorder.
Method LEV was evaluated in placebo-controlled, monotherapy trials that included 738 patients with Cognitive Disorders, of whom 319 were ≥65 years, and 1,609 patients with Anxiety Disorders, of whom 169 were ≥65 years. Data are reported as comparison of the incidence of specific adverse effects in the LEV and placebo groups (where the incidence was ≥5% in the LEV group).
Results Common problems in the Cognitive group were asthenia (7.1%), somnolence (4.5%), urinary tract infection (4.1%), dizziness (3.3%), and headache (1.3%). Common problems in the Anxiety group were headache and tremor (5.2%), urinary tract infection (4.1%), weight loss (4.0%), anorexia, pharyngitis, and abdominal pain (3.8%), insomnia (3.0%), vomiting (2.4%), and oedema (2.0%). In comparison, the younger group of patients with epilepsy who received LEV reported somnolence (6.4%), infection (5.9%), asthenia (5.6%), dizziness (4.7%), pharyngitis (2.2%), and pain (0.7%). The type and incidence of adverse effects reported by older patients were lower than reports from the predominantly younger epilepsy patients taking multiple AEDs.
Conclusion LEV was well tolerated by older patients with central nervous system disorders other than epilepsy. No problems occurred among these older patients that were not seen in the epilepsy population, nor were the rates higher. These data indicate that adverse effects associated with LEV were minimized when the drug was used as monotherapy, even in this vulnerable population.

SC 306

Seizures (Sz) after ischemic stroke (IS): a 2-year prospective study

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Introduction The purpose of our study was to analyse the frequency and risk factors (RF) of early seizures (ES) and late-onset seizures (LS).
Method All patients with IS admitted to neurological clinic between September 1, 1997 and April 1, 1998 were followed up for 2 years or until death.
Results The cohort consisted of 328 patients. Sz occurred in 32 (9.75%), ES – in 20 (6.1%), LS – in 18 patients; 30% of patients with ES subsequently had LS. In the univariate analysis significant differences between patients with and without ES were found for: age 70 – 79, moderate severity of stroke, hypertension, atrial fibrillation (AF). ES were associated with recurrent stroke (RS) and severe/moderate deficit in the late restoration period. With multiple logistic regression, AF was a significant RF for ES, and ES were a strong predictive factor for RS. 20% of patients with ES died during the first month of stroke compared to 8.4% of patients without ES. Cumulative risk of LS was 3.27% at 1 year and 5.70% at 2 years. In the univariate analysis significant RF for LS were: age 50 – 59, mild/moderate stroke, AF, and smoking. With multivariate analysis, only AF was a significant RF for LS.
Conclusion ES occurred in 6.1% of IS patients. Only AF was a significant RF for ES, while ES were a strong predictive factor for RS and LS. Cumulative risk of LS was 5.7% after 2 years of stroke.

Ageing and dementia 2

SC 307

Age-related white matter changes as a predictor of disability in the elderly: The LADIS (Leukoaraiosis and DISability) project

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Introduction Age-related White Matter Changes (ARWMC) as detected by brain imaging are associated with cognitive, motor, mood, and behaviour disturbances, all conditions related to disability in the elderly. The LADIS (Leukoaraiosis And DISability) project is a Concerted Action supported by the European union within the V Framework Program. 13 European centres collaborate with the aim to evaluate ARWMC as independent determinant of transition to disability in the elderly.
Method 800 subjects/patients aged 65 – 84 with ARWMC of different severity and no/mild disability, will be enrolled in 4 settings (stroke, dementia, geriatrics, population), assessed at baseline, and followed-up for 3 years. Subjects will be evaluated at baseline with standard clinical and functional tests (including tests for cognitive and motor functions and tests for depression). These tests will be repeated yearly for 3 years. MRI study is performed at baseline and repeated at the end of the follow-up in order to evaluate the progression ARWMC.
Results Outcome events including death, dementia, stroke, and depression will be registered. The relative risk of transition to disability and the risks of death, dementia, stroke, and depression will be estimated in the 3 severity ARWMC groups adjusting for other determinants of disability. Transnational harmonization of clinical and MRI assessments of ARWMC are ongoing and will be a further deliverable from this collaborative project.
Conclusion Clinical and radiological data will serve for identifying strategies for preventing and treating ARWMC thus contributing to reduce the burden of dependent aging in Europe.

SC 308

Detecting mild cognitive impairment (MCI) patients with the DemTect®

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Introduction The DemTect®, a new screening instrument (Kessler et al., 2000), consists of five subtests: word list learning, number transcoding, digit span (reverse), supermarket task, and delayed recall of the word list. The following cognitive domains are assessed: verbal short- and long-term memory, number processing, language, working memory, cognitive flexibility, and speed of information processing. This study repre-

sents a comparison of the performance of healthy control subjects (CG) with patients with mild cognitive impairment (MCI) on the DemTect® subtests.
Method 99 subjects were enrolled. 38 had a diagnosis of MCI, without dementia. The remaining 61 participants were healthy control subjects without cognitive impairment (CG). Both groups were comparable in age: MCI, 74.91 (SD=5.79) years; CG, 74.81 (SD=6.31) years. The MMSE score of the MCI group was 27.76 (SD=1.13), versus 27.91 (SD=1.74) in the CG. This difference was not statistically significant.
Results The MCI group demonstrated significantly lower ($P<0.01$–$P<0.001$) scores on all five DemTect® subtests than the CG (MCI vs CG: word list 9.01 vs 11.3; transcoding 3.1 vs 3.73; verbal fluency [supermarket task] 14.5 vs 22.90; digit span 4.3 vs 4.98; delayed recall 1.6 vs 3.3).
Conclusion In contrast to the MMSE, the DemTect® is a very useful tool for the identification of patients with mild cognitive impairment. The sensitivity of the DemTect® over the MMSE reveals that MCI patients may have cognitive deficits in addition to impaired memory.
Literature
Kessler J, Calabrese P, Kalbe E, Berger F (2000). DemTect: Ein neues Screening-Verfahren zur Unterstützung der Demenzdiagnostik. Psycho; 26:343–347.

SC 309

Anosognosia in mild Alzheimer's disease: revelations by FDG-PET

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Introduction We examined regional cerebral glucose uptake in mild AD patients, who, in addition, exhibited anosognosia (lack of awareness of symptoms). FDG-PET was utilized by using a new cognitive stressor, the Emotional Counting Stroop Test (ECS). Previous studies suggest that the Stroop Test evokes selective attention, which is believed to be mediated by the Anterior Cingulate Cortex (ACC) (Posner, 1996).
Method 10 mild AD patients were selected based on the MMSE score between 20 and 24. The FDG-PET scans were performed 20 minutes after undergoing the ECS, a cognitive task specialized for functional neuroimaging. A baseline PET scan and the Anosognosia Questionnaire (a questionnaire developed to objectively evaluate anosognosia in AD) were administered on separate occasions. Quantitative image subtraction was done using SPM99 software.
The co-registration of PET images with the patients' MRI scans was performed to more accurately identify areas of altered glucose metabolism.
Results 6 patients exhibited anosognosia as identified by the Anosognosia Questionnaire. A significant loss of inferior ACC and right posterior parietal glucose uptake was identified in 5 of the 6 anosognosic AD patients ($p<.01$). The magnitude of the glucose uptake loss in the ACC correlated positively with anosognosia score in mild AD ($p<.05$). However, when assessing the subtracted FDG-PET images in all of the AD patients additional areas of altered glucose uptake were identified.
Conclusion This is the first study to date which employs FDG-PET in conjunction with objective anosognosia assessment to identify the potential neural substrate of anosognosia in mild AD. Therefore, anosognosia may represent a specific defect in selective attention in AD.

