Gemeinsame Jahrestagung Schweizerische Neurologische Gesellschaft (178. Tagung) Schweizerische Gesellschaft für Klinische Neurophysiologie und SVEPTA Fortbildung

Réunion annuelle commune Société Suisse de Neurologie (178e réunion) Société Suisse de Neurophysiologie Clinique et ASATEP Formation continue

Abstracts
Lugano, 31. Mai–2. Juni 2007

Freie Mitteilungen SNG

Session: Donnerstag, 31.5.2007, 14.30–15.00 Uhr

Gene expression profiling in vasculitic neuropathy

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Background: DNA microarray analysis is a powerful tool for simultaneous analysis and comparison of gene regulation in normal and diseased tissues. Little is known about pathomechanisms of vasculitic neuropathy and in particular in non-systemic vasculitis there are no disease markers.

Methods: Nerve biopsies from 8 patients with vasculitic neuropathy were included in this study. As controls biopsy specimens were obtained from individuals who did not suffer from polyneuropathy. Total RNA was isolated and a biotin-labelled cRNA was generated for differential expression analysis on the Hu 133A 2.0 Affymetrix chip.

Results: In vasculitic nerves 201 genes were differentially regulated compared to control nerves. There was a striking upregulation of mRNA of genes involved in immune regulation and inflammation. Of special interest are members of the complement family (complement component 1 and 4A), members of the MHC class II group, proteolytic enzymes like granzyme K, and granzyme A and matrix-metalloproteinase 9, adhesion molecules like CD52, immunoglobulins, TNF-beta and the chemokine family.

Conclusion: We demonstrate an impressive upregulation of genes involved in immunity and inflammation in vasculitic neuropathy. Thus gene expression profiles may reveal mechanistic clues to the molecular pathogenesis of vasculitic neuropathies.

Anti-Ma2 positive limbic encephalitis with granulomatous cerebral angiitis

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Paraneoplastic central nervous system involvement associated with serum anti-Ma2 antibodies is known to present as either limbic, diencephalic or brainstem encephalitis. We report on a 27-year-old male with a progressive diencephalic syndrome. Cerebral MRI showed T2 hyperintense lesions around 3rd ventricle and in the right temporal lobe. Combined antiviral, tuberculostatic and corticosteroid therapy was administered with no beneficial effect. An exhaustive clinical, laboratory and imaging search for a putative autoimmune or neoplastic aetiology yielded but some microcalcified foci in the left testis. Diagnostic brain biopsy from right parahippocampal gyrus indicated noncaseating granulomatous CNS angiitis involving both $CD4^+$, $CD8^+$ T-lymphocytes and $CD68^+$ macrophages. Histology was interpreted as consistent with neurosarcoidosis, and Infliximab was given. The patient succumbed 6 months following onset of disease, permission for autopsy was not granted. Retrospective analysis of collected serum and CSF samples disclosed high titres of anti-Ma2 antibodies. We interpret the above constellation as one fulfilling the criteria of "definite paraneoplastic CNS disease", as defined by Dalmau et al. (i.e. either classic or non-classic paraneoplastic manifestation without known malignant disease, yet with presence of a well-characterised antineuronal antibody). To the best of our knowledge, this is the first documented case of granulomatous CNS angiitis of paraneoplastic origin.

McLeod myopathy revisited – more neurogenic and less benign

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Objective: The X-linked McLeod neuroacanthocytosis syndrome (MLS) is a rare multisystem disorder assigned as "benign" McLeod myopathy [1]. MLS is caused by mutations in the XK gene which shares important homologies with ced-8, a cell death effector gene in C. elegans. With this study we assessed the clinical, genetic and neuromuscular findings of a large series of McLeod patients.

Methods: 11 McLeod patients including the initial index patient participated in the study. The patients originated from Germany, Switzerland, Chile, the United States and Japan. Clinical findings were evaluated by the local examinators. Formalin-fixed tissue was available from all patients and fresh-frozen skeletal muscle from 10 of them. The samples were processed according to standard histology protocols.

Results: All but one patient had elevated serum CK levels. 9 patients had areflexia at

least at the lower limbs without sensory symptoms. Muscle weakness and atrophy of different degree was present in 9 patients and was disabling in 3 patients. 8 patients developed a choreatic movement disorder and 6 patients had psychiatric manifestions. Cognitive decline of variable degree also was found in 6 patients. Upon muscle biopsy all patients had neurogenic changes of variable degree but only 2 patients showed evidence for clear myopathic changes. There were no specific histological findings and the expression of structural muscle proteins was not altered.

Conclusion: MLS is a disabling disorder resembling Huntington's disease with additional neuromuscular manifestations of variable degree. Muscle biopsy findings consistently demonstrated neurogenic changes, whereas myopathic alterations were only found in few patients. Our findings suggest that creatine kinase elevation, myatrophy and weakness may reflect a motor neuropathy rather than a myopathy in the majority of McLeod patients.

Literature

1 Swash M, Schwartz MS, Carter ND, Heath R, Leak M, Rogers KL. Benign X-linked myopathy with acanthocytes (McLeod syndrome). Brain. 1983;106:717–33.

Freie Mitteilungen SGKN

Session: Freitag, 1.6.2007, 09.00–09.30 Uhr

Clinical evoked potential imaging in multiple sclerosis

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Evoked potentials (EP) are used to evaluate the functional integrity of sensory pathways. Despite its potential value in early diagnosis and prognosis of multiple sclerosis (MS), it has become less significant, due to its low sensitivity and specificity. Clinical EP are recorded from few electrodes and their interpretation is restricted to few parameters. In research laboratories EP are recorded from a large array of electrodes and results are defined in terms of spatio-temporal dynamics and estimated electric brain sources. We aim to introduce these techniques into clinical applications and to define more objective and sensitive parameters. In a standardised protocol we record somatosensory EP (SSEP) evoked by median nerve electrical stimulation and full-field pattern-reversal visual EP (VEP) with a 256 channel EEG. For each EP component we quantify potential map's topography, strength and latency of maximal strength. In healthy subjects 4 successive components are defined for the SSEP and 5 for the VEP, defining each component's mean and standard deviation. Patients' data are then compared to these values. The probability that a parameter significantly deviates from the norm is determined by z-score statistics. Patients with MS recorded presented pathological VEP and/or SSEP according to our criteria. We conclude that high-resolution SSEP and VEP mapping is feasible in a clinical setting and the defined parameters may be more sensitive than conventional EP recordings.

Evidence for a sympathetic origin of idiopathic periodic leg movements in sleep

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Background: Idiopathic periodic leg movements in sleep (i-PLMS) are frequently accompanied by autonomic and EEG-signs of arousal, but it is not clear whether i-PLMS are the cause or the consequence.

Methods: Spectral EEG- and heart rate-variability (HRV) before and during leg movements were analysed in polysomnographies (PSG) of patients with periodic leg movements (n = 8; i-PLMS), obstructive sleep apnoea syndrome (n = 7, RRLMS) or normal PSG (n = 9; Non-PLMS).

Results: In all types of leg movements an increased HRV started up to 8 seconds before movement onset followed by an increased Delta-activity, then showing an increased Theta-, Alpha-, Beta- and Gamma-activity, and ending with a decreased spindle-activity after movement onset. Only low frequency HRV oscillations correlated with PLMS amplitude and index. Delta-synchronisation and HRV had greater peaks for i-PLMS and RRLMS than for Non-PLMS, whereas Gamma-synchronisation began 1–2 seconds earlier for Non-PLMS and RRLMS than for i-PLMS.

Conclusion: All leg movements in sleep were preceded by autonomic changes occurring before EEG arousals favouring an origin on brainstem level. Autonomic activation was most pronounced for i-PLMS and correlated with PLMS magnitude. EEG signs clearly preceded muscle activity in Non-PLMS and RRLMS, but began only shortly before or at the same time as i-PLMS. Therefore, i-PLMS are more likely to be triggered directly by sympathetic processes than by a cortical arousal.

Focal minimal convulsive status epilepticus with bilateral periorbital myocloni – a paradoxon?

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An 88-year-old lady was hospitalised because of a first generalised epileptic seizure in the context of fever of unknown origin. She was successfully treated with valproate and benzodiazepines. One week later, she developed a permanent painful twitching of the left side of her face. The mimic musculature, including the orbicularis oculi, orbicularis ori muscles and the platysma contracted with a frequency of about one Hertz. On close inspection, parts of the right-sided periorbital muscles also showed contractions synchronised to the left side. The EEG revealed right hemispheric slowing but no continuous epileptiform activity. In addition, correlating with the visible contractions, muscle potentials on both sides were recorded in the frontal traces corroborating the clinical findings of bilateral involvement. The MRI displayed hyperintense DWI signals in the right parietal region and signs of increased cerebral blood flow, findings compatible with a focal status epilepticus (FSE). Extensive laboratory examinations including CSF were normal.

A diagnosis of FSE with minimal convulsive features and bilateral involvement of the periorbital musculature was made. The aetiology of the FSE remained unresolved. Treatment was difficult and included valproate, propofol, midazolam and phenytoin. The patient was discharged on levetiracetam and oxcarbacepine.

