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Conference Report

Abstracts of the 2024 Annual Meeting of the Swiss Neurological Society (SNS): Quo Vadis Neuroinflammation? From Pathophysiologic Advances to Novel Treatment Strategies

Swiss Neurological Society (SNS) †

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Abstract: On behalf of the SNS, we are pleased to present the Abstracts of the Annual Meeting which is held at the Congress Center in Basel, Switzerland, from 6–7 June 2024. In total, 83 abstracts were selected, whereof we include 8 abstracts for the Plenary Sessions, 6 abstracts for the SAYN GemSession, 30 abstracts for Poster flash presentations, and 39 abstracts as ePosters. We congratulate all the presenters on their research work and contributions.

Keywords: neurology; stroke; cerebrovascular; movement disorders; neurodegenerative; neuroinflammatory; neuroinfectious diseases; neuromuscular; neurodegenerative; neurovascular; neurotrauma; neuroimmunology; neuro-oncology; spine and pain; biological psychiatry; epilepsy and sleep disorders; neuropsychology; behavioral neurology; clinical neurophysiology; headache; neuropathology; neurorehabilitation

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O01

Serum Biomarkers Capture Disease Progression in Multiple Sclerosis

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Aims: Blood biomarkers that capture disease progression independent of relapse activity (PIRA) in MS are lacking. The aim of our study was to investigate the longitudinal dynamics of serum glial fibrillary acidic protein (sGFAP) and neurofilament light chain (sNfL) levels in people with MS (PwMS) starting B cell depleting therapy (BCDT), and to study the association with future PIRA events.
Methods: Longitudinal data from 318 patients (1302 samples) under BCDT were leveraged from the Swiss MS Cohort. Serum GFAP levels were also determined in 2861 healthy controls (4943 samples), which served as a reference to calculate age-, sex- and BMI-adjusted Z scores allowing quantification of the deviation from normal. Biomarker levels were measured using an ultrasensitive Simoa assay in patients prospectively starting ocrelizumab or rituximab. Prognostic power of biomarkers at median one year after start of BCDT and their longitudinal dynamics in relation to PIRA were investigated.
Results: During a median of 4.1 [IQR: 3.0, 5.0] years from BCDT treatment initiation, 22.7% of PwMS experienced at least one PIRA event. Increased sGFAP levels (Z score > 1) one year after treatment initiation were associated with an increased hazard risk of PIRA (HR = 1.9 95% confidence interval [1.1, 3.1], $p = 0.015$), whereas increased sNfL levels were not associated with increased risk ($p = 0.41$). Longitudinally, on-treatment sGFAP levels increased (estimate 0.61 Z score units per 10 years of follow-up time [0.39, 0.83], $p < 0.001$), and were higher in PwMS experiencing PIRA (estimate 0.38 Z score units [0.06, 0.71], $p = 0.023$) compared with those remaining stable. Different sNfL Z scores slopes were found in patients with PIRA vs. stable disease (interaction $p = 0.008$) with an average decrease of 0.98 Z score units per 10 years observed in stable patients (estimate -0.98 [-1.32, -0.64], $p < 0.001$), while elevated levels in PwMS later experiencing PIRA remained unaffected by BCDT.
Conclusions: Elevated serum GFAP, but not sNfL levels one year after BCDT initiation were prognostic of PIRA. The two biomarkers also displayed significantly different dynamics after starting BCDT; in patients later experiencing PIRA both sGFAP and sNfL levels remained higher than in PwMS with stable disease. Our findings emphasize the value of sNfL and especially sGFAP for capturing and prognosticating risk of disease progression in MS.

O02

Antithrombotic Treatment for Cervical Artery Dissection: An Individual Patient Data Meta-Analysis of the CADISS and TREAT-CAD Randomised Trials

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Aims: Cervical artery dissection is the most common cause of stroke in the young. To date, there is no conclusive evidence on which antithrombotic therapy should be used to treat patients. We aimed to investigate the efficacy and safety of antiplatelets (aspirin) and anticoagulants (vitamin K antagonists) in preventing early recurrent stroke in cervical artery dissection patients.
Methods: We performed a preplanned individual patient data meta-analysis on the two randomised controlled trials CADISS and TREAT-CAD (registered in PROSPERO CRD42023372742). The primary outcome was a composite of (i) any stroke, (ii) death, and (iii) major bleeding (extra- or intracranial) at 90 days follow-up. The components of the composite outcome were also secondary outcomes. Subgroup analyses based on baseline characteristics with a putative impact on the outcome were performed. We performed logistic regression using the maximum penalized likelihood method including interaction in the subgroup analyses.
Results: 444 patients were included in the intention-to-treat (ITT) population and 370 patients in the per-protocol (PP) population. Baseline characteristics were balanced. There was a non-significant tendency for there to be fewer primary endpoints in those randomised to anticoagulation, 3/218 (1.4%), vs. aspirin, 10/226 (4.4%), OR = 0.33 (95% CI 0.08–1.05), $p = 0.061$. In comparison with aspirin, anticoagulation was associated with fewer recurrent strokes, 1/218 (0.5%) vs. 9/226 (4.0%), OR = 0.16 (95% CI 0.02–0.69), $p = 0.012$, and more bleeding events, 2 vs. 0.

