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Managing editor:
Dr. Nadine Leyser, nleyser@emh.ch

Director of publications:
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Neurology

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Rue Saint-Martin 7
CH-1003 Lausanne

Production
Schwabe AG
Farnsburgerstrasse 8
Postfach 832, 4132 Muttenz
Tel. +41 (0)61 467 85 85, Fax +41 (0)61 467 85 86
e-mail: druckerei@schwabe.ch

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1

Ataxia-telangiectasia: a "disease model" to understand cerebellar control of vestibular reflexes

A.A. Tarnutzer[1], A.G. Shaikh[2], S. Marti[1], A. Palla[1], T.O. Crawford[3], D. Straumann[1], J.P. Carey[3], K.D. Nguyen[3], D.S. Zee[3]
[1]Zurich University Hospital, Zurich, Switzerland, [2]Case Western Reserve University, Cleveland, United States, [3]The Johns Hopkins University, Baltimore, United States

Introduction: Experimental animal models suggest that modulation of the amplitude and direction of vestibular reflexes are important functions of the vestibulo-cerebellum and contribute to the control of gaze and balance. These critical vestibular functions have been infrequently quantified in human cerebellar disease.
Methods: In 13 patients with ataxia-telangiectasia (A-T), a disease associated with profound cerebellar cortical degeneration, we found abnormalities of several key vestibular reflexes. The rotational vestibulo-ocular reflex (VOR), transduced by the semicircular canals was measured during earth-vertical, constant-velocity, on-axis rotations with the body upright (yaw), supine, or left-ear-down (LED). Vestibulo-collic reflexes (VCR) were assessed using a surrogate vestibular response mediated by the saccule, cVEMPs (cervical vestibular evoked myogenic potentials) in which auditory clicks induce changes in activity from the sternocleidomastoid muscle.
Results: The VOR gain (eye velocity/head velocity) was abnormally increased in all patients. There was also an abnormal eye velocity directed along the axes orthogonal to that of head rotation, called VOR cross-coupling. Five patients, in whom eye movements along all three axes could be measured, did not align the axis of eye rotation with that of head rotation during the VOR elicited in all three planes of rotations. In eight of ten patients, the amplitude but not the threshold or latency for cVEMPs was increased, indirectly suggesting an increased gain of VCR.
Conclusions: Increased gains of the VOR and VCR suggest that long-term adaptation of the amplitudes of not only the canal but also otolith-mediated vestibular reflexes is impaired in patients with vestibulo-cerebellar lesions. Abnormal VOR cross-coupling and impaired spatial alignment of the eye and head rotation axes suggests an inability to generate a veridical central estimate of the orientation of the head. Degeneration of the Purkinje neurons in the vestibulo-cerebellum probably underlies these deficits. Quantifying vestibulo-ocular and vestibulo-collic reflexes in patients with various cerebellar diseases not only offers insights into how the vestibulo-cerebellum functions in healthy humans but can provide valuable surrogate biomarkers for monitoring progression of the cerebellar disease and efficacy of its treatment.

2

Copeptin as prognostic serum biomarker in different acute stroke treatment settings: an interim analysis

G. M. De Marchis[1], M. Katan[2], A. Weck[1], H. P. Mattle[1], M. Seiler[1], M. Christ-Crain[3], B. Müller[5], M. Arnold[1]
[1]Department of Neurology, Inselspital, Bern, Switzerland, [2]Department of Neurology, University Hospital, Basel, Switzerland, [3]Department of Endocrinology and Clinical Nutrition, Univ. Hospital, Basel, Switzerland, [4]Research Department, BRAHMS GmbH, Berlin, Germany, [5]Department of Internal Medicine, Aarau, Switzerland

Aim: This ongoing prospective study aims to evaluate Copeptin as prognostic serum biomarker in different acute stroke treatment settings (conservative or thrombolysis).
Background: In a recent prospective study, we demonstrated that Copeptin is a novel independent predictor of functional outcome and mortality after acute ischemic stroke. However, the subgroup of patients undergoing thrombolysis was too small to draw final conclusions.
Methods: We analyzed the data of 457 patients with ischemic stroke admitted to the stroke unit of the Inselspital Bern between March 2009 and July 2010. Totally, 295 patients were treated conservatively, 162 patients with thrombolysis. Copeptin levels were measured within 24 hours of symptom onset. After three months, we assessed unfavorable outcome (modified Ranking scale [mRS] >/=3) and mortality.
Results: In conservatively treated patients, Copeptin values were higher in patients with an unfavorable outcome compared to patients with favorable outcome (26.3 pmol/l, IQR 9.8–81.6 versus 9.0 pmol/l, IQR 4.4–19.6, p <0.0001), as well as in patients who died compared to surviving patients (60.6 pmol/l, IQR 24.8–128.2 versus 9.6 pmol/l, IQR 4.7–24.9, p <0.0001). In logistic regression analysis, Copeptin predicted functional outcome (OR 2.14, 95% CI 1.13–4.06, p = 0.01) and mortality (OR 3.56, 95% CI 1.56–8.11, p <0.0001) independently of known stroke risk factors. In patients treated with thrombolysis, Copeptin values were increased in patients with an unfavorable outcome compared to patients with favorable outcome (31.9 pmol/l, IQR 15.8–31.9 versus 12.4, IQR 5.7–54.0, p = 0.004), as well as in patients who died compared to surviving patients (56.3 pmol/l, IQR 18.3-120.5 versus 17.8, IQR 7.06–52.9, p = 0.007). However, Copeptin did not independently predict functional outcome (RR 1.31, 95% CI 0.71–2.41, p = 0.38), or mortality (RR 1.92, 95% CI 0.90–4.12, p = 0.09).
Conclusion: Copeptin independently predicts functional outcome and mortality in patients with ischemic stroke and conservative treatment. However, in this interim analysis Copeptin did not reach statistical significance in patients treated with thrombolysis.

3

Intracranial Hemorrhage, Outcome and Mortality after Intra-Arterial Therapy for Acute Ischemic Stroke in Patients under Oral Anticoagulants

G. M. De Marchis[1], S. Jung[1], G. Colucci[2], N. Meier[1], U. Fischer[1], A. Weck[1], M.-L. Mono[1], A. Galimanis[1], H. P. Mattle[1], G. Schroth[3], M. Arnold[1], C. Brekenfeld[3]
[1]Department of Neurology, Inselspital, Bern, Switzerland, [2]Haematology and Central Haematology Laboratory, Inselspital, Bern, Switzerland, [3]Department of Neuroradiology, Inselspital, Bern, Switzerland

Background and Purpose: Use of intravenous tissue plasminogen activator (tPA) for acute ischemic stroke is restricted to patients with an international normalized ratio (INR) less than 1.7. However, a recent study showed an increased risk of symptomatic intracranial hemorrhage (sICH) after intravenous tPA use in patients with oral anticoagulants (OAC) even with an INR less than 1.7. The present study assessed the risk of sICH, clinical outcome and mortality after intra-arterial therapy (IAT) in patients with and without OAC at time of stroke onset.
Methods: Consecutive patients treated with IAT from December 1992 to October 2010 were included. Clinical outcome and mortality were assessed 90 days after stroke onset. Patients with and without baseline OAC were compared.
Results: Overall, 714 patients were treated with IAT. Twenty-eight patients (3.9%) were under OAC at time of symptom onset. Median INR in the OAC group was 1.79 (interquartile range [IQR] 1.41–2.3) and 1.01 (IQR 1.0–1.09, P <0.0001) in the group without OAC. Patients treated with OAC at admission underwent more often mechanical-only IAT than patients without OAC (46.4% vs. 12.8%, P <0.0001). Comparing patients with and without baseline OAC use, we did not find any statistical difference in the rate of sICH (7.1% vs. 6.0%, P = 0.80), unfavorable outcome (modified Rankin score 3 to 6) (67.9% vs. 50.9%, P = 0.11), and mortality (17.9% vs. 21.6%, P = 0.58).
Conclusion: OAC use at baseline did not significantly increase the risk of sICH after IAT, nor the risk of unfavorable outcome and mortality 90 days after IAT.

4

Therapeutic potential of proteasomal inhibition in dysferlinopathies with missense mutations

B. A. Azakir[1], S. Di Fulvio[1], M. Sinnreich[1]
[1]Department of Neurology, University Hospital, Basel, Switzerland

Objective: Dysferlin is a transmembrane protein implicated in surface membrane repair of muscle cells. Mutations in dysferlin cause the progressive muscular dystrophies Miyoshi Myopathy, Limb Girdle Muscular Dystrophy 2B, and distal anterior compartment myopathy. Dysferlinopathies are inherited in an autosomal recessive manner, and many patients with this disease harbor missense mutations in at least one of their two pathogenic DYSF alleles. These patients have significantly reduced dysferlin levels or lack the protein in skeletal muscle, suggesting that dysferlin encoded by mis-sense alleles is rapidly degraded by the cell's quality-control system. We reasoned that mis-sense mutated dysferlin, if salvaged from degradation, might be biologically functional.
Methods: We used a dysferlin deficient human myoblast culture harboring the common Arg555Trp mis-sense allele and a DYSF non-sense allele, as well as control human myoblast cultures

harboring either two wild-type or two non-sense alleles. We measured dysferlin protein levels, resealing kinetics of laser-induced plasmalemmal wounds, myotube formation, and cellular viability after treatment of the human myoblast cultures with the proteasome inhibitors Lactacystin or Velcade (Bortezomib).
Results: We show that endogenous Arg555Trp mis-sense mutated dysferlin is degraded by the proteasomal system. Inhibition of the proteasome by Lactacystin or Velcade rescues Arg555Trp mis-sense mutated dysferlin from degradation. This salvaged protein is functional as it restores plasma membrane resealing in patient derived myoblasts, and reverses their deficit in myotube formation. Velcade and Lactacystin did not cause cellular toxicity at the regimen used.
Conclusions: Our results indicate that proteasomal inhibition may provide a viable therapeutic strategy for patients harboring certain dysferlin mis-sense mutations.