SC 310

Patients with vascular dementia differ from patients with Alzheimer's disease with respect to population characteristics and pattern of cognitive decline

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Introduction Published data about the rate of cognitive decline and characteristics of patients with "pure" vascular dementia (VaD) have been limited. The objective of our study was to examine the population characteristics and pattern of cognitive decline in patients with VaD enrolled in randomised, double-blind, placebo-controlled, 24-week trials of the efficacy and tolerability of donepezil (Studies 307 and 308).
Method Enrolled patients had probable or possible VaD, classified according to NINDS-AIREN criteria. Patients were excluded if they had a diagnosis of Alzheimer's disease (AD).
Results 219 patients were enrolled; 73% had probable VaD and 27% had possible VaD. At screening, patients had a mean Hachinski score of 9.7. 73% of patients had had an abrupt onset of cognitive symptoms. 60% of patients had a history of at least one stroke, 17% had a history of transient ischemic attack. Vascular risk factors were prominent and included hypertension (70%), smoking (62%), and hypercholesterolemia (39%). Almost all patients had abnormal CT or MRI scans. Placebo-treated patients with VaD maintained cognitive function (ADAS-cog LS mean change from baseline score at Week 24 [observed cases], −0.10; n=310). This contrasts with the cognitive decline observed in placebo-treated patients with AD in donepezil trials (ADAS-cog LS mean change from baseline score at Week 24, 0.94; n=491).
Conclusion The patients enrolled in these trials had probable or possible VaD and a broad range of cardiovascular disease, and therefore differ from those enrolled in AD trials. Placebo-treated patients with VaD, in contrast to placebo-treated patients with AD, demonstrated stable cognitive function over 24 weeks.

SC 311

Global cognitive function and dementia in acute stroke and seven years after. The influence of age, stroke severity, stroke recurrence and stroke risk factors. A community-based study.

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Introduction Stroke may lead to impairment of global cognitive function and dementia. In a large community-based stroke cohort we evaluated risk factors for developing dementia following stroke.
Method In the community-based Copenhagen Stroke Study of 1197 acute stroke pts MMSE was tested in the acute state and at follow-up 7 years after. MMSE was used as a marker of dementia. Scandinavian Stroke Scale (SSS) was used to determine stroke severity. Relevant stroke risk factors were evaluated. Multivariate statistics were entertained.
Results Mean age was 74 years; at follow-up 81 years. MMSE was significantly related to stroke severity.
1) Acute state: SSS 0–14: MMSE 9; SSS 15–29: MMSE 12; SSS 30–44: MMSE 24; SSS 45–58: MMSE 24.
2) Follow-up: SSS 0–14: MMSE 9; SSS 15–29: MMSE 22; SSS 30–44: MMSE 24; SSS 45–58: MMSE 26.
Predictors of decline of MMSE over time were: *Age* MMSE decreased 0.7 point per 10 years increase (p=0.03). *Stroke se-*

verity MMSE decreased 1.0 point per 10 points decrease of SSS (p=0.02). *Hypertension* MMSE decreased 1.8 points (p=0.04). *Stroke* recurrence MMSE decreased 2.2 points (p=0.04). *MMSE in the acute state* MMSE decreased 6.6 points per 10 points decrease. Other stroke risk factors and leucoaraiosis had no influence.
Conclusion Change in MMSE over time was predicted by age, stroke severity, previous stroke, hypertension, and MMSE in the acute state. Atrial fibrillation, leucoaraiosis, and previous stroke had no independent influence. The study points to possibilities of preventing global cognitive impairment and dementia after stroke in particular hypertension.

SC 312

Intrathecal infusion test in the detection of normal pressure hydrocephalus

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Introduction We wanted to examine the frequency of pathological intrathecal infusion tests in the population of patients who were admitted to our department with a possible normal pressure hydrocephalus (NPH), and the proportion of patients who later had a shunt-operation.
Method All patients who had an intrathecal infusion test at the Department of Neurology, in the period 1991–2001 were included. The tests were performed according to the modified procedure of Katzman and Hussey. The initial resting pressure and mean increase in pressure during the 10 minutes of infusion were measured. The results from the tests were classified into 3 groups: normal, possible pathological and definite pathological.
Results During the 11 years 324 tests were performed. 168 tests were normal, 60 possible pathological and 96 definite pathological. In the group with pathological tests 16% of the patients were under 60 years of age, 23% 60–70 years, 47% 70–80 years, and 14% over 80 years of age. 56% of the patients with definite pathological tests, 20% with possible pathological tests and 14% with normal tests, later had a shunt-operation.
Conclusion NPH is a dementia that can be reversed with a shunt-operation. An early diagnosis is important. The intrathecal infusion test is a simple diagnostic procedure of significance. However, other factors also seem to influence in the decision regarding surgery.

Headache and pain

SC 313

Prevalence and diagnosis of migraine in a primary care setting

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Introduction This prospective, international, open-label study examined the association of headache impact and migraine diagnosis in subjects presenting to primary care physicians (PCP) with headache. Additionally, migraine prevalence in this primary care setting was ascertained.
Method Headache sufferers presenting to a PCP completed a headache impact test, a headache survey, and a productivity questionnaire. Then the PCP, using customary diagnostic practice, evaluated them, grouping them as being previously diagnosed migraine, newly diagnosed migraine, non-migraine primary headache, and secondary headaches. Newly diagnosed and non-migraine subjects completed diaries for their first 6 headaches. At study end, an expert panel reviewed the diaries, providing a final IHS diagnosis.
Results From 700 headache presenters (outside of US) who completed the screening phase, 82% (575/699) received a migraine diagnosis from their PCP; 170 were newly diagnosed subjects and 405 had been previously diagnosed. Non-migraine primary headache diagnosis comprised 92 subjects. Diaries were completed by 149 newly diagnosed migraineurs and 67 non-migraine subjects. Expert panel review of the diaries revealed that the initial migraine diagnosis in the newly diagnosed group was correct in 85% (126/148) of cases. Diary review of the non-migraineurs, as initially diagnosed by PCP's, revealed that 61% (41/67) could be reclassified as migraine (1.1/1.2).
Conclusion In the absence of headache diary information, PCP's appear to be too conservative in diagnosing migraine. When diagnosis (excluding migrainous) was made, it was correct 85% of the time. In contrast, 61% of non-migraine diagnosis by PCP's was in fact migraine (excluding migrainous).

SC 314

Headache associated with sexual activity: demography and clinical features

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Introduction The objective of our study was to provide demographical and clinical data about idiopathic headache associated with sexual activity (HSA) by analysing the second largest case series reported to date.
Method Between 1996 and 2001, 37 patients with a diagnosis of HSA were questioned by a structured interview.
Results The mean age at onset of the disease was 36.8 (±10.7) years. There were a clear male preponderance (2.7:1) and two peaks of age of onset. A first peak was between the 20th and 24th (n=8), a second between the 35th and 44th (n=16) year of age. 8 patients suffered from HSA type 1 (dull subtype) which gradually increased with progressing sexual excitement. The remaining (n=29) suffered from HSA type 2 (explosive subtype). The pain was predominantly bilateral (27/37) and diffuse or occipitally (33/37) located. In HSA type 2, there was a high co-morbidity with migraine (12/29), benign exertional headache (16/29), and tension-type headache (14/29). In contrast, HSA type 1 only had a co-morbidity with tension-type headache (4/8, $p<0.05$).
Conclusion Mean age at onset, a male preponderance, a predominantly bilateral and occipital pain, and a higher frequency of HSA type 2 are in concordance with the literature. For the first time, we found two peaks for the age of onset. The high co-morbidity of HSA type 2 with migraine and benign exertional headache might give interesting insights into its aetiology.

