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Wissenschaftliches Komitee
Comité Scientifique

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GemSession (SAYN)
Donnerstag | Jeudi 28.09.2017, 16:30-17:30

M01*
Motifs in the tau protein that control conformation and binding to microtubules determine pathological effects that are distinct from phosphorylation and aggregation

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Background and objectives:
The abnormal deposition of pathogenic forms of tau protein in the brain is a main feature and a major determinant of cognitive decline in many neurodegenerative disorders including Alzheimer's disease and frontotemporal lobar degeneration. However, the molecular mechanisms by which tau protein induces neurodegeneration remain debated. A gain of toxic function through hyperphosphorylation and aggregation or a loss of normal function are the major divergent hypotheses. By comparing the effects of different mutants of tau protein both in vivo and in vitro, our experiments aim at disentangling the molecular events leading to tau toxicity.

Material and methods:
We generated AAV viral vectors encoding the wild type human tau protein, the P301 S disease-related mutant or a 2P mutant that is not able to fold into β-sheet conformation. We overexpressed these variants in the mouse forebrain. Using histological, biochemical and ultrastructural analysis, we assessed at different time points, the deposition of phosphorylated and aggregated forms of tau, as well as the induced pathology. Resulting changes in animal behavioral performances were determined using specific tasks. The molecular effects of these forms of tau were also studied at the cellular level in primary neuronal cultures.

Results:
The P301 S mutation induces tau aggregation and progressing motor deficits. In contrast, wild-type tau is more heavily hyperphosphorylated and causes behavioral impairments that do not progress over time. However, these behavioral defects are rescued when β-sheet breaking proline residues are inserted in the microtubule-binding domain of tau. This tau mutant is poorly phosphorylated and promotes microtubule stabilization.

Conclusion:
The regulation of the binding of tau to microtubules through conformational changes may play a role in the developing pathology, possibly upstream aggregation and hyperphosphorylation of tau. Therefore these results may guide the design of novel therapeutic approaches to enhance binding to the cytoskeleton, and prevent downstream pathogenic events.

M02*
The diagnostic burden of Primary Angiitis of the Central Nervous System- a monocentric, retrospective study

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Background
Although being an extraordinary rare condition, Primary Angiitis of the Central Nervous System (PACNS) is an important differential diagnosis of various CNS lesions. Due to neurological morbidity and potential mortality a fast diagnosis is essential. However, the current diagnostic criteria leave space for misdiagnosis and are even harder to follow in the clinical routine.

Material & Methods
Retrospectively, we analysed 20 patients who were admitted between 2006-2016 to our neurological department and were suspected of suffering from PACNS due to clinical and radiological evaluation. Demographic data, paraclinic diagnostics – with a special emphasis on brain and leptomeningeal biopsy -, the kind of immunosuppressive treatment and the clinical course thereafter were collected by chart review.

Results:
On clinical presentation, neuropsychological or cognitive symptoms were frequently (15/20 patients) linked to the suspicion of PACNS. 17 patients had a cerebral angiography (MR or digital substraction angiography) result "typical" for PACNS.
In 10 cases (50%) a combined meningeal and parenchymal brain biopsy was performed. The demographic data (e.g. median age, gender distribution) were similar in both groups (biopsy vs. non-biopsy).

Following diagnostic work-up, 3 patients in each group were treated for PACNS with all 6 patients presenting with a relapsing-remitting course in the follow-up despite immunosuppressive therapy. Four of these (2 in each group) presented with recurrent neuropsychological and/or cognitive symptoms.

Remarkably, brain biopsy did not confirm PACNS in any of these cases. Hence, in only 3 of the 10 cases it helped to find a differential diagnosis as one of the major goals of brain biopsy with the remainder having unspecific histological results.

Discussion
Our retrospective study demonstrates the difficulties neurologists encounter in the diagnostic approach of PACNS.

Unfortunately, combined leptomeningeal and parenchymal brain biopsy was not supportive to confirm the diagnosis of PACNS, but at least excluded important differential diagnoses. Therefore, the diagnosis of PACNS still relies on clinical suspicion and the course of the disease (relapsing-remitting, progressive) with neuropsychological symptoms being frequent. Baseline and follow-up radiological findings were neither sensitive nor specific for PACNS. In summary, our experience from this small study underlines frequent challenges and hurdles in the diagnosis of PACNS.

M03*
Secular trends in procedur stroke or death risks of stenting versus endarterectomy for symptomatic carotid stenosis - a pooled analysis of randomised trials

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Background and aims:
Stroke risk associated with carotid disease may have decreased over the past decades. It is less clear whether this is also true for the procedural risk of revascularisation.

Methods:
We analysed temporal changes in procedural risks among 4599 patients with symptomatic carotid stenosis treated with carotid artery stenting (CAS; n=2327) or endarterectomy (CEA; n=2272) in four randomised trials between 2000 and 2008, using generalised linear mixed models with a random intercept for each source trial. Models were additionally adjusted for age and other baseline characteristics predicting treatment risk. The primary outcome event was any procedural stroke or death, defined as occurring within 30 days after treatment.

Findings:
The procedural stroke or death risk in the CEA group decreased significantly over time (unadjusted OR per year 0.83, 95% CI 0.74-0.94, p=0.007), while the change in CAS risk was not significant (unadjusted OR 0.96, 95% CI 0.88 -1.04, p=0.34). After adjustment for baseline characteristics, the results remained essentially the same (CEA: OR 0.81, 95% CI 0.72-0.92, p=0.003; CAS: OR 0.96, 95% CI 0.88 -1.05, p=0.31). The treatment effect of CAS vs. CEA changed significantly over time (interaction p=0.04).

Conclusion:
The risk of stroke or death associated with carotid endarterectomy for symptomatic carotid stenosis decreased over time, independent of clinical predictors of procedural risk. There was no significant change in procedural risk of carotid stenting.

M04*
Isolation and characterization of autoreactive CD4+ T cells in patients with narcolepsy with cataplexy

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Background:
Narcolepsy with cataplexy is a hypothalamic disorder caused by the selective loss of neuronal cells of the posterior hypothalamus that produce the neuropeptide hypocretin (HCRT). As a result, HCRT-1 levels in cerebrospinal fluid (CSF) are low or undetectable in >95% of patients. Accumulating lines of evidence, including a strong association with the HLA-DQB1*06:02 haplotype, support the notion that narcolepsy is an immune-mediated disorder that manifests in genetically predisposed individuals upon exposure to environmental factors. The involved cellular and humoral mechanisms are still unclear.

Aim:
To identify autoreactive T cells from narcolepsy patients by combining antigenic stimulation, T cell receptor (TCR) deep sequencing and T cell cloning.

Patients and methods:
21 patients with narcolepsy with cataplexy (14/17 with low/undetectable CSF HCRT-1, 15/18 HLA DQB*0602 positive) and 14 controls (all HLA-DQB1*0602 positive) were studied. T cells from the blood of narcolepsy patients or healthy donors were initially expanded polyclonally with mitogen and IL-2 in microcultures to generate T cell

libraries that were subsequently screened for their reactivity against a set of neuronal antigens. When available, T cells from CSF were also polyclonally expanded. Next-generation TCR sequencing was performed on total T cells from blood and CSF as well as on autoreactive T cells.

Results:
CD4+ T cell clones reactive against HCRT and other neuronal antigens expressed by HCRT-producing neurons were found in all narcolepsy patients but in none of the healthy controls. Moreover, immunodominant epitopes of the autoantigens were also identified. Finally, autoreactive T cell clonotypes could be tracked in the blood and CSF of narcolepsy patients.

Conclusions:
We provide first evidence of autoreactive CD4+ T cell clones that can recognize HCRT and other neuronal antigens in the blood and CSF of patients with narcolepsy with cataplexy. Further studies are needed to understand the role of these cells in the pathogenesis of the disease and the implications of this observation for the (early) diagnosis and (immunomodulatory) treatment of narcolepsy.

M05*
Objective measures to discriminate nonorganic from idiopathic hypersomnia: a systematic review

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Background and aims
Nonorganic hypersomnia (NOH) and idiopathic hypersomnia (IH) are disorders characterized by a "hypersomnolence" which cannot merely be explained by a disturbed sleep, insufficient sleep, a general medical condition or medication use. "Hypersomnolence" refers either to excessive daytime sleepiness (EDS) or to prolonged need for sleep, or both. The two ambiguous entities are mainly differentiated by the presence/absence of a psychiatric disorder.

Despite the bidirectional pathogenetic relationship which certainly exists between psychiatric and sleep complaints, "hypersomnolence" as assessed by objective measures may differ between NOH and IH patients. This review aimed to evaluate whether and which objective sleep-wake measures facilitate the diagnostic differentiation between NOH and IH.

Methods:
Sixty-six out of 546 studies revealed by the search met the eligibility criteria. These requested objective measures either in NOH or IH, or from both groups.

Results:
In the polysomnography, NOH patients had a longer sleep latency (SL), a shorter total sleep time (TST), and a lower sleep efficiency (SE) in comparison to patients with IH, who additionally showed cognitive impairment after abrupt awakening due to sleep inertia. Furthermore, in NOH patients the SL was also longer in the MSLT and the inactivity index in the actigraphy greater in comparison to IH patients.

The differences between the two patient groups are significantly affected by the inclusion criteria of the corresponding studies. The objective measures found in NOH patients resembled those found in IH patients much more if rather strict diagnostic criteria were applied to diagnose NOH, and if the Epworth sleepiness score was used to clearly define EDS. On the other hand, the objective measures found in IH patients resembled those described in NOH patients if less strict criteria were used to diagnose IH, i.e. if the diagnosis was purely based on prolonged sleep duration but did not necessarily require an elevated Epworth sleepiness score.

Conclusions:
Rather than representing two strictly different entities, NOH and IH may represent a continuum and the published differences in objective measurements primarily depend on the presence or absence of EDS as a diagnostic requirement. We speculate, that studies on NOH that do not require this criterion of EDS may show deviant results due to the inclusion of psychiatric patients suffering from insomnia and tiredness.

M06*
Neurological complications of acute virus E infection (NEUROCAVE): results from a Swiss prospective study

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Background:
An association between acute hepatitis E virus (HEV) infection and neurological complications, including neuralgic amyotrophy (NA) and Guillain-Barré syndrome (GBS), emerged in the last years.

Aim:
We studied the clinical features, frequency and management of neurological complications related to acute HEV infection.

Methods:
All adults consecutively diagnosed with acute hepatitis E (HEV IgM+ and IgG+; RNA+/-since 2015 underwent

neurological examination. In case of neurological involvement, lumbar puncture, EMG, brachial plexus and cervical MRI, and cervical ventral root high-resolution ultrasound (US) were performed. We included 68 patients (39 males, 13 females) and followed them for 6 months.

Results:
The estimated mean incubation time for HEV infection was 2-3 weeks. HEV RNA (genotype 3) was detected by PCR in sera from 25 patients. The mean latency between acute hepatitis and NA was 5-10 days. Overall, 16 patients had NA, one a forme fruste of NA, 23 severe myalgia, one transverse myelitis, one GBS (after concomitant infection with HEV and CMV). NA was bilateral (although asymmetric) in 10 cases and more common in males (13/16). Common MRI findings in NA were T2-hyperintensity and gadolinium enhancement of affected muscles (supraspinatus, infraspinatus, trapezius and deltoid). EMG studies demonstrated a predominant upper trunk (C5-C6) involvement of the brachial plexus. The US showed enlargement of the affected cervical ventral roots and of the median nerve at upper arm, with patchy fascicle swelling. Cerebrospinal fluid analysis was performed in 6 patients with NA, showing increased protein count in 3 cases and increased cell count only in one case. Five patients with bilateral NA had a transient serum monoclonal peak IgM. Eight patients with severe bilateral NA were treated in the acute phase with intravenous immunoglobulins, whereas four with unilateral involvement received oral prednisone for 2-3 weeks. All treated patients improved within one month in terms of pain reduction and increased muscle strength. There was no exacerbation of HEV under immunomodulatory treatment. Two patients with mild NA and patients with myalgia recovered within 2 months without treatment.