Conclusions: This IPD analysis of all currently available RCT data found no difference between anticoagulants and antiplatelets in preventing early recurrent events. However, the trend towards better outcomes with anticoagulants suggests that larger trials are required. These should include more modern forms of antithrombotic therapy, including direct oral anticoagulants (DOACS) and dual antiplatelet therapy.

O03

Eculizumab Use in Neuromyelitis Optica Spectrum Disorders: Real-World Data from a European Cohort

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Background: Attack prevention is crucial to avoid disability accumulation in neuromyelitis optica spectrum disorders (NMOSD). Eculizumab, an inhibitor of the terminal complement cascade, was highly effective in preventing attacks in a phase III trial in aquaporin-4 (AQP4)-IgG seropositive (+) NMOSD, but real-world data are only emerging.
Aims: To evaluate the effectiveness and safety of Eculizumab in a real-world setting in Germany and Austria.
Methods: Annualized attack rate (AAR), expanded disability status scale (EDSS), magnetic resonance imaging (MRI), adverse events including mortality, and tolerability of meningococcal vaccinations were retrospectively evaluated in patients with AQP4-IgG+ NMOSD (n = 52), MOG-IgG-associated disease (MOGAD, n = 2), and double-seronegative NMOSD (n = 1) treated with Eculizumab between December 2014 and April 2022.
Results: Fifty-five patients (84% females, age 55.1 $\pm$ 15.8 years) received Eculizumab for 14.7 (IQR 8.1–21.3) months. Fourty patients (73%) received meningococcal vaccination before starting Eculizumab, nine with concomitant oral prednisone and 31 without. Ten of the latter (32%) experienced attacks shortly after vaccination (9.6 $\pm$ 8.6 days). In contrast, no post-vaccinal attack occurred in the nine patients vaccinated while on oral prednisone as well as in 22 patients who were (re-)vaccinated while on Eculizumab. During Eculizumab therapy, 87% of patients were attack-free. The median AAR decreased from 1.0 (range 0–4) in the two years preceding Eculizumab to 0 (range 0–1.4; $p < 0.001$). Add-on immunosuppressants in 13/55 (24%) patients showed no advantage in AAR compared to Eculizumab monotherapy. EDSS from start to last follow-up during Eculizumab treatment was stable (median 6.0), and the proportion of patients with new T2- or gadolinium-enhancing MRI-lesions in the brain and spinal cord decreased. Seven (13%) patients experienced serious infections. Five patients (9%; median age 53.7 years) died on Eculizumab treatment: one from myocardial infarction, one from ileus with secondary sepsis and three in the context of systemic infections, including one from meningococcal sepsis. The discontinuation rate overall was 20%.
Conclusions: Eculizumab proved to be highly effective in preventing NMOSD attacks. An increased risk of attacks following meningococcal vaccination prior to treatment start and potentially fatal systemic infections during Eculizumab must be considered. Further research is necessary to explore the

O04

CHIT1 at Diagnosis Predicts Faster Disability Progression and Reflects Early Microglial Activation in Multiple Sclerosis

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Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system (CNS) characterized by considerable heterogeneity in disease course. Therefore, prediction of long-term outcome and treatment stratification remain some of the major challenges in MS care. In this study, we investigated five microglia and macrophage markers—chitotriosidase (CHIT1), chitinase-3-like protein 1 (CHI3L1), soluble triggering receptor expressed on myeloid cells 2 (sTREM2), glycoprotein non-metastatic melanoma protein B (GPNMB) and C-C motif chemokine ligand 18 (CCL18)—in the cerebrospinal fluid (CSF) at diagnostic lumbar puncture in a large, longitudinal cohort of 192 MS patients. Through multi-time-point disability assessments, mixed-effects models and a machine learning approach, we showed that CHIT1 in the CSF is a robust predictor for faster disability progression. Using single-cell/nucleus transcriptomics, we found CHIT1 to be predominantly expressed by a distinct microglia subset, located primarily in active MS lesions. These CHIT1+ microglia

displayed an early-activated, transitional cell state enriched for pathways involved in lipid clearance and metabolism. Neuropathological evaluation of post-mortem MS brain tissue confirmed that the CHIT1 protein is produced by lipid-laden phagocytes in actively demyelinating lesions, also in early disease stages. Altogether, we provide a rationale for CHIT1 as an early biomarker for faster disability progression in MS, facilitating patient stratification and therapy selection.