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Triptan use is not associated with increased risk of severe vascular events in migraine patients

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Introduction It has been speculated that triptan use might increase risk of ischemic events through vasoconstriction. Our main objective was to estimate rates of ischemic events in relation to triptan use among migraineurs and compared with non-migraineurs.
Method We conducted a retrospective cohort study of ischemic events and mortality among 130,411 migraineurs and 130,411 matched non-migraineurs, using United Healthcare's medical claims data from 1995–1999, and the National Death Index. Rate ratios (RRs) incorporate adjustment for demographics, cardiovascular history, ergot alkaloid use, and other factors.
Results Migraineurs and non-migraineurs had identical rates of myocardial infarction (MI): 1.4/1000 person-years. There was no increase in risk of MI with current (RR 0.80, 95% CI 0.58–1.11) or recent (RR 1.15, 95% CI 0.71–1.87) triptan use. Migraineurs had 67% more strokes than non-migraineurs (RR 1.67, 95% CI 1.31–2.13). Neither current (RR 0.90, 95% CI 0.64–1.26) nor recent (RR 0.84, 95% CI 0.46–1.55) triptan use was associated with risk of stroke. Current ergot use was associated with a moderate increase in risk of stroke (RR 1.49, 95% CI 0.93–2.41). History of migraine was not associated with all-cause mortality. There was no increase in all-cause mortality with current (RR 0.64, 95% CI 0.45–0.89) or recent (RR 1.01, 95% CI 0.63–1.64) triptan use.
Conclusion Use of triptans was not associated with increased risk of any ischemic events, including MI and stroke, or mortality. Consistent with previous studies, migraineurs had an elevated risk of stroke, compared with non-migraineurs. There is a suggestion for concern regarding ergot drugs and cerebral ischemic events.

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Reduced headache impact after three months of sumatriptan migraine therapy in the primary care setting

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Introduction The Headache Impact Test (HIT-6) was developed to quantify the impact of headache on patients' life. Sumatriptan has proven clinical efficacy; we aimed to evaluate its effect on reducing headache impact.
Method In a 15-country prospective study aimed to assess the association of HIT-6 scores with migraine diagnosis in the predominantly primary care setting (PCS), migraine subjects received sumatriptan 50mg (S50, n=595) for 3 months. At study end, changes in HIT-6 scores were evaluated for the overall study sample. To adjust S50 effect estimate for potential study effect using a conservative approach, the incremental change in HIT scores among subjects who were triptan naïves (TNs, n=457) over subjects who were prior sumatriptan users (PSUs, n=138) before the study was examined using analysis of covariance adjusting for gender and baseline score.
Results The study sample (n=595) consisted of 84% female, mean age 39 years. Prior to the study a majority of subjects (77%) did not use triptans, of which 83% used over-the-counter analgesics. At study end, mean HIT-6 score for the overall sample was significantly reduced from 65 (SD=6) to 59 (SD=8) ($p<0.0001$). After adjusting for potential study effect, reductions in HIT-6 scores during the study for TNs remains to be significantly greater than PSUs by 2.5 (95% CI: 1, 4) ($p<0.001$).
Conclusion Sumatriptan reduced headache impact beyond migraine pain and associated symptoms in triptan-naïve migraineurs.

SC 317

Topiramate prophylaxis in patients suffering from migraine with aura: results from a randomized, double-blind, placebo-controlled trial

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Introduction Topiramate, a broad-spectrum antiepileptic drug, has demonstrated efficacy in migraine prophylaxis in several pilot trials.
Method We conducted a multicenter, randomised, double-blind, placebo-controlled study of topiramate in migraine prophylaxis. A total of 213 patients were initially randomised in a 2:1 ratio to topiramate or placebo. Study medication was titrated weekly in 25-mg increments over 8 weeks to 200 mg/day or to the maximum tolerated dose, followed by a 12-week maintenance period. A subset of patients (n=75) experienced aura or migraine with aura (n=46 topiramate, n=29 placebo) at some point during the trial. The protocol defined analyses used ANCOVA with baseline monthly migraine rate as covariate.
Results For the ITT population (n=211), the protocol defined repeated measures were not sensitive enough to detect drug-placebo differences. Among patients with any aura, topiramate treated patients exhibited a significantly greater reduction in monthly migraine rate ($P=.018$) and migraine days/month ($P=.04$) compared to placebo treated patients.
Conclusion The results of this study suggest that migraine prophylaxis with topiramate may be more effective in patients with aura compared to those without aura.

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Efficacy of eletriptan in subjects who previously demonstrated lack of response to oral sumatriptan: a randomised, placebo-controlled study

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Introduction Eletriptan is a selective 5-$HT_{1B/1D}$ agonist previously shown to be effective in the acute treatment of migraine[1-3]. This study investigated the efficacy of eletriptan in a subset of patients from a previous study who discontinued sumatriptan due to lack of response.
Method A subgroup analysis was performed in a double-blind, parallel-group study of patients who previously had an insufficient response to sumatriptan (n=317). Subjects received

40mg eletriptan (E40; *n*=140), 80mg eletriptan (E80; *n*=121) or placebo (*n*=56) for the treatment of 1–3 migraine attacks.
Results Results are reported as E40, E80 and placebo. Two-hour headache response rates for eletriptan 40mg and 80mg were significantly greater than placebo (57%, 70%, 31%; $P<0.005$ E40, $P<0.0001$ E80). Both E40 and E80 provided rapid onset of action, with higher headache response at 1h (36%, 48%, 15%; $P<0.01$ E40, $P=0.0001$ E80). The 2h pain-free rate was significantly higher with eletriptan (30%, 46% and 4%; $P<0.005$ E40, $P=0.0001$ E80). Headache response was sustained, with no recurrence or need for rescue medication (37%, 45%, 13%; $P<0.005$ E40, $P<0.0005$ E80). Eletriptan demonstrated significantly superior sustained pain-free relief (21%, 28%, 4%; $P<0.05$ E40, $P<0.005$ E80). Treatment-related adverse events were generally mild to moderate and transient. Both eletriptan doses had significantly greater treatment acceptability than placebo (63%, 67%, 17%; $P<0.0001$ both comparisons).
Conclusion Eletriptan 40mg and 80mg were shown to be highly effective and well-tolerated in treating migraine patients who previously discontinued sumatriptan due to inadequate response.
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Movement disorders 2

SC 319

Brain activation during complex finger tapping in patients with writer's cramp: a functional MRI study.