Conclusions:
In this prospective study we demonstrate that the neurological complications of acute HEV genotype 3 infection are frequent among patients, especially in males. Pain improves with intravenous immunoglobulins or prednisone.

Freie Mitteilungen II | Communications libres II
Freitag | Vendredi 29.09.2017, 08:15-09:45

M07
Vitamin D supplementation differentially affects seasonal multiple sclerosis disease activity

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Background and objectives:
Low ultraviolet-B (UVB) radiation causes hypovitaminosis D, which is a known risk factor for multiple sclerosis (MS) and associated with MS disease activity (Hanwell & Banwell 2011). Our objective is to test whether vitamin D supplementation is most effective in lowering disease activity during the period of the year with low UVB radiation and consequently low serum 25-hydroxyvitamin D3 (25(OH)D3) concentration.

Subjects and Methods:
Retrospective analysis of medical records from our outpatient department identified 40 MS patients with available data of at least 6 months before and during oral vitamin D supplementation. Serum 25(OH)D3 concentration was analyzed using immunoassay. UVB radiation data was provided by the local government. Annualized and quarterly relapse rates before and during vitamin D supplementation served as outcome parameters.

Results:
During vitamin D supplementation (18,950 international units/week (mean, SD 3,397)), serum 25(OH)D3 concentration increased by 51 nmol/L and the UVB related seasonal variability of 25(OH)D3 levels ceased (rho = -0.13, $p > 0.05$). Furthermore, the annualized relapse rate decreased by approximately 50%. This decrease remained significant after adjusting for immunotherapies, vitamin D supplementation, MS Phenotype, sex, age and disease duration (regression coefficient for vitamin D supplementation, -0.24; 95% confidence interval, -0.61 to -0.02; $p = 0.04$). Notably, the reduction in relapse rates was almost solely driven by the prominent reduction of the quarterly relapse rate in late winter/early spring, when 25(OH)D3 levels of non-supplemented patients were the lowest.

Conclusions:
Our study demonstrated the modulation of seasonal MS disease activity through vitamin D supplementation. Given the prominent reduction of the quarterly relapse rate in late winter/early spring, our data indicate a beneficial effect of supplementing MS patients with vitamin D, especially during this period of the year.

M08
Rivaroxaban plasma levels in patients with acute ischemic stroke and intracerebral hemorrhage

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Background:
In patients with acute stroke taking Rivaroxaban, we explored whether plasma levels of Rivaroxaban (RivLev) (i) differed between type of stroke and (ii) were associated with clinical and laboratory characteristics.

Methods and Results:
Multicenter explorative registry-based study (Novel-Oral-Anticoagulants-In-Stroke-Patients collaboration;NOA-CISP;ClinicalTrials: NCT02353585) of patients with stroke taking Rivaroxaban and RivLevs measured on admission. We explored a) whether RivLev expressed as continuous or categorical variable differ with stroke type (acute ischemic stroke [AIS], intracerebral hemorrhage [ICH]), b) factors modifying RivLev, c) the accuracy of distinct INR-thresholds to predict RivLev$\leq$100ng/ml, a threshold for the use of thrombolysis, and d) the influence of RivLev on stroke severity. Regression models with Odds Ratios (OR)[95%-CI] were used for statistical analyses; RivLevs were expressed as median[IQR].

Among 241 patients (age 80[IQR73-84], 49% females; median time-from-onset-to-admission 2 hours[IQR1-4.5hours], RivLev 89ng/ml[31-194]), 190 had AIS and 51 had ICH. RivLev did not differ neither as continuous (AIS: 85ng/ml [30-204] versus ICH: 102 ng/ml [51-165]; OR 1.00[95%-CI 0.997 -1.002] nor as categorical variable (RivLevtrough($\leq$137ng/ml): AIS 66.3% versus ICH 66.7%, ns). RivLev correlated with Rivaroxaban dosage and inversely with renal function and time-since-last-intake (each $p<.05$) but neither with age nor sex. The specificity to predict RivLev$\leq$100ng/ml with INR$\leq$1.0/$\leq$1.1/$\leq$1.4 was 25.7%/42.9%/90.5% while the sensitivity was 98.9%/89.4%/55.3%, respectively. AIS-patients with RivLev$\leq$100ng/ml had higher odds for severe strokes (NIHSS>15;OR 2.433[1.094-5.846], $p<.05$).

Conclusions:
AIS and ICH patients under Rivaroxaban had comparable RivLev with 2/3 of the ICH-patients having low RivLev. Dosage, renal function and time-since-last-intake determined RivLev. Prior to therapeutic decisions, RivLev should be measured.

M09
Dopamine depletion changes the interplay between nucleus reticularis thalami and motor thalamus in rat: new insights for parkinson's disease pahtophysiology

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Background:
In the basal ganglia cortical loop, two thalamic nuclei, the motor thalamus (MTh) and the nucleus reticularis thalami (NRT), are critically modulated by the dopamine (DA). Despite their key roles, there is little evidence on their neuronal electrophysiological properties and the changes induced by DA depletion states.

Methods:
In order to shed some light on the functional properties of MTh and NRT, we investigated single neuronal activity in normal and acute tetrodotoxin (TTX) and 2 weeks after chronic 6-hydroxydopamine (6-OHDA) DA depletion states induced by their infusion in the medial forebrain bundle, respectively. The recordings were performed during stable cortical slow wave activity (SWA), with the aim to investigate the MTh and NRT-cortical coupling. We collected a total of 23 MTh and 13 NRT neurons in control animals, 28 MTh and 8 NRT neurons from 6-OHDA-treated animals and 34 MTh cells in TTX-treated animals. Microdialysis was performed from MTh for GABA detection before and after TTX infusion.

Results:
We found that after 6-OHDA-induced chronic DA depletion the NRT neuronal firing rate increased with a parallel decrease of burst activity. The MTh activity was instead largely unaffected by 6-OHDA-lesion whilst it was decrease by acute TTX-DA depletion. Accordingly, the GABA extrasynaptic levels within the MTh resulted significantly increased after TTX infusion.

Of note, in normal condition the MTh showed a phase-locked activity with the cortex that was reduced in 6-OHDA animals. On the contrary, the coupling between MTh and cortex became stronger phase-locked after acute DA depletion. Concerning the NRT-SWA coupling, it remained weak in normal and 6-OHDA animals.

Conclusions:
These results suggest a chronic compensatory mechanism that rebalances the acutely decrease of MTh activity with a parallel decoupling of the MTh-cortical interplay.

On the other hand, the NRT is largely unaffected by the cortex and its increased activity are likely due to a reduced inhibitory tone from the DAergic afferents.

M10
Therapeutic drug monitoring for intravenous levetiracetam in status epilepticus: a tool to guide management?

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Introduction:
Intravenous levetiracetam (LEV) is widely used in the treatment of status epilepticus (SE). Loading dose is used in order to quickly reach therapeutic serum levels. We analysed the correlation between LEV serum levels after the loading dose and clinical response.

Material and Methods:
Retrospective analysis of our prospective SE registry. We included all patients with available serum levels measured less than 36 hours after the loading dose. A Bayesian/maximum likelihood approach based on a population pharmacokinetic model was used to estimate mean LEV exposure. Clinical response was defined as LEV being the last antiepileptic drug (AED) introduced in the 24 hours before SE cessation. We compared serum levels and mean LEV exposure between responders and non-responders. The correlation was adjusted for other available clinical data recorded prospectively.

Results:
Between February 2015 and April 2016, we included 29 patients with 29 serum levels within 36 hours. We also

included 45 later serum levels within 7 days for calculation of the pharmacokinetic model. No differences were found in serum levels (median 19.5 versus 21.5 mg/l; p=0.7) or calculated mean LEV exposure (median 25.8 versus 36.2 mg/l, p=0.7) between responders and non-responders. Correction for SE severity did not alter the absence of relationship. The LEV loading doses were correlated with the calculated LEV mean exposures but not with the measured serum levels.

Discussion:
Serum levels and calculated exposure of LEV cannot be used as predictors of clinical response. Moreover, serum levels are not correlated with the loading dose itself due to LEV short half-life (6-8 hours). This questions the use of serum levels to assess the LEV loading dose.

M11
Video-rating to quantify Limb Ataxia in Multiple Sclerosis

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Background:
In Multiple Sclerosis (MS) the Expanded Disability Status Scale (EDSS) is commonly used to determine disability but suffers from low inter- and intra-rater reliability (1). Supporting such assessments with computer systems based on machine learning are one possibility for improvement but require alternative methods to capture consistent clinical judgement (2). We recorded videos of MS patients performing the Finger-to-Nose Tests (FNT) to use them as a reference for grading the severity of limb ataxia based on the Neurostatus-EDSS definitions (3).

Objective:
To investigate whether the use of predefined reference videos representing degrees of severity of limb ataxia can improve disability ratings.

Methods:
Twenty-six neurologists from Bern and Basel rated 60 videos of MS patients performing the FNT, recorded using a Microsoft Kinect™ 1 camera. Ratings were based on the Neurostatus-EDSS definitions of limb ataxia, performed at baseline and after six weeks. The neurologists were randomized into two groups: one group using the reference videos for rating, the other rated without reference videos. The inter-rater consistency and test re-test agreement were determined.

Results:
The use of reference videos made neurologists more consistent. We found that the spread of average ratings was lower using reference videos (standard deviation=0.12; range=0.40) than without reference videos (standard deviation=0.26; range=0.88), which resulted in a statistically significant difference in standard deviation (F-test; p=0.013). Similarly, use of reference videos increased the intraclass correlation coefficient for inter-rater agreement from 0.756 (without reference videos; 95%CI 0.756-0.871) to 0.816 (95%CI 0.674-0.829). Short-term intra-rater agreement measured as percentage of identical ratings was $75 \pm 22\%$ with and $79 \pm 18\%$ without reference videos. Long-term intra-rater agreement was similar between the two groups, $68 \pm 9\%$ with and $69 \pm 11\%$ without reference videos. No significant association was found between rater experience.

Conclusions:
The results of this study show a significant improvement in consistency when using preselected reference videos to rate upper limb ataxia measured with the FNT. Hence, this may represent a method to rate movements in a more consistent way, particularly in the context of clinical research, or for training machine learning algorithms.

M12
Time to diagnosis of multiple sclerosis in Switzerland: Observational data from the Swiss Multiple Sclerosis Registry (SMSR)

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Background:
International MS registry data suggest that time from MS symptom onset to diagnosis has decreased over the past two decades in parallel with novel diagnostic guidelines. Nevertheless, time to diagnosis remains substantial in many European countries, with averages between 1.1 [1] to 3.6 [2] years. Using data from the newly established Swiss Multiple Sclerosis Registry (SMSR), we examine time to diagnosis and time trends in Switzerland.