Freie Mitteilungen SNG

Session: Freitag, 1.6.2007, 10.40–11.15 Uhr

Limb girdle, pseudomyopathic autoimmune myasthenia gravis: does it exist?

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"Limb girdle" myasthenia includes familiar and autoimmune forms and is considered a rare clinical presentation. Patients complain of proximal weakness without oculobulbar involvement and without fluctuations.

This "pseudo-myopathic" clinical presentation of MG often leads to diagnostic difficulties, unnecessary invasive exams, in particular muscle biopsy, and most of all to treatment delay.

We describe 2 cases of proximal autoimmune myasthenia:

A young 12-year-old girl who developed progressive difficulties of ambulation followed by appearance of mild proximal shoulder girdle palsy. Only at the age of 16 the diagnostic of proximal autoimmune myasthenia was made and treatment began.

The second case is of a 58-year-old female with progressive proximal muscle weakness, in whom "limb girdle" myasthenia was diagnosed and thymoma disclosed.

These two cases confirm that the diagnosis of myasthenia should be considered in both young and elderly patients with proximal muscular deficit and without a history of fluctuations because of important therapeutic and prognostic consequences.

The clinical history of these 2 cases and the review of the literature are discussed.

Comparison of pramipexole (PPX) versus levodopa/benserazide (L/B) in the treatment of restless legs syndrome (RLS). A double-blind randomised Swiss multi-centre crossover trial

C. L. Bassetti, J. Mathis, J. Schwander, F. Bornatico, P. Fuhr, for the Swiss RLS Study Group

Background/aims: Efficacy and safety of a non-ergot dopamine agonist was never directly compared with levodopa in a randomised double-blind trial in patients with RLS. The aim of the present study was to determine the non-inferiority of PPX compared to a dual release formulation of L/B in the treatment of idiopathic RLS. Primary objective was the change in frequency of periodic limb movements while in bed calculated as mean PLMI of both legs (PLMIbed) after 4 weeks of treatment, as assessed by actigraphy (over 3 consecutive nights, baseline and end of treatment). Secondary outcomes included changes in International RLS Scale (IRLS).

Patients and methods: Patients with idiopathic RLS were recruited from 6 accredited sleep centres in Switzerland. In a 14-week double-blind, crossover study patients were randomly assigned to the sequence PPX (0.25–0.75 mg) and L/B dual release (L/B 125–375 mg) or vice versa. A 2-week wash-out period preceded the two 4-week treatment periods. A dose adjustment was done during the first 15 days of each period. The trial ended with a 2-week follow-up period.

Results: 67 patients were randomised for the study whereof 39 completed the study according to protocol. The mean doses of L/B and PPX were 240 ± 74 mg/d and 0.488 ± 0.14 mg/d, respectively. Baseline PLMIbed scores were comparable between treatment groups (21.5 ± 14.9 PPX vs 21.1 ± 17.0 L/B). PPX proved to be non-inferior in comparison to L/B on the primary endpoint PLMIbed (median: –8.1 PPX vs –4.9 L/B; p = 0.00015). Even not powered for superiority there was a strong trend for a better improvement with PPX in the PLMIbed (p = 0.065) and IRLS score (–7.2 ± 9.5 PPX vs –4.0 ± 7.5 L/B; p = 0.054). Patients with an IRLS score >20 at baseline (26.3 ± 3.8 PPX vs 26.5 ± 4.3 L/B) showed a clearly higher reduction for PPX (–8.5 ± 7.7 PPX vs –4.3 ± 5.4 L/B; p = 0.0467). There were no related serious adverse events and no unexpected safety observations were made.

Conclusions: Pramipexole was not inferior to levodopa/benserazide in reducing PLMIbed. Both showed similar efficacy and safety in the treatment of idiopathic RLS. These results have to be seen in the context that L/B was given as a combination of an immediate and retard formulation.

Identification of first Swiss desminopathy families using systematic muscle imaging in myofibrillar myopathies

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We performed systematic muscle imaging to characterise the pattern of muscle involvement in 20 patients with a desmin gene mutation and compared these findings with 23 patients with myofibrillar myopathies (MFM) caused by myotilin, filamin c, ZASP and Œ ± B-Crystallin (Œ ± BC) gene mutations. All desminopathy and Œ ± BC patients showed a characteristic pattern with predominant involvement of the gluteus maximus, sartorius, gracilis, semitendinosus and peroneal group muscles. In contrast, muscle imaging in patients with myotilin, filamin c and ZASP mutations showed predominant affection of the vastus intermedius, vastus medialis, adductor magnus, semimembranosus, biceps femoris, soleus, medial gastrocnemius and tibial anterior muscles. Our data suggest important differences of muscle involvement between patients with gene mutations coding for intermediate filament (associated) proteins and Z-disc proteins. Furthermore, using this time- and cost-effective approach for the identification of MFM patients suitable for direct gene, we could identify the first Swiss families with desmin mutations. Additionally, 5 Swiss patients presenting with the second pattern were identified and myotilin, ZASP and filamin-c gene analysis are currently underway.

Poster SNG und SGKN

Session: Freitag, 1.6.2007, 13.00–14.00 Uhr

P 01 An unexpected and fatal differential diagnosis of acute bilateral leg pain

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A 65-year-old patient was referred to our emergency department with rapidly progressive pain of the upper legs. He had a previous history of colon carcinoma with pulmonary and spinal skeletal metastasis, which had remitted one year before under radio- and polychemotherapy.

On admission he appeared distressed, but cardiovascularly stable and afebrile. Inspection and neurological examination of the limbs was unremarkable, except for slight swelling of the right thigh. The laboratory work-up revealed leukocytosis and elevated values for CRP (288 mg/l, <8) and CK (488 U/L, <170). A few hours after symptom onset he developed fever, abdominal tenderness as well as discoloration and massive swelling of the right lateral thigh and left lower leg. An emergency CT scan was performed, which revealed bilateral muscular gas gangrene with extended myonecrosis of the right vastus lateralis.

Despite intravenous antibiosis and radical surgical debridement, the patient died 24 hours later of multiple organ failure due to severe sepsis caused by *Clostridium septicum.* The inital symptoms had been caused by non-traumatic clostridial myonecrosis, a rare condition associated with colonic neoplasia. This case illustrates the fulminant nature of gas gangrene and although it is an uncommon diagnosis, it is essential to take this diagnosis into consideration in patients with intestine carcinomas and to initate management early.

P 02 Focal posterior cerebral artery dissection presenting with subarachnoid haemorrhage: case report and review of the literature

P. Agazzi, C. Städler, S. Tschuor, D. Boscherini

Ospedale Regionale Lugano

Introduction: PCA artery dissection is a rare occurrence. Accurate diagnosis is important for appropriate clinical management. We present a dissection of P2 segment of PCA in association with a diving episode and responsible of a subarachnoid haemorrhage.

Case report: A 16-year-old boy, after a dive in a swimming pool with no evidence of head trauma, presented an abrupt onset of severe neck pain irradiating to the occipital region. Patient vomited once. Headaches persisted and he presented to the emergency department. Neurological showed no focal deficits. Head CT scan showed a subarachnoid bleeding restricted to the right ambiens cistern.

CTA scan did not depict an evidence cause of bleeding. MR angiography showed an irregular narrowing of right P2 segment compatible with focal dissection. DSA did not add consistent information. Clinical course was uneventful with a clinical and imaging follow-up at one year.

Discussion: PCA dissection presents usually with occipital headaches and pain in the posterior cervical region with or without ischaemic signs. PCA dissections occur near the P1-P2 junction. Mild head trauma has often been reported in such setting. Isolated focal PCA dissections present more rarely with haemorrhagic events. Conservative medical treatment is a rule and surgical or endovascular approaches are seldom necessary.

P 03 Nichtepileptische Anfälle nach (fraglichem) Kopftrauma – exemplarische Fälle aus der Versicherungsmedizin

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Nach einer traumatischen Hirnverletzung («mild traumatic brain injury», MTBI, oder einer Hirnkontusion) sind epileptische Anfälle mit einer Häufigkeit von 1,5 bis 17% (5-Jahres-Prävalenz) beschrieben (Lit.: Annegers et al., N Engl J Med 1998).

In der Literatur wurde auch das Auftreten von psychogenen, nichtepileptischen Anfällen (PNEA) nach einem Kopftrauma beschrieben (Westbrook et al., Epilepsia 1998).

Bei 2 von 5 hier vorgestellten Fällen mit PNEA konnte die Art des Kopftraumas nicht restlos gesichert werden, bei allen 5 Fällen waren keine posttraumatischen Veränderungen in der Bildgebung des Kopfes und keine epilepsietypischen Veränderungen im EEG nachweisbar. Drei Patienten zeigten zum Unfallzeitpunkt oder kurz danach eine Bewusstseinsveränderung, in insgesamt 3 Fällen traten im Verlauf rezidivierende anfallsartige Ereignisse auf. Die Anfallssemiologie zeigte ein breites Spektrum von Phänomenen: Bewusstseinstrübung mit und ohne motorische Entäusserungen, synkopenartige Zustände, zum Teil mit Symptomen, die an eine Angststörung oder eine organische Schwindelerkrankung erinnerten.