5

Post stroke motivational impairment and apathy: predictive neuroanatomical factors

Jean-Benoît Epiney[1], Lucien Rochat[2], Martial Van Der Linden[2], Jean-Marie Annoni[1,3,4]
[1]Faculty of Biology and Medicine, and university hospital University of Lausanne, Switzerland, [2]Faculty of Psychology, and Medecine, [3]University of Geneva, [4]Department of Medicine, University of Fribourg

Background: Motivational impairments are described in 19 to 55% of post-stroke patients, but few studies have described the relationships between specific symptoms of apathy and localisation of the lesions.
Objective: To assess the relationships between site of lesion and three dimensions of apathy (lack of interest, loss of initiative and emotional blunting) and between apathy and sensitivity to positive reinforcement.
Methods: 32 post-stroke patients were assessed by using a standard measure of apathy (the Apathy Inventory), a specific task measuring sensitivity to cued positive reinforcement (Cued-reinforcement reaction-time task CRRT), as well as a global measure of cognitive functioning and a measure of working memory. Anatomical sites of lesion were classified according to the results of MRI or CT-scan.
Results: Frontal/temporal lesions were associated with loss of interest and thalamic lesions were associated with emotional blunting. No relationship was found between basal ganglia lesions and apathy. Sensitivity to reinforcement was reduced in patients with higher emotional blunting and lack of interest scores. However, high NIHSS (NIH Stroke Scale) was also related to frontal/temporal lesions and loss of interest, indicating that stroke severity might play a special role in some dimensions of apathy.
Conclusion: Apathy is not an uncommon clinical manifestation after stroke. Although some trends were found in our study, further studies need to assess which particular lesion causes each subcomponent of apathy. According to our result, sensitivity to reward is affected in apathy and is possibly a consequence of emotional blunting resulting in loss of interest. The complexity of neuro-functioning and psychology of motivation is still challenging. (Supported by the Swiss National Foundation grant no. 325100-118362)

6

Ergebnisse der endovaskulären Behandlung des akuten ischämischen Hirninfarktes bei 748 Patienten

Caspar Brekenfeld, Heinrich-Paul Mattle, Jan Gralla, Marcel Arnold, Simon Jung, Urs Fischer, Gerhard Schroth
Department Neuroradiology, Inselspital Bern, Switzerland

Hintergrund: Ziel der akuten Hirninfarkttherapie ist die rasche Rekanalisation der verschlossenen Hirnarterie. Neben der systemisch verabreichten Thrombolyse stehen auch endovaskuläre Revaskularisationsverfahren zur Verfügung, die – bei höherem materiellen, zeitlichen und personellen Aufwand – eine bessere Rekanalisationsrate versprechen.
Fragestellung: Häufigkeit der Verschlüsse in verschiedenen Gefässterritorien und deren Einfluss auf die Prognose für den Patienten. Auftreten von Komplikationen. Evaluation der Prädiktoren für ein gutes Endresultat 3 Monate nach Therapie.
Methoden: Retrospektive Auswertung der prospektiv geführten Datenbank, die alle am Inselspital Bern endovaskulär behandelten Patienten mit einem akuten ischämischen Hirninfarkt seit 1992 beinhaltet. NIHSS bei Eintritt, Zeit bis zur Behandlung, Verschlussort, Kollateralen, kardiovaskuläre Risikofaktoren, Rekanalisationsrate, symptomatische intrazerebrale Hämatome und der funktionelle Status des Patienten nach 3 Monaten gemessen anhand der modifizierten Rankin Skala gingen in die Analyse ein.
Ergebnisse: 748 Patienten (44,7% Frauen) mit 3-Monats Follow-up nach endovaskulärer Therapie eines akuten ischämischen Schlaganfalls wurden analysiert. Verschlusslokalisationen waren bei 84,5% der Patienten das vordere, bei 15,5% das vertebrobasiläre Stromgebiet. Verschlüsser der Arteria carotis interna lagen bei 24,9%, des Mediahauptstammes bei 52,4% vor. Die endovaskuläre Therapie behinhaltete in 13,9% ausschliesslich mechanische Verfahren, in 54,1% die ausschliessliche Gabe eines Thrombolytikums und 32% eine Kombination dieser Verfahren. Symptomatische Hirnblutungen wurden in 4,8% der Patienten beobachtet. Die Mortalität betrug 22,7%, die Häufigkeit eines guten Endresultates (mRS 0-2) 46%. Erfolgreiche Rekanalisation, niedriger Aufnahme-NIHSS und jüngeres Alter waren hoch signifikante Prädiktoren eines guten Endresultates 3 Monate nach Therapie.
Schlussfolgerung: Die endovaskuläre Hirninfarkttherapie erlaubt die Kombination verschiedener Rekanalisationsverfahren und führt dadurch zu einer verbesserten Rekanalisationsrate, die signifikant mit einem besseren Endresultat für den Patienten verbunden ist. Die Rate symptomatischer Hirnblutungen nach Therapie ist mit weniger als 5% gering.

7

Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data

*Carotid Stenting Trialists' Collaboration**

Leo H Bonati[1], Joanna Dobson[2], Ale Algra[3], Alain Branchereau[4], Gilles Chatellier[5], Gustav Fraedrich[6], Willem P. Mali[7], Hermann Zeumer[8], Martin M. Brown[9], Jean-Louis Mas*[10], Peter A. Ringleb*[11], *Contributed equally to the report*
[1]Department of Neurology and Stroke Unit, University Hospital Basel, Switzerland, [2]Medical Statistics Unit, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK, [3]Department of Neurology and Julius Centre for Health Sciences and Patient Care, University, Medical Centre Utrecht, Netherland, [4]Department of Vascular Surgery, Hôpital Timone Adultes, Marseille, France, [5]Clinical Research Unit, Hôpital Européen Georges Pompidou, Université René Descartes, Paris, France, [6]Department of Vascular Surgery, Medical University, Innsbruck, Austria, [7]Department of Radiology, University Medical Centre Utrecht, Netherlands, [8]Department of Diagnostic and Interventional Neuroradiology, University Hospital Hamburg-Eppendorf, Hamburg, Germany, [9]Department of Brain Repair and Rehabilitation, Institute of Neurology, University College London, London, UK, [10]Department of Neurology, Hôpital Sainte-Anne, Université Paris Descartes, INSERM, UMR894, Paris, France, [11]Department of Neurology, University Hospital Heidelberg, Germany

Background: Results from randomised controlled trials have shown a higher short-term risk of stroke associated with carotid stenting than with carotid endarterectomy for the treatment of symptomatic carotid stenosis. However, these trials were underpowered for investigation of whether carotid artery stenting might be a safe alternative to endarterectomy in specific patient subgroups. We therefore did a preplanned meta-analysis of individual patient data from three randomised controlled trials.

Methods: Data from all 3433 patients with symptomatic carotid stenosis who were randomly assigned and analysed in the Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial, and the International Carotid Stenting Study (ICSS) were pooled and analysed with fi xed-eff ect binomial regression models adjusted for source trial. The primary outcome event was any stroke or death. The intention-to-treat (ITT) analysis included all patients and outcome events occurring between randomisation and 120 days thereafter. The per-protocol (PP) analysis was restricted to patients receiving the allocated treatment and events occurring within 30 days after treatment.
Findings: In the first 120 days after randomisation (ITT analysis), any stroke or death occurred significantly more often in the carotid stenting group (153 [8.9%] of 1725) than in the carotid endarterectomy group (99 [5.8%] of 1708, risk ratio [RR] 1.53, [95% CI 1.20–1.95], p = 0.0006; absolute risk difference 3.2 [1.4–4.9]). Of all subgroup variables assessed, only age significantly modified the treatment effect: in patients younger than 70 years (median age), the estimated 120-day risk of stroke or death was 50 (5.8%) of 869 patients in the carotid stenting group and 48 (5.7%) of 843 in the carotid endarterectomy group (RR 1.00 [0.68–1.47]); in patients 70 years or older, the estimated risk with carotid stenting was twice that with carotid endarterectomy (103 [12.0%] of 856 vs 51 [5.9%] of 865, 2.04 [1.48–2.82], interaction p = 0.0053, p = 0.0014 for trend). In the PP analysis, risk estimates of stroke or death within 30 days of treatment among patients younger than 70 years were 43 (5.1%) of 851 patients in the stenting group and 37 (4.5%) of 821 in the endarterectomy group (1.11 [0.73–1.71]); in patients 70 years or older, the estimates were 87 (10.5%) of 828 patients and 36 (4.4%) of 824, respectively (2.41 [1.65–3.51]; categorical interaction p = 0.0078, trend interaction p = 0.0013].
Interpretation: Stenting for symptomatic carotid stenosis should be avoided in older patients (age ≥70 years), but might be as safe as endarterectomy in younger patients.
Funding: The Stroke Association.

P01

A case of isolated cerebellar damage 20 years after radiation therapy of a pharyngeal carcinoma

R.I.F. Iancu Ferfoglia[1], H.E. Emond[1], MIVG Vargas Gomez[1], P.P. Pollak[1]
[1]Geneva University Hospitals (HUG), Geneva, Switzerland

Delayed radiation injury of the central nervous system is a severe adverse event. Long term damage of radiotherapy is in part due to the total dose, dose fraction and treatment volume. Advanced age is one of the common risk factors. Most often, delayed effects of radiation therapy may lead to severe irreversible neurological consequences affecting generally more than one brain structure. Demyelination, global cerebral atrophy, minor-to-severe cognitive deficits and necrosis of the brain parenchyma are some of the frequent brain damages. We report the case of an 80-year-old man who developed an isolated static and kinetic cerebellar syndrome 20 years after radiation therapy. He received a total dose of 70 Gray with mixed electron and photon beams on a left palatine tonsillar carcinoma with homolateral jugular ganglionic metastasis. The patient was admitted in January 2011 following progressive worsening ataxia and bilateral dysmetria. We performed a magnetic resonance imaging showing an isolated cerebellar atrophy with Fluid-attenuated-inversion-recovery (FLAIR) hypersignal of the vermis. There were no signs of leucoencephalopathy. A lumbar puncture showed no pleocytosis and normal IgG index. The anti-Hu, anti-Ri, and anti-Yo antibodies were absent. There was no family history of cerebellar ataxia and the patient was negative for the Fragile X-associated tremor/ataxia syndrome (FXTAS) premutation. A total body FDG PET/CT imaging showed no signs of neoplasia and a local pharyngeal examination did not show any evidence of relapsing tumor. A delayed adverse event of radiation therapy such as the isolated cerebellar damage described in this report is an extremely rare entity in the medical literature.