Methods:
The SMSR is a nation-wide registry for adult persons with MS. Since its launch in June 2016, it has enrolled over 1'400 persons with MS and collected 1'150 baseline questionnaires. Data are obtained via self-administered online- and paper surveys and include years of symptom onset and diagnosis, setting of diagnosis, first symptoms as well as

demographic data. Participants with a year of diagnosis between 1997 and 2016 were included. Temporal trends were assessed across 4 periods (1996-2000; 2001-2005; 2006-2010; 2011-2016), reflecting changing guidelines for the diagnosis of MS [3–5]. Factors associated with longer time to diagnosis (>2 years versus <2 years) were assessed using multivariable logistic regression with age, sex, diagnostic setting, type of first symptoms, and MS type as potential confounders.

Results:
Of 807 patients with MS diagnosis between 1997 and 2016, we included 795 patients with plausible diagnostic dates. Number of diagnoses (average time to diagnosis) across time-periods was as follows: 136 (5.0), 132 (3.3), 212 (3.7) and 315 (3.5) respectively (test for linear trend in time to diagnosis over the 4 periods: p-value = 0.011). This temporal trend - although mainly caused by longer times to diagnosis during the first period - was confirmed by multivariate logistic regression (OR for linear trend: 0.87 [0.76 -1.00]). Furthermore, PPMS (OR: 3.28 [1.77-6.08]), depression as a first symptom (1.79 [1.11-2.90]) and older age (1.76 [1.49-2.07]) were associated with longer intervals to diagnosis. By contrast, gait problems (0.59 [0.42-0.83]) and paresthesia (0.68 [0.50-0.94]) as first symptoms were associated with earlier diagnosis.

Conclusions:
Time to diagnosis decreased in Switzerland after the introduction of the 2001 McDonald guidelines, but with no clear trend thereafter. Although time to diagnosis was similar to other European countries, significant potential for improvements may still exist.

M13
The molecular signature of parkinsonism in patients with gait disorders

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Background:
Gait disorders are frequently associated with parkinsonism in older adults. However, their molecular substrates and the clinical impact of parkinsonism have not been described. This cross-sectional study aims to compare the CSF total tau, Aβ1-42, and phosphorylated tau levels in patients with gait disorders with and without parkinsonism and to study the clinical role of parkinsonism on gait and cognition.

Methods:
Patients with neurological gait disorders, who accepted to perform a lumbar puncture, were consecutively included in this cross-sectional study. CSF biomarkers were measured by ELISA in 49 patients with gait disorders (77.7 $\pm$ 6.6 years; 32.7% women). Spatio-temporal gait parameters were quantified with an optoelectronic system and cognition with a comprehensive neuropsychological assessment. Parkinsonism was defined by presence of bradykinesia and at least one of the following signs among muscular rigidity, rest tremor or postural instability.

Results:
Parkinsonism was identified in 14 patients (28.6%). CSF Aβ1-42 level was decreased in patients with parkinsonism (β:-189.4; 95%CI [-352.3;-26.6]; p = 0.024) even after adjusting for age, gender, comorbidities and total white matter burden; while CSF total tau and phosphorylated tau levels were similar between patients with and without parkinsonism. Patients with parkinsonism presented decreased attentional and executive performances but similar gait parameters compared to those without parkinsonism.

Conclusions:
Parkinsonism in patients with gait disorders represents a phenotype related to amyloidopathy, as demonstrated by decreased CSF Aβ1-42 level. Among patients with gait disorders, the subgroup with parkinsonism displays impaired cognition, but similar quantitative gait parameters compared to the subgroup without parkinsonism.

M14
Increased uncertainty about the direction of gravity in bilateral vestibulopathy correlates with residual utricular function

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Background and aims:
Gait imbalance and oscillopsia are major complaints in patients with bilateral vestibular deficits (BVD), and has been linked to increased variability in the perceived direction of gravity due to deficient vestibular (otolithic) input. The aim of this study is to compare the accuracy and precision of the perceived direction of gravity for vision-dependent and vision-independent tasks in patients with BVD.

Materials and methods:
Adjustment errors and trial-to-trial variability for different psychophysical tasks were obtained in patients with BVD (n=10) and compared to healthy controls (n=10). Subjective visual vertical (SVV) and subjective haptic vertical (SHV) were measured in different roll orientations (0°, $\pm$45°, $\pm$90°) and subjective postural adjustments along perceived earth-vertical and earth-horizontal were collected. Patients with bilaterally absent ocular vestibular-evoked myogenic-potentials (oVEMPs) were compared to those with (partially) preserved oVEMP-responses.

Results:
While variability depended on roll-angle for both patients and controls, variability was larger in patientsfor both for

the SVV ($p<0.001$) and the SHV ($p=0.004$). Patients with bilaterally absent oVEMP-responses had higher SVV ($p=0.024$) and SHV ($p=0.006$) variability compared to those with (partially) preserved utricular function. Self-positioning along earth-horizontal was more variable in BVD-patients compared to controls ($p<0.001$), while this was not true for adjustments along perceived earth-vertical ($p=0.420$). Again variability was higher in those subjects with bilaterally absent oVEMP responses compared to residual (partial) utricular function ($p=0.032$). There was a significant correlation in variability for patients for the SVV and the SHV (R2=0.61, slope=1.06 [95%-CI=0.80 -1.54]). Differences in adjustment errors between patients and controls were minor.

Conclusions:
The discrepancy between significantly decreased precision but preserved accuracy of verticality-estimates in patients compared to controls is most likely due to the bilaterality of vestibular deficits. With variability correlating amongst all three paradigms and also with oVEMP-responses, this emphasizes the role of bilaterally intact utricular input for precise verticality perception.

M15
Strabismus Measurements with Novel Video Goggles

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Background and Aims:
Measurement of ocular motility and alignment is essential for the diagnosis of cranial nerve palsies and comitant strabismus. The traditional Hess screen test is time-proven for documenting squint angles at different gaze directions, but the test is subjective and requires good patient cooperation.

Materials and Methods:
We designed novel strabismus video goggles with built-in laser target projection and LCD shutters for automated alternate occlusion of the eyes. We measured 41 adults and children $\geq$6 years with acquired paralytic strabismus (third, fourth and sixth nerve palsies) or comitant strabismus and 17 healthy volunteers, and compared the results to the Hess screen test.

Results:
Measurements with strabismus video goggles and Hess screen test were closely comparable across patients and healthy controls, reproducing the individual strabismus patterns. Unlike with Hess screen testing, measurements with the strabismus video goggles were even possible in patients with comitant strabismus and visual suppression.

Conclusions:
The novel strabismus video goggles are simple, fast and accurate in measuring ocular deviations and the results are closely comparable to the conventional Hess screen test. The device can be used in patients with visual suppression, who are not suitable for the Hess screen test, as well as children as young as 6 years of age.

Poster | Posters
P01* - P12*: Kandidaten für den Déjérine-Dubois-Preis
P01* - P12*: Candidats pour le prix Déjérine-Dubois

P01*
Sleep-wake changes and disturbances and their impact on the short- and long-term outcome of stroke - a two-center prospective observational cohort study: Update on the descriptive analysis of the first 360 patients

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Background:
Sleep-wake disturbances (SWD) including sleep disordered breathing (SDB), insomnia, and restless legs syndrome (RLS) are associated with increased cardio-cerebrovascular morbidity and mortality. Few observations suggest that SWD are frequent in stroke and detrimental for its outcome.

The aim of this study is to assess prospectively and in a large cohort of patients 1) the prevalence of SWD after stroke or transient ischemic attack (TIA), and 2) their impact on outcome in the first 2 years after the acute event.

Patients and methods:
We plan to include ~500 patients with TIA or ischemic stroke from the Departments of Neurology in Bern and Lugano. Stroke characteristics, cardiovascular risk profile and sleep disordered breathing are assessed during the acute phase. At 3, 12 and 24 months sleep-wake habits/disturbances, psychiatric and cognitive changes, stroke outcome and the occurrence of new cardio-cerebrovascular events are assessed by interviews and questionnaires. In about 1/5 of the entire sample objective testing including blood pressure variability and endothelial function are performed during the acute phase as well as at 3 and 12 months post stroke.

Results:
Since August 2015 a total of 360 patients (63% male, 37% female, 314 in Bern and 46 in Lugano) with ischemic stroke (83%) or TIA (17%) were recruited. Mean age of patients was 65 years (SD 13 years, range 21-86 years) with mean NIHSS-scores of 3.5 (SD 4.7, range 0-40) at admission and 1.4 (SD 2.5, range 0-19) at discharge. At the 3 months follow-up visit (completed by 252 patients) the modified Rankin Scale (mRS) was < 2 in 77% of patients.

In the acute phase, the mean AHI was 14/h (SD 15, range 0-83); the AHI was >20/h in 26% and >30/h in 15% of patients. At 3 months, excessive daytime sleepiness (Epworth Sleepiness Score ≥10) was reported by 15%, fatigue (Fatigue Severity Scale >4.0) by 28%, and insomnia complaints (Insomnia Severity index >14 and ≥10) by 6-25% of patients. The diagnostic criteria for RLS were fulfilled by 5% of patients.

Conclusions:
Preliminary results of this ongoing study suggest a high prevalence of sleep disordered breathing, excessive daytime sleepiness and fatigue but not of RLS in the first 3 months after stroke. Prevalence of insomnia complaints is moderate. Their evolution over time and impact on stroke, cognitive, psychiatric and cardiovascular outcome remains unclear at this time.

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P02*
Identification of a Novel Blood Biomarker Panel for Improved Mortality Prediction in Acute Ischemic Stroke

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Background:
We investigated a preselected set of 92 candidate blood biomarkers that have been implicated in different key processes of vascular biology, including inflammatory responses, angiogenesis and other processes, to predict post-stroke mortality. Based on the most promising markers we aimed to create a novel biomarker panel for risk stratification.

Method:
In this prospective cohort study, we simultaneously measured 92 biomarkers within 72 hours of symptom onset in 320 stroke patients by a novel proximity extension assay technique (Proseek Multiplex CVD III, Olink Proteomics, Uppsala, Sweden). The primary outcome measure was mortality within 90 days. To identify the most promising biomarkers we first estimated the association of each biomarker by using logistic regression models adjusting for multiple testing. The remaining markers were then used to create a panel. Within the panel each biomarker was weighted according to the sum of the differences from the median. We fitted regression models to estimate odds-ratios and 95% confidence intervals (OR, 95% CI) for the association of the panel with mortality. The discriminatory accuracy was assessed with the area under the receiver-operating-characteristic curve (AUC).

Results:
Of the 320 patients 11.6% died within 90 days after stroke. After correction for multiple testing 16 biomarkers were selected to create the panel. After adjustment for demographic and vascular risk factors the panel remained independently associated with mortality (OR 1.14, 1.05 – 1.24 95% CI) and improved the discriminatory accuracy to predict

mortality (AUC of 0.89, 0.85 – 0.94 95% CI, to 0.92, 0.89 - 0.96 95% CI), as compared to the clinical prediction model alone.

Conclusions:
We identified a novel blood biomarker panel which improved mortality prediction beyond established demographic and vascular risk factors after acute ischemic stroke. These results need to be validated in a larger independent cohort study.

P03*
Does cerebellar dysfunction contribute to tremor in Parkinson's disease?

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Background
Rest tremor in Parkinson's disease (PD) is disabling and responds often incompletely to conventional therapy. The pathogenesis remains largely unknown. Functional imaging, neurophysiology and structural studies, and stereotactic surgery point to an involvement of the cerebellum and the cerebello-thalamo-cortical pathway, but the precise nature remains unknown. These functional changes in the cerebellum may include pathological and compensatory mechanisms.