Es empfiehlt sich bei Anfällen, die nach einer leichten Hirnverletzung (MTBI) auftreten, neben der Frage der Unfallkausalität auch Fragen bezüglich einer eventuell vorliegenden psychogenen Störung zu klären.

P 04 Serum and cerebrospinal fluid prostaglandin D synthase levels in disorders with and without excessive daytime sleepiness: a prospective study

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Somnogenic prostaglandin D2 is catalysed by prostaglandin D synthase (PGDS). In a preliminary study we found decreased cerebrospinal fluid (CSF) PGDS levels in patients with excessive daytime sleepiness (EDS). Another study, contrariwise, observed elevated PGDS levels in serum of narcoleptic patients. In this prospective study, therefore, we systematically performed lumbar punctures and simultaneous blood withdrawal between 9 and 11 a.m. for PGDS determination in 22 consecutive patients with neurological disorders with EDS (42 ± 18 years, 10 men) and in 22 consecutive neurological patients without EDS (49 ± 16 years, 11 men). In all patients EDS was quantified by Epworth Sleepiness Scale (ESS). CSF PGDS levels were significantly lower in EDS patients (13 ± 2 mg/L) than in non-EDS patients (19 ± 9 mg/L, $p = 0.007$). ESS scores were inversely correlated with CSF PGDS levels ($r = -0.48$; $p = 0.001$). In serum we found no differences between groups (EDS: 0.6 ± 0.3; non-EDS: 0.6 ± 0.1; $p = 0.36$). Age and gender did not influence PGDS levels. Together with our published preliminary findings in other patients, this prospective study demonstrates a CSF PGDS deficiency in neurological patients with excessive daytime sleepiness. In serum, where concentrations are much lower, we found no differences between EDS and non-EDS patients. Further studies are needed to provide better understanding of the role of the prostaglandin system in sleep-wake regulation.

P 05 Is there a morphological substrate of Parkinsonian rest tremor? A voxel-based morphometry study

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Objective: To investigate morphological substrates of rest tremor in Parkinson's disease (PD). Rest tremor is a hallmark of PD. Its pathogenesis remains incompletely understood. Nigrostriatal dopaminergic deficiency correlates with bradykinesia, but not with rest tremor. It is hypothesised that an interaction of basal ganglia- and cerebello-thalamo-cortical circuits may cause rest tremor.

Methods: We investigated 24 men (median, range [y], age 62, 55–70, at onset 55, 42–67, disease duration 7, 3–20) with mild to moderate PD (HY 2–3). Exclusion criteria were advanced PD (HY 4–5), dementia and other significant brain pathology. Patients with tremor (n = 14) and without (n = 10) were compared. Clinical and neuropsychological profile was similar, except for more prevalent motor fluctuations (90 vs 14%, $p < 0.01$) and impaired balance (100 vs 50%, $p < 0.01$) in those without tremor. Voxel-based morphometry of 3T T1-MRI, pre-processed according to an optimised protocol using SPM2, was performed. The resulting normalised grey matter volume distributions of the two groups were tested for local differences by a voxel-wise ANCOVA.

Results: Grey matter density is decreased in quadrangular lobe and declive of the cerebellum in PD with tremor ($p < 0.05$).

Conclusion: These results demonstrate for the first time morphological changes in the cerebellum in PD with rest tremor and underscore the involvement of the cerebellum and cerebello-thalamo-cortical circuit in the pathogenesis of rest tremor.

P 06 Different cortical activation in writer's cramp in homozygote twins during a simple non-affected motor task

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Objective: To compare motor-induced BOLD-signals with fMRI in a patient with late-onset writer's cramp (WC) and cervical dystonia and in his non-affected monozygote, twin brother. Anomalies during non-affected motor behaviours have been sparsely reported. In case of heredity we expected comparable disturbed BOLD-responses during dystonia-free task performance, assuming sub-clinical motor abnormalities in both brothers.

Methods: Brain imaging was performed with a 3T MR Philips scanner in a standard block design during performance of a tonic power grip of the left or right hand.

Results: The non-affected twin showed normal activation patterns in sensory and motor areas including contralateral M1, SI and SMA during task performance. In the affected twin no such activation was observed while using the right or left hand, except for contralateral supramarginal gyrus activity during task performance with the left, subsequently affected hand.

Conclusion: The lack of significant activity during performance of a simple motor task agrees with previous reports and also supports the assumption that motor abnormalities in WC can be observed sub-clinically. The lack of cortical activation during performance with the left hand in the affected twin points to a behavioural component in the pathogenesis of hand dystonia as opposed to a genetic predilection.

P 07 Drugs and myasthenia

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A young woman, with well-compensated generalised myasthenia, had a worsening of symptoms upon short exposure to norfloxacine, requiring 2 years of therapy with steroids accompanied by many side effects.

We were asked by many physicians and patients with myasthenia about the safety of several common and uncommon drugs. In

absence of many answers we tried, however, to complete and reassume already existing lists, suggesting which drugs should be avoided or used as alternatives in this disease.

For several classes of drugs, unfortunately, there are not, in the literature, indications about their safety of use in myasthenia.

We submitted the list to the Swiss neurologists, asking them for improvements or their experiences using this list.

The following list is the results of this work and it is possible to download the list on the following webpage: www.farmacovigilanza.epatologia.ch → Farmacovigilanza → Presentazioni, pubblicazioni, vario → Vario → Farmaci controindicati o permessi nella miastenia.

P 08 Arachnoid cyst with intracystic haemorrhage and subdural haematoma: case report and literature review

D. Bervini, D. Boscherini, S. Tschuor, C. Tosi

Ospedale Regionale Lugano

Introduction: Arachnoid cysts (AC) are usually asymptomatic. Very rarely they can become symptomatic due to cyst enlargement or haemorrhage, often after head trauma. In such cases bleeding is confined to the subdural space, but intracystic haemorrhage has rarely been observed.

Case report: Six years before admission a patient aged 49 was diagnosed with a right temporal arachnoid cyst with MRI for frontal headaches. He presented with an acute onset of right frontal headache and after admission we assisted to a progressive clinical deterioration consistent with an intracranial hypertension syndrome (GCS = 7). There was no history of a head trauma. CT scan revealed a hyperdense mass located in the right middle fossa and Sylvian fissure. There was a thinning of the temporal squama. An MR examination showed the presence of a cystic lesion in the right middle cranial fossa, with high signal intensity. During surgery the haematoma and intracystic blood clots were removed. The cyst wall was partially excised. Complete neurological recovery, imaging normalisation and functional reintegration was achieved.

Discussion: ACs can become symptomatic due to cyst enlargement or haemorrhage. The combination of intracystic bleeding with subdural haematoma has been reported to our knowledge in only 38 such cases. There was predilection for the left side and the male sex. The average age was 25.6. More than half had a history of a previous head injury.

P 09 S90L BSCL2 mutation causing Silver syndrome with optic nerve involvement

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We report a 35-year-old female who presented in our motor neuron clinic with a history of walking difficulties since early childhood. On examination she had distal symmetric wasting and weakness in the hands. In her legs there was increased muscle tone, bilateral symmetric hyperreflexia, extensor plantar responses, spastic gait and pes cavus. Neurophysiological findings were consistent with a pure axonal and motor neuropathy and central motor conduction time to the legs was prolonged.

One year later she presented again with a blurred vision of her left eye. Visual acuity was reduced to 50% and VEPs were markedly prolonged. MRI of the optic nerve and brain and CSF analysis including oligoclonal bands were normal. Mutation analysis excluded a mitofusin 2 (MFN 2) gene mutation but revealed a heterozygous BSCL2 S90L mutation consistent with the neuromuscular phenotype described in Silver syndrome. Clinical and genetic analysis of further family members is currently underway.

Optic nerve involvement has been reported in some axonal hereditary motor (sensory) neuropathies (MFN 2, e.g.) but has not yet been observed in patients with BSCL 2 mutations. Therefore, our observations expand the clinical phenotype of BSCL2 mutations carriers.

P 10 Spontaneous multifocal cervical liquor leakage causing an intracranial hypotension syndrome – case report

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A 39-year-old woman presented with a 4-week history of progressive postural headache accompanied by dizziness and vomiting. By lying down all symptoms relieved. The patient was afebrile with no apparent meningeal signs and any trauma. No focal neurological signs were noted. Cerebral and spinal MR imaging revealed a diffuse pachymeningeal contrast enhancement. Spontaneous intracranial hypotension was suspected on the basis of clinical and neuroradiological findings confirmed by a low CSF pressure at lumbar puncture. Other causes of leptomeningeal diseases were excluded. Conservative treatment including bed rest, intravenous volume administration and intravenous coffeine as well as oral administration of prednisone was continued over one week with short lasting success. However, 3 weeks later headaches relapsed. A CT-myelography now revealed a CSF leakage at the cervical level C1-2 as well as at C6-7. After an epidural blood patch at the level C1 and C2 postural headaches disappeared after several days. Months later the patient was still in remission of her symptoms and follow-up MRI scans showed a persisting epidural CSF accumulation at C1-2 and cervico-thoracal but no more dural enhancement. These clinical and radiological findings are most likely the result of in the meantime occurred balance between CSF loss and production. This case seems to be the first one describing two independent, spontaneous cervical CSF leakages causing an intracranial hypotension syndrome.