P02

Amnesia due to Fornix Infarction – a Case Report

Dr. med. Julia Walch[1], Dr. med. Philip Siebel[1], Prof. Dr. med. Barbara Tettenborn[1]
[1]Klinik für Neurologie, Kantonsspital St. Gallen, Schweiz

Introduction: Transient global amnesia (TGA) is a clinical disorder, characterized by sudden-onset anterograde amnesia, amnesia of the recent past and repetitive questioning, usually lasting from 1 to 24 hours. Alertness and personal identity as well as contact with the environment and capability of high-level mental performance are typically preserved differentiating classic TGA from TGA mimics. The etiology remains obscure, but it has been suggested to be migrainous or epileptic in nature or ischemic following venous congestion. Hyperintensities in hippocampus on DWI and T2 weighted MR images are found in some patients. Although TGA is considered abenign disorder, the TGA mimics can be more worrying.
Case Report: We report a case of a 71-year-old woman, who was admitted to us because of a sudden-onset loss of memory and disorientation in time. She asked repeatedly same questions and had an anterograde amnesia. We saw her about 3 days later, were she still presented with anterograde amnesia and was disoriented in time. Further clinical neurological examination was unremarkable. Neuropsychological testing revealed an impaired episodic memory, reduced cognitive flexibility and slow executive processing. Laboratory results were normal apart an elevated cholesterol. Echokardiography and Duplexsonography of the extracranial arteries were normal. Computertomography of the Head showed no pathological findings, whereas MRI showed bilateral DWI + lesions in the fornix. To separate an inflammation from an ischemia we repeated the cerebral MRI one week later. It confirmed ischemia, which was suspectd in the first MRI. TGA mimic by fornix infarction has been described earlier as a rare differential diagnosis not as benign as classic TGA. Amnesia due to fornix infarction, as described before, affected other regions like septohippocampal fibres at the same time. Therefore the morphological source of this clinical picture remained unclear. In our case isolated fornix ischemia showed a clinical picture of TGA, suggesting that the fornix and not septohippocampal fibres are responsible for a clinical TGA syndrome.
Conclusion: A transient global amnesia, which lasts longer than expected could be due to isolated fornix infarction.

P03

Analysis of velocity in sleep state space shows hemispheric EEG asymmetries in slow wave sleep of healthy subjects

L.I. Imbach[1], E.W. Werth[1], U.K. Kallweit[1], J.S. Sarnthein[1], R.P. Poryazova[1], C.B. Baumann[1]
[1]University Hospital Zürich, Zürich, Switzerland

Introduction: Human sleep is mainly considered to be a global brain state. Nevertheless, hemispheric asymmetries in sleep EEG recordings have been described by conventional sleep EEG analysis. With this approach, however, dynamic properties of sleep are poorly represented. To examine dynamic aspects of regional EEG variability in healthy human sleep, we implemented state space analysis (a novel frequency-based EEG analysis method) and analyzed regional differences of velocity in state space, as a measure of local behavioral state instability.
Methods: We analyzed sleep recordings (8 channels, whole-night polysomnography) of 7 healthy, right-handed volunteers in a 2-dimensional state space, which was optimized by statistical modeling for best differentiation of behavioral states. Velocity in state space was determined, based on a 5s epoch time frame for each channel. In slow wave sleep, the spatial distribution of velocity was further examined by comparison of interhemispheric and fronto-occipital derivations, respectively.

Results: Interhemispheric comparison of absolute velocity showed a fluctuating pattern between left and right sided electrodes in slow wave sleep, with a slight, but significant overall preference for one side in each individual in frontal derivations (3 left, 4 right hemispheric predominance). On the other hand, analysis of speed ratios in a fronto-occipital axis (F3-O1), showed a uniform speed gradient with significantly higher velocities in occipital, as compared to frontal electrodes in all recordings.
Conclusions: The conserved topography of the 2-dimensional state space in all derivations allows us to determine and compare regional velocity measures in sleep state space. The observed fronto-occipital velocity gradient for all individuals indicates significantly higher state instability for occipital derivations, as compared to frontal electrodes. On the other hand, interhemispheric comparison of velocity measures in frontal electrodes show a fluctuating pattern between the left and right hemisphere, which could be interpreted as a continuous rhythm of alternating hemispheric dominance.

P04

Assessment of post-stroke fatigue: The Fatigue Scale for Motor and Cognitive Functions (FSMC)

M.H. Hubacher[1], P.C. Calabrese[2], C.B. Bassetti[3], A.C. Carota[4], I.K.P. Penner[5]
[1]Cognitive Psychology, Basel, Switzerland, [2]Neuropsychology and Behavioural Neurology, Lugano, Switzerland, [3]Neurology, Lugano, Switzerland, [4]Neurology, Lausanne, Switzerland, [5]Cognitive Psychology and Neurology, Basel, Switzerland

Introduction: Post-stroke fatigue (PSF) is an important but still controversial issue. Today there is only few knowledge on the nature of PSF and its association with depression and cognitive deficits. PSF prevalence is estimated at 30–70% and the negative influence on quality of life is well documented. However, studies conducted so far applied fatigue questionnaires with a main focus on the physical component while not accounting for the cognitive aspect. The aim of the present study was to characterize fatigue over the acute phase of stroke by a newly developed fatigue instrument (FSMC: Fatigue Scale for Motor and Cognitive Functions) which considers both physical as well as cognitive fatigue and to relate fatigue findings to measures of depression and cognition.
Methods: Eight rehabilitation centres in Switzerland agreed to participate in the study. Thirty-one stroke patients (F/M = 6/25; age range = 35–76 y; ischemic/haemorrhagic stroke = 28/3) were recruited by their treating physician. The neuropsychological examination was on average performed 50.65 days after the stroke event (SD = 31.57). Fatigue was assessed by two already existing scales (Fatigue Severity Scale (FSS); Modified Fatigue Impact Scale (MFIS)) and by the FSMC, depression by the Beck Depression Inventory Fast Screen (BDI-FS) and cognitive performance by the Brief Repeatable Battery of Neuropsychological Tests (BRB-N). The Nine-Hole-Peg Test (9HPT) and the 25-foot walk test provided quantitative functional data of finger dexterity and gait.
Results: Depending on the different fatigue scales, prevalence ranged between 16.1% and 58.1%. Depression correlated significantly with all fatigue instruments. Among the applied fatigue scales, a relevant relationship between lesion localisation and fatigue severity could only be found for the FSMC. Patients with cortical lesions scored higher on the cognitive subscale of the FSMC, while patients with subcortical lesions scored higher on the physical subscale. For cognition and upper and lower extremity functions again the best differentiation was found for the two subscales of the FSMC.
Conclusions: The present study aimed to assess cognitive and motor dimensions of PSF by applying a new fatigue instrument and by relating it to depression and cognitive performance. A comparison between FSMC and two commonly applied fatigue scales revealed a superior sensitivity for prevalence rates, lesion localisation, as well as cognitive and physical functioning.

P05

Beneficial Outcome of Natalizumab-associated Progressive Multifocal Leukoencephalopathy (PML) and Herpes Simplex Virus Type 2 (HSV-2) Meningoencephalitis in a Multiple Sclerosis (MS) Patient

I.J. Jelcic[1], N.B. Braun[1], HF Fischer[1], B.S. Schuknecht[2], M.W. Weller[1], M.L. Linnebank[1]
[1]Department of Neurology, University Hospital Zurich, Zurich, Switzerland, [2]Diagnostic and Vascular Neuroradiology, Medizinisch Radiologisches Institut Zürich, Zurich, Switzerland

Introduction: Natalizumab treatment has been established for therapy escalation in relapsing-remitting MS (RRMS). PML and PML-associated immune reconstitution inflammatory syndrome (PML-IRIS) are relatively rare, but severe, and in a substantial number of cases even fatal complications of natalizumab therapy. Here, we describe the clinical course and therapeutic regimen in a patient with RRMS, who developed a HSV-2 meningoencephalitis and prolonged PML-IRIS in the context of natalizumab therapy.
Methods: Case report.
Results: A 40-year-old, male RRMS patient experienced fever and meningism due to HSV-2 meningoencephalitis after two years of relapse- and progression-free natalizumab treatment. Magnetic resonance imaging (MRI) showed a new T2-hyperintense lesion in the left occipital lobe. The symptoms were treated effectively with valaciclovir. Two months later he complained of increased light sensitivity and slightly distorted vision in the right lower visual field. JC virus (JCV) DNA was detected in the CSF. MRI showed progression of the occipital lesion, consistent with the diagnosis of PML. Plasma exchange for natalizumab removal was performed and mefloquine therapy was installed. Two months later he developed modest fever, flu-like symptoms and an acute loss of vision in the right visual field. MRI showed contrast enhancement of the PML lesion. Hence, PML-IRIS was diagnosed. The symptoms remitted after high-dose methylprednisolone (MP) treatment. The PML-IRIS relapsed 2 and 5 months, each time after discontinuation of MP, but vanished after reinstallation of MP. Low-dose MP, mefloquine and valaciclovir were continued for nearly 11 months. Additionally, glatiramer acetate treatment was started for prophylaxis of MS relapses six months after PML-IRIS onset. Two months after cessation of MP treatment, PML-IRIS has not reoccurred and PML has not progressed. Magnetic resonance spectroscopy (MRS) showed gliosis of PML lesions. His disability status remained stable in comparison to PML onset.
Conclusions: Early and aggressive treatment of PML-IRIS may result in beneficial outcome. The combination of clinical symptoms and laboratory, MRI as well as MRS findings may help to titrate long-term MP treatment for prevention of PML-IRIS reoccurrence. The role of concomitant brain infections in the pathogenesis of PML remains unclear. We strongly recommend to look also for other brain infections than PML, if new MS atypical lesions occur during natalizumab treatment.