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Introduction The objective of our study was to investigate the cerebral activation pattern during complex finger tapping in patients with writer's cramp.
Method We studied 11 patients with writer's cramp and 11 age-matched control subjects. All patients and controls were right-handed. Subjects had to tap individual fingers against the thumb pad in a fixed sequence (second-fourth-third-fifth) with the dominant and the non-dominant limb at their maximum speed. Right and left hand were studied in separate sessions. The fMRI experimental paradigm consisted of multiple 15-second epochs of baseline (rest) and activation (movement), in a boxcar configuration. Image processing and statistical analysis of the fMRI time-series data were performed using SPM99.
Results Both groups performed more taps with the dominant than the non-dominant hand. Patients performed a smaller number of finger taps than controls with both dystonic and non-dystonic hand ($F_{group}=145$; $F_{side}=21$; for both values $p<0.001$) and made more errors than controls ($F_{group}=11.4$; $p<0.01$). During movements of the dystonic hand patients activated bilateral premotor areas (BA6) and the left inferior parietal lobule (BA40) more than controls ($p<0.001$). In addition to these areas, during movements performed with the non-dystonic (and non dominant) hand patients also showed increased activation of the superior parietal (BA7) and insular cortex bilaterally.
Conclusion The performance of complex finger movements is abnormal in both hands in patients with writer's cramp. This abnormality is associated with an increased activation of the premotor and parietal cortex.

SC 320

Phenotypic characterization of dyt 13-related primary torsion dystonia in a large Italian family

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Introduction A large Italian family, affected by idiopathic torsion dystonia was investigated. The family was first examined in 1994. In 2001, a novel PTD locus named DYT13 was identified on chromosome 1(1p36.13–36.32), as associated with the phenotype segregating in this family.
Method The family, including 45 family members and 11 spouses, was examined for the first time in 1994. Each subject underwent complete neurological evaluation and was blood sampled for DNA analysis. All the members were re-evaluated on March 2000.
Results In 1994, 8 individuals received a diagnosis of definite dystonia and 6 of probable dystonia. After the second evaluation, 3 more individuals had developed a definite dystonia. Inheritance of PTD was autosomal dominant, with affected individuals spanning 3 consecutive generations and male-to-male transmission. The age at onset ranges from 5 to 45 years. Onset occurred either in the cranio-cervical region or in the upper limb. Progression was mild and disease course relatively benign for all affected individuals (just two cases had generalization). Affection of the lower body was rarely significant. No "anticipation" was observed in younger generations neither in the age of onset nor in severity. Some of the affected members presented rapid jerky, myoclonic-like movements.
Conclusion At present, the linkage of PTD and DYT13 locus has been detected only in this family. The phenotypic presentation of DYT13-PTD in 11 subjects belonging to a large Italian family is variable, but includes few prevalent features: early age at onset, upper body presentation of symptoms, mild severity of disease even in subjects with generalized dystonia.

SC 321

Role of levodopa on experimental pain in Parkinson's disease (PD): a positron emission tomography study

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Introduction Physiopathology of pain in PD is not well known. Painful symptoms could be in part due to central modification of nociception and that the dopaminergic deficit would be expected to eliminate the inhibitory influence on thalamocortical nociceptive activity. The objective of our study was to assess the effect of levodopa on cerebral activity during experimental nociceptive stimulation in PD patients and to compare pain threshold before and after administration of levodopa.
Method We performed $H_2{}^{15}O$ PET analyses of cerebral blood flow on six PD patients (66±8 years) while they received alternate noxious and innocuous right hand cold water stimuli during OFF dopaminergic treatment and after levodopa administration

(ON). Orders of cold stimuli and OFF/ON periods were randomised. For each patient cold stimuli were determinated using a visual analogue scale from 0 to 10. Noxious cold stimulus was defined as temperature inducing painful sensation superior or equal to 3 and innocuous stimulus was the previous value plus 10°C.
Results For most of the patients during OFF period, painful stimulation (9.3±1.2°C) induced increases of CBF in left parietal cortex, left motor and lateral premotor cortex, supplementary motor area, cingulum and brainstem. During ON period, only an increase of CBF in cingulate gyrus was elicited by pain stimulation (6.2±2.4°C). In OFF period, pain threshold was higher than in ON period (levodopa mean dose=225±61 mg) ($p=0.01$).
Conclusion Levodopa could reduced pain induced-activation in nociceptive pathways and raised pain threshold in PD patients suggesting that dopaminergic deficit could be involved in central processing of pain in PD.

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The adverse effects of L-dopa-induced dyskinesias on the quality of life (QoL) of patients with Parkinson's disease (PD): a prospective European study

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Introduction Previous studies have shown that dopamine agonists can reduce the risk of L-dopa induced dyskinesia. We evaluated the impact of L-dopa-induced dyskinesias on (QoL) in patients with Parkinson's disease.
Method A 6-month, multicentre, observational study was conducted in France, Germany and the United Kingdom. We measured dyskinesias using 2 scales: the Unified Parkinson's Disease Rating Scale (UPDRS, section IVa) and the Goetz Dyskinesia Rating Scale (GDRS). QoL was assessed using the Short-Form 36 (SF-36) and the Parkinson's Disease Quality of Life (PDQL) scales. Depression was evaluated using the Montgomery Asberg Depression Rating Scale (MADRS), and activities of daily living (ADL) using the UPDRS (section II). Statistical analysis included the use of multiple regression models to assess the impact of dyskinesias on QoL, while taking into account the effects of fluctuations, disease progression and country.
Results A total of 321 patients were enrolled at 63 centres: 63% of patients were male, mean age was 64 (±9) years, and mean disease duration was 8.7 (±5.6) years. There was a wide spectrum of clinical presentations ranging from no motor complications to fluctuations and severe dyskinesias. Higher dyskinesia scores on section IVa of the UPDRS were associated with a significant decrease in the QoL measures on the SF-36 subscales, as well as its two summary scales (physical component scale $p=0.0089$, mental component scale $p=0.0021$). Similarly, higher dyskinesia scores (UPDRS and GDRS) were associated with significant reductions in scores on the PDQL subscales; in particular, dyskinesias had a negative effect on the scores of the two subscales that were not symptom based (social functioning [$p=0.0002$ UPDRS; $p=0.0012$ GDRS] and emotional functioning [$p=0.0011$ and $p=0.0233$, respectively]). Dyskinesias also had an adverse effect on depression; higher scores on dyskinesia scales were associated with worsening depression on the MADRS ($p=0.0034$ for UPDRS and $p=0.0478$ for GDRS). On the other hand, dyskinesia scores had no significant effect on patients' ADL scores.
Conclusion L-dopa induced dyskinesias have adverse effects on the QoL of patients with Parkinson's disease. These effects are particularly important in terms of their negative impact on the psychological well-being of patients. Treatment strategies proven to reduce the risk of dyskinesia (use of dopamine agonists as early therapy) might help to diminish the adverse consequences of dyskinesias on the QoL of patients with Parkinson's disease.
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Hedonistic homeostatic dysregulation: screening in an Italian Parkinson's disease population

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Introduction Hedonistic homeostatic dysregulation (HHD) is a neuropsychiatric disorder that has recently been described in patients with Parkinson's disease (PD). The clinical syndrome of HHD includes symptoms of self-medication, drug hoarding, hypersexuality, behavioural disorders (aggression), mood disorders (depression, anxiety, hypomanic state) and an alterated perception of motor state.
Method To better evaluate the prevalence of this phenomena in PD, we have designed a short screening questionnaire that has been filled in at the control visits at our PD clinic. The questionnaire consisted of 3 parts: demographic data; presence of dyskinesias; 5 questions about 1- self-medication and assumption of extra dose of dopamine replacement therapy (DRT), 2- mood disorders, 3- behavioural disorders, 4- compulsive behaviours, 5- hypersexuality.
Results Over a 4-month period, 202 patients with PD have been screened; 114 were male, mean age was 68.1 y (range 42–89), mean duration of disease 7.3 y (1–30), mean Hoehn and Yahr score 2.2 (1–4). Of this cohort of PD patients, 43.6% (n=88) presented with mood disorders; 5.5% (n=11) abused DRT; 5.5% (n=11) showed behavioural disorders; 3,0% (n=6) compulsions; 2.0% (n=4) alterations of sexual behaviour. According to our data we have selected 6 (3.0%) patients who presented with abuse of DRT associated with mood and behavioural disorders, suggesting a possible diagnosis of HHD.
Conclusion HHD is a rare condition though extremely distressing for the patients, its family and social environment. We are evaluating in detail the selected patients to confirm diagnosis and consequently optimise pharmacological treatment.