P 11 Gamma-hydroxybutyrate (GHB) promotes functional recovery and alters expression of neuroplasticity-related genes in a mouse-model of stroke

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Background/aim: GHB, a drug used in humans to promote slow-wave sleep and treat narcolepsy, has been suggested to be neuroprotective in animal models of stroke. The present study aimed to assess the potential role of GHB in a mouse ischaemic model in promoting functional recovery after stroke and to search for underlying molecular mechanisms.

Methods: The mouse transluminal ischaemia model, i.e. 30-minute occlusion of the middle cerebral artery, was used. GHB (100 mg/kg, twice/day, 8 hours apart) or saline were given intraperitoneally for 10 days with the first injection at the reperfusion. Rotarod and grip-strength tests were used for evaluating motor activities and Taqman real-time PCR was for assessing expression of several neuroplasticity-related genes including GAP43, c-jun, neurocan and ephrin B1.

Results: Striatal ischaemia resulted in significant decreases in the body weight, the forelimb grip-strength and rotarod activity. GHB-treated mice regained the body weight and the grip-strength after 3 weeks of recovery, whereas in saline-treated mice the decreases remained over 5 weeks. There was no difference in the recovery of the rotarod activity for the two groups. Taqman PCR assay showed that GHB decreased expression of c-jun and neurocan by 2–4 folds, respectively, in the injured striatum compared with the saline group.

Conclusions: GHB appears to accelerate functional stroke recovery and to change ischaemia-induced expression profiles of neuroplasticity-related genes.

P 12 Awareness of sleepiness prior to falling asleep

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Introduction: Sleepiness-induced motor vehicle crashes are one of the most important causes of severe accidents and death. Prevention of such accidents deserves a better understanding of why sleepy people continue to drive a motor vehicle and if they are aware of the sleepiness prior to falling asleep.

Methods: Of 12 healthy students (mean age 24.1, SD 1.7; 6 women) each underwent 4 maintenance-of-wakefulness trials (MWT) after total sleep restriction. The instruction was: "Your task is to indicate your sleepiness at the first appearance of sleepiness symptoms and to stay awake." Sleep (>15 sec) and microsleeps (MS; 3–15 sec) were scored in the EEG.

Results: Overt sleep was scored in 44 trials and MS in the remaining 4 trials. In 22 trials MS or sleep appeared before the subject indicated subjective sleepiness (45.8%). Only 4 subjects did indicate their subjective sleepiness before sleep onset in all 4 trials. Females indicated their sleepiness prior to sleep onset more (70.8%) as compared to male subjects (37.5%) ($p < 0.02$).

Conclusion: Our unexpected finding, that sleep onset was missed almost in 50% of all trials, might have major impact on prevention strategies of sleepiness-induced motor vehicle crashes. If our finding will be confirmed in a larger group of subjects, prevention does have to also focus on the reason why some persons do not report their sleepiness and gender differences may be an important issue.

P 13 Human vascular endothelial growth factor protects axotomised retinal ganglion cells in vivo by activating ERK-1/2 and Akt pathways

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Based on its trophic effects on neurons and vascular cells, vascular endothelial growth factor (VEGF) is a promising candidate for the treatment of neurodegenerative diseases. To evaluate the therapeutic potential of VEGF, we here examined effects of this growth factor on the degeneration of axotomised retinal ganglion cells (RGCs), which, as CNS-derived neurons, offer themselves in an excellent way to study neuroprotection in vivo. Making use of a transgenic mouse line that constitutively expresses human VEGF under a neuron-specific enolase promoter, we show that (1) the VEGF-transgenic retina overexpresses human VEGF, (2) RGCs carry the VEGF receptor-2 and (3) vascular networks in normal and axotomised VEGF-transgenic (tg) retinas do not differ from control animals. After axotomy RGCs of VEGF-tg mice were protected against delayed degeneration, as compared with wild-type littermates. Western blots revealed increased phosphorylated ERK-1/2 and Akt and reduced phosphorylated p38 and activated caspase-3 levels in axotomised VEGF-transgenic retinas. Intravitreous injections of pharmacological ERK-1/2 (PD98059) or Akt (LY294002) inhibitors showed that VEGF exerts neuroprotection by dual activation of ERK-1/2 and Akt pathways. In view of axotomy-induced RGC death occuring slowly and considering that RGCs are CNS-derived neurons, we predict the clinical implementation of VEGF in neurodegenerative diseases of both brain and retina.

P 14 Increased CSF MCP-1 and IL-8 levels in ALS patients

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Objectives: ALS is classically assumed to be a neurodegenerative disorder. Inflammation has been observed in CNS tissue in ALS patients. We investigated the expression of proinflammatory chemokines in ALS – as compared to non-inflammatory neurological disease (NIND) patients.

Methods: We analysed 9 chemokines, eotaxin, eotaxin-3, IL-8, IP-10, MCP-1, MCP-4, MDC, MIP-1b and TARC in serum and CSF of 20 ALS- and 20 NIND-patients.

Results: MCP-1 and IL-8 levels in CSF in ALS were significantly higher than in NIND (1304 pg/ml versus 1055 pg/ml; $p = 0.013$ and 22.7 pg/ml versus 18.6 pg/ml; $p = 0.035$, respectively). The expression of MCP-1 and IL-8 were higher in CSF than in serum ($p < 0.001$). CSF/serum albumin ratio showed no correlation to chemokine levels. There was a trend towards higher MCP-1 CSF levels in ALS patients with shorter time between first symptoms and diagnosis ($p = 0.083$).

Conclusions: We confirmed previous findings of increased MCP-1 levels in CSF of ALS patients. Furthermore, increased levels of IL-8 in CSF suggest a stimulation of a proinflammatory cytokine cascade after microglia activation. We found a tendency for higher MCP-1 values in patients with a shorter diagnostic delay, who are known to also have a shorter survival. This finding may suggest an association of higher MCP-1 levels with rapidly progressing disease. Larger follow-up studies are needed to evaluate the value of chemokines as disease markers in ALS.

P 15 Primary Persistent Visual Disturbance (PPVD) in patients without migraine

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Objective: To describe patients with PPVD (also known as visual snow) but without the diagnosis of migraine, including clinical characteristics, imaging and metabolic findings and therapeutic response to anticonvulsants.

Background: PPVD is clinically distinct from persistent visual migraine aura. It was described – outside the ophthalmological and psychiatric context – in association with migraine and without metabolic or imaging abnormalities.

Design/methods: Clinical evaluation, imaging and electroencephalographic studies (⅔ patients) and cerebrospinal fluid (CSF) analysis (⅔ patients).

Results: We studied 3 patients (2 men, one woman) who presented in our tertiary care headache unit between January and September 2006 because of persistent visual disturbances for several years without fulfilling the criteria for migraine according to International Headache Society criteria. Two of them had been referred by an ophthalmologist. Magnetic resonance imaging (T_1-, T_2-weighted, FLAIR and DWI), MR spectroscopy and EEG studies were normal. CSF analysis revealed a slightly elevated protein (0.57 g/l) in one patient as an isolated abnormality. CSF lactate was normal in all patients. Treatment with lamotrigine (2 patients) or topiramate (one patient) was not effective.

Conclusions/relevance: PPVD can occur without migraine and without any evidence for epilepsy or an underlying inflammatory, metabolic or mitochondrial disorder, and is difficult to treat.

P 16 A case of chronic inflammatory demyelination polyneuropathy revealing a low-grade mantellar lymphoma, 30 years after radio- and chemotherapy for Hodgkin lymphoma

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The association of chronic inflammatory demyelinating polyneuropathy (CIDP) and haematopoietic proliferative disorders is well documented in literature. Moreover, the correlation with monoclonal gammopathy of unknown significance (MGUS) is relatively frequent and presents some distinct clinical and electrophysiological features.

We describe a case of CIDP preceding by 6 months the appearance of monoclonal gammopathy and one year the development of chronic lymphoproliferative disorder (mantellar-cell lymphoma) in a 60-year-old patient, 30 years after a complete recovery from Hodgkin lymphoma.

This case is a testimony that in front of the diagnosis of CIDP the clinician should

consider the accurate work-up for the haematopoietic proliferative disorders.

In our case the appearance of CIDP as a sentinel of lymphoproliferative disorder permitted its early diagnosis, however, introduction treatment for lymphoma did not influence the clinical course of polyneuropathy.

P 17 Isolated acalculia with impaired size estimation after subcortical frontal lesion

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Background: Acalculia is a rare disorder and normally described with parietal lesion.

Case report: A 79-year-old woman with an ischaemic stroke of the left anterior corona radiata and putamen presented rapidly regressive motor aphasia. A striking inability to calculate and estimate sizes persisted, however.