P06

Cognition and Brain Atrophy in Multiple Sclerosis (COBAMS) – An Ultrasound based Approach

M. Müller[1], J. Voss[1], P. Wicki[1], P. Stellmes[1]
[1]Luzerner Kantonsspital, Luzern, Switzerland

Introduction: In patients with multiple sclerosis (MS) cognitive decline corresponds to brain atrophy as assessed by magnetic resonance imaging (MRI). Compared to MRI brain atrophy can be assessed similarly with transcranial ultrasound (TCS). In COBAMS, we address the aim whether TCS can reliably recognize brain atrophy over a 3 years term, and if so, whether the observed atrophy correspond to clinical changes (disease duration, EDSS, MSFC, Brief Repeatable Battery, BDI, FMSC). In this, we report our baseline methodical TCS results and a first comparison to MS patients.
Methods: The width of the 3. ventricle (3V) and of the lateral horns of the side ventricle (LHSV) correspond to brain atrophy with atrophy the more advanced the wider the width. In 38 healthy persons (male 13, female 25; mean age, 35 years, age range 22–55 years) the width of the 3V and of the LHSD were measured in the axial insonation plane in which the hyperechogenic pineal gland was visible and the 3V walls were parallel. Part of the study was an interobserver evaluation in 16 of the 38 controls. For a first estimation of its usefulness 8 MS patients (1 male, 7 female; age range, 23–51 years; EDSS range 1–3.5; disease duration from first diagnosis 1–31 years) were investigated.

Results: Between the observers correlation coefficient were high in the assessment of the width of 3V (r = 0.96) and LHSV (r = 0.82). Bland and Altmann plots demonstrated no outliners indicating good agreement. In the controls, the mean (± SD) width of the 3V was 3.3 (±0.77) mm, that of the LHSV 17.5 (±1.9) mm; for both, there was no age dependency. In the MS patients only the 3V (4.17 + 2.1 mm) correlated with increasing EDSS (r = 0.67), duration of disease (r = 0.73).
Conclusion: Our findings are well in agreement with earlier investigations [1, 2]. Assessing especially the width of the 3V as an index of brain atrophy seems an reliable, stable and, hence, a promising tool for long term evaluation of MS patients.
1 Wollenweber FA, et al. Width of the third ventricle assessed by transcranial sonography can monitor brain atrophy in a time- and cost-effective manner – Results from a longitudinal study on 500 subjects. Psychiatry Res. 2011 Jan 31. [Epub ahead of print].
2 Berg D, et al. The correlation between ventricular diameter measured by transcranial sonography and clinical disability and cognitive dysfunction in patients with multiple sclerosis.
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P07

Diagnosis of subcortical vascular dementia: Is history of stroke a necessary requirement?

Antje Bischof, Stephan Ulmer, Alphonse Probst, Ludwig Kappos, Andreas U. Monsch, Marc Sollberger

Objective: To characterise patients diagnosed with subcortical vascular dementia using clinical, neuroimaging, and CSF measures, thereby testing and comparing the current diagnostic criteria of subcortical vascular dementia.
Background: Vascular dementia is thought to be the most common cause of dementia after Alzheimer's disease (AD) in older individuals. In contrast to AD, reliable and easily applicable diagnostic criteria for VaD are still controversially discussed. The commonly used NINDS-AIREN criteria as well as the criteria proposed by Erkinjuntti require evidence of a cognitive syndrome related to relevant cerebrovascular disease on clinical and radiological grounds. Herein, the history of stroke is an important criterion to demonstrate the temporal relationship between the onset of dementia and cerebrovascular disease.
Methods: We applied the NINDS-AIREN criteria and criteria proposed by Erkinjuntti for subcortical vascular dementia. In addition, to strengthen the diagnostic accuracy, only patients showing no pattern of CSF markers (i. e. t-tau, p-tau, and amyloid beta$_{1\text{-}42}$) suggestive for Alzheimer's disease kept the diagnosis of subcortical vascular dementia.
Results: 6 patients fulfilled the neuroimaging and clinical criteria of either NINDS-AIREN or Erkinjuntti and showed no pattern of CSF markers suggestive for Alzheimer's disease. Of these 6 patients, only 1 patient fulfilled the criteria of having either a history of stroke or focal neurological signs such as a hemiparesis or a Babinski reflex. The other 5 patients' histories were suggestive for a neurodegenerative disease.
Conclusions: Our observations challenge the importance of a positive history of stroke or neurological signs suggestive of a previous stroke in the diagnosis of subcortical vascular dementia. Refined neuroimaging criteria together with a neuropsychological profile typical for subcortical brain disease and CSF markers for neurodegenerative diseases should be applied and assessed for their validity in the diagnosis of subcortical vascular dementia in larger prospective studies.

P08

Dysferlinopathy in Switzerland: Clinical features and new genotypes

J.A. Petersen[1], M. Dunnand[1], D. Fischer[1], W. Kress[1], T. Kuntzer[1], H.H. Jung[1]
[1]University Hospital Zurich, Zurich, Switzerland, [2]Lausanne University Hospital (CHUV), Lausanne, Switzerland, [3]University Hospital Basel, Basel, Switzerland, [4]of Human Genetics, University of Wuerzburg, Wuerzburg, Germany, [5]Lausanne University Hospital (CHUV), Lausanne, Switzerland, [6]University Hospital Zurich, Zurich, Switzerland

Introduction: Dysferlin, the protein product of the dysferlin gene (DYSF), is absent or drastically reduced in patients with the following autosomal recessive muscle disorders: limb girdle muscular dystrophy type 2B (LGMD2B), Miyoshi myopathy (MM) and distal anterior compartment myopathy. Ethnic clusters have been described in Jews from Lybia and the Caucasus region as well as in Italian and Spanish populations.
Methods: We retrospectively assessed clinical data from patients followed up in 3 Swiss Neuromuscular Centers (Basel, Lausanne and Zurich) who had the following inclusion criteria: Swiss origin, progressive weakness in distal or proximal muscles, with absent or reduced dysferlin in immunohistochemistry or on western blot and mutations in the DYSF gene. Data on family pedigrees, clinical features, age and symptoms at onset, disease duration, muscle strength according to the Medical Research Council (MRC) and CK levels as well as muscle biopsy and mutational analyses results were collected.
Results: Eight patients were found to include our criteria: 6 (four women) presented with LGMD2B phenotype and 2 (one woman) presented with a proximo-distal phenotype, but phenotypes varied within the same family. Disease onset was in late adolescence or early adulthood (19.3 ± 4.6 years). CK levels were markedly elevated (10470 ± 9340 IU/L, range 2200–23000). In six patients, two disease-causing mutations were identified. In two patients, one mutation was detected without identification of the second deleterious allele. Four patients out of 2 non-related families originating from Central Switzerland carried the identical mutation c. 3031+2T>C, 3 of them being homozygous. Four patients from 3 different families carried the mutation c.1064_1065delAA heterozygous. One novel mutation was identified (c. 2869C>T).
Conclusion: Our study confirms the heterogeneous phenotype of the DYSF mutations and the usual huge elevation of CK levels. Furthermore, a possible founder effect was discovered for at least two mutations (c. 3031+2 T>C, c.1064_1065delAA). These findings are important for genetic counselling and could enable a molecular diagnosis of LGMD2B in Swiss patients.

P09

Expert-based algorithm for the screening of cognitive deficits in multiple sclerosis patients

P. Calabrese[1], J.M. Annoni[1], A. Baumann[1], T. Haefeli[1], C.P. Kamm[1], M. Koch[1], M. Yildiz[1], R. Müri[1]
[1]Neurocentro della Svizzera Italiana, Lugano, Switzerland, [2]Université de Fribourg, Fribourg, Switzerland, [3]Private practice, Langenthal, Switzerland, [4]Private practice, Bern, Switzerland, [5]University of Berne, Bern, Switzerland, [6]Private practice, Luzern, Switzerland, [7]Kantonsspital, St. Gallen, Switzerland, [8]University of Berne, Bern, Switzerland

Cognitive dysfunctions are knowon to affect about 50% of MS-patients. They may occur even in early phases of disease and have often a great impact on daily life. They tend to increase slowly over time thus forcing the affected patients to reduce e.g. their working-time. There is a strong need to identify patients with cognitive deficits early since this may have implications for drug treatment and/or neuropsychological training.
We present an expert-based proposal of an algorithm aimed to detect cognitive disturbances in individuals with MS as early as possible. It was concluded by consensus that the diagnostic approach should consider practical issues, such as brevity of the used screening tools, single-domain vs. composite tests, etc. to make them largely applicable but nontheless meeting methodological standards. By bearing these prerequisites in mind the workgroup came up to propose a two-step approach, considering a cognitive screening with a short standardized test if a) MS-patients complain subjectively about cognitive failures or b) clinical routine examination raises suspicion on cognitive performance. In a second step the cognitive performance may be further explored in detail by comprehensive psychometric batteries when cognitive dysfunction is evidenced by screening. The proposed algorithm, together with some potential screening tools which were selected on the aforementioned basis is presented in detail.

P10

Facial nerve palsy and anti-Ku autoantibodies

R. Sutter[1], B. Mengiardi[2], D. Benz[3], I. Heijnen[4], L. Kappos[1], D.T. Winkler[1]
[1]Department of Neurology, University Hospital Basel, Basel, Switzerland, [2]IMAMED, Radiologie Nordwest, Basel, Switzerland, [3]Department of Rheumatology, University Hospital Basel, Basel, Switzerland, [4]Division of Medical Immunology, Laboratory Medicine, University Hospital Basel, Basel, Switzerland

Introduction: Autoantibodies against nuclear protein Ku are rare and thought to be mostly related to connective tissue diseases and overlap syndromes. A first report on three patients has recently implied a potential association of facial nerve palsy and anti-Ku antibodies.