Objective
This study aims to investigate the potential role of cerebellar dysfunction in the pathogenesis of tremor in Parkinson's disease (PD).

Methods:
Cerebellar function can be tested by the eyeblink classical conditioning (EBCC), a form of associative motor learning, which depends on the integrity of the cerebellum and the olivo-cerebellar circuit. Fifteen PD patients with tremor (PD+tremor) and fifteen without (PD-tremor) were investigated compared to age-matched healthy controls. We assessed the associative motor learning in a delayed classical conditioning paradigm.

Results:
Our findings suggest an impaired EBCC both in the PD-tremor and PD+tremor compared to healthy controls, which do not differ regarding tremor. The rate of associative motor learning ranges widely from being preserved to complete abolition which appears to correlate rather with the disease progression.

Conclusion:
There is an impaired associative motor learning in PD suggesting a potential cerebellar dysfunction, which does not contribute to tremor pathogenesis. This cerebellar dysfunction may progress along with the neurodegenerative process in PD, which needs to be further explored.

P04*
Proenkephalin A (PENK-A) adds no incremental prognostic value after acute ischemic stroke

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Objective:
Proenkephalin (PENK-A) is a stable precursor fragment of the enkephalin neuropeptide family involved in blood brain barrier disruption and apoptosis. Plasma levels of PENK-A were previously associated with poor outcome after ischemic stroke in a pilot study1. The aim of this study was to validate PENK-A as potential novel prognostic biomarker in an independent prospective larger cohort.

Method:
PENK-A levels were measured within 72 hours of symptom onset in 320 consecutively enrolled ischemic stroke patients at a tertiary stroke centre in Switzerland. The primary outcome measures were functional outcome (assessed by the modified Rankin Scale) and mortality within 90 days. For the association between PENK-A and the primary outcomes, logistic and cox proportional regression analyses were fitted to estimate odds ratios (OR), hazard ratios (HR) and 95% confidence intervals (CI), respectively.

Results:
Among the 320 patients 41% had an unfavourable outcome (mRS >2) and 12% died within 90 days. In the univariate analysis PENK-A levels were significantly associated with both outcome measures, however after adjusting for demographic and vascular risk factors, PENK-A was no longer independently associated with functional outcome and mortality (OR 1.5 (95%CI: 0.15-15.52; p=0.72) and HR 1.29 (95%CI: 0.16-10.35; p=0.81). The strongest confounding factors for the association of PNEK A with both outcome measures were age, cardiac-comorbidities and renal-insufficiency.

Conclusion:
Among patients with acute stroke PENK-A does not serve as an independent prognostic marker. Therefore, previous observations could not be confirmed. This study underlines the importance of independent validation studies in the assessment of blood biomarkers.

P05*
The variability of the cerebellar-cortical interaction: A paired-pulse stimulation study

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Objective:
The aim of this study is to investigate the cerebellar-cortical inhibition (CBI) in healthy participants using the paired-pulse stimulation paradigm.

Background:
Paired-pulse transcranial magnetic stimulation (PP-TMS) allows the investigation of brain excitability in humans. More specifically, applying a conditioning subthreshold stimulus (CS) 1-6 ms before the test suprathreshold stimulus (TS) can lead to intra-cortical inhibition (Ugawa et al., 1995). Recent studies have shown that there is a suppression of intracortical inhibition in patients with Parkinson disease (PD). However, TMS studies have shown variability in MEP responses which pose a problem to the interpretation and utility of the paradigm. This study aims to investigate this variability in healthy participants. The result will provide insights of PP-TMS paradigm as a potential protocol for the investigation of the cerebello-thalamo-cortical activity in diseases such as PD.

Methods:
We explored the CBI using a cerebello-cortical PP TMS paradigm in 12 healthy participants. A suprathreshold test stimulus (TS) was applied over the motor cortex after the subthreshold conditioning stimulus (CS) applied over the ipsilateral cerebellum with an inter-stimulus interval (ISI) of 5 ms. The CS was set to 90% and the TS to 100% of rest motor threshold (rMT).

Results:
CBI was shown in 5 out 12 of the participants (-17,8% 13,5% SD), whereas a facilitation was shown in the 7 others participants (+36,3% 20% SD).

Conclusions:
These results suggest a great variability of cerebello-cortical interaction which may even be facilitatory contrary to the current model of CBI. This highlights inter-indivual differences to be further explored and may also predict effects of cerebellar stimulation.

P06*
Abnormalities of brain evoked potentials in patients with and without neuropathic pain after spinal cord injury

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Background and aims:
Neuropathic pain (NP) often affects individuals with spinal cord injury (SCI) disturbing their daily life. Here, we report the contribution of laser evoked (LEPs), ultra-late LEPs (uLEPs) and contact heat evoked potentials (CHEPs) techniques for quantifying the neurological dysfunction and identifying possible differences between persons with and without NP.

Methods:
24 SCI individuals (12 each group) were examined. Inclusion criteria: traumatic SCI below T1, at- or below-level SCI NP for pain group. Groups were matched by age, sex, lesion level and the AIS grade. LEPs and uLEPs measurements were done with Tm-YAG laser stimulation of the skin and CHEPs with heat-foil thermode, applied to: hand (control site) and test site (dermatome of altered sensation). LEPs, uLEPs and CHEPs were recorded from a single scalp electrode at Cz. Components were identified and analysed.

Results:
LEPs and CHEPs components (latencies, amplitudes) from the control site were normal and showed no differences between groups and were abnormal (absent) in 9 out of 12 patients in both groups from the test site. uLEPs reaction times (RT) analysis showed a diffuse distribution in group without pain in contrast to bimodal distribution in group with pain.

Conclusions:
LEPs, uLEPs and CHEPs methods were able to detect abnormalities of spino-thalamic tract in both groups of patients with SCI. From uLEPs RT results, we could suggest that patients with NP have partial nerve fiber preservation with abnormal functions causing pain, whereas patients without pain have total loss and therefore no pain.

P07*
Hemoglobin decrease and anemia in acute stroke treatment

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Background and Purpose:
Anemia is associated with worse outcome and survival in conservatively treated ischemic stroke patients, but the impact of anemia in intravenous thrombolysis or endovascular treatment has hardly been addressed. The aim of this study was to analyze the role of anemia on infarct evolution and outcome in acute stroke treatment.

Methods:
1158 consecutive patients treated between 2011 and 2015 were included. Baseline data and 3 months outcome assessed with the modified Rankin Scale were recorded prospectively. In a subset of 345 patients baseline DWI MRI lesion volumes were measured semi-automatically and in 135 of them final infarct volumes. Multivariable and linear regression analysis were used to determine predictors of outcome and infarct growth.

Results:
712 patients received endovascular treatment and 446 intravenous thrombolysis. Lower hemoglobin at baseline, at 24 h, and nadir until day 5 predicted poor outcome (OR 1.150 -1.279) and higher mortality (OR 1.131 -1.237) independently of treatment. Decrease of hemoglobin after hospital arrival, mainly induced by hemodilution, predicted poor outcome and had a linear association with final infarct volumes and the amount and velocity of infarct growth. Infarcts of patients with newly evolving anemia were twice as large as infarcts with normal hemoglobin levels.

Conclusion:
Anemia at hospital admission and any hemoglobin decrease affect outcome in acute stroke treatment negatively, probably by enlarging and accelerating infarct growth. Our results imply a possible adverse effect of hemodilution on penumbral evolution. Whether decrease of hemoglobin in acute stroke treatment could be avoided and avoidance improves outcome should be studied prospectively.

P08*
Fast-Track Versus Open-End Hospitalizations for Patients with Non-Disabling, Acute Ischemic Stroke Requiring Hospitalization

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Background & Aims:
Fast-track hospitalizations for patients with non-disabling, acute ischemic stroke (AIS) bear the potential to expedite return to daily life while optimizing the use of healthcare resources. This study aims at assessing the feasibility and safety of fast-track hospitalizations among patients with non-disabling AIS.

Design & Methods:
Retrospective cohort study on patients hospitalized in the Stroke Center of the University of Basel, Switzerland, between January 1st, 2014 and December 31st, 2015. Fast-track hospitalizations were defined as $\leq$72 hours. Patients with non-disabling AIS were those discharged directly home, i.e. not to a rehabilitation facility. The primary endpoint was the rate of unplanned rehospitalizations for any reason within 3 months from the index hospital discharge.

Results:
During the study period, 1'402 patients were hospitalized for AIS. Of these, 532 patients (38%) had a non-disabling AIS, and their median length of hospitalization was 6 days (IQR: 4-9). Fast-track hospitalizations have been realized among 15% of the analyzed patients with non-disabling AIS (80/532). Patients discharged per fast-track had less severe AIS, were treated less frequently with thrombolysis, and had a lower comorbidity index. The rates of unplanned rehospitalization within 3 months from hospital discharge did not differ between fast-track (8.8%) and open-end hospitalizations (8.6%). After adjusting for stroke severity, thrombolysis rate, and comorbidity, the difference in the rehospitalization odds remained non-significant.

Conclusion:
Among patients with non-disabling AIS, fast-track hospitalizations are feasible and do not seem to be associated with a higher risk of unplanned rehospitalizations.

P09*
Serum amyloid A – a novel predictor of stroke associated infections

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Backround & Aim:
The use of novel blood biomarkers to identify patients, vulnerable for post-stroke infections, may help to implement treatment more rapidly thus eventually reducing mortality. We addressed the value of Serum Amyloid A – Protein (SAA) in prediction of stroke-associated infections as compared to established inflammatory biomarkers.

Material & Method:
In this prospective, multicenter cohort-study we measured SAA of ischemic stroke patients within 72 h of symptoms onset. Patients with signs of infection on admission or before stroke onset were excluded. The primary outcome measure was any stroke-associated infections occurring within 5 days of hospital admission. Infections were diagnosed according to the criteria of the U.S. Centers for Disease Control and Prevention.

Results:
Of 283 patients, 60 (21.2%) developed an infection after onset of stroke. In the univariate analysis SAA was associated with the development of any infection with an OR of 1.51 95% CI, 1.26 – 1.82. After adjusting for all other predictors which were significantly associated with any infection (P-value cut off $\leq$ 0.001), SAA remained and independent predictor (adj. OR 1.36 95% CI, 1.02 – 1.82). Adding SAA to the regression model, the discriminatory accuracy improved, from 0.75 95% CI, 0.67 – 0.82 to 0.76 95% CI, 0.68 – 0.83 p<0.04 (likelihood ratio test). The addition of SAA to the multivariate model led to an NRI of 0.31 95% CI, -0.06 – 0.58.

Conclusion:
Among ischemic stroke patients, serum Amyloid A- Protein measured on admission is a novel independent predictor of infection after stroke. SAA improved the prediction model of patients who developed any infection.

P10*
Sensory abnormalities in unaffected area in individuals with spinal cord injury with and without neuropathic pain, a quantitative sensory testing study

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Background and aims:
Sensory profiling is suggested to understand mechanisms of neuropathic pain (NP). Therefore, quantitative sensory testing (QST) was compared in persons with spinal cord injury (SCI) with and without NP.

Methods:
QST according to the DFNS protocol was applied to 24 individuals with traumatic SCI below T1 (12 each group) on hand (control site) and test site (dermatome of altered sensation). For sensory function loss and gain score (LOGA) was applied. Ratings are L: loss, G: gain, 1: thermal, 2: mechanical, 3: thermal and mechanical symptoms. Groups were matched by age, sex, lesion level and AIS grade.