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A biochemical marker for Parkinson's disease

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Introduction As the majority of neurodegeneration in PD occurs before motor dysfunction develops, the development of neuroprotective treatments for PD are hindered by current diagnostic methods based on motor signs. The death of central dopaminergic neurons results in the release of the intraneuronal pigment neuromelanin (NM). We hypothesised that the release of NM might stimulate a specific immune response and developed a novel enzyme-linked immunosorbant assay (ELISA) to quantify such a response. The aim of this project was to investigate

the efficacy of this test in discriminating PD subjects from healthy controls.
Method PD patients and healthy age- and sex-matched controls were recruited from Australian and German populations. PD was confirmed using the Unified Parkinson's Disease Rating Scale and a positive response to L-dopa in the absence of atypical signs. Collected sera were analysed using our novel ELISA test for anti-NM antibodies.
Results The ELISA response was significantly higher in the PD patients compared with healthy controls in both populations (Australian population; p=0.005, German population; p=0.001). The response was specific for catecholaminergic-based compounds and was unaffected by age or gender of the subject. The response was associated with disease severity, being higher in the early clinical stages.
Conclusion This test represents a novel and objective method to identify a specific immune response indicating the death of central dopaminergic neurons. As loss of pigmented neurons occurs primarily prior to the onset of motor symptomatology we propose that this test may represent a biochemical marker for preclinical PD.

Neuroimaging

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Positron emission tomography studies in patients referred with suspected Creutzfeldt-Jakob disease

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Method PET was performed in 15 patients with the tentative clinical diagnosis of Creutzfeldt-Jakob disease (CJD). [18F]-2-fluorodeoxyglucose (FDG) was used to assess changes in regional brain glucose metabolism indicative of neuronal death and the monoamine oxidase B inhibitor, N-[11C-methyl]-L-deuterodeprenyl (DED) was used to assess astrocytosis.
Results The diagnosis of definite CJD was confirmed in 6 patients. In 1 patient with probable CJD prion resistant protein could not be demonstrated. In further patients with probable CJD no autopsy was allowed. In the patients with definite or probable CJD, FDG and DED gave, in comparison with normal controls, a typical pattern of pronounced decrease of glucose metabolism regionally, indicative of cell death, accompanied by a similar increase in DED binding, indicating astrocytosis. These changes were most pronounced in the cerebellar, frontal, occipital and parietal cortex whereas the pons, the thalamus and the putamen were less affected and the temporal cortex appeared relatively unaffected. In the 6 other patients, the clinical examination was unable to confirm the diagnosis of CJD. In 3 of them a high regional cerebral glucose metabolic rate was noticed in parts of the brain, the temporal lobes and basal ganglia in particular. 1 had Sjögren's syndrome, 1 had suffered of paraneoplastic limbic encephalitis. The third spontaneously recovered. In the last 3 patients the deprenyl-binding was normal despite the hypometabolic glucose pattern similar to that seen in the CJD patients.
Conclusion A combination of a high regional deprenyl binding and a low regional glucose metabolism seems to be indicative of CJD.

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High resolution imaging of gene expression by positron emission tomography (PET)

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Introduction The objective of our study was to non-invasively quantitate herpes simplex virus type 1 thymidine kinase (HSV-1-tk) gene expression mediated by double-gene co-expression constructs by new generation ECAT HRRT and microPET scanners at high spatial resolution.
Method Multi-functional imaging genes consisting of the HSV-1-tk gene linked to the green fluorescent protein (gfp) gene by gene fusion or by an internal ribosome entry site were retrovirally transduced into rat F98 glioma cells. F98-TG17 (tkgfp fusion), F98-TIG (tkIRESgfp) and F98-GIT (gfpIREStk) glioma cells were sorted by fluorescence activated cell sorting (FACS) and their relative GFP-expression was quantified. The level of TK-expression was assessed after intravenous administration of 9-(4-[18F]fluoro-3-hydroxymethyl-butyl)guanin (FHBG; 250 μCi/rat; 50 μCi/mouse) into nude rats (n=4) and nude mice (n=4) bearing subcutaneous growing transduced F98 gliomas.
Results In cell culture, the relative level of GFP-expression mediated by F98-GIT cells was 2- to 3-fold higher than in F98-TIG cells indicating IRES-mediated impaired cap-independent translation of the second gene. In contrast, F98-TIG cells accumulated 2- to 3-fold more FHBG than F98-GIT cells demonstrating a good correlation between both quantitative assays for IRES-mediated GFP- and TK-expression in culture and in vivo.
Conclusion Subtle differences of HSV-1-TK expression due to different locations of the tk-gene within multiple-gene constructs can be differentiated by high-resolution FHBG-PET. Proportional IRES-mediated co-expression of TK with a therapeutic gene substituting the gfp-gene will enable indirect in vivo imaging of therapeutic gene expression even with the tk-gene located at the "weak" position downstream from the IRE site.

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Comparison of DW/PW-MRI and PET in acute ischemic stroke: early identification of penumbra and irreversible damage

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Introduction The main target of therapeutic strategies in acute stroke trials is the functionally impaired but still viable tissue, i.e. the penumbra. DW- and PW-MRI have become powerful tools in acute stroke trials. However, the quantitative assessment

of perfusional thresholds and irreversible lesion volume remain important methodological issues. MRI findings were validated on PET results to improve reliability in acute stroke imaging.
Method In 10 patients DW- and PW-MRI were performed within 8 h after ischemic stroke and after 24 h. MRI-based definition of hypoperfusion volume and lesion size was compared to CBF, CMR02, and flumazenil binding (FMZ).
Results The volume of reduced CMRO2 corresponded to DWI lesion size. Reduced FMZ binding could be larger than the DWI defect at first measurement and correlated to the permanent infarct. The area of critically reduced CBF extended beyond the defect on initial DWI and PWI but correlated to lesion size on DWI after 24h.
Conclusion These preliminary data in a small patient group allow the comparison of multitracer PET and DW/PW-MRI in the acute phase of ischemic stroke. PET imaging provides the earliest and most reliable detection of irreversible neuronal damage and penumbra tissue. However, in most instances MRI enables a fair estimate of ischemic compromise.