Method: We tested mental and written mathematical operations: addition, subtraction, multiplication, division and evaluated the patient's ability to transcode numbers and to estimate quantities (weights, lengths and speed of different objects).

Results: Performance was similar in oral and written tasks. While conceptual mathematical knowledge (understanding and use of arithmetical principles) and mathematical facts seemed intact, the patient had severe difficulties with mathematical procedures essential for processing numbers. Division was most disturbed, followed by subtraction and multiplication. Addition was less affected. Even the processing of single digits was deficient. Important judgment errors were observed in the estimation of quantities.

Conclusion: A subcortical left frontal lesion may provoke isolated severe persistent acalculia and impaired size estimation.

P 18 Phenotypic variability in gamilial amyotrophic lateral sclerosis (ALS) patients carrying the SOD L144F mutation

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Amyotrophic lateral sclerosis (ALS) is inherited in 10% of cases (fALS). In about 20% of these fALS cases a SOD mutation is detectable. Currently 106 different mutations are known. Between 2001 and 2006 we have screened 25 fALS cases for SOD mutations and have identified 2 SOD families.

One of the families immigrated from the Balkan and showed a TTG to TTC transposition. In the Swiss family the L144F mutation showed a novel TTG to TTT transposition in two cousins.

Phenotypic variability exists between and within the families.

Survival time in one affected Swiss cousin (a) was 42 years after symptom onset, whereas her cousin (b) as well as 2 other family members followed the typical clinical course.

The cousin (a) with long survival showed primarily lower motoneuron signs and initially carried the diagnosis of spinal muscular atrophy (SMA). Bulbar symptoms were moderate with only slight atrophy of her tongue and moderately exaggerated masseter reflex. Genetic analysis revealed negative results (SMA, SCA). The patient deceased at the age of 72.

The cousin (b) with the more typical clinical course shows combined lower und upper motoneuron signs in lower and upper limbs. Bulbar symptoms are predominantly upper motoneuron typ.

Conclusion:
- SOD mutations seem to be rare among Swiss fALS cases.
- The L144F mutation may be associated with extreme long survival time with high intrafamilial variability.
- Predominance of the lower motoneuron signs does not preclude ALS.

P 19 Excessive daytime sleepiness in patients with Parkinson's syndrome and sleep-wake complaints

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Introduction: Excessive daytime sleepiness (EDS) is common in patients with Parkinson's syndrome. Age, gender, severity of the neurodegenerative process, night-time disturbances and therapy are implicated in the pathophysiology of EDS. In a group of patients a narcolepsy-like phenotype has been suggested.

Methods: Thirty-five patients (27 male) with Parkinson's syndrome (22 with idiopathic Parkinson's disease and 13 with atypical parkinsonism) underwent video-polysomnography and multiple sleep latency test (MSLT). EDS was also assessed by Epworth sleepiness scale (ESS). The patients were referred to the sleep centre for different reasons, 19 because of EDS.

Results: Twenty-one patients had ESS $\geq$10, of whom 19 were men. Ten patients had mean sleep latency (MSL) in MSLT $\leq$5 minutes, of whom 9 were men. Male patients had higher ESS scores (although not statistically significant) and shorter MSL in MSLT ($p = 0.035$). Sleep-onset REM (SOREM) was observed in only 2 patients (5/149 nap opportunities, 3.4%). Slightly negative correlation was found between MSL and the dopamine agonist dose. The amount of REM sleep correlated positively with MSL and negatively with ESS score. Apnoea/hypopnoea index was slightly correlated to the ESS score.

Conclusion: In this sample of patients EDS was common and related to male sex, quantity of REM sleep, dopamine agonist dose and sleep-related breathing disturbances. As SOREM was rare, narcolepsy-like phenotype seems unlikely in this group of patients.

P 20 Sleepwalking in Parkinson's disease

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Objective: To report the occurrence of adult-onset ("de novo") sleepwalking (SW) in a series of 5 patients with idiopathic Parkinson's disease (PD).

Methods: Five patients with adult-onset SW out of 165 consecutive patients with PD were identified over a period of 2 years. These patients underwent a systematic clinical assessment of their extrapyramidal and sleep problems which included standard questionnaires, clinical examination and estimation of PD severity (motor score of the unified Parkinson's disease rating scale [UPDRS III] and Hoehn and Yahr stage [HY]). In 4 out of 5 patients a video-polysomnography (PSG) was recorded and scored according to international criteria.

Results: There were 3 women and 2 men with an age of 67 ± 14 years (mean ± SD, range 46–81). The mean UPDRS III was 24 ± 10 (range 10–35) and the mean HY was 2.6 ± 1.1 (range 1–4). Medications in these patients included levodopa (n = 5), dopamine agonists (n = 4), SSRI antidepressants (n = 3) and hypnotics (n = 3). All patients had at least one concomitant sleep-wake disorder including REM-sleep behaviour disorder (RBD) (n = 4) and insomnia (n = 3). In all but one patient the latency between onset of PD and appearance of SW was >4 years.

Conclusion: Adult-onset SW is not uncommon in PD and may arise from a complex disturbance of arousal and motor control in sleep secondary to brainstem neurodegeneration.

P 21 Long-term prognosis of myasthenia gravis in old patients with severe internistic and surgical complications

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In myasthenic patients, especially with the severe generalised form, systemic complications can lead to serious life-threatening events.

We describe 2 cases of late-onset generalised myasthenia, with bulbar and respiratory involvement, who had several internistic and surgical complications, both related and independent of the disease and its treatment with consequent great number of myasthenic exacerbations.

Both patients repetitively required intensive care unit hospitalisation and prolonged intubation and their clinical conditions were often so seriously compromised to consider the arrest of invasive life support.

However, they are still alive after many years, at the age of 79 and 88, actually self-sufficient, without myasthenic symptoms and without myasthenic treatment.

Despite the progress in the myasthenia gravis treatment since the introduction of inhibitors of cholinesterasis, ventilatory sup-

port, thymectomy and IVIG plasmapheresis, myasthenic exacerbations are still an important challenge for clinicians who must often deal with dramatic life-threatening events.

However, the myasthenic exacerbations themselves do not necessarily change the long-term prognosis of the disease so the maximal treatment should always be considered, even in apparently desperate situations.

P 22 Association of chronic inflammatory demyelinating polyneuropathy (CIDP) and a spinal form of multiple sclerosis (MS) in a young patient: a diagnostic and therapeutic challenge

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Subclinical central nervous system demyelination in chronic inflammatory demyelinating polyneuropathy has been reported, especially in young patients, but association between CIDP and clinically active multiple sclerosis is rare and can be a diagnostic and therapeutic challenge for the clinician.

Recently, there has been a rising interest for the association between MS and CIDP because of possible CIDP-like polyneuropathy development in patients with MS treated with interferon beta.

In contrast, some CIDP patients resistant to other therapies may benefit from interferon beta treatment.

We describe a case of a 19-year-old girl with a subacute-onset CIDP who has developed, 10 years later, at the age of 29, the relapsing-remitting multiple sclerosis with predominant medullar involvement, actually treated with interferon beta.

Peculiar clinical and therapeutic aspects of the case and a review of the literature are discussed.

P 23 Association of environmental factors with the onset of status epilepticus

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Objective: To test whether non-medical, environmental factors influence the frequency of admissions of patients with status epilepticus (SE) to the intensive care unit (ICU).

Methods: Retrospective statistical analysis (using Poisson-regression and likelihood ratio tests) of all admissions of patients with SE to the ICU of a tertiary care centre during three years with regard to daytime, weekday, season, moon cycle and weather conditions.

Results: Data from 184 patients (mean age 57 years [18–89]) showed a significant ($p < 0.001$) diurnal pattern with a peak of admissions between 4 to 5 p.m. and a minimum in the early morning. The weekly pattern was significant ($p = 0.045$) with admissions peaking on Thursdays/Fridays and the lowest rate at weekends. There was no monthly or seasonal pattern. The pattern of admission across moon cycle was statistically significant, peaking at day 3 after new moon ($p = 0.003$), with a weaker peak 7 days after full moon and a minimum 3 days before new moon. While temperature, sunshine and wind force did not significantly influence the admissions, relative humidity was a significant protective factor, with a 2% average decline in admissions per 1% increment in humidity.

Conclusion: Admissions of patients with SE on ICU are significantly associated with several environmental factors. Contrary to public belief, SE did neither peak at full moon nor at new moon, but some days after new moon. The reasons for the associations observed remain to be elucidated.

P 24 To be or not TB

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We present a case of a 68-year-old immunocompetent man, hospitalised with the diagnosis of multiple brain metastasis of unknown origin. The initial diagnostic work-up resulted in the diagnosis of a kidney tumour in the setting of a horseshoe kidney. Following to several sterile leucocyturias since more than a year, a specific TB search was performed on urine, permitting the diagnosis of renal tuberculoma. Despite the absence of pathological results in LCR studies (negative TB cultures and PCR), we suspected a disseminated CNS tuberculosis. The subsequent anti-tubercular therapy resulted in the remission of both kidney "tumour" and cerebral "metastasis", indirectly confirming our suspicion of CNS tuberculomas as a dissemination of renal TB.