Methods: To report a case of a 40-years-old man with recurrent facial nerve palsy and high titers of anti-Ku autoantibodies without overt connective tissue disease.
Results: Robust contrast enhancement of the right facial nerve was seen by magnetic resonance imaging during the patient's second episode of peripheral facial nerve palsy (fig. 1A). Indirect immunofluorescence on human epidermoid type 2 (HEp-2) cells showed prominent patchy homogeneous nucleoplasmic and nucleolar staining (fig. 1B). Further analysis by line immunoassay confirmed the presence of anti-Ku antibodies (fig. 1B insert).
Conclusions: Anti-Ku antibodies might play a role in a subset of patients with facial nerve palsy. Facial neuropathy may even be a leading neurological symptom in patients with high titers of anti-Ku autoantibodies. Further studies are necessary to determine whether the presence of anti-Ku antibodies in patients with peripheral facial nerve palsies is just a rare coincidence or pathogenic.
Key words: facial nerve palsy, autoimmune antibodies, Anti-Ku antibodies, cranial nerve, neuropathy

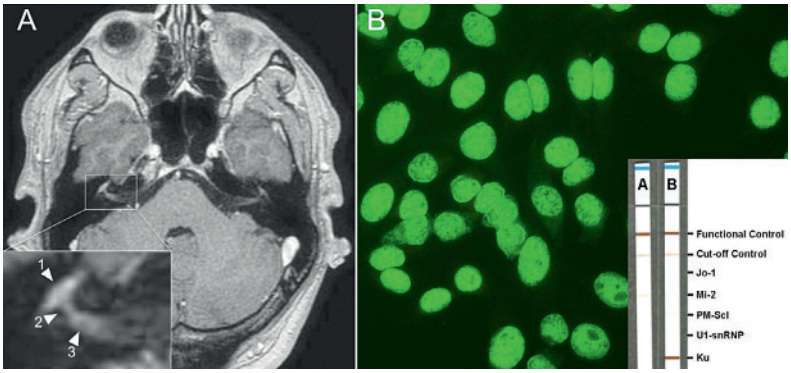

Figure 1 A and B
A) Contrast-enhanced axial T1-weighted MR image (3D-Turbo-Field-Echo) of the intratemporal facial nerve: MR imaging shows strong enhancement of the right facial nerve in the distal intrameatal segment (1), the labyrinthine segment (2) and an intensely enhancing and thickened geniculate ganglion region (3).

B) Anti-Ku antibodies immunofluorescence: Anti-Ku antibodies revealed by indirect immunofluorescence on HEp-2 substrate cells, demonstrating patchy/homogeneous nucleoplasmic and nucleolar staining (large image). Specificity for Ku was confirmed by line-blot immunoassay (insert). Blots were incubated with serum from a healthy control individual (C) and the patient (P).

P11

Functional mapping of cortical language areas with functional MRI in individual subjects

F. Grouiller[1], M. Genetti[1], K. Schaller[2], L. Spinelli[2], M. Seeck[2], C.M. Michel[1]
[1]Functional Brain Mapping Laboratory, UNIGE, Geneva, Switzerland, [2]Neurology and Neurosurgery Department, HUG, Geneva, Switzerland

In the last two decades, several tasks for fMRI-based non-invasive mapping of brain language areas for presurgical evaluation have been proposed. However, while hemispheric lateralization of language has become reliable and concordant with invasive procedures in clinical populations, reliable individual localization of crucial language areas within the dominant hemisphere still remains challenging. Here, we present the data of 22 right-handed, healthy subjects who performed an auditory semantic decision task including congruent, incongruent and non-sense short sentences (Astesano et al., 2004) in an fMRI event-related design. The group analysis revealed activations in the left superior temporal and left inferior frontal gyri corresponding to Wernicke and Broca's areas, respectively. Moreover, these areas were also activated in most of the individual subjects. We conclude that this semantic decision task is a promising paradigm for robust localization of crucial language are as in individual subjects. The short duration and the simplicity make it particularly suitable for patients with cognitive impairments.
Reference: Astesano C, Besson M, Alter K. Cogn Brain Res. 2004.

P12

Involvement of pain and reward systems in medication-overuse headache

Franz Riederer, MD[1], Marvin Marti, MS[1], Roger Luechinger, PhD[2], Rupert Lanzenberger, MD[3], Jan von Meyenburg, MD[4], Andreas R. Gantenbein, MD[1], Spyridon Kollias, MD[4], Charly Gaul[5], Peter S. Sándor MD[1,6]
[1]Department of Neurology, Headache Unit, University Hospital Zurich, Switzerland, [2] Institute for Biomedical Engineering, University and ETH Zurich, Switzerland, [3]Department of Psychiatry and Psychotherapy, Medical University Vienna, Austria, [4]Institute of Neuroradiology, University Hospital Zurich, Switzerland, [5]Department of Neurology, Headache Clinic, University Essen, [6]RehaClinic, Bad Zurzach/Baden, Switzerland

Medication-overuse headache (MOH), a significant medical problem, most frequently evolves from episodic migraine, the mechanisms remaining unclear. Patients with MOH frequently fulfil diagnostic criteria of substance dependence and are comorbid with other substance related disorders. Thus neurobiological similarities between MOH and substance dependence have been suggested. Using voxel-based morphometry, we searched for structural abnormalities related to pain and reward. High-resolution structural MRIs were compared between 29 patients with both, MOH and migraine, according to IHS diagnostic criteria and healthy age- and sex-matched controls. Comorbid anxiety and depression were assessed with the HADS. In patients, we observed a significant increase of grey matter volume (GMV) bilaterally in the thalamus, the ventral striatum, the hippocampus, the middle cingulum, the inferior cerebellum, and the periaqueductal grey matter of the midbrain. We found a significant GMV decrease in prefrontal regions, the left insula, and the left temporal pole. Patients and controls had distinct patterns of grey matter covariance in pain processing and modulatory regions, suggesting altered functional connectivity. In patients with MOH, we found structural changes in pain processing regions including the brainstem. Furthermore, we found grey matter changes in fronto-striatal systems. This is compatible with the concept of dependence as a disease maintaining factor in patients with MOH.
Key words: migraine, medication-overuse headache, voxel-based morphometry, substance dependence

P13

Natalizumab is effective in multiple sclerosis: three-year real life data

U. Kallweit[1], I. Jelcic[1], N. Braun[1], H. Fischer[1], B. Zörner[1], B. Schreiner[1], A.A. Sokolov[1], M. Linnebank[1]
[1]University Hospital Zurich, Zurich, Switzerland

Introduction: Natalizumab therapy of relapsing-remitting multiple sclerosis has been shown to be effective in a reduction of the clinical relapse rate and probability of disability progression. However, real life longitudinal data, especially on patients with a high EDSS at baseline, are rare.
Methods: A retrospective, observational, single-center study was carried out. We analyzed data from 64 (47 females) consecutive MS patients, according McDonald criteria. Disease severity was measured using EDSS. Mean age was 41 years (±10 SD, range 22–68 years). In 16/64 (25%) patients, natalizumab was used as first line treatment.
Results: After one year of treatment (n = 64), EDSS decreased by 0.47 points (p = 0.047), the annualized relapse rate (ARR) by 82% (p <0.001). After two years (n = 41), EDSS was still reduced by 0.28 (not significant) and ARR by 69% (p <0.001). After three years (n = 23), EDSS was reduced by 0.26 (not significant), ARR by 77% (p <0.001). EDSS and ARR reduction did not depend on baseline ARR (1–2 vs. >2) or EDSS (<4 vs. 4).
Conclusion: These real life data reinforce that natalizumab is effective over years, reduces ARR and stabilizes EDSS independently from baseline data.

P14

Non-invasive drug-monitoring: Determination of valproic acid concentration in breath via extractive electrospray ionization mass spectrometry (EESI-MS)

A. Disko[1], G. Gamez[2], L. Zhu[2], H. Chen[3], V. Azov[4], K. Chingin[2], R. Zenobi[2], G. Krämer[1]
[1]Schweizerisches Epilepsie-Zentrum, Zürich, Switzerland, [2]Department of Chemistry and Applied Biosciences, ETH, Zürich, Switzerland, [3]Department of Applied Chemistry, East China Institute of Technology, Fuzhou, China, [4]University of Bremen, Bremen, Germany

Introduction: Drug monitoring of antiepileptic drug serum concentration is common practice in epileptol-ogy. However some patients such as children or mentally handicapped people do not toler-ate regular blood withdrawals well. Since extractive electrospray ionization mass spectrome-try has already been successful in detecting drugs and their metabolites in breath in real time, we tested if this is also possible for valproic acid and its metabolites.
Methods: In six epilepsy patients receiving valproic acid we repeatedly measured valproic acid metabo-lites in breath via EESI-MS. Subsequently, as a control, we took blood samples to measure total and free valproic acid serum concentration.
Results: We managed to detect hydroxy-valproic acid-lactone in breath as a novel biomarker for drug monitoring of valproic acid. We showed a linear and sufficient correlation (R2 = 0.89) between the correlation of metabolites in breath and free valproic acid serum concentration.
Conclusion: Our study showed that analysis of breath can be used for drug monitoring of valproic acid. The method has many advantages: it is non-invasive, pain free and can give results in real time.

P15

Postpartal Marchiafava-Bignami disease – a case report

Philip Siebel[1], Ansgar Felbecker[1], Julia Walch[1], Johannes Weber[2], Barbara Tettenborn[1]
[1]Department of Neurology, Cantonal Hospital St. Gallen, Switzerland, [2]Department of Radiology, Cantonal Hospital St. Gallen, Switzerland

Introduction: Marchiafava-Bignami disease (MBD) is a rare neuropsychiatric disease of malnourished alcoholics, pathologically characterized by callosal lesions of demyelinization and necrosis. The clinical course of the patients is variable and may be acute, subacute or chronic and is typically marked by cognitive dysfunction, spasticitiy, gait instability and dysarthria as well as disconnection syndromes. Whereas in the past diagnosis was possible only postmortem, nowadays different stages of the disease have been investigated by MRI revealing high intensitiy areas in fluid-attenuated inversion recovery (FLAIR), T2 and diffusion-weighted MRI imaging (DWI) and decreased signal in T1. Although numerous etiological hypotheses have been proposed the pathophysiology of MBD remains unclear. Few cases of MBD in non-alcoholics are described supporting the hypothesis that ethanol is not the sole causative agent.
Case Report: We report a 28 year old woman, who gave birth to a healthy boy two weeks before admission. She reported about intermittent spasticity in her left limbs. There was no alcohol or drug abuse in her personal history, pregnancy as well as childbirth was uncomplicated. Physical and neurological examinations were normal. Laboratory tests showed no abnormalities, especially normal sodium values at admission and in the past. Vitamin status (Vitamin B1, B6, Vitamin D) and cerebrospinal fluid were normal. Due to substitution folic acid, Vitamin B12 and copper were slightly elevated. MRI showed a typical lesion in the splenium of the corpus callosum as described above. On the basis of history, clinical presentation and MRI findings Marchiafava-Bignami disease was diagnosed and administration of thiamine and other vitamins of the B-complex was started. A second MRI ten days later showed symmetrical progression of the lesion in the splenium. Clinical findings had not changed and only neuropsychological examination revealed slight cognitive defects. We started intravenous high dose steroids for 5 days tapering the dosis p.o. over a period of 6 days. The long term follow-up has to be evaluated.
Conclusion: Marchiafava-Bignami disease may appear in non alcoholics without evidence of malnutrition and may be associated with postpartal changes of blood homeostasis.