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Functional imaging of visually guided hand movements

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Introduction Imaging studies in humans suggest that visuomotor control of forelimb and eye movements involves reciprocal connections between striate, extrastriate, parietal, motor and frontal areas related to movement performance and visuospatial coding of movement direction. The aim of our study is to investigate the functional role of the human extrastriate visual area V5 in the control of visually guided hand movements and the interaction between extrastriate visual areas, basal ganglia, parietal and motor areas by using functional MRI (fMRI).
Method 9 right-handed, healthy subjects performed visually guided hand movements, either tracking a horizontally moving target or performing a centre out task to a stationary target by moving a cursor using a MRI compatible joystick. Subjects' eye and hand movements were monitored during scanning. Brainvoyager 4.4 was used for data analysis.
Results Our results show significant neural activations in area V5 during visually guided hand tracking movements. Visuomotor tracking with central fixation versus replay condition engaged a neural network involving left sensorimotor cortex, bilateral SMA, pre-SMA, dorsal premotor cortex, intraparietal cortex, as well as left basal ganglia, thalamus and right anterior cerebellum. The centre out task activated the same areas, but the basal ganglia and thalamus to a greater degree and less so the premotor cortex. Additional activation in the right red nucleus was evident.
Conclusion Our results indicate that visual monitoring during tracking and reaching requires the involvement of area V5.
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SC 329

Functional brain mapping of the sensorimotor cortex: an fMRI study

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Introduction We wanted to implement a vibrotactile-stimulation-paradigm within the MR-environment for functional brain diagnosis in patients with severe motor deficits.
Method Experiments were performed on a 1.5Tesla whole-body scanner. The vibrotactile-stimulation-paradigm was a 50Hz vibrotactile stimulus with an amplitude of 2mm applied via pneumatic tube to the right and left palm. The vibrating device is an electromotor with 50W performance and 6000U/min. A single examination consisted of two fMRI measurements, where the right and the left palm were vibrated. The whole study was performed in 20 healthy, right-handed male and female volunteers (age range 25–45 years). Statistical analysis was done with SPM99.
Results Vibratory stimulation of the right and left palm revealed contralateral activation of the primary motor cortex (MI), the primary and secondary somatosensory cortex (SI and SII) and the premotor area (PM). The supplementary motor area (SMA) within the frontal lobe was bilaterally activated. An ipsilateral activation foci was seen within the gyrus frontalis superior near the interhemispheric fissure, within the PM and the SI and SII. The strongest activation was found within the SI and SII followed by the MI. The PM and the SMA showed only weak activation.
Conclusion Vibratory stimulation to the right and left palm can lead to an activation response not only of sensory cortex, but also to an activation response of the motor cortex. This holds promise for the vibratory stimulation to be applied for functional brain mapping of the sensory motor cortex in patients with severe motor deficits.

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Investigations on the human central sympathetic pathway through the brainstem using a new method of three-dimensional mapping on the basis of digital post-processing MRI

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Introduction Information on the brainstem segment of the central sympathetic pathway is sparse. Experimental studies suggest integrative centres in the dorsolateral pontine tegmentum and in the medulla oblongata. To study the central sympathetic pathway in man we applied a new method of three-dimensional brainstem mapping using digital post-processing MRI by

superimposing brainstem lesions onto the appropriate sections of an anatomical atlas and an idealized brainstem model.
Method 258 prospectively recruited patients presenting with acute signs of brainstem ischemia underwent biplane T2- and EPI-diffusion weighted MRI with slice direction parallel and perpendicular to a brainstem slice selection of the stereotactic anatomical atlas of Schaltenbrand and Wahren. The individual slices were normalized and projected into the digitalized anatomical atlas. Lesions were then imported into a three-dimensional model of the human brainstem consisting of 5286 volume elements ("voxels") for correlation analysis.
Results 32 of the 258 patients showed a Horner's syndrome due to acute brainstem ischemia. Only 2/32 patients had pontine lesions sparing the medulla, 14 had pontomedullary lesions, 16 medullary lesions. Correlation analysis showed significantly affected voxels in the dorsal medulla oblongata. Lesion site contacted or overlapped the area of the dorsomedially located Nucleus tractus solitarius (NTS) in 82% of the patients on one or more atlas slice levels.
Conclusion In this first in vivo study important relay centres of the central sympathetic pathway could be localised in the medullary complex of the NTS, one of the integrative centres suspected from experimental animal studies.

Sleep disorders

SC 331

Sleep apnoea in ischaemic stroke: a prospective study

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Introduction Sleep apnoea can be responsible for various changes that can play an important role in precipitating stroke. We aimed to prospectively evaluate the presence of sleep apnoea syndrome (SAS), delineate its subtype, and evaluate its management in recent stroke.
Methods We investigated 50 patients with acute stroke and 27 subjects as a control. We obtained data reflecting risk factors and Epworth Sleeping Scale (ESS) by interviewing every subject and his/her spouse. Severity of stroke was assessed by Scandinavian Stroke Sclae (SSS). Patients and control were subjected to overnight sleep study using portable AutoSet device. Arterial blood gases were estimated for very patient and control.
Results 30 patients had supratentorial and 20 had infratentorial infarctions. Among the supratentorial group, 7 (23.3%) had obstructive SAS, while in infratentorial group 6 (30%) had central and 5 (25%) had obstructive SAS. No significant difference was found between obstructive SAS, central SAS, and control groups as regards age, BMI, other risk factors, while ESS was significantly higher in obstructive than in central and control groups. Sleep respiratory study parameters were significantly higher among obstructive than central SAS and control groups. No relationships were found between sleep apnoea and the topographical parenchymatous location of the neurological lesion. On the other hand, significant correlation was found between severity of stroke and severity of SA. All patients with obstructive SAS showed significant improvement after nasal continues positive air pressure (CPAP) ventilation, and those with central SAS improved significantly with bilevel positive airway pressure (BiPAP).

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Hypocretin dysfunction and sleep disturbances in neurological diseases

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Introduction Hypocretins 1 and 2 are newly discovered neuropeptides that play an important role in the regulation of sleep. Recent human studies documented a high sensitivity and specificity of undetectably low CSF hypocretin levels in idiopathic narcolepsy-cataplexy cases.
Method 20 patients with narcolepsy-cataplexy, 4 cases with Niemann-Pick disease and 3 patients suffering from Prader-Willi syndrome underwent sleep study (nocturnal v-PSG and MSLT). In all of the patients HLA oligotyping with DQB1*0602 positivity was done, hypocretin-1 measurement in CSF was provided and the values were correlated with controls.
Results MSLT mean value in patients suffering from narcolepsy-cataplexy was 3.06±2.3 min, number of SOREMs/5 was 2.5±1.57. With the exception of 2 cases (one of the both with signal peptide hypocretin mutation) the others were HLA DQB1*0602 positive. 17 out of 20 patients had undetectable CSF hypocretin-1 level, in one case the level was very low (75 pg/ml). Only 1 patient showed normal and 1 even elevated CSF hypocretin-1 level. The diagnostic specificity of this examination for narcolepsy was 90%. Out of 4 Niemann-Pick disease cases only one with clinical signs of cataplexy was HLA DQB1*0602 positive. CSF hypocretin-1 level in this group was significantly diminished ($p<0.05$) in comparison with the controls. Patients suffering from Prader-Willi syndrome (n=3) revealed a diminished CSF hypocretin-1 level in correlation with duration of the disease and severity of sleep disturbance.
Conclusion Hypocretin deficiency can be found besides narcolepsy-cataplexy also in sleep disorders developing as a consequence of lateral hypothalamic area damage.