Results:
Mean values of QST parameters did not differ between groups. At the test site, both groups showed loss of function for CDT, WDT, TSL, MDT and/or VDT. LOGA scores were abnormal in all pain patients and in 11/12 of the pain-free group. Most frequent LOGA score was L3G0 (6/12: pain group, 7/12: pain-free group). In addition, patients from both groups had also abnormalities in the control site: Loss of function for MDT and/or VDT. LOGA scores were abnormal in 11/12 (pain group) and in 9/12 (pain-free group). Most frequent LOGA score for control site was L2G0 (5/12: pain group) but very heterogeneous in the pain-free group.

Conclusions:
Our study confirms altered spinothalamic and dorsal column functions below the level of injury independent of NP. Unexpectedly, abnormalities in dorsal column functions were also detected at the control site for both groups indicating changes in sensory processing rostral to the spinal lesion.

P11*
Mechanical thrombectomy using the new ERIC is similarly effective compared to the established stent retrievers in patients with acute ischemic stroke and large vessel occlusion

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Objective:
Mechanical thrombectomy in patients with acute ischemic stroke and proximal vessel occlusion in the anterior circulation using stent retrievers (SR) is highly effective and safe. The new Embolus Retriever with Interlinked Cages (ERIC)– designed to prevent the captured clot from shearing off during retraction – demonstrated efficacy and safety in smaller case series. The aim of this study was to assess efficacy of ERIC compared to SR in acute stroke patients with large vessel occlusion of the anterior circulation at the Stroke Center of Cantonal Hospital Aarau (Switzerland).

Method:
A single-center, open-label, retrospective cohort study of 132 consecutive patients with proven acute large vessel occlusion of the anterior circulation between 01/2014 – 06/2016. Primary outcome was successful recanalization (TICI 2b/3). Secondary outcome was good clinical outcome at discharge and 90 days (mRS Score of 0- 2).

Results:
91 patients were treated with ERIC. Successful recanalization rates were comparable in ERIC (88%) and SR (90%) treated patients (p=0.69). Clinical outcome was similarly beneficial in both groups (ERIC 49.4%, SR 42.5%, p=0.48)

Conclusion:
ERIC and SR show to be similarly effective in acute ischemic stroke with large vessel occlusion. ERIC might further strengthen the current armentarium of mechanical thrombectomy devices.

P12*
Neuro Elutax SV® Drug Eluting Balloon vs. Wingspan® Stent System in Symptomatic Intracranial High-grade Stenosis

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Aim:
Intracranial atherosclerotic stenosis is a well-known cause of ischemic stroke. Following the SAMMPRIS trial, medical treatment is favored over stenting. Drug eluting balloons (DEB) are widely used in coronary angioplasty showing better results than bare-surface balloons. There is little evidence of DEB employment in intracranial stenosis, especially of paclitaxel-eluted balloons (pDEB). The Elutax SV® (Aachen Resonance) is the first CE certificated pDEB for intracranial use. This study compared the pDEB Elutax® to angioplasty with the Wingspan® Stent System.

Methods:
A single-center, open-labeled, retrospective cohort-study of 19 patients with symptomatic intracranial high-grade stenosis either treated with pDEB Elutax® or Wingspan®/Gateway® from a tertiary stroke center in Switzerland.

Results:
42% patients (n=8) received pDEB Elutax®. Median clinical follow-up was 10 months for the Wingspan® Stent and 9.5 months for Elutax® (p=0.36). No differences were found in the clinical baseline characteristics with a median stenosis grade of 80% for the Wingspan® Stent and 81% for the Elutax® (p=0.87). The compound endpoint "ischemic re-event and restenosis" was significantly lower for Elutax® (13% vs 64%; p=0.03, OR 0.08 (CI: 0.007-0.93; p=0.043) compared to the Wingspan® Stent System.

Conclusion:
The pDEB ElutaxSV® may be a promising alternative treatment for patients with symptomatic high-grade intracranial stenosis showing a significantly lower recurrence rate compared to the Gateway®/Wingspan® with a similar safety profile. Further studies will be needed to definitively elucidate the role of pDEB in the management of symptomatic intracranial high-grade stenosis.

P13
Alpha synuclein characterization in skin biopsy as biomarker of Parkinson Disease

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Objectives:
The diagnosis of PD lays on clinical signs of motor involvement that appear later on in the disease when most of the substantia nigra neurons are already lost. Hence, there is a need for a biomarker that can identify patients at the beginning of disease or at risk of developing PD. We aim to establish skin biopsies in PD as a specific method for identifying physiological and pathological forms of alpha-synuclein (a-syn) linked to the progression of the disease.

Methods:
We started a three year-longitudinal, observational, controlled study in which we collect clinical data and skin biopsy at three anatomical sites (ankle, thigh and cervical area) in patients with PD patients. Immunofluorescence and biochemical analysis of a-syn, phosphorylated a-syn (p-asyn) and a-syn oligomers in skin nerves and intraepidermal nerve fiber density are assessed.

Results:
Fifty subjects have been enrolled so far. Preliminary results show that PD patients have significant differences in the amount of pathology-associated forms of a-syn in dermal nerves in comparison to healthy subjects. Furthermore, there is a significant axonal denervation in the cervical area which positively correlates to disease duration. Dermal denervation is stronger than epidermal nerve loss, in accordance to the localization of pathological a-syn deposits mainly in dermal autonomic structures.

Conclusions:
A-syn detection and characterization in skin biopsy is an easily accessible biomarker for Parkinson disease. Larger patients' number and longer follow-up are needed to establish the specificity and sensitivity of the technique.

P14
Absolute lymphocyte count recovery in patients with relapsing-remitting multiple sclerosis (RRMS) treated with cladribine tablets 3.5 mg/kg in CLARITY and CLARITY Extension

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Background and Objectives:
In CLARITY, cladribine tablets (CT) significantly reduced relapse rates, disability progression and MRI measures of disease activity over 2 years. The most commonly reported adverse event was lymphopenia, consistent with the mechanism of action for CT. The objective of the present

study was to investigate the absolute lymphocyte count (ALC) in patients with RRMS receiving 2 years of treatment with CT 3.5 mg/kg (CT3.5).

Materials and Methods:
Data from patients randomised to CT3.5 for 2 years in CLARITY or CLARITY Extension including time spent in the PREMIERE registry (N=685) were pooled to provide long-term follow-up data. Data from patients randomised to placebo in CLARITY and followed up in CLARITY Extension and PREMIERE are also reported (PBO; N=435).

Results:
At baseline (start of CLARITY or CLARITY Extension), median (Q1–Q3) ALC was 1.86×109/L (1.50–2.29) for CT3.5 and 1.91×109/L (1.54–2.32) for PBO. During Year 1, ALC in CT3.5 reached a nadir at 9 weeks post-treatment [1.00×109/L (0.80–1.30)]. At the end of Year 1 (48 weeks), median ALC had increased to 1.21×109/L (0.95–1.50). During Year 2, ALC in CT3.5 reached a nadir 7 weeks after re-treatment [0.81×109/L (0.60–1.04)], increasing to 1.03×109/L (0.80–1.30) at the end of Year 2 (96 weeks). At the end of Years 3 and 4 (144 and 192 weeks), ALC in the CT3.5 group (with no further treatment) increased to 1.36×109/L (1.02–1.65) and 1.40×109/L (1.10–1.81), respectively, reaching a final median ALC of 1.76×109/L (1.17–2.65) after 6.5 years (312 weeks). In PBO patients, median ALC values were between 1.69×109/L (1.45–2.05) and 1.95×109/L (1.59–2.38).

Conclusions:
Rapid reductions in ALC after CT3.5 treatment in Years 1 and 2 were followed by gradual returns toward baseline. Median lymphocyte counts were within normal range beyond Year 2 (96 weeks) in all patients for whom follow-up data are available.

P15
Testing head rotation and flexion is useful in Functional Limb Weakness

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Background:
Functional (psychogenic) Neurological Disorders (FND) are common and should be diagnosed using positive diagnostic features of internal inconsistency. There is however a lack of objective data regarding motor signs and a lack of signs relating to motor disorder affecting the upper body and neck.

Objective:
To provide specificity and sensitivy data on two axial motor signs: the sterno-cleido-mastoid and platysma signs.

Methods:
Thirty patients with DSM-5 motor FND and 40 organic controls with unilateral weakness were prospectively included. The SCM functional sign and platysma organic signs were systematically tested and compared between groups.

Results:
The SCM has a high specificity 90% (CI 77-96%) to detect FND when the platysma sign has 100%(CI:88-100%) to detect organic weakness. The co-occurrence of a positive SCM and a negative platysma sign in patients with unilateral weakness carries a 95% specificity (CI:83-99%) and 63% sensitivity(CI:44-80%).

Conclusion:
The SCM test and platysma signs can be used for the diagnosis of motor FND. The extent to which they add value to other validated signs (such as Hoovers) should be further evaluated.

P16
Swiss Survey on Parkinson's Disease patients: results from the feasibility evaluation of SYNAPSES (StudY to observe SafiNAmide in clinical Practice during the firSt post-commErcialization phaSe) study

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Introduction and aim
Safinamide is an α-aminoamide derivative, orally administered, with dopaminergic and non-dopaminergic actions. It is indicated for the treatment of patients with idiopathic PD as add-on therapy to a stable dose of levodopa alone or in combination with other PD medications in mid-to-late-stage fluctuating patients.

Here we describe the design of a Drug Utilization Study on safinamide conducted during the first post-commercialization phase, and the results of the study feasibility conducted in Switzerland.

Methods:
SYNAPSES study is an ongoing, observational, European, multicentre, retrospective-prospective cohort study. The primary objective is to describe the occurrence of adverse events in patients treated with safinamide in real-life

conditions, overall and stratified by age (>75) and relevant concomitant conditions.

Secondary objectives include the description of patients characteristics treated with safinamide according to clinical practice and safinamide treatment patterns in real-life setting.

The study will observe 1600 patients in 140 centres across 7 European countries, during 1 year after safinamide treatment initiation.

To evaluate the feasibility of conducting SYNAPSES study, Swiss neurologists underwent a phone structured interviews from December 2015 to May 2016. Sites were selected for the phone interview among the most relevant ones for PD management in Switzerland. Statistics are provided as overall proportions.

Results:
Among 5 Swiss sites selected for participating in the survey, 900 out of 1400 PD patients followed in 2015 were in fluctuating mid-to-late stage and had received a stable dose of levodopa. MAOB-inhibitors have been administered to 280 (31%) patients. Concomitant hepatic impairment and ophthalmological history were reported for 30 (3.3%) and 10 (1.1%) patients, respectively.

The portion of patients aged >75 years was 18% (N=160). Patients suffering from psychiatric conditions receiving fluoxetine or fluvoxamine therapy were 13 (1.4%).

Conclusion:
The quali-quantitative survey confirmed the feasibility of the study in Switzerland in the selected sites. The SYNAPSES study will improve the knowledge about safinamide safety profile and treatment patterns.

P17
Efficacy of Cladribine Tablets 3.5 mg/kg in High Disease Activity (HDA) Subgroups of Patients with Relapsing Multiple Sclerosis (RMS) in the CLARITY Study

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Background and Objectives:
In the CLARITY study, treatment with cladribine tablets (CT) vs placebo showed strong efficacy in a large cohort of patients with RMS over 2 years. Patients with HDA are at higher risk of relapses and disability progression; post hoc analysis of CLARITY may provide insights into the efficacy of CT in those patients. The objective of the present study was to compare the effects of CT 3.5 mg/kg (CT3.5) vs placebo in subgroups of CLARITY patients selected using two HDA definitions.