P16

Reduced Synaptic Strength and Lower Neuronal Synchronization after Acute Hemispheric Stroke

R.P. Poryazova[1], R.H. Huber[2], R.K. Khatami[3], E.W. Werth[1], P.B. Brugger[1], C.L.B. Bassetti[4]
[1]Department of Neurology, University Hospital Zurich, Zurich, Switzerland, [2]University Children's Hospital Zurich, Zurich, Switzerland, [3]Sleep centre, Clinic Barmelweid, Barmelweid, Switzerland, [4]Neurocenter of Southern Switzerland (EOC), Lugano, Switzerland

Introduction: Functional recovery after stroke depends on the adaptive plasticity of the human brain. There is strong evidence that sleep contributes essentially to brain plasticity and learning. Slow waves (SW) are the main feature of non-rapid eye movements sleep (NREM). They are cortically generated and reflect the synchronization of neuronal activity. It has been suggested that the slope of SW is a marker of synaptic strength. We aimed at investigating SW activity in patients with acute hemispheric cortical stroke and comparing it to healthy controls.
Methods: Eight patients with hemispheric cortical stroke (six left and two right) and eight age and gender matched controls underwent high-density EEG (hd-EEG) examination with 128 electrodes during sleep. The recordings in all patients were performed within seven days after stroke. The slope of SW was calculated as the amplitude of the most negative peak divided by the time until the next zero crossing.
Results: In patients with hemispheric stroke, statistical nonparametric mapping showed a significantly reduced slope of SW over the affected in comparison to the non-affected hemisphere in a paramedian frontocentral region. Additionally, the slope of slow waves was reduced over a similar region in patients in comparison to healthy controls in a t-test.
Conclusion: The reduced slope of SW over the affected hemisphere after hemispheric cortical stroke in comparison to non-affected hemisphere and to healthy controls suggests decreased synaptic strength and lower neuronal synchronization over a frontocentral region, roughly corresponding to the location of the ischemic damage.
Support: The study is supported by the Zurich Center for Integrative Human Physiology (ZIHP).

P17

Signs of autoimmune demyelination in the CNS after octreotide treatment in a patient with metastatic meningioma

S.R. Schreglmann[1], I. Jelcic[1], M. Linnebank[1], M. Weller[1]
[1]Department of Neurology, University Hospital Zurich, Zurich, Switzerland

Introduction: Octreotide is a long-acting somatostatin analog which is approved for the treatment of various gastrointestinal syndromes of hormone hypersecretion. Since somatostatin receptors are present on most meningiomas, octreotide has been suggested as a salvage treatment for patients with recurrent meningioma with confirmed presence of somatostatin receptors by octreotide SPECT or PET studies. We report the history of a patient with metastatic somatostatin receptor-positive meningioma who developed a demyelinating autoimmune reaction in the CNS after octreotide therapy.
Methods: Case report.
Results: A 52-year old, female polyallergic (latex, NSAR, hayfever, contrast agent) patient with multiple somatostatin receptor-positive intracranial meningiomas and histologically confirmed pulmonary metastases was subjected to subcutaneous octreotide treatment. She developed new intermittent bilateral paraesthesia in the L3-L5 dermatomes at 21 days after the first exposure to octreotide which was given at 0.1 mg 3x/d s.c.for 25 days. MRI scans revealed three periventricular and subcortical T2-hyperintense lesions without contrast enhancement not noticed previously and two spinal lesions (no previous spinal scan). Repeated lumbar punctures revealed CSF changes in accordance with chronic inflammation at base line [and 6 months later]: normal cell count (4 [3]/µl), elevated IgG index (1.6 [1.06]; norm: <0.7), positive CSF oligoclonal bands (OCBs; serum negative), elevated CSF/serum index for HSV IgG (5.07 [5.98]), [measles IgG 6.62] and CMV IgG (4.06 [4.16]; norm: 1.9), negative HCV and CMV PCR and a partly positive measles/rubella/zoster (MRZ) reaction (elevated CSF anti-measles and rubella IgG titres). Anti-CNS antibodies and a vasculitis screening were unremarkable. An ischaemic, infectious or paraneoplastic cause of the spinal and cerebral lesions was thus unlikely.

Conclusion: We report symptoms and signs of focal demyelination after octreotide treatment in a patient with metastatic meningioma. The onset of clinical symptoms as well as MRI and CSF changes were suggestive of an immune process triggered by somatostatin administration. Polyspecific intrathecal antibody production, elevated IgG index and positive OCBs suggest a chronic autoimmune reaction which may be a rare, but relevant risk of octreotide treatment in polyallergic patients.

P18

TIA like episodes in acute small cortical subarachnoidal haemorrhage probably due to amyloid angiopathy

S. Reinle[1], M. Tröger[1], L. Remonda[2], L. Boxheimer[2], U.W. Buettner[1], H. Hungerbühler[1]
Department of Neurology[1] and Department of Neuroradiology[2], Cantonal Hospital Aarau

Introduction: Recently there has been described a syndrome with TIA like episodes in acute small cortical subarachnoidal haemorrhage (SAH) , mostly due to cerebral amyloid angiopathy. The genesis of the transient sensomotor hemispheric symptoms is unclear. Pathophysiologically a spreading depression should be taken in account.
Methods: Case series.
Results: We give report on four patients, one women and three men from 77 to 81 years old, with recurrent transient sensomotor hemispheric symptoms in small cortical SAH's. There was no sign of cerebral ischaemia or epilepsy. 3 of 4 patients had signs of old cortical SAH's in other location and cortical/subcortical microbleeds in the blood sensitive images of MRI. 1 patient had a documented history of 4 small cortical SAH's during the last 5 years. He developed an intracerebral haematoma a few days after the last episode, and the other patients were symtomfree after a few weeks without antiepileptic drugs.
Conclusions: We describe four additional patients with TIA-like episodes due to acute small cortical SAH's. In most patients you can see signs of old small SAH's and cortical/ subcortical microbleeds in the MRI. The cause of the TIA-episodes is unclear, a spreading depression can be discussed. The prognosis of the quite uniform syndrome seems to be good. Since amyloid angiopathy is the cause in most cases, the patients are at risk for intracerebral haematoma.

P19

Acute ischemic stroke in children and young adults

S. Bigi[1], U. Fischer[2], E. Wehrli[1], H.P. Mattle[2], E. Boltshauser[4], S. Bürki[1], P.Y. Jeannet[5], J. Fluss[6], P. Weber[7], K. Nedeltchev[2], M. El-Koussy[3], M. Steinlin[1], M. Arnold[2]
[1]University Children's Hospital, Department of Pediatric Neuroloy, Berne, Switzerland, [2]University Hospital, Department of Neurology, Berne, Switzerland, [3]University Hospital, Department of Neuroradiology, Berne, Switzerland, [4]University Children`s Hospital, Department of Pediatric Neurology, Zurich, Switzerland, [5]University Children's Hospital, Department of Pediatric Neurology, Lausanne, Switzerland, [6]University Children's Hospital, Department of Pediatric Neurology, Geneva, Switzerland, [7]University Children's Hospital, Department of Pediatric Neurology, Basel, Switzerland

Introduction: The aim of this study was to compare children and young adults with acute ischemic stroke (AIS) in two large registries.
Methods: We compared clinical characteristics, stroke etiology, work-up and outcome (mRS at 3–6 months) in children (1 month–16 years) and young adults (16.1–45 years) with AIS. Data of children were collected prospectively in the nationwide Swiss NeuroPediatric Stroke Registry, young adults in the Bernese stroke database. Outcome (mRS) and stroke severity (PedNIHSS) in children were assigned retrospectively.
Results: From 01/2000 to 12/2008 128 children and 199 young adults suffered an AIS. Children were more likely to be male than young adults (62%/49%, p = 0.023) and had less frequently hypertension (p = 0.001), hypercholesterolemia (p = 0.003) and a family history of stroke (p = 0.048). Stroke severity was similar in children and young adults (median PedNIHSS/NIHSS 5/6; p = 0.102). Stroke etiology (original TOAST classification) was more likely to be „other determined cause" in children than in young adults (51%/29%; p <0.001). Cervicocerebral artery dissections were less frequent in children than in young adults (10%/23%; p = 0.005). Outcome at 3–6 months did not differ between children and young adults (p = 0.907): 59% of children and 60% of young adults had a favorable outcome (mRS 0-1). Mortality was similar among children and young adults (4%/6%; p = 0.436). In multivariate analysis, low PedNIHSS/NIHSS was the most important predictor of favorable outcome (p <0.001).
Conclusions: Even though stroke etiology and risk factors in children and young adults are different, stroke severity and clinical outcome were similar in both groups.