P 25 Electrophysiological surrogate markers for primary progressive multiple sclerosis (PPMS) – cross-sectional analysis of 23 patients

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Background: Approximately 10% of patients with multiple sclerosis follow a primary progressive course. Disease progression in these patients is assessed by clinical examination. Serial MRI are of limited value, as signs of inflammation are less prominent in PPMS than in other forms of MS.

Objectives: To determine the relationship between evoked potentials (EP) and disability in PPMS patients.

Methods: 23 patients with a definite diagnosis of PPMS, a median Expanded Disability Status Scale (EDSS) of 4 (2.5–6.5) and a mean disease duration of 5.2 years (0.1–19.3 years) underwent visual, somatosensory and motor evoked potentials and a standardised neurological examination. Spearman rank correlation was used to examine the association between EP and clinical measures.

Results: EDSS values correlated strongly with the sum of z-transformed EP latencies ($rho = 0.736$; $p < 0.001$) and the number of pathological EP test results ($rho = 0.717$; $p < 0.001$).

Conclusions: Multimodal EP studies generate objective quantifiable data that correlate well with clinical disability in PPMS patients, even if the sample size is small. This may be related to the predominance of spinal cord involvement in most PPMS patients, since spinal pathology is relatively well represented in MEP and SEP alterations. To establish whether multimodal EP can serve as valid surrogate markers for future clinical trials in PPMS, the presented cross-sectional analysis needs to be supplemented by longitudinal observations.

P 26 Parameters of decision for the management of disease modifying treatment in multiple sclerosis in daily practice: an observational programme

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Background: The aim of this prospective observational programme was to describe the day-to-day neurologist's practice in terms of follow-up and treatment strategy of patients with relapsing-remitting multiple sclerosis (RRMS).

Methods: Patients were treated with any one of the registered disease-modifying drugs (DMD) as prescribed by the treating neurologist. Data on neurological status, clinical and magnetic resonance imaging (MRI) outcomes, and the determinants for treatment decisions were captured in a structured questionnaire for every follow-up visit occurring during the 1-year observation period. Visits were stratified according to whether a change in the therapeutic strategy had occurred or not; these two groups were then analysed for differences in the neurologist's decision determinants.

Results: 307 patients (951 documented visits) were evaluated. Stratification resulted in 893 visits without and 48 visits with a recorded therapeutic change. Patients with a subsequent change in DMD treatment had a higher baseline mean EDSS score and had experienced a higher average number of relapses in the 2 years prior to enrolment. The determinants for change with the highest rating of importance were frequency and severity of relapses, disability progression and changes in tolerance.

Conclusions: This analysis provides an insight into Swiss neurological daily practice and the tools and thresholds used to evaluate DMD treatment strategies therein.

P 27 Blood glucose levels after ischaemic stroke in patients with and without sleep apnoea

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Background/aims: The aim of our study is to investigate changes in blood glucose in patients with acute ischaemic stroke and their relationship to sleep apnoea (SA) severity and type.

Patients/methods: We included 29 consecutive patients with acute ischaemic stroke, in whom fasting blood glucose level was repeatedly assessed at day 1, 2, 3, 4, 7 and 19 after admission in the same period of time (between 6 and 10 a.m.). Stroke severity on admission and stroke outcome at discharge were recorded. Respirography was performed in the first night and scored according to standard criteria.

Results: The mean age was 62 ± 12 [25–83], 19 (66%) were male. Blood glucose on admission was 7.4 ± 2.9 [4.1–19.9] and 6.4 ± 2.0 [4.6–11.1] at day seven. We found a significant correlation between glucose at day seven and apnoea-hypopnoea index ($p = 0.002$; $r = 0.622$), central apnoea index ($p = 0.009$; $r = 0.556$) and oxygen desaturation index ($p < 0.0001$; $r = 0.751$) independent of cardiovascular risk factors, age and body-mass index. Glucose at day seven correlated with stroke severity on admission ($p = 0.004$; $r = 0.607$) and with functional disability at discharge ($p = 0.017$; $r = 0.528$).

Conclusions: Glucose level at day seven after ischaemic stroke is an independent predictor of stroke severity and outcome, and is associated with severity of SA, central apnoeas and oxygen desaturations. Further studies are needed to test the hypothesis that these findings may reflect an increased sympathetic activity possibly related to sleep apnoea.

P 28 Correlation between sleep EEG and cognitive functions after hemispheric ischaemic stroke

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Background: The aim of the study is to elucidate the association between changes in sleep EEG and alteration of cognitive functions in patients with ischaemic stroke.

Methods: We studied 11 consecutive patients with first-ever hemispheric ischaemic stroke admitted within 3 days after symptoms onset. Stroke volume was assessed by MR imaging. Sleep EEG and nocturnal breathing were examined with a validated portable system. Cognitive function was evaluated using a standardised battery of tests. A second examination of sleep EEG and cognitive function was performed in 9 patients at least 3 months after stroke. The patients were compared with 5 gender- and age-matched healthy controls.

Results: Mean age was 43 ± 12 years (range 18–60), 4 were males. In 5 patients stroke was right-sided, in 6 left-sided. Mean volume of the stroke lesion was 82 ± 66 ml (range 5–200). In the acute stroke phase a significant correlation between (1) sleep efficiency and attention ($p = 0.039$), (2) amount of REM sleep and verbal fluency ($p = 0.016$) was found. A significant improvement of sleep efficiency ($p = 0.005$), verbal fluency ($p = 0.009$) and nonverbal fluency ($p = 0.02$) was found in the control examination. In the chronic phase we observed a correlation between amount of REM sleep and visual learning ability ($p = 0.017$).

Conclusion: The results suggest the presence of a link between changes in sleep EEG pattern and alteration of cognitive functions during the acute and the recovery phase after hemispheric stroke.

P 29 Flexor myoclonus of the arm due to posttraumatic syringomyelia

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We report the case of a segmental myoclonus of the right arm in a posttraumatic syringomyelia, exclusively triggered by pain. A 33-year-old man developed non-painful paraesthesias and hypaesthesia at the shoulder-girdle and in both arms 2 years after a complete transverse spinal cord injury at the fourth thoracic level. Within few months repetitive involuntary flexion movements of the right arm developed, exclusively triggered by spontaneous as well as afflicted intense pain in the right arm. The clinical exam showed hyporeflexia of upper extremities (more on the right side), a right-sided sensory level for touch, pain and temperature at the 4th thoracic level in addition to the known complete transverse spinal cord syndrome at the 6th thoracic level. Median nerve sensory evoked potentials were normal, but cutaneous silent period in the right hand was attenuated. EEG showed an intermittent bifrontal slowing but no epileptiform potentials. MRI and SPECT of the brain were normal. MRI of the cervical spine revealed a syringomyelia from the second cervical segment down to the spinal cord lesion. After the syringo-peritoneal drainage, pain and involuntary movements decreased clearly and were followed by a stable clinical course in the subsequent months.

This case shows segmental flexor myoclonus in an upper extremity, most likely caused by disinhibition of the flexor reflex due to a posttraumatic cervical syringomyelia.

P 30 Multidrug resistance-associated protein (Mrp)-1: a gateway for drugs to the stroke brain

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Purpose: ATP-binding cassette (ABC) transporters are ATP-dependent flippases located at the blood-brain barrier (BBB) that are involved in the elimination of drugs from the brain. While the majority of transporters are expressed on the luminal surface of the endothelium, carrying drugs from the brain back into the blood against concentration gradients [1], some transporters, including multidrug resistance-associated protein (Mrp)-1 (also termed ABCC1), predominantly exhibit abluminal localisation on vascular endothelium. Until now, the function of these abluminal transporters remained largely unclear.

Methods and results: To elucidate the implication of Mrp-1 for the pharmacotherapy of ischaemic stroke, we submitted adult C57bl/6 mice to 30 and 90 min of middle cerebral artery (MCA) occlusion [1]. Immunohistochemical studies and Western blots using enriched capillary fractions showed that Mrp-1 expression was decreased in ischaemic brain at 3–12 h after reperfusion onset. Delivery of the Mrp-1 substrates 17,EG and GSNO immediately after MCA occlusion resulted in a dose-dependent decrease (17,EG) or increase (GSNO) in brain injury, compared to vehicle-treated control mice. Deactivation of Mrp-1 both by pharmacological inhibition with MK571 or genetic knockout completely blocked the injury effects of 17,EG and GSNO, indicating that Mrp-1 was required for the brain entry of both pharmacological compounds.

Conclusions: Our data suggest that Mrp-1 serves as gateway for drugs into the stroke brain. We predict that the selection of drugs acting as substrates of abluminal, but not luminal ABC transporters may greatly facilitate pharmacological therapies in brain diseases.