Materials and Methods:
CLARITY patients randomized to CT3.5 (N=433) or placebo (N=437) were retrospectively analyzed using two different HDA definitions based on relapse history, prior treatment, and MRI characteristics. Patients were categorized according to whether they had experienced a high relapse rate ([HRR] $\geq$2 relapses in the previous year) regardless of prior treatment, or a HRR with/without treatment failure ([HRR/TF] $\geq$2 relapses in the previous year, or $\geq$1 relapse in previous year while on DMD therapy and $\geq$1 T1 Gd+ or $\geq$9 T2 lesions).

Results:
In the overall CLARITY population, CT3.5 reduced the risk of 6-month confirmed EDSS progression by 47% (HR=0.53, 95% CI: 0.36; 0.79) vs placebo. A larger risk reduction for CT3.5 vs placebo of 82% was seen (HR=0.18 each, 95% CI: 0.08; 0.44 and 0.07; 0.43) in the HRR subgroup (p=0.0036 nominal significance vs non-HRR) and the HRR/TF subgroup (p=0.0037 nominal significance vs non-HRR/TF), indicating greater responsiveness to CT3.5 in patients identified by these criteria. Similar patterns were observed for time to 3-month EDSS progression. ARR was lower with CT3.5 than placebo in the overall population (RR=0.42, 95% CI: 0.33; 0.52), and even lower with HRR (RR=0.32, 95% CI: 0.22; 0.47) and HRR/TF (RR=0.33; 95% CI: 0.23; 0.48), each p<0.0001 vs placebo). Strong treatment effects on radiological markers were observed in each HDA subgroup.

Conclusions:
In the CLARITY study, patients identified by HDA criteria showed clinical and MRI responses to CT3.5 that were generally better than, or at least comparable with, the outcomes seen in the overall CLARITY population.

P18
Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Erenumab (AMG 334) in Migraine Prevention: Primary Results of the STRIVE Trial

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Objective:
To evaluate the efficacy and safety/tolerability of erenumab (AMG 334), a fully human anti-CGRP receptor monoclonal antibody, in a phase 3 trial of subjects with episodic migraine (EM) (NCT02456740).

Methods:
In this multinational, double-blind, placebo-controlled trial, adults with EM (n = 955) were randomized 1:1:1 to subcutaneous monthly placebo or erenumab 70 mg or 140 mg for 24 weeks. The primary endpoint was change from baseline in mean monthly migraine days (MMDs) over weeks 13-24.

Secondary endpoints were $\geq$ 50% reduction in MMDs, change in mean acute migraine-specific medication days, and change in mean Physical Impairment (PI) and Impact on Everyday Activities (EA) scores (as measured by the Migraine Physical Function Impact Diary [MPFID]). P-values for pairwise comparisons of each erenumab dose with placebo are presented. Statistical significance was determined after adjustment for multiple comparisons.

Results:
Subjects reported 8.3 MMDs at baseline and experienced -3.2, -3.7, and -1.8-day reductions in the 70 mg, 140 mg, and placebo groups, respectively ($p < 0.001$ for both). A $\geq$ 50% reduction in MMDs was achieved by 43%, 50%, and 27% in the 70 mg, 140 mg, and placebo groups ($p < 0.001$ for both), and monthly acute migraine-specific medication days were reduced by -1.1, -1.6, and -0.2 days ($p < 0.001$ for both). Subjects had improved PI scores (-4.2, -4.8, -2.4 points in the 70 mg, 140 mg, and placebo groups; $p < 0.001$) and EA scores (-5.5, -5.9, and -3.3 points; $p<0.001$). The safety/tolerability profile of erenumab was similar to placebo; subjects most frequently reported nasopharyngitis, upper respiratory tract infection, and sinusitis.

Conclusion:
Erenumab 70 mg and 140 mg significantly reduced migraine frequency and use of migraine specific medications, reducing migraine's impact on physical impairment and everyday activities compared with placebo in this EM trial. Numerically greater efficacy was observed for the 140 mg dose consistently across all endpoints.

P19
The contribution of the blink reflex on diagnostic value in patients with trigeminal neuralgia and/ or temporomandibular joint disorder

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Background & Aim:
Temporomandibular joint (TMJ) disorder is divided in two separate subgroups: osteoarthritis and variations of anterior disc displacement. Recognizing conditions such as TMJ disorder and trigeminal neuralgia (TN) is important for managing non-dental orofacial pain. The aim of this study was to evaluate the diagnostic value of blink reflex in a sample of patients with TMJ disorders and trigeminal neuralgia (TN).

Material & Methods:
Forty two patients who were examined for clinical symptoms and signs of orofacial pain of non-dental origin participated in this study which was carried out between 2001 and 2016 in cooperation between the neurological outpatient clinic for pain and a subspecialist dental practice for orofacial pain. TMJ diagnosis (all patients with osteoarthritis except one patient with disc displacement) was confirmed by means of magnetic resonance imaging (MRI). As a part of an interdisciplinary collaboration, the patients underwent neurological diagnostics, including blink reflex. The study included 21 patients (group G-1; mean age 58.3 years, only one male patient) with determined co-morbidity of TMJ disorder and TN, and 23 patients (group G-2; mean age 56.4 years, 5 male patients) with only idiopathic TN confirmed. Pain intensity was rated on a visual-analogue scale (VAS with range 0-10). Reflex blinks were measured by electrographic recordings of the evoked muscle action potentials. The level of anxiety was evaluated by Spielberger's psychological measuring instrument State-Trait Anxiety Inventory (STAI).

Results:
The groups G-1 and G-2 of patients did not differ according to age ($p>0.05$). TMJ pain on the VAS amounted to 6.91 in patients of G-1. There were no differences ($p>0.05$) regarding the TN related pain on the VAS between G-1 patients (9) and G-2 patients (8.74). Blink-reflex parameters were almost equally abnormal in G-1 patients (40%) and G-2 patients (39.1%). Similar values of high anxiety scores

were found in both groups of patients - STAI 1: 45.19/46.57 and STAI 2: 46.05/43.39 respectively (p>0.05).

Conclusion:
Although TMJ diagnosis is the most common gold standard for MRI, there is no gold standard for assessing neuropathic pain caused by idiopathic NT. The absence of confirmation of trigeminal nerve abnormalities by blink reflexes (positive finding in about 40% of patients in both groups) confirms the fact that TN is not related to large myelinate fiber dysfunction.

P20
Patient-Reported Outcomes in Chronic Migraine Patients Receiving Placebo or Erenumab (AMG 334) in a Phase 2, Randomized, Double-blind Study

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Objective:
To evaluate patient-reported outcomes in a phase 2 clinical trial of erenumab (AMG 334) for chronic migraine (CM) (NCT02066415).

Background:
Migraine is a disabling disease associated with substantial burden on patients and society. Erenumab is a fully human anti-CGRP receptor monoclonal antibody in clinical development for migraine prevention.

Design/Methods:
667 adults with CM were randomized (3:2:2) to monthly subcutaneous placebo or erenumab 70 mg or 140 mg. Primary and secondary endpoints were assessed at week 12. Exploratory endpoints included: change from baseline in migraine-specific QoL measured by the Migraine-Specific Quality-of-Life Questionnaire (MSQ), headache impact measured by the Headache Impact Test (HIT-6), and migraine-related disability measured by the Migraine Disability Assessment Test (MIDAS). No formal hypothesis was tested; p-values (placebo vs erenumab dose-groups) are descriptive.

Results:
Baseline scores were similar between groups. Improvements were observed for all endpoints in both erenumab groups at week 12. The mean (95% CI) changes for placebo vs 70 mg and 140 mg groups, respectively, were 11.8 (9.4,14.1) vs 17.7 (14.9,20.6), p=0.002 and 19.1 (16.3,22.0), p<0.001 for MSQ role function-restrictive scores, 8.9 (6.8,11.0) vs 13.0 (10.5,15.6), p=0.013 and 13.8 (11.3,16.4), p=0.003 for MSQ role function-preventive scores, and 9.9 (7.3,12.5) vs 18.2 (15.0,21.3), p<0.001 and 18.8 (15.6,21.9), p<0.001 for MSQ emotional-function scores. Mean changes in HIT-6 scores were -3.1 (-3.9,-2.3) for placebo vs -5.6 (-6.5,-4.6), p<0.001 for both erenumab groups. Corresponding mean changes in the placebo, 70 mg, and 140 mg dose-groups were -7.5 days (−12.4,-2.7) vs -19.4 days (-25.2,-13.6), p=0.002 and -19.8 days (-25.6,-14.0), p=0.001 for MIDAS days of lost productivity, -5.2 days (-8.0,-2.4) vs -10.3 days (-13.6, -6.9), p=0.023 and -10.2 days (−13.6,−6.8), p=0.024 for MIDAS-absenteeism, and -1.9 days (-4.7,0.8) vs -9.3 days (-12.6,-6.1), p<0.001 and -9.9 days (-13.2,-6.7), p<0.001 for MIDAS-presenteeism.

Conclusions:
Erenumab-treated CM patients experienced consistent and clinically significant improvements in migraine-specific QoL and reductions in headache impact and disability.

P21
Brain Volume Loss Correlates With Long-term Disability Worsening in Patients With MS: SIENA Analysis of TEMSO MRI Data

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Objective:
In TEMSO (NCT00134563), Structural Image Evaluation using Normalisation of Atrophy (SIENA) analysis showed that teriflunomide, a once-daily oral immunomodulator for relapsing-remitting MS (RRMS), significantly reduced brain volume loss (BVL) vs placebo. Here, we further investigate the association between BVL and long-term disability worsening (DW) in TEMSO and its extension (NCT00803049).

Materials and Methods:
Blinded SIENA analysis of patient scans from TEMSO (N=969) determined BVL in Year 1 and Year 2.

A 13-trial meta-analysis evaluating correlation between treatment effects on BVL and DW in patients with RRMS was updated to include SIENA analysis of BVL in TEMSO.

To evaluate the predictive value of BVL during the first 2 years on 12- and 24-week confirmed DW (CDW) over 5 years, the total population (n=709) was categorized into quartiles (Q1–Q4) defined by percentage brain volume

changes from baseline to Year 2. Probability of DW was derived from Kaplan–Meier estimates. Quartiles were compared using Cox's proportional hazards model (adjusted for covariates).

Results:
Following SIENA analysis of BVL in TEMSO, treatment effects on DW and BVL correlated more strongly vs the original meta-analysis (coefficient of determination for relationship between BVL and DW strengthened from 0.48 to 0.61).

In quartile analyses, Q4 (most BVL from baseline to Year 2) had a significantly higher probability of 12- and 24 week CDW after 5 years vs Q1 (least BVL): Q1 vs Q4 hazard ratios, 0.611 (95% confidence interval [CI] 0.432, 0.865; P=0.0055) and 0.566 (95% CI 0.386, 0.830; P=0.0036) for 12- and 24-week CDW after 5 years, respectively.

Conclusions:
These analyses support the correlation between BVL and (long-term) CDW and the effects of teriflunomide on these outcomes, as well as highlight the predictive value of BVL earlier in the disease course.

P22
Durable efficacy of cladribine tablets in patients with multiple sclerosis: analysis of relapse rates and relapse-free patients in the CLARITY and CLARITY Extension studies

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Background & Objectives:
In CLARITY, giving CT annually for 2 years, significantly reduced relapse rates and slowed disability progression vs PBO. The objective of the present study was to assess the efficacy of 2-years' additional treatment with cladribine tablets (CT) or placebo (PBO) in patients with relapsing multiple sclerosis (RMS) in an extension (EXT) to the CLARITY trial.