O05

Senescent Fibro-Adipogenic Progenitors Are Potential Drivers of Pathology in Inclusion Body Myositis

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Aims: This study aimed to investigate the role of cellular senescence in the pathogenesis of Inclusion Body Myositis (IBM), a unique form of idiopathic inflammatory myopathy characterized by distinct clinical features and resistance to conventional treatments. Specifically, the focus was on understanding how senescence of tissue-resident cells contributes to disease progression in IBM, independent of inflammatory activity.
Methods: Histopathological analysis was conducted by comparing samples from IBM patients, non-diseased controls, and immune-mediated necrotizing myopathy patients. Single nuclei RNA sequencing was employed to deconvolute and study muscle-resident cell populations, with a particular emphasis on fibro-adipogenic progenitors (FAPs). The study also investigated changes in the transcriptomic landscape of IBM, particularly in the myogenic compartment.
Results: The histopathological analysis revealed that cellular senescence is a prominent feature in IBM, primarily affecting non-myogenic cells. Single nuclei RNA sequencing identified a specific cluster of FAPs demonstrating key hallmarks of senescence, including a pro-inflammatory secretome, p21 expression, increased β-galactosidase activity, and engagement of senescence pathways. IBM muscle cells exhibited a distinct pro-inflammatory phenotype with intracellular complement activity and expression of immunogenic surface molecules. Additionally, alterations in the transcriptomic landscape of IBM were observed, including a pronounced loss of type 2A myofibers and rarefication of acetylcholine receptor expressing myofibers.
Conclusions: This study highlights the altered phenotypical landscape of muscle-resident cells in IBM, with FAPs identified as the primary senescent cell type. The findings suggest that senescent FAPs, rather than myofibers, play a crucial role in IBM pathogenesis. The study also unveils potential mechanisms linking FAP senescence to skeletal muscle cell dysfunction, including changes in collagen composition, specifically the loss of collagen type XV expression. Understanding these cellular processes may provide insights for developing targeted therapeutic approaches for IBM.

O06

Trial of N-Acetyl-l-Leucine in Niemann–Pick Disease Type C

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Background: Niemann–Pick disease type C (NPC) is a rare lysosomal storage disorder with an unmet medical need. The agent N-acetyl-l-leucine (NALL) improves lysosomal and metabolic dysfunction, showing both symptomatic and disease-modifying effects (Kaya et al., 2021).
Aim: To evaluate the safety and efficacy of N-acetyl-l-leucine (NALL) for NPC.
Methods: In this double-blind, placebo-controlled, crossover trial, we randomly assigned patients 4 years of age or older with genetically confirmed NPC in a 1:1 ratio to receive NALL for 12 weeks, followed by placebo for 12 weeks, or to receive placebo for 12 weeks, followed by NALL for 12 weeks. NALL or matching placebo was administered orally two to three times per day, with patients 4 to 12 years of age receiving weight-based doses (2 to 4 g per day) and those 13 years of age or older receiving a dose of 4 g per day. The primary end point was the total score on the Scale for the Assessment and Rating of Ataxia (SARA; range, 0 to 40, with lower scores indicating better neurologic status). Secondary end points included scores on the Clinical Global Impression of Improvement, the Spinocerebellar Ataxia Functional Index, and the Modified Disability Rating Scale. Crossover data from the two 12-week periods in each group were included in the comparisons of NALL with placebo.
Results: A total of 60 patients 5 to 67 years of age were enrolled. The mean baseline SARA total scores used in the primary analysis were 15.88 before receipt of the first dose of NALL (60 patients) and 15.68 before receipt of the first dose of placebo (59 patients; 1 patient never received placebo). The mean (±SD) change from baseline in the SARA total score was -1.97 ± 2.43 points after 12 weeks of receiving NALL and -0.60 ± 2.39 points after 12 weeks of receiving placebo (least-squares mean difference, -1.28 points; 95% confidence interval, -1.91 to -0.65; $p < 0.001$). The results for the secondary end points were generally supportive of the findings in the primary analysis. The incidence of adverse events was similar with NALL and placebo, and no treatment-related serious adverse events occurred.
Conclusions: Treatment with NALL for 12 weeks led to better neurologic status than placebo. A longer treatment period is needed to determine the neuroprotective effects of this agent in patients with this devastating disease. (Funded by IntraBio; ClinicalTrials.gov number, NCT05163288; EudraCT number, 2021-005356-1.