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Effects of gabapentin on restless legs syndrome accompanied by nocturnal pain: results of a double-blind, crossover study with polysomnographic control in 24 patients

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Introduction Several open studies have suggested the therapeutic efficacy of gabapentin (GBP) in restless legs syndrome (RLS)[1,2]. This double-blind study investigated efficacy and effective dose of GBP in RLS and examined the role of nocturnal pain in predicting GBP response.
Method 24 patients with RLS (International Restless Legs Syndrome Study Group [IRLSSG] criteria)[3] underwent 6 weeks of treatment with GBP or placebo (PLB) following a randomised, double-blind, crossover design. GBP was initiated at 600mg/d and increased by 600mg/d every 2 weeks if clinically required. Patients were assessed at baseline with a visual analog scale for pain (VAS-P) and the IRLSSG rating scale. Based on a threshold score of 20mm on the VAS-P, patients were classi-

fied as either pain-RLS (P-RLS) or not pain-RLS (NP-RLS). Both rating scales were completed every 2 weeks. Sleep studies were performed after each treatment period.
Results The mean IRLSSG-rating score for GBP patients was 53% lower than for PLB patients. The mean effective dose of GBP was 1855mg/d. GBP also increased total sleep time, sleep efficiency, and stage 3 sleep, and reduced periodic leg movements of sleep (PLMS) (all $p<.05$). Additionally, the percentage of NP-RLS increased with GBP (62% to 81%) but remained stable with PLB ($p<.01$).
Conclusion GBP is an effective treatment for RLS. The presence of nocturnal pain predicts a better response to GBP. Normalization of sleep and PLMS-index can be observed following GBP treatment.
Literature
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The impact of restless legs syndrome (RLS) on sleep and cognitive functioning

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Introduction RLS is a serious neurological disorder with primary morbidities involving sleep loss and extreme discomfort, which may impact on cognitive abilities. To date, no studies have systematically assessed the burden of RLS on sleep and cognition. This study assesses the impact on these parameters compared with a normative population (norms).
Method The Medical Outcomes Study Sleep and Cognition scales were administered to 85 patients with primary RLS referred to a specialist clinic. Scores from this group were compared with published norms (N=3053). As recommended in the literature, a 0.5 SD determined a minimally clinically important difference.
Results The majority (64.5%) of patients were women; the mean (±SD) age was 62.4 (±14.0) years; 67.1% reported experiencing RLS symptoms almost daily. Sleep scores for the RLS group were 19 points (approximately 1 SD) worse than the norms. Cognition scores for the RLS group were 14 points (0.5 SD) worse than the norms. Sleep and cognition scores for RLS patients were even worse if RLS symptoms first began to appear before the age of 45 years (deficit of four additional points). A significant correlation between sleep loss and cognition was noted ($p<0.05$).
Conclusion RLS poses a clinically significant burden to patients in terms of sleep loss and cognitive functioning, which should be considered when evaluating RLS treatment. The early-onset phenotype was more impaired. This is consistent with research noting the biological differences between early- and late-onset RLS phenotypes. Future studies will further establish the cognitive and sleep impact of RLS.

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Cabergoline in restless legs syndrome (RLS) – a double-blind placebo-controlled multicenter dose-finding trial

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Introduction Augmentation or time-shifting of symptoms after starting therapy may limit the clinical use of l-dopa (LD) and short-acting dopamine agonists (DA) in RLS. Trials suggest an inverse correlation between half-life and incidence of augmentation, favouring DAs with longer half-lifes, like cabergoline (CAB, t1/2: 65h).
Method 86 patients with moderate to severe RLS were stratified into 4 treatment groups receiving placebo, 0.5mg, 1mg and 2mg CAB once daily.
Results Demographic characteristics were comparable in all groups: duration of RLS: 220.4±158.2 months, previous LD/DA use: 60.7/44%, RLS severity at night: 6.5±1.9. Between baseline and week 5 all three CAB treatment groups showed a clinical improvement of 1) RLS severity at night (0.5mg: 6.7±1.8 vs. 2.3±2.8, p=0.0046; 1mg: 6.0±1.3 vs. 1.9±2.5, p=0.0085; 2mg: 7.0±2.3 vs. 2.2±3.2, p=0.0016), in contrast to placebo (6.2±2.0 vs. 4.8±3.2). Similar results have been found for the RLS severity before bedtime (0.5mg: p=0.0426; 1mg: p=0.0041; 2mg: p=0.0137), 3) RLS severity at day (0.5mg: p=0.3512; 1mg: p=0.0126; 2mg: p=0.0021), 4) IRLSSG rating scale (0.5mg: p=0.0013; 1mg: p=0.0017; 2mg: p=0.0032) and 5) satisfaction with sleep (0.5mg: p=0.0449; 1mg: p=0.0561; 2mg: p=0.0038). AEs with possible relationship to any study drug were comparable among groups; no serious AE occurred.
Conclusion Cabergoline is a highly efficacious and well tolerated option for the treatment of RLS patients. While even low doses of 0.5mg CAB given once daily in the evening led to a significant improvement of RLS symptoms at night, a single evening dose of 2mg covers RLS symptoms over the whole 24h period.

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Transient restless legs syndrome (RLS) can be induced by spinal anaesthesia – a prospective study.

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Introduction Restless Legs Syndrome (RLS) is a frequent neurological disorder with prevalence about 10%. The following study is based on several patients describing RLS after undergoing surgery in spinal anaesthesia. The aim of this study was to examine the possible relationship between RLS and spinal anaesthesia in a prospective way, to assess the incidence and time course of RLS after spinal anaesthesia and to identify possible predictors.
Method We examined 202 consecutive patients undergoing spinal anaesthesia for various surgical reasons. We regarded prospectively the presence and severity of RLS symptoms with Irlssg criteria and severity scale 48–72 h post surgery, after one week, one month, 3 and 6 months. At the first contact a detailed medical history including prior RLS symptoms and current drug treatment was obtained. Additionally, blood biochemical parameters and the total blood count were taken from the patients' histories.
Results 161 of the patients had no prior history of RLS symptoms. From this group 14 patients (8.7%; 95% CI 5.0–13.3) developed first onset RLS after spinal anaesthesia. The RLS symptoms were transient with a mean duration of 33±30 days. Regarding the group of patients with pre-existing RLS (n=41) 4 of them developed a marked deterioration of RLS symptoms. Low MCV and MCH were identified as predictors of RLS symptoms after spinal anaesthesia ($p<0.02$).
Conclusion Transient RLS can be caused by spinal anaesthesia.

Cognitive neurology

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Neuropsychological impairments acute and seven years after stroke The Copenhagen Stroke Study

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Introduction Neuropsychological impairments are significant contributors to the handicap of the stroke patient. We wanted to study their presence late after stroke in a 7-year follow-up study.
Method In the community-based Copenhagen Stroke Study of 1197 acute stroke patients neuropsychological impairments (aphasia, apraxia, hemineglect, anosognosia, orientation and global cognitive function (MMSE ≤24)) were tested on admission and at follow-up 7 years later. Stroke severity was measured on admission and at follow-up using the Scandinavian Stroke Scale (SSS, 0–58).
Results 1197 patients were included (mean age 74 sd 5 years). 324 pts (27%) were alive at follow-up (84 sd 8 months). 166 (53%) accepted to participate. 24 had suffered a new stroke. In total 142 pts were included in the study (mean age at stroke onset 66 sd 14 years). Participants had less severe strokes on admission (SSS 47><SSS 44 years, p=.03). No significant age difference between participants (66 sd 14 years) and non-participants (68 years sd 18 years). No significant difference in frequencies of neuropsychological impairments on admission.
Frequencies of neuropsychological impairments acute and after 7 years were: Aphasia 38%/21%; orientation 23%/14%; apraxia 7%/6%; hemineglect 16%/12%; anosognosia 16%/12%; MMSE ≤24 42%/25%. In 53% a specific impairment or MMSE ≤24 was present.
Conclusion The frequency of neuropsychological impairments late after stroke is surprisingly high and contributes to the handicap in more than half of the long-term survivors.