Materials and Methods:
In CLARITY EXT, patients who had received PBO in CLARITY were assigned to CT 3.5mg/kg body weight; those who received CT (3.5 or 5.25mg/kg) in CLARITY were re-randomised (2:1) to CT 3.5mg/kg or PBO. Annualised relapse rates (ARR) and proportions of patients qualifying relapse free were compared at different times (i.e. CLARITY vs CLARITY EXT) within the same treatment groups: patients treated with CT 3.5mg/kg in CLARITY and PBO in CLARITY EXT (n=98); CT 3.5mg/kg in CLARITY and CT 3.5mg/kg in CLARITY EXT (n=186); CT 5.25mg/kg in CLARITY and CT 3.5mg/kg in CLARITY EXT (n=186); PBO in CLARITY and CT 3.5mg/kg in CLARITY EXT (n=244).

Results:
No significant differences in ARR were seen for CLARITY vs CLARITY EXT except in patients who received PBO in CLARITY and CT 3.5mg/kg in CLARITY EXT (0.26 vs 0.10, $p<0.0001$). During CLARITY EXT, >70% of patients in each group qualified relapse free; the only significant difference between CLARITY and CLARITY EXT was seen in patients treated with PBO in CLARITY and CT 3.5mg/kg in CLARITY EXT (58.0% vs 79.6%, $p<0.0001$).

Conclusions:
Comparing CLARITY with CLARITY EXT demonstrates that CT produced durable clinical benefits: patients who received CT in CLARITY and PBO in CLARITY EXT maintained low relapse rates throughout. Patients who received CT in CLARITY and CT in CLARITY EXT showed no additional benefit vs CT treatment in CLARITY only. For patients who received PBO in CLARITY, switching to CT in CLARITY EXT significantly reduced ARR and increased the proportion of relapse-free patients.

P23
Synergistic effect of Vitamin D on Methylprednisolone-induced T-cell apoptosis

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Background:
Methylprednisolone (MPS) pulse therapy is the first-line therapy of MS-relapses. Nevertheless, some patients do not adequately respond to treatment. Thus, strategies to improve glucocorticoid (GC) efficacy are needed, especially in GC-resistant MS patients. Vitamin D (VD) deficiency is a risk factor for MS. In this context, we investigated the effects of 1,25(OH)2D3 (VD) on MPS-induced apoptosis in T-cells, one presumed mechanism of GC action in MS.

Methods:
The influence of VD (100nM, 1 μM) on MPS-induced apoptosis (MPS 2.5 mM) was investigated in vitro in

steroid resistant Jurkat cells (T-cell leukemia; n=5). C57BL/6 mice were treated in vivo with VD (20ng/d for 3 days) or vehicle control. Afterwards, splenic T-cells were isolated and incubated in vitro with MPS for 24 hours (6nM, 60nM and 600nM; n=5). Blood samples from 7 MS patients with steroid responsive and 5 MS patients with steroid resistant relapses with indication for plasma exchange were collected after MPS pulse therapy. T-cells were incubated in vitro for 72 hours with VD (10nM) and MPS (75 μM). In all experiments apoptosis was measured by flow cytometry using Annexin V/PI staining.

Results:
In Jurkat cells, VD monotherapy did not induce apoptosis compared to DMSO-control. However, VD augmented MPS-induced apoptosis dose dependently 1.37 (p>0,05) to 1.92-fold (p<0,05) .The synergistic effect of VD and MPS was also present in mice pre-treated with VD in vivo (x-fold increase of T-cell apoptosis: VD20ng+MPS 6nM (1.8-fold, p<0.05), VD20ng+60nM (1.7-fold, p<0.05), VD20ng+600nM (1.2-fold, p>0.05)). In MS patients with GC-responsive relapses, MPS-induced T-cell apoptosis in vitro was 48.5% (SD 17.8, p>0.05). Further VD did not lead to any additional effect on MPS-induced T-cell apoptosis (p>0.05) in GC-responsive patients. In contrast, patients without sufficient MPS response during MS relapse showed an increase of MPS-induced T-cell apoptosis in vitro from 38% (IQR 15.65) to 40.6% (IQR 14.3) by co-incubation with VD (p<0,05).

Conclusion:
This study showed an effect of VD on MPS-induced apoptosis in Jurkat cells, murine and human T-cells. This may indicate approaches to enhance efficacy of MPS-treatment in MS patients with steroid-resistant relapses.

P24
Broken heart syndrome as clinical correlate of MS disease activity - a case report

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Background:
Takotsubo Cardiomyopathy (TC) can be associated with relapsing remitting multiple sclerosis (RRMS), representing a diagnostic challenge. We present a case of rapid evolution of acute heart failure (AHF) as manifestation of RRMS with no other clinical signs for demyelinating inflammatory CNS disease, diagnostic work-up and therapeutic strategy.

Methods:
Case presentation including clinical and paraclinical data, longitudinal evaluation of AHF as measured by thransthoracic echocardiography (TTE) and findings incl. MRI leading to RRMS diagnosis. The therapeutic strategy is compared to cases in literature.

Results:
A 17 year-old female patient presented at the emergency department with dyspnoea, sweating and general malaise. In TTE, an acute left ventricular dysfunction (LVD) of 15% was detected. Coronary angiography was normal. Due to respiratory distress, artificial ventilation was necessary. Endomyocardial biopsy showed vacuolisation without other pathology indicating stress-induced cardiopathy. Adrenal/renal MRI showed no signs of phaeochromocytoma or renal artery stenosis.

Medical history revealed transient left arm paresis two years before and 2 episodes of partially remitting vertigo and right sensory hemisyndrome some weeks prior to a AHF. Brain MRI showed multiple acute and chronic inflammatory demyelinating lesions with extensive brainstem involvement, especially an acute lesion in the medulla oblongata fulfilling McDonald Criteria 2010. Lumbar puncture and exclusion of alternative diagnoses revealed no abnormalities. LV function improved to 55% after 5 days of symptomatic treatment for AHF.

Steroid pulse therapy was given at day 6-8 after onset AHF. Immunomodulatory therapy was installed (dimethylfumarate) after 6 weeks. TTE controls after 1, 3 and 6 months showed normal LV function. To date, no new neurological symptoms have occurred.

Conclusion:
Life threatening TC can represent dramatic early onset of RRMS and is here reported to be the first symptom leading to medical consultation. Concordant to a cases described in the literature our patient showed a medullary lesion on brain MRI probably responsible for altering the sympathetic neural regulation, subsequently leading to sympathetic overactivation. Awareness about the potential association of TC to RRMS, prompt diagnosis and early treatment are essential.

P25
Rationale, Design and Methods of the TREAT-MS study

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Randomized controlled trials (RCTs) are the "gold standard" for generating evidence of the efficacy and safety of a drug. However, enrolment criteria, timelines, and atypical

comparators of RCTs limit relevance to standard clinical practice. Real-world data (RWD) provide longitudinal information on comparative effectiveness and tolerability of drugs, as well as their impact on resource use, medical costs, pharmaco-economic outcomes, and patient-reported outcomes. Regarding alemtuzumab, the collected data from clinical studies provide a sound body of evidence on the efficacy and the safety profile in the treatment of RRMS. However, data on the utilization and the treatment outcomes of the drug under clinical practice conditions are limited to few reports on small cohorts. Here we describe the rationale, design and methods of the recently established non-interventional open, uncontrolled, prospective, multicenter, and long-term study TREAT-MS (non-interventional long-Term study foRobsErvAtion of Treatment with Alemtuzumab in active relapsing-remitting MS).The main goal of TREAT-MS is to establish a broader real-world dataset on the utilization and safety, effectiveness, quality of life and other aspects of the drug in every day clinical practice. The study encompasses a risk management plan to recognize and counter each occurring adverse effect as early as possible, which will also support physicians who treat MS patients with alemtuzumab in their daily clinical practice. TREAT will additionally investigate how the risk management plan is transferred into clinical practice which is crucial for alemtuzumab with necessary long term monitoring.

P26
Case Report: A rare cause of third cranial nerve palsy

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Introduction:
Neurovascular compression syndromes are most commonly seen in affection of the 5th cranial nerve (CN V) causing trigeminal neuralgia, followed by CN VII (hemifacial spasm), CN VIII (vestibular paroxysmia) and CN IX (glossopharyngeal neuralgia). Affection of other cranial nerves is less common. We report a case of CN III palsy due to direct vascular compression by the posterior cerebral artery (PCA).

Clinical presentation:
A 41-year old previously healthy male patient presented with episodic painless diplopia, disturbed vision and ptosis of his right eyelid. He suffered two episodes with sudden-onset lasting 5 and 20 minutes. He was symptom-free between the attacks. During the third episode clinical examination revealed features of isolated right third nerve palsy with mydriasis, ptosis and gaze paralysis of adduction, elevation and depression. The patient had no history of diabetes, migraine or contact to parasympatholytics. Imaging studies (cranial CT, CT angiography, Doppler ultrasonography) showed no hints for relevant atheromatosis, stroke, intracranial hemorrhage, aneurysm or tumor. Laboratory studies and cerebrospinal fluid were normal. Cranial MRI disclosed neurovascular compression of the right oculomotor nerve by the P1 segment of the right PCA. Clinical follow-up visits showed spontaneous resolution of his episodes.

Conclusion:
Isolated CN III palsy due to direct vascular compression is a rare but clinically very important condition. It is most commonly caused by aneurysms, while compression by the PCA is less common. Cranial MRI is essential for diagnostics. The use of carbamazepine might be considered as therapeutical option according to other neurovascular compression syndromes.

P27
Case Report: Overlap of neuromyelitis optica spectrum disorder with autoimmune encephalitis and persistency of high-titer antibodies against Myelin Oligodendrocyte Glycoprotein

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Background:
Antibodies against myelin oligodendrocyte glycoprotein (MOG Ab) are increasingly recognized in pediatric patients with acute disseminated encephalomyelitis (ADEM), adults with neuromyelitis optica spectrum disorders (NMOSD), in uni- or bilateral optic neuritis (ON), multiple sclerosis (MS) and anti-N-methyl-D-aspartate receptor antibodies (NMDA Ab) positive encephalitis. We present a case of a 17-year-old patient with overlap of NMOSD with high-titer MOG Ab and NMDA Ab negative autoimmune encephalitis.

Methods:
Clinical course and paraclinical features (blood, cerebrospinal fluid, MRI, EEG, optic coherence tomography (OCT), anti-MOG testing with cell-based assay). The follow-up comprises 28 months.

Results:
The 17-year-old patient developed bilateral ON with involvement of the chiasma (confirmed by MRI and OCT) occurring four weeks after a flu-like infection. He fully recovered after high-dose steroid therapy.

Two months later, he experienced a generalized epileptic seizure followed by three consecutive seizures during the next month.

Shortly after the last seizure, spastic paraparesis, sensory symptoms, micturition complaints, cognitive impairment, and aphasia manifested. MRI showed encephalitis with predominantly left-hemispheric extensive cerebral lesions with restricted diffusion and subacute longitudinal myelitis with partial contrast enhancement.

High-titer MOG Ab were detected and remained positive after 13 and 25 months, also under immunosuppressive treatment. Aquaporin 4 antibodies (AQP4 Ab), NMDA Ab, onconeural and neuronal surface antibodies were negative. Blood and CSF parameters including oligoclonal bands were normal. He recovered after high-dose steroid therapy and rehabilitation within two months. In next three months, three seizures occurred under anticonvulsants. Two weeks after the last seizure, he developed a new short-segment myelitis with sensory symptoms and resolution after high-dose steroid therapy. After initiation of azathioprine, he has remained stable without residual symptoms for currently 23 months.

