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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.

SC 105

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.
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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.

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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.