P20

Bridging Therapy in Patients with Acute Stroke and Confirmed Arterial Occlusion/Pseudoocclusion of the Internal Carotid Artery and M1-Segment of Middle Cerebral Artery: intravenous Thrombolysis with Alteplase, Stenting of Internal Carotid Artery, Mechanical Recanalisation, Local and Systemic Application of Tirofiban
A Single-Center Retrospective Analysis

Till Betz[1], Luca Remonda[2], Stephan Wetzel[2], Michael Diepers[2], Guido Schwegler[1], Ulrich W. Buettner[1], Manuela Ernst[1], Hansjörg Hungerbühler[1]
Department of Neurology[1] and Departement of Neuroradiology[2], Cantonal Hospital Aarau

Purpose: Strokes due to acute occlusion of the internal carotid artery (ICA) in combination with occlusion of the middle cerebral artery (MCA) usually respond poorly to systemic thrombolysis and the prognosis often is not favourable. A combined approach with intravenous (iv) thrombolysis and stenting of the occluded ICA and endovascular mechanical removal of thrombotic material seems to be a promising alternative. Few data exist in this field.
Materials and Methods: 2010 we reviewed data of 10 consecutive acute stroke-patients with ICA (probably due to macroatheromatosis) and M1 segment occlusion of the MCA (probably due to arterio-arterial embolisation). Patients with carotid T occlusion were excluded. All patients received a cerebral angiography. The M1 occlusion of 1 patient had fully recanalised after iv. thrombolysis; In patients with good collaterals present no recananalisation of the still occluded ICA was attempted. All other patients with still occluded or near occluded MCA and ICA were treated with combined revascularisation approches. In all patients stenting of the ICA was performed, periprocedural Tirofiban was used locally (bolus) and systemically and thrombus material was removed mechanically by aspiration and different devices (mostly penumbra device). Except of patients with relevant bleeding all received Tirofiban for 24–48 hours. Subsequently it was replaced by a medication with Aspirin and Clopidogrel. Modified Rankin Scale (mRS) scores at 90 days were recorded to assess functional outcome.
Results: 2 women and 7 men were included in the study. Mean patient age was 60 years (52–78); median National Institute of Health Stroke Scale score on admission was 13 (3–24); Successful recanalisation of the ICA with stenting and the M1 part of MCA (Thrombolysis in Myocardial Infarction [TIMI] score II and III) was achieved in all patients (100%). After 3 month 5 patients had mRS 0-2 (56%), 3 mRS 3-4 (33%), 1 died. As complication two large space-occupying bleedings occured, one of the patient with an initial NIHSS Score 21 and a large Media-

Infarction died, the other was operated with a decompressive craniectomy. After 3 months the mRS was 4. During the first 3 months the ICA and MCA remained open with exception of 1 patient, in whom the ICA one day after the intervention was again occluded without clinical deterioration (MCA remained open).
Conclusion: A bridging or combination therapy for patients with acute ICA occlusion/pseudoocclusion and M1 occlusion of MCA due to macroatheromatosis and arterio-arterial embolism with iv thrombolysis, stenting of the ICA, mechanical removal of thrombus material and periprocedural local and systemic application of tirofiban led in most patients to a favourable outcome.

P21

Contrast enhanced ultrasound of carotid plaque neovascularisation: accuracy of visual analysis

A.V. Viaccoz[1], H.M. Muller[1], I.K. Kuzmanovic[1], C.B. Bonvin[1], D.M. Mugnai[2], N.M. Murith[2], K.B. Burkhardt[3], M.B. Bochaton-Piallat[3], R.S. Sztajzel[1]
[1]Neurology, University Hospital Geneva, Geneva, Switzerland, [2]Cardiovascular Surgery, University Hospital Geneva, Geneva, Switzerland, [3]Pathology, University Hospital Geneva, Geneva, Switzerland

Background: To evaluate whether neovascularisation of the carotid plaque may be accurately assessed by visual analysis of contrast enhanced ultrasound imaging and to correlate these findings with a time to peak analysis program and with histopathology.
Methods: Patients with >50% symptomatic or >60% asymptomatic stenoses were included. Ultrasound examination (Antares apparatus, Siemens) included assessment of degree of stenosis and contrast (Sonovue) enhanced imaging using a cadence CPS program. Contrast enhancement was evaluated visually by 4 investigators (grade 0: no, grade 1: intermediate and grade 2: extensive enhancement). Positive agreement (at least 3 unanimous investigators) was correlated to a time to peak analysis (program written in MATLAB). Intensity was expressed as the difference between minimum and maximum level of intensity within the region of interest of the plaque measured at the peak of microbubbles concentration. A histopathological examination (microvessel CD34 staining) was completed whenever endarterectomy was performed.
Results: Thirty-six patients, 18 symptomatic and 18 asymptomatic, were included (mean age 74.5). Interobserver agreement was of 94%. The grade of contrast enhancement assessed visually correlated with the mean delta value: grade 0 (n = 16) with 0.015, grade 1(n = 13) with 0.03 and grade 2 (n = 7) with 0.04 (grade 0 vs 2, p <0.001). In 22 patients, a histopathological examination was carried out. Median value of CD34 + area was larger in patients with grade 2 in comparison with grade 1 or grade 0 (respectively 21.5 vs 12.5 and $11.5x10^{-3}$ mm^2); a statistical difference however was not obtained.
Conclusion: Visual analysis of contrast enhanced ultrasound imaging seems accurate with a high ratio of interobserver agreement and correlated significantly with a time to peak analysis program. A larger number of patients is needed however in order to confirm these results and to demonstrate a relationship with histopathological findings.

P22

D-Dimer Levels in Spontaneous Internal Carotid Artery Dissection

C. Gaechter[1], A. Mendez[2], A.R. Huber[2], M. Diepers[3], D. Muentener[1], H. Hungerbuehler[1]
[1]Department of Neurology, Kantonsspital Aarau, Aarau, Switzerland, [2]Department of Laboratory Medicine, Kantonsspital Aarau, Aarau, Switzerland, [3]Department of Neuroradiology, Kantonsspital Aarau, Aarau, Switzerland

Introduction: It is well-known that d-dimer levels are usually very high in acute aortic dissection. We investigated whether this relationship can also be detected in spontaneous internal carotid artery dissection (sICAD).
Methods: We retrospectively analysed 16 consecutive patients admitted to our Neurology department from 2008 to 2010 with sICAD, diagnosed clinically and by magnetic resonance imaging or computed tomography. D-Dimer testing on admission was done in 11 of these patients. We also collected data on d-dimer levels from 5 patients with spontaneous aortic dissection treated at our clinic.
Results: 3 of 11 sICAD patients had elevated d-dimer levels (range 0.19 mg/l – 2 mg/l), whereas all of the patients with aortic dissection had very high levels (maximum 191 mg/l).
Conclusions: In contrast to aortic dissection, sICAD does not regulary lead to elevated d-dimer levels. This might be due to a smaller surface of the injured vessel and the fact that a significant communication between the true and the false lumen is often absent, which could prevent a relevant activation of the extrinsic pathway of the coagulation cascade.

P23

Early recanalization rate of acute middle cerebral artery occlusion after intravenous thrombolysis

Ernst M, MD (A); Anõn J, MD (B); Remonda L, MD (B); Buettner UW, MD (A); Hungerbühler H, MD (A).
Departments of Neurology (A) and Neuroradiology (B) Kantonsspital Aarau, Aarau

Introduction: We evaluated the early recanalization rate after intravenous (IV)thrombolysis in patients with acute middle cerebral artery (MCA) occlusion.
Methods: All patients with M1-MCA occlusions (defined up to trifurcation) receiving IV recombinant tissue plasminogen activator (rt-PA) in the period 2009–2010 admitted to the department of Neurology (n = 35) were reviewed retrospectively. To analyze there canalization rate (according to Thrombolysis In Myocardial Infarction flow grades [TIMI 2/3] and Mori grading system [MORI 3/4]) after IV rt-PA we selected those patients which received a cerebral angiography (CAG) in the context of a bridging therapy.
Results: 26 patients were scheduled for a CAG (in 3 patients the CAG was cancelled because of a considerable clinical improvement and probably spontaneous recanalization confirmed 24hours later by ultrasound). 9 patients had not been considered for a CAG because of different reasons. The 23 selected subjects receiving a CAG had a median baseline NIH Stroke Scale of 14.3 and the mean age was 68 years. 15 patients had a proximal M1-MCA occlusion (65.2%) and 8 patients had a distal M1-MCA occlusion (34.8%). The mean time to initiation of IV rt-PA was 53.5 minutes. The mean time from beginning IV rt-PA to the first imaging of M1-MCA in CAG was 142.2 minutes (range 53–270 min). 3 patients (13%) had a recanalization after IV rt-PA. Two of them had still a M2-MCA occlusion. In summary 3 patients scheduled for a CAG and 3 patients undergoing a CAG had a early recanalization after IV rt-PA.
Conclusions: A low rate (23.1%) of early recanalization was observed in patients with M1-MCA occlusion after IV rt-PA alone. For most of the patients an intravenous thrombolysis wasn't a sufficient therapy. Other therapeutic options are needed (bridging therapy, local reperfusion therapy alone, more efficient thrombolytic drugs).

P24

Gene expression profiling in the cortex of spontaneously hypertensive rats shows abnormal metabolisms and reduced hypoxic/oxidative stress tolerance capacities

Marie-Françoise Ritz, Caspar Grond-Grinsbach, Stefan Engelter, Philippe Lyrer
Neurology Clinic, University of Basel, Basel

Objectives: Cerebral small vessel disease (SVD) is an important cause of stroke, cognitive decline and vascular dementia (VaD). The molecular mechanisms involved in the development and progression of SVD are not yet completely understood. As hypertension is one of the major risk factors for developing the disease, Spontaneously Hypertensive Rats (SHR) are considered a good experimental model for the study of neuropathological changes appearing in the brain, as they share several similarities with essential hypertension in human. We previously described cellular differences in the brain of this rat strain such as imbalance between the number of blood microvessels and astrocytes at the level of the neurovascular unit in young, pre-hypertensive SHR, leading to signs of neuronal hypoxia in the brain of older animals [1].
Methods: To identify genes and pathways involved in the development of small vessel disease, we performed comparison of gene expression in the cortex of 2 and 9-month-old SHR with age-matched normotensive Wistar Kyoto (WKY) rats using oligonucleotide-based microarray technology. Quantitative qPCR was used to confirm the differences in expression for selected genes.