Conclusion:
This case suggests overlap of MOG ab positive NMOSD and autoimmune encephalitis negative for NMDA Ab. There are rare cases of autoimmune encephalitis associated with MOG ab, still, further investigations are needed to elucidate, whether MOG ab or other antibodies contribute to pathogenesis. This case confirms the need of long-term immunosuppressive therapy to achieve remission in MOG Ab NMOSD.

P28
Cladribine tablets in the treatment of patients with multiple sclerosis: an integrated analysis of safety from the multiple sclerosis clinical development program

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Background and Objectives:
Treatment with cladribine tablets in the CLARITY, CLARITY Extension and ORACLE-MS studies demonstrated efficacy vs placebo across a spectrum of patients with both early and relapsing multiple sclerosis (RMS). The adverse event (AE) profiles from these individual studies have been presented elsewhere. Pooling safety data for integrated analyses is an established route to a comprehensive characterisation of the safety profile of a therapy. The objective of this study was to report the emergent overall adverse event (AE) profile from an integrated pool of safety data collected in trials which evaluated cladribine tablets as monotherapy, in patients with early or RMS.

Materials and Methods:
The monotherapy oral cohort (patients who received cladribine tablets only) was derived from CLARITY, CLARITY Extension, ORACLE-MS and the PREMIERE registry, and included 923 patients who received cladribine tablets 3.5 mg/kg: 3432.65 patient years exposure for this dose. 641 patients received placebo in this cohort (2025.97 patient years). Adjusted adverse events incidences per 100 patient years (Adj-AE per 100PY) were calculated for the integrated analyses.

Results:
The mean study period for patients was 194 weeks in the monotherapy oral 3.5 mg/kg cohort and 165 weeks in the placebo cohort; age (36.5 years), proportion of females (66.3%) and prior disease modifying drug experience were balanced among groups. Adj-AE per 100PY rates for cladribine 3.5 mg/kg and placebo were: treatment emergent AE (TEAE): 103.3 and 94.3; TEAEs leading to discontinuation: 2.1 and 1.1; serious AEs: 4.0 and 3.6; serious AEs leading to death: 0.26 and 0.25. With regard to the known, expected events with cladribine treatment, Adj-AE per 100PY for lymphopenia (preferred term) were 7.94 (3.5 mg/kg) and 1.06 (placebo), and for system organ class of infection and infestations, 24.93 (3.5 mg/kg) and 27.05 (placebo); herpes zoster (preferred term), 0.83 (3.5 mg/kg) and 0.20 (placebo). Adj-AE per 100PY for the system organ class of neoplasms, benign, malignant and unspecified were 1.14 and 1.01, for cladribine and placebo, respectively.

Conclusions:
The AE profile for cladribine tablets 3.5 mg/kg as a monotherapy has been well-characterised in a pooled population of patients with early and active MS. Lymphopenia was expected from the mode of action of cladribine

P29
Rapidity of Onset of Ocrelizumab Clinical Efficacy in Relapsing Multiple Sclerosis

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Objective:
To assess the dynamics of onset of ocrelizumab effect on the risk of relapse over time and relapse rate by epoch compared with interferon beta-1a (IFNβ-1a) in the pooled OPERA I and OPERA II studies in relapsing multiple sclerosis (RMS).

Background:
In RMS, rapid control of clinical disease activity is an important treatment goal to minimize subsequent disability worsening. Ocrelizumab, a humanized monoclonal

antibody that selectively targets CD20compared with IFNβ-1a over 96 weeks in two identical phase III trials in RMS (OPERA I and OPERA II). + B cells, was superior in reducing clinical and MRI measures of disease activity.

Design/Methods:
In the OPERA studies, patients were randomized 1:1 to receive intravenous ocrelizumab 600 mg every 24 weeks or subcutaneous IFNβ-1a 44 μg three times weekly for 96 weeks. The primary endpoint in the individual studies was annualized protocol-defined relapse rate (ARR) by Week 96. The risk of first onset of protocol-defined relapse at various time points, and ARR through Week 96 and at 8-, 24- and 48-week epochs in the pooled OPERA studies were evaluated in post-hoc exploratory analyses.

Results:
In the pooled analysis, ocrelizumab reduced ARR from baseline to Week 96 by 46.5% vs IFNβ-1a (0.156 vs. 0.291; p<0.0001). Kaplan–Meier analysis showed that ocrelizumab reduced the cumulative probability of relapse vs IFNβ-1a as early as Week 8 (hazard ratio: 0.02 vs. 0.04, p=0.0142). Reductions in ARR with ocrelizumab vs IFNβ-1a were also observed in the baseline−Week 8 (0.12 vs. 0.27; p=0.0045), baseline−Week 24 (0.18 vs 0.30; p=0.0009) and baseline−Week 48 (0.16 vs. 0.30; p<0.0001) epochs.

Conclusions:
In a pooled analysis of the OPERA studies, ocrelizumab reduced relapse occurrence vs IFNβ-1a throughout 96 weeks, with significant reductions observed by Week 8.

P30
Safety of Ocrelizumab in Multiple Sclerosis: Updated Analysis in Patients with Relapsing and Primary Progressive Multiple Sclerosis

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Objective:
To report updated safety data from the controlled and open-label extension (OLE) periods of the clinical trials of ocrelizumab in relapsing (RMS) and primary progressive (PPMS) multiple sclerosis.

Background:
The safety and efficacy of ocrelizumab have been characterized in Phase III trials in RMS (OPERA I and OPERA II) and PPMS (ORATORIO). Ongoing safety reporting on disease-modifying therapies for MS is crucial to understanding the long-term benefit-risk profile.

Design/Methods:
The OPERA studies randomized patients (1:1) to ocrelizumab 600 mg every 24 weeks or subcutaneous interferon beta-1a (IFNβ-1a) 44μg three times weekly for 96 weeks. ORATORIO randomized patients (2:1) to ocrelizumab 600 mg or placebo every 24 weeks for >120 weeks. Phase III patients completing the controlled treatment period could enter an ocrelizumab OLE phase. A phase II study in RRMS randomized patients (1:1:1:1) to ocrelizumab 600 mg, ocrelizumab 2000 mg, placebo, or intramuscular IFNβ-1a through Week 24, followed by ocrelizumab every 24 weeks through Week 96; after a treatment-free period, eligible patients entered a long-term OLE administering ocrelizumab 600 mg every 24 weeks. Safety outcomes are reported for all patients dosed with ocrelizumab in phase II and III MS clinical trials, including patients who switched to ocrelizumab from comparators.

Results:
As of 20 January 2016, 2279 MS patients received ocrelizumab, resulting in 5711 patient-years (PY) of exposure. Reported rates per 100PY (95% confidence interval) were: adverse events (AEs) 242 (238, 246), serious AEs 6.97 (6.30, 7.69), infections 73.6 (71.4, 75.9), serious infections 1.80 (1.47, 2.19), and the incidence rate of malignancy was 0.440 (0.285, 0.649). A June 2016 data cut available for malignancies shows an incidence rate of 0.402 (0.263, 0.589).

Conclusions:
The updated safety profile in the ocrelizumab MS all-exposure population is generally consistent with the controlled treatment period for the RMS and PPMS populations. Additional data from ongoing follow-up will be reported.

P31
The Association Between Confirmed Disability Progression and Patient-Reported Fatigue in PPMS Patients in the ORATORIO study

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Objective:
To describe changes in fatigue in patients with/without 12-week confirmed disability progression (CDP) and the impact of ocrelizumab on this measure.

Background:
Fatigue is commonly reported by patients with multiple sclerosis (MS); however, its relationship with CDP is not well understood in patients with primary progressive MS (PPMS).

Design/Methods:
In ORATORIO, the self-reported Modified Fatigue Impact Scale (MFIS) was administered at baseline, Week 48, and Week 120; 12-week CDP (defined as an increase of $\geq$1/$\geq$0.5 points on the Expanded Disability Status Scale if the baseline score was $\leq$5.5/>5.5 points, respectively) was assessed throughout the trial. The relationship between changes in fatigue and 12-week CDP was assessed in the combined treatment groups through analysis of covariance (ANCOVA), adjusting for baseline MFIS score, region, and age group. This ANCOVA was then stratified by treatment group.

Results:
Patients with CDP had a significantly greater increase in fatigue from baseline than patients without CDP (adjusted mean [95% CI] 3.763 [1.479, 6.047] vs –0.978 [–2.941, 0.986]; p=0.0003). A similar pattern was seen across the MFIS subscales: physical (p=0.0001), cognitive (p=0.0241), and psychosocial (p=0.0042). In patients without CDP, ocrelizumab-treated patients had a significantly greater decrease in fatigue from baseline compared with placebo-treated patients (adjusted mean [95% CI] –2.849 [–4.848, –0.850] vs 0.893 [–2.166, 3.952]; p=0.0337). In patients with CDP, the increase in fatigue from baseline was numerically lower in ocrelizumab- vs placebo-treated patients (adjusted mean [95% CI] 2.662 [–0.049, 5.373] vs 4.864 [1.623, 8.106]; p=0.28).

Conclusions:
In ORATORIO, CDP was strongly associated with increased fatigue, underlining the importance of preventing disease progression in patients with PPMS. Furthermore, the significant reduction in fatigue reported by patients without 12-week CDP while treated with ocrelizumab compared with placebo suggests a beneficial effect of ocrelizumab, even in those PPMS patients without documented disease progression.

P32
Teriflunomide in Routine Clinical Practice: Study Design and Baseline Characteristics of the TACO Study

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Objective:
Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting MS (RRMS). Two phase 3 studies in patients with relapsing forms of MS (TEMSO, NCT00134563; TOWER, NCT00751881) showed consistent efficacy across key clinical and MRI outcome measures (MRI assessed in TEMSO only) and a well-characterized safety profile. The phase 4 TACO study (Teriflunomide in RRMS patients Assessing Clinical benefit and patient-reported Outcomes in real-life medical practice) will assess patient-reported outcomes (PROs) and clinical measurements in a real-world setting in a Swiss RRMS cohort. Here we describe baseline characteristics of patients enrolled in the TACO study.

Materials and Methods
TACO is a national, prospective, single-arm, multicenter, open-label study that evaluates PROs in patients with RRMS receiving teriflunomide once daily in Switzerland. Study duration is 24 months (12-month core study; 12-month extension follow-up) with a target recruitment of 70 patients from 12 centers. The primary outcome is quality of life measured by the validated Multiple Sclerosis Impact Scale (MSIS-29) questionnaire. Secondary outcome variables include relapses, disability progression as well as fatigue (Fatigue Scale for Motor and Cognitive Functions), depression (Hospital Anxiety and Depression Scale), and cognition (Multiple Sclerosis Neuropsychological Screening Questionnaire). Safety, adherence to safety monitoring, treatment satisfaction, and health economic outcomes are also evaluated.

Results:
As of June 25, 2017, 56 patients were enrolled in the study. The mean (standard deviation; SD) age was 51.01 (12.93) years, and 64% of the patients were female. The mean (SD) time since first symptom was 14.35 (10.50) years; mean (SD) baseline Expanded Disability Status Scale score was 2.4 (1.3).

Conclusions
TACO will provide valuable information on the current use of teriflunomide in the Swiss clinical setting, including PROs, safety, and efficacy. These outcomes will complement data from other studies of teriflunomide in the real-world setting.

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