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Illusory contours and specific regions of human extrastriate cortex: evidence from rTMS.

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Introduction fMRI studies showed that perception of illusory contours is associated with extrastriate cortex activation prevailing on the right side. 1 Hz rTMS is able to induce lasting inhibition of cortical activity. The objective of the study was to investigate the role of extrastriate cortex in illusory contour perception inducing 1 Hz rTMS interference in healthy subjects.
Method We studied 8 healthy subjects (4 M, 4 F; mean age: 41±10.5; range 25–55 yr). 1 Hz rTMS (600 pulses) was given through a figure-of-eight coil over right and left occipital cortex (O1 and O2 of 10/20 EEG system) at 90% motor threshold intensity. To control for unspecific rTMS effects, sham magnetic stimulation on the same sites was given. Subjects underwent computerized task requiring perception of illusory and real contours of Kaniztsa squares in baseline and after rTMS. After stimulus presentation the subject made a forced-choice decision about the regularity or irregularity of stimulus contours by hitting, as soon as possible, one of two keys on a keyboard. Reaction times (RT) were measured.
Results Right occipital stimulation significantly increased RT for illusory contour perception (p<.0001 vs. all other experimental conditions at Duncan's post-hoc). On the other hand, no significant RT changes were observed in the other experimental conditions with respect to the baseline.
Conclusion 1Hz rTMS of right extrastriate cortex can disrupt perception of illusory contours and the effect appears to be side-specific, being evident only after O2 stimulation. This rTMS study supports the critical role of right extrastriate cortex in intermediate vision.

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Alteration of effector versus side of movement: a contingent negative variation (CNV) study

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Introduction Earlier research has explored the impact of several stimulus- and set-related parameters on brain activation as measured by the amplitude of the Contingent Negative Variation (CNV). Little is known, however, about the impact of the previous trial on the CNV of the forthcoming trial and how a previous movement affects brain activation preparing the next movement. Our study was designed to examine such effects of alteration of finger (from index to middle, and vice versa) and hand (from left to right, and vice versa) independently from each other.
Method CNV was recorded in 20 right-handed healthy subjects using a visual/visual S1-choice paradigm. An earlier informative stimulus instructed for side and finger of the following movement and was followed 3s later by an imperative stimulus providing the command to move. Subjects had to respond to each imperative stimulus with a unilateral flexion movement made with index or middle finger of one hand. Every finger of a previous trial could be followed by the same or every other finger in the next trial with equal probability. CNV was analysed with respect to finger and hand of the present and the preceding movement.
Results Our results show that: (1) a change of the side of movement is associated with a widespread increase of negativity contralateral to the currently prepared movement. (2) After a change of finger, a more focal increase of negativity occurs over temporoparietal areas contralateral to the currently prepared movement. (3) A change of finger results in higher negativity over the left hemisphere.

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The prevalence of Fahr's disease among patients presenting with Parkinson-like syndrome and mild cognitive impairment

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Introduction Absence of response to Levodopa is considered as one of the most important factors to reconsider a diagnosis of Parkinson Disease (PD). Fahr's disease (idiopathic basal ganglia calcification) is a rarely reported condition among the abovementioned cases. The objective of our study was o identify the most common causes of Mild Cognitive Impairment with extrapyramidal signs not responding to Levodopa treatment
Method We retrospectively reviewed the personal files of 138 patients with clinically definite PD with dementia (Calne et al, 1992), treated for a period of 1 year with L-Dopa as the main

therapy. All patients were re-examined at 6 and at 12 months after presentation in our outpatient clinic. We performed regular evaluations with the UPDRS. Patients not responding to Levodopa treatment have undergone a full investigation, including neuroimaging studies and a neuropsychological evaluation (MMSE, SKT tests and ADAS cog).
Results Of the 138 patients, 27 were identified as non-responders to Levodopa after 1-year treatment. From these patients, 11 were identified as probable Alzheimer Disease (AD) (NINCDS-ADRDA criteria), 7 as probable Lewy Body Disease (LBD) (McKeath and al, 1996), 2 as Multiple System Atrophy, 5 as Fahr's Disease and 1 as pseudodementia.
Conclusion Fahr's disease is a rare, yet underdiagnosed, cause of Parkinson-Like Syndrome non-responding to Levodopa. Taking into account the facility of the diagnosis with neuroimaging studies, as well as the familial-hereditary character, we propose that detailed neuroimaging studies (especially a CT-scan) in association with neuropsychological investigation should be performed in all of those patients, and possibly in their relatives as well.

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Evaluation of executive functions in Parkinson's disease by conditioned choice reaction time testing

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Introduction Parkinson's disease (PD) causes cognitive changes that may occur early (Cooper et al, 1991; 1994) or even precede motor symptoms. These changes involve mainly frontal executive functions. We tested the validity of a new computer based conditioned choice reaction time test (CCRTT) for quantitative evaluation of executive functions in PD. The CCRTT demands establishment of arbitrary associations between visual and auditory signals, quick changes of these associations and refrainment from automatic responses. This new test is objective, quantitative, independent of linguistic skills, simple to administer and culture-independent.
Method 19 early PD patients and 21 age-matched controls were tested. The patients had significantly slowed visual and auditory choice reaction times.
Results When tested on learnt associations between visual cues and auditory stimuli, patients were as fast as controls. In the final test condition the learned visual-auditory associations were reversed unexpectedly in 25% of the trials. Both patients and controls became slower in the regular trials and were further slowed in the reversed trials (patients: $p=0.001$, controls: $p=0.00004$). Marked differences between the two groups were found in the regular ($p=0.002$) and reversed ($p=0.003$) trials.
Conclusion The results show that PD patients are able to use learnt associations in order to shorten their auditory reaction time down to normal. However, they required extra time to switch their planned response in the reversed condition. This is consistent with their perseverance, as demonstrated by computer-administered WCST. We conclude that this new CCRTT is a sensitive and valid test for executive capabilities.

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Attention and short-term memory in patients with mild to moderate traumatic brain injuries

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Introduction Mild to moderate traumatic brain injuries (TBI) represent 75% of head injuries. Long-lasting symptoms are reported in 14 to 88% of such patients. Since imaging techniques, EEG, and neurological examination reveal no signs of cerebral damage, there are controversies about the existence of cognitive deficits in such patients.
Method We developed computerised tests for visual attention and short-term memory assessment. We compared the results of 37 patients with TBI and 57 controls.
Results Our results show that the registration of correct answers is not sensitive enough to discover cognitive deficits in TBI patients, but significant difference is found in results of recognition reaction time ($p<0,05$) measured with Sternberg Memory Scanning Paradigm and time of reaction to visual stimulus ($p=0,0348$) measured with Choice Reaction Time Task.
Conclusion We showed that it is possible to measure the reduced efficiency of TBI patients in performing the same task as controls. This can be and objective measure of mental slowness that TBI patients often report.