Results: This analysis revealed significant downregulations in the expression of genes involved in the energy and lipid metabolisms, in mitochondrial function, in oxidative stress, and in hypoxia preconditioning in 2 as well as 9-month old SHR. Moreover, genes involved in endothelial proliferation were overexpressed in both SHR groups, confirming our histological observations.
Conclusions: These results indicate that the brains of SHR suffer from mitochondrial dysfunction, energy failure and increased oxidative stress. These observations suggest that SHR may be unable to tolerate hypoxia-like conditions, and may be more vulnerable than WKY to high-energy consumption conditions. This genetic analysis gives new insights about pathways accounting for the development of deep ischemic infarcts observed in small vessel disease which will ultimately lead to the establishment of preventive therapeutic options for patients at risk.
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P25

Intra-arterial thrombolysis beyond the 6 hours time window, in wake-up and unclear-onset stroke

S. Jung[1], U. Fischer[1], M.L. Mono[1], J. Gralla[2], A. Galimanis[1], O. Findling[1], M. El-Koussy[2], G.M. DeMarchis[1], A. Weck[1], C. Brekenfeld[2], G. Schroth[2], H.P. Mattle[1], M. Arnold[1]
[1]Neurology, Bern, Switzerland, [2]Neuroradiology, Bern, Switzerland

Background: Intra-arterial thrombolysis (IAT) is an efficacious therapy in acute ischemic stroke when administrated within 6 hours of symptom onset (SWA <6 h). Whether IAT should also be performed in patients presenting after 6 hours (SWA >6 h), in those who woke up with their stroke (WUS) or with unclear-onset of stroke (UOS) remains unknown. The aim of this single-center study was to evaluate the efficacy and safety of IAT in these treatment groups.
Methods: 682 consecutive patients with ischemic stroke treated with IAT were included in the study. Evaluation criteria were excellent clinical outcome (modified Rankin scale 0–1), favourable outcome (modified Rankin scale 0–2) and mortality at 3-months. Additionally vessel recanalization and rates of intracerebral and systemic haemorrhages were recorded. Analysis of differences in outcome and complication between the groups was performed in univariate and multivariate regression analyses.
Results: 540 SWA <6 h, 96 SWA >6 h, 30 WUS and 16 UOS patients were treated. Baseline characteristics were similar apart from a higher NIHSS score in the UOS group and more vertebrobasilar occlusions in SWA >6 h, WUS and UOS compared to SWA <6 h. Outcome and bleeding complications did not differ between SWA <6 h and SWA >6 h, WUS or UOS in univariate or multivariate analysis.
Conclusions: IAT is an effective and safe therapy option in selected patients beyond stroke guidelines. Optimal criteria for patient selection, especially in WUS have to be addressed in further trials.

P26

IV Thrombolysis and Statins

The Statins in Thrombolysis-Study-Group: Stefan T. Engelter, MD[1], Lauri Soinne, MD[2], Peter Ringleb, MD[3], Hakan Sarikaya, MD[4], Régis Bordet, MD[5], Jörg Berrouschot, MD[6], Celine Odier, MD[7], Marcel Arnold, MD[8], Gary A. Ford, MD[9], Alessandro Pezzini, MD[10], Andrea Zini, MD[11], Kirsi Rantanen, MD[2], Andrea Rocco, MD[3], Leo H. Bonati, MD[1], Lars Kellert, MD[3], Daniel Strbian, MD[2], Anett Stoll, MD[6], Niklaus Meier, MD[8], Patrik Michel, MD[7], Ralf W. Baumgartner, MD[4], Didier Leys, MD[5], Turgut Tatlisumak, MD[2], Philippe A. Lyrer, MD[1]
From the Departments of Neurology, University Hospitals Basel, (Switzerland)[1], Helsinki (Finland)[2], Heidelberg (Germany)[3], Zurich (Switzerland)[4], University Lille Nord de France, UDSL (EA1046), Lille (France)[5], Altenburg (Germany)[6], Lausanne (Switzerland)[7], Bern (Switzerland)[8], Newcastle University and Newcastle-upon-Tyne Hospitals NHS Foundation Trust, Newcastle (UK)[9], Brescia (Italy)[10], and Nuovo-Ospedale-Civile «S. Agostino-Estense», Modena (Italy)[11]

Background: Prior use of statins may affect functional outcome and intracranial hemorrhage (ICH) rates in stroke patients receiving IV thrombolysis (IVT).
Methods: In a pooled analysis of 11 IVT-databases we compared outcomes between statin users and nonusers. Main outcome measures were excellent 3-month-outcome (modified Rankin scale 0–1) and intracranial hemorrhage (ICH) in three categories. We distinguished all ICHs (ICH_{all}), symptomatic ICH based on the criteria of the ECASS-II-trial ($SICH_{ECASS-II}$) and those of the NINDS-trial ($SICH_{NINDS}$). Unadjusted and adjusted odds ratios (OR) with 95%-confidence-intervals were calculated.
Results: Among 4012 IVT-treated patients 918 (22.9%) were statin users. They were older, more often male, and more frequently had hypertension, hypercholesterolemia, diabetes, coronary heart disease, and concomitant antithrombotic use compared with nonusers. Fewer statin users (35.5%) than nonusers (39.7%) reached an excellent 3-month-outcome ($OR_{unadjusted}$ 0.84 [0.72–0.98], p = 0.02). After adjustment for age, gender, blood pressure, time-to-thrombolysis, and stroke severity, the association was no longer significant (0.89[0.74–1.06], p = 0.20). ICH occurred by trend more often in statin users (ICH_{all} 20.1% versus 17.4%; $SICH_{NINDS}$ 9.2% versus 7.5%; $SICH_{ECASS-II}$ 6.9% versus 5.1%). This difference was statistically significant only for $SICH_{ECASS-II}$ (OR = 1.38 [1.02–1.87]). After adjustment for age, gender, blood pressure, use of antithrombotics, and stroke severity, the $OR_{adjusted}$ for each category of ICH (ICH_{all} 1.15 [0.93–1.41]; $SICH_{ECASS-II}$ 1.32 [0.94–1.85]; $SICH_{NINDS}$ 1.16 [0.87–1.56]) showed no difference between statin users and nonusers.
Conclusion: In stroke patients receiving IVT, prior statin use was neither an independent predictor of functional outcome nor ICH. It may be considered as an indicator of baseline characteristics that are associated with a less favorable course.

P27

Optimization of arterial wall imaging on 3-Tesla MRI for diagnosis and follow-up of cerebral vasculitis

M. El-Koussy[1], J. Mathys[2], A. Rieke[1], C. Brekenfeld[1], J. Gralla[1], C. Kiefer[1], H.P. Mattle[2], G. Schroth[1]
[1]Dept. of Neuroradiology, University of Bern, Bern, Switzerland, [2]Dept. of Neurology, University of Bern, Bern, Switzerland

Introduction: Conventional MRI findings suggestive of cerebral vasculitis are rather non-specific. These range from vessel irregularities to cerebral parenchymal changes. A more optimized approach would include systematic imaging of the arterial vessel wall, which would allow for standardized follow-up studies to monitor disease progress and response to treatment.
Methods: The MRI was performed on a 3-Tesla clinical scanner (Magnetom Verio, Siemens, Erlangen, Germany). In addition to the standard MRI and the MR-angiographic series, the following sequences were performed; isotropic ultrathin heavy-T2-weighted sequence (CISS), time-of-flight MR-angiography (ToF-MRA) before and after intravenous gadolinium administration as well as double inversion recovery, dark blood (DIR-DB), fat suppressed T2 and gadolinium enhanced T1-weighted images. Co-registration of the sequences was performed to provide an even more accurate understanding of the pathological process.
Results: Two cases were followed-up by several MRI studies utilizing the aforementioned technique. In a documented case of cerebral vasculitis with symptomatic stenosis involving the distal segment of the left internal carotid artery as well as the A1- and M1-segments of the ipsilateral anterior and middle cerebral arteries respectively several acute ischemic lesions were depicted on diffusion-weighted images with corresponding hypoperfusion on the perfusion time-to-peak map. The follow-up revealed progressive stenosis of the affected arteries, especially the M1-segment of the left middle cerebral artery. There was obvious wall thickening and enhancement involving the aforementioned arteries. The images were of good quality and could be reproduced over several follow-up studies.
Conclusion: An optimized MRI technique for vessel wall imaging can allow for standardized follow-up examinations for cerebral vasculitis, thus guiding further diagnostic work-ups and therapeutic decisions.The MRI sequences in this work were optimized for higher magnetic field scanners, e.g. 3-Tesla MRI, however they can be performed at 1.5-Tesla.

P28

Risk of very early recurrent cerebrovascular events in symptomatic carotid stenosis – Is there a need for emergency endarterectomy within the first hours after symptom onset?

M.L. Mono[1], I. Steiger[1], O. Findling[1], M. Reinert[2], A. Galimanis[1], D. Kuhlen[2], J. Beck[2], M. El-Koussy[3], C. Brekenfeld[3], G. Schroth[3], U. Fischer[1], K. Nedeltchev[1], H.P. Mattle[1], M. Arnold[1]
[1]Department of neurology, Inselspital, University Hospital and University of Bern, Bern, Switzerland, [2]Department of neurosurgery, Inselspital, University Hospital and University of Bern Inselspital, Bern, Switzerland, [3]Department of neuroradiology, nselspital, University Hospital and University of Bern, Bern, Switzerland

Background: The very early risk of recurrent cerebrovascular events in hospitalised patients with symptomatic carotid stenosis (SCS) is largely unknown. Therefore, the benefit from emergency carotid intervention (CI) within the first hours after symptom onset in patients with SCS is undetermined.
Methods: Ninety-four patients admitted to our stroke unit within 48 hours after symptom onset with a non-disabling stroke, transient ischemic attack (TIA) or amaurosis fugax (AF) and SCS ≥50% underwent CI (90% carotid endarterectomy, 10% carotid artery stenting). The recurrence rate of stroke, TIA or AF was determined at 48 h, 7 and 14 days. In case of CI, procedure-related cerebrovascular events were assessed.
Results: Mean time from admission to CI was 7.1d (SD ± 6.86). 21 patients (22.3%) were treated within 48 h of symptom onset. Overall 15 recurrent cerebrovascular events occured in 12 patients (12.7%) between admission and CI: Two strokes-in-progression (2.1%), 5 TIAs (5.3%) and 1 AF (1.1%) within the first 48 h (total 8.5%); 1 stroke (1.1%) and 1 TIA (1.1%) between 48h-7d (total 2.1%) and 5 TIAs between 7–14 d (5.3%). The overall risk of procedure-related cerebrovascular events was 4.3% (3 strokes and 1 TIA). Patients with CI <48 h were not at increased peri-procedural risk (4.8% vs. 4.1%, P = 0.896).
Conclusions: The risk of early stroke recurrence in hospitalised patients with symptomatic carotid stenosis was quite low. Further studies are needed to determine whether very early CI may further decrease the rate of recurrent stroke without increasing peri-procedural complications.