O07

Risk of Stroke Associated with Cerebral Microbleeds in Different Subtypes of Ischemic Stroke and TIA

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Aims: In ischemic stroke patients, cerebral microbleeds (CMBs) are associated with an increased risk of recurrent ischemic stroke (IS) and intracerebral hemorrhage (ICH). However, little is known whether this risk varies among different stroke etiologies.
Methods: We performed a sub-analysis from the Microbleeds International Collaborative Network (MICON) pooled individual patient data cohort on patients with IS and available index etiology based on the TOAST classification. The primary outcome was the composite of IS or ICH during follow-up, the secondary outcome was the stroke subtype respectively. We used a Cox regression hazard model to compare the impact of CMBs in different stroke etiologies adjusted for potential confounders.
Results: We included 12133 patients with available TOAST classification (mean age 70 ± 12, 41.5% female) with a total follow up time of 18340 person-years. In cardioembolic stroke, CMBs were associated with the primary outcome (aHR [95% CI] 1.49 [1.18–1.89], $p = 0.001$) and ICH (aHR 3.12 [1.62–5.99], $p = 0.001$), and weakly associated with IS (aHR 1.30 [0.99–1.72], $p = 0.06$). CMBs were associated with ICH but not IS in patients with undetermined (including competing) etiologies (aHR 8.59 [1.61–45.8], $p = 0.012$). In large-artery-arteriosclerosis, the presence of CMBs was not associated with the primary or secondary outcomes. In patients with small vessel occlusion a high load of CMBs ($\geq$5 CMBs)—but not the presence of CMBs alone–was associated with the primary outcome (aHR 2.0 [1.19–3.36], p =0.008) and ICH (aHR 7.38 [2.07–26.2], $p = 0.002$)—but not IS.
Conclusions: The prognostic impact of CMBs may vary according to the index stroke etiology. In stroke patients with an index event classified as undetermined etiology as well as cardioembolic the risk of ICH was elevated in patients with CMBs.

O08

The Role of B Cell Activating Factor (BAFF) Following B Cell Depletion in Multiple Sclerosis

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Aims: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. The strong involvement of B cells in the pathogenesis of MS has been underscored by the success of CD20+ B cell depleting treatments. Initation of B cell depleting therapies lead to a significant increase in levels of B cell activating factor (BAFF) in the serum of MS

patients. BAFF is a crucial factor for strengthening B cell self-tolerance and for inducing regulatory B cells. Yet, the role of BAFF as prognostic factor for treatment response in B cell depleted MS patients is unknown.
We aim to investigate the role of BAFF following CD20 depletion on the expansion of regulatory B cells in MS and the use of BAFF serum levels as biomarker for treatment response in B cell depleted MS patients.
Methods: We conducted a retrospective, longitudinal study measuring BAFF serum levels of 166 MS patients from two different centers (discovery and replication cohort) by commercial ELISA before and under treatment with the monoclonal CD20 depleting antibodies Ocrelizumab or Rituximab. We correlated serum BAFF levels to standardized clinical outcome parameters, including the prognostic value of serum BAFF levels for long-term progression independent of relapse activity (PIRA). Further, we performed phenotypic characterization of B cell subsets in the blood of MS patients before and under B cell depletion using high dimensional flow cytometry.
Results: BAFF levels increased significantly with a peak within 6–12 months after the initiation of B cell depleting therapy. Overall, BAFF increases were lower in progressive MS patients compared to relapsing-remitting MS patients and in patients with a longer disease duration. PIRA was preferentially observed in patients with lower increases in serum BAFF following anti-CD20 therapy.
Conclusions: BAFF serum levels might serve as a novel prognostic biomarker for PIRA in B cell depleted MS patients. Since PIRA is considered as a clinical correlate of grey matter (GM) pathology, these observations might indicate that high BAFF levels correlate with less GM pathology.

O09

Timing and Location of Recurrent Intracerebral Haemorrhage

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Introduction: Mechanisms underlying recurrent intracerebral haemorrhage (ICH) are poorly understood. We aimed to assess timing and location (adjacent [adjICH] vs. remote to a previous ICH [remICH]) of