Literature

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P 31 Three complications of an intrathecal morphine pump in a single patient

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A patient who underwent the implantation of an intrathecal morphine pump for the treatment of chronic, intractable post-traumatic

pain in a shoulder had three complications after the procedure. A cerebrospinal fluid (CSF) fistula developed around the intrathecal catheter, presenting with a subcutaneous fluid collection in the abdomen around the site of the pump. Two wound revisions in the back were needed to close the fistula. Painful bilateral leg oedema, severe enough to impede walking, also developed. This was found to be directly related to the intrathecal morphine dose, regressing after the dose was lowered. Finally, there was also intermittent lancinating radicular pain in both legs, which gradually resolved spontaneously. Of these three complications, only the last one is widely known. A CSF fistula presenting with an abdominal seroma has apparently not been reported before, and leg oedema due to intrathecal morphine has been described in only one report, though it is probably much more common than recognised. The occurrence of all of these problems in a single patient underscores the fact that the insertion of morphine pumps is not entirely unproblematic and should only be undertaken for well-conceived indications, in well-informed patients and by experienced hands.

P 32 A case of slowly progressive gait ataxia with positive anti-disialosyl-antibodies

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A 56-year-old man was admitted because of slowly progressive distal paraesthesias and severe ataxia of the lower extremities.

Neurological examination revealed severe painless symmetrical sensory impairment of the lower extremities with a profound loss of vibration sense but no weakness. Deep tendon reflexes were absent. He presented with a broad-based ataxic gait. Upper extremities and cranial nerve examination were normal.

Sensory nerve action potentials (SNAPs) were normal. Somatosensory evoked potentials (SSEP) of the tibial nerve could neither be recorded from thoracolumbal nor cortical whereas the SNAPs in the poplitea were normal suggesting a lesion proximal to the dorsal root ganglion, probably postganglionic sensory nerve roots and dorsal columns.

Anti-disialosyl-antibodies were positive. Infections, solid tumours, paraneoplastic conditions, diabetes and Sjögren's syndrome were excluded by specific investigations. The patient showed a moderate improvement to IVIg therapy.

The differential diagnosis involves other cases of sensory ataxic neuropathies and disorders of dorsal root ganglion. However, sensory neuropathies and ganglionopathies are characterised by abnormalities of sensory nerve action potentials whereas in our case the SNAPs were normal.

To our knowledge this is the first case of chronic progressive gait ataxia with positive anti-disialosyl-antibodies and IVIg response affecting the postganglionic sensory nerve roots and dorsal columns.

P 33 A new test to measure upper limb apraxia in stroke (TULIAS): a reliability study

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Currently, few scales are available to evaluate forelimb apraxia and they only partly cover behavioural aspects of praxis production. Therefore, the aim of the present study was to assess inter-rater reliability of a comprehensive clinical test of upper limb apraxia (TULIAS) recently developed in our Clinic.

A cohort of 52 patients with ischaemic stroke was prospectively studied. The TULIAS test incorporates imitation and pantomime of transitive (tool use), intransitive (communicative) and meaningless gestures. The assessment, requiring 20 min, was recorded on video and scored by 2 investigators. Inter-rater reliability was calculated by intra-class correlation coefficient (ICC) and weighted kappa statistics. Cronbach's Alpha was used to measure internal consistency.

The findings demonstrated a good to excellent inter-rater reliability for total score and 6 subtests (ICCs >0.80). Internal consistency was good for 4 subtests (alpha values >0.70), and moderate (0.65) to less consistent (0.58) for 2 subtests. For inter-rater reliability at item level (n = 48) all but 5 items had acceptable to excellent degree of agreement (weighted kappa's >0.60).

These results show that the TULIAS test is a reliable instrument to systematically assess upper limb praxis, justifying further validation. The test can be easily applied and is therefore useful in clinical practice and for research purposes.

P 34 Neurolymphomatosis as a single sign of tumour recurrence in a patient with diffuse large B-cell lymphoma of the testis

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A 40-year-old man presented with progressive asymmetric brachialgia and peripheral paresis of the right arm over 6 weeks. The pain was of neuropathic origin with burning sensations and deterioration at night time. Moreover, he suffered from weight loss and extensive sweating. One year ago, he was diagnosed as having a diffuse large B-cell lymphoma of the testis and was treated with chemotherapy until remission. On examination we found an axonal polyneuropathy and a painful radicular syndrome of the spinal roots C6 and C7. CSF showed elevated cell count, elevated protein and high lactate value, suggestive of leptomeningeal metastasis. MRI- and FDG-PET-scans revealed infiltration of the right brachial plexus and concomitant lymph node enlargement. Multiple biopsies of the lymph nodes confirmed the diagnosis of malignant and non-malignant infiltration of the right brachial plexus leading to the diagnosis of neurolymphomatosis. As diffuse large B-cell lymphomas harbour a high tropism to peripheral nerves and the CNS, the rare diagnosis of neurolymphomatosis should be kept in mind in tumour patients with neuropathic pain syndromes beside other conditions like borreliosis and varicella zoster infection.

P 35 Behaviourally induced insufficient sleep syndrome: a case series of 31 patients

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Introduction: Behaviourally induced insufficient sleep disorder (BIISD) occurs when an individual persistently fails to obtain the amount of sleep required to maintain normal levels of alertness and wakefulness.

Objective and method: This study presents the results of the post hoc evaluation of 31 consecutive patients who received the diagnosis of BIISD in our Sleep Disorders Centre.

Results: Mean age of the BIISD patient was 39.0 ± 11.8 years (mean ± SD). 23/30 were males. Mean ESS was 14.8 ± 3.2. ESS was less than 10 in 3 patients, between 10 to 14 in 11 and higher than 14 in 17 patients. Time in bed (TIB) estimation based on the SQ revealed TIB of 7:11 h ± 1:08 h during weekdays and 8:30 h ± 1:18 h on weekend. TIB estimation based on actigraphy recordings revealed significantly shorter TIB on weekdays and on weekends (weekday: 6:38 h ± 0:44 h, weekend: 7:53 h ± 1:18 h) compared to TIB taken from the SQ. In this population the PSG recording revealed short sleep latency 8.4 ± 7.9 minutes and high sleep efficiency (91.5 ± 16.7%). MSLT mean sleep latency was 5.7 ± 3.6 minutes. Sleep-onset REM (SOREM) episodes with 2 and more SOREM were present in 5 patients. MWT mean sleep latency was very variable (range: 2.4–20 minutes).

Conclusion: The results of this case series indicate that sleep prolongation on weekends and high-quality sleep during night sleep (short sleep latency and high sleep efficiency) are not sufficient enough to reduce EDS in this patient group; however, these measures characterise BIISD.

P 36 Fatal outcome in a patient suffering from statin-induced rhabdomyolysis, hypothyroidism and inclusion body myopathy

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We report the case of a 73-year-old woman who developed progressive clinical signs of proximal symmetrical tetraparesis under treatment of HMG-CoA reductase inhibi-

tor. Additionally, the patient suffered from untreated hypothyroidism. CK values were above 20 000 U/l and EMG studies showed a myopathic pattern. The first muscle biopsy revealed subacute rhabdomyolysis and regeneration of muscle fibres consistent with the diagnosis of a toxic myopathy. Inflammatory signs were not found. Replacement of statins, substitution of thyroid hormones and treatment with steroids led to initial clinical improvement and reduction of CK values.

After five-month follow-up tetraparesis relapsed. EMG again showed a generalised myopathic pattern of proximal extremity muscles. A second muscle biopsy now revealed progressive rhabdomyolysis and additionally rimmed vacuoles as characteristical signs of inclusion body myopathy (IBM). On a second look at the first biopsy rimmed vacuoles could now also be detected in small numbers. Initial high-dose steroid therapy and azathioprine were given with a marked and lasting drop of CK values, but without clinical benefit until now. The aetiology and pathogenesis of statin-induced myopathy is still poorly understood and therapeutic options are rare. Concomitant IBM and hypothyroidism were confounding factors for the bad outcome in our patient, possibly pointing towards a subgroup of patients with a higher likelihood of complications on statin therapy.

P 37 Therapy refractory voltage-gated potassium channel antibody (VGKC-Ab) negative neuromyotonia with generalised lymphadenopathy

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We report the case of a 65-year-old man who suffered from progressive myokymia in both legs. Besides undulating wormlike rhythmic movements he complained of severe muscle cramps and hyperhidrosis. On examination he showed no pareses, no signs of ataxia or brainstem abnormalities. Apart from absent ankle jerks no reflex abnormalities were found. Sensory symptoms consisted of pallanaesthesia. During the following 2 weeks myokymia was also present in the upper extremities and the facial muscles. EMG studies revealed spontaneous douplet, triplet and multiplet motor unit discharges as well as fasciculation and fibrillation potentials. Nerve conduction studies showed characteristic afterdischarges and signs of axonal polyneuropathy. VGKC-Ab were negative. A thymoma or a lung cancer was excluded, but on CT scans we found lymphadenopathy of the mediastinum and the abdomen. Biopsies revealed a picture of reactive cell changes but no malignant cells, granulomes or Langerhans' cells. CSF was normal despite a slight elevation in proteine, which we referred to the degenerative changes of the spine. We started therapy with carbamazepine and phenytoin as well as IVIGs (0.4 g/kg body weight) with virtually no effect. In contrast to the ineffectivity of recommended membrane stabilising anticonvulsants and immunmodulating IVIGs in our patient only immunosuppressive treatment with steroids led to an improvement of neuromyotonia as well as lymphadenopathy of still unknown origin.

P 38 NogoA deficiency aggravates brain injury after transient focal cerebral ischaemia in mice

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Purpose: NogoA is an axonal outgrowth inhibitor, the deactivation of which enhances brain plasticity and recovery under pathophysiological conditions including ischaemic stroke and spinal cord trauma. In order to characterise the effect of NogoA deficiency on brain injury, we submitted wildtype (wt) and NogoA-/- mice to 30 min of middle cerebral artery (MCA) occlusion.

Methods and results: Out of 8 mice in each mouse line, 0 wt and 3 NogoA-/- animals died during the first three days after the stroke. The surviving 5 NogoA-/- animals exhibited exacerbated deficits in a grip strength motor force test. Compared with wt mice (n = 8), the density of TUNEL+ was increased in the striatum of NogoA-/- animals (n = 5). Conversely, the percentage of surviving striatal neurons was significantly reduced by NogoA deficiency. In order to rule out that aggravation of brain injury was due to vascular alterations induced by the NogoA deficiency, we prepared histochemistries for CD31 and VEGFR-2, which are markers for brain capillaries and newborn capillaries, respectively. The density of CD31+ and VEGFR-2+ capillaries did not differ between both mouse lines. To elucidate mechanisms underlying the effects of NogoA-/-, Western blots with tissue samples obtained from the ischaemic and contralateral non-ischaemic striatum were performed. These blots revealed elevated levels of phosphorylated ERK1/2 in the ischaemic striatum of NogoA-/- compared with wt mice. Levels of total ERK1/2, total and phosphorylated JNK1/2, as well as total and phosphorylated p38 did not differ between both animal groups. Additionally, intracellular GTPase, RhoA and RhoB were higher in ischaemic brain of NogoA-/- animals than controls.

Conclusion: Our present study exhibits an acute injury-aggravating effect of NogoA deficiency.

P 39 Transgenic erythropoietin (Epo) protects from focal cerebral ischaemia by a dual pathway involving both ERK-1/-2 and Akt

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Apart from its haematopoietic function, Epo exerts neuroprotective activity upon brain ischaemia. We examined the mechanisms mediating Epo's neuroprotective activity in vivo, making use of a transgenic mouse line, tg21, that constitutively expresses human Epo in the brain without inducing polycythaemia. tg21 animals and their wt controls were submitted to 90 or 30 minutes of intraluminal middle cerebral artery occlusion (MCAo). Brain injury and cell signalling were assessed at 24 (90 min) or 72 (30 min) hours of reperfusion. Cell signalling inhibitors for MAP kinase / ERK-1/-2 (PD98059) and Akt (Wortmannin) were i.c.v. applied. We show that human Epo is expressed in the cortex and striatum of tg21 mice and that neurons carry the Epo receptor. After MCAo, Epo potently protected brains of tg21 mice against ischaemic injury, both whether longer-lasting (90 min) and mild (30 min) ischaemias were imposed. Histochemical studies revealed that Epo induced an activation of Jak-2, ERK-1/-2 and Akt signalling in the ischaemic brain, which was associated with elevated Bcl-XL and decreased NO synthase (neuronal and inducible) levels. STAT-5 activity, on the other hand, was not increased. I.c.v. injections of PD98059 or Wortmannin showed that both ERK-1/-2 and Akt were required for Epo's neuroprotective activity, antagonisation of either pathway completely abolishing tissue protection. The dual activation of ERK-1/-2 and Akt is crucial for Epo's neuroprotective function.

P 40 Mononeuritis multiplex due to a necrotising vasculitis diagnosed with a biopsy of the cutaneus antebrachii nerve

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Background: Among patients with vasculitic neuropathy the combination of superficial peroneal nerve and peroneus brevis muscle biopsy has a sensitivity of approximately 60%. However, due to the multifocal involvement of nerves, the peroneal nerve might not be involved.

Case report: A 25-year-old female patient presented with dysaesthesias in the left palm and a very painful left elbow. She has been suffering from several episodes of tingling and painful paraesthesias as well as weakness in both distal upper extremities for eight years. The lower extremities were never involved. Her symptoms lasted usually up to one month; however, the remissions were usually incomplete. The neurological examination showed an asymmetrical sensorimotor neuropathy of the ulnar nerve in both hands and the median nerve in the left hand with involvement of the pronator teres muscle. Laboratory screening showed positive lupus anticoagulants, anticardiolipin antibodies, ANAs and antibodies to double-stranded DNA. Electrophysiological studies confirmed an older bilateral axonal lesion of the ulnar nerve and a fresh axonal lesion of the left

median nerve. The biopsy of the left n. cutaneus antebrachii revealed a necrotising vasculitis. A diagnosis of a lupus-like disease with nerve vasculitis was made. After the biopsy the patient only noticed a slight hypaesthesia in the ulnar forearm without pain. Treatment with methylprednisolon and mycophenolate was initiated.

Conclusion: As illustrated by our case, only upper extremities may be affected in nerve vasculitis. As a consequence, biopsy of the n. cutaneus antebrachii may be the only possibility to diagnose a necrotising vasculitis associated with mononeuritis multiplex.

P 41 A project and a model for a stroke unit in southern Switzerland

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In the region of southern Switzerland (350 000 inhabitants) the public health is united under a unique administrative structure (Ente Ospedaliero Cantonale-EOC) composed mainly of 4 regional hospitals (Ospedale Regionale di Lugano-ORL, Ospedale Regionale Bellinzona e Valli-ORBV, Ospedale Regionale di Locarno-ODL, Ospedale Regionale Beata Vergine di Mendrisio-OBV). These hospitals treat patients with special problems in a network, with subspecialities present only in some of them, like a "multisite hospital". The ORL has a neurological and neurosurgical department, the others have an internal (ORBV) or external (OBV, ODL) neurology consultant. All four hospitals have an intensive care unit, an internal medicine department and a radiology unit with a CT scan. MRI is available in two (ORL, ORBV), cerebral digitalised angiography in one (ORL). Actually only a part of the 600 patients with acute stroke arriving yearly in the EOC-hospitals are treated by a neurologist in dedicated beds and only one hospital (ORL) has a stroke team respecting international standards of organisation.

In charge of the Direction of the EOC the "SUN-EOC" developed a model for the acute treatment of patients with stroke in southern Switzerland considering these local particular conditions.

We present this model of "multisite stroke unit", which includes the creation of:

1. A central stroke unit (ORL) with dedicated beds for acute stroke patients of the region of Lugano and selected cases from the whole area of southern Switzerland (examples: complex cases, patients requiring neurosurgery or urgent carotid surgery).
2. Three local stroke teams (ORBV, ODL, OBV) taking directly on charge routine cases, with the possibility of systemic thrombolysis and in close collaboration with the central stroke unit.
3. One clinical nurse specialist in vascular neurology to improve the quality of patient care and nursing practice in all 4 hospitals.
4. Common guidelines in vascular neurology, valid for all hospitals.
5. Continuous education programme for the staff of all hospitals of EOC, coordinated by the central stroke unit.
6. The developing of "telemedicine" facilities to allow a better communication between different stroke unit teams and the central stroke unit.
7. Collaboration with a specialised rehabilitation clinic (Clinica Hildebrand in Brissago) for rapid post-acute neurorehabilitation.

P 42 Cognitive virtual reality-based neurorehabilitation in acute stroke patients

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Purpose: In this study we perform a preliminary evaluation of the therapeutic efficacy of a novel virtual reality (VR)-based neurorehabilitation system for stroke patients with moderate to severe arm paresis. The therapy system is designed to stimulate the cortical networks involved in action recognition and imagery by providing patients with visual stimuli based on movement observation combined with overt actions.

Methods: Six stroke patients were recruited (ages 29–65 years, 4 male/2 female, 4 with paresis on non-dominant side) from the acute stroke treatment unit of the University Hospital Zurich. After neurological assessment and neuroimaging each patient was treated from the first week after stroke onset for up to 5 weeks with an interactive VR system equipped with task-oriented gaming scenarios. In addition to standard clinical assessment and records of kinematic arm movements during performance of the game, patients completed questionnaires to rate their own enjoyment of the system and their performance in the game.

Results: Over the course of treatment individual patients showed improved performance in the neurological tests (NIHSS mean increase 3.2 ± 1.7 SD, mRS mean increase 2.8 ± 0.8, Kunesch score mean increase 6.6 ± 5.6), reflecting functional recovery of the paretic arm. Improvements in neurological scores were reflected in their performance in the gaming scenarios, as measured by increases in the game difficulty parameters while maintaining constantly high scores. Questionnaires revealed that patients enjoy working with our system, that they found it easy to use and that they were optimistic about their prospects for future recovery. It was also found that self-assessment of performance correlates with the evolution of selected clinical scores.

Conclusions: While the efficacy of our system relative to other therapeutic approaches needs further evaluation, our initial results suggest that our VR system is well accepted by patients. This result opens the door for the development of a home-based, low-cost therapeutic system for the treatment of acute stroke patients. Our results also open the possibility of our system being used for simultaneous therapy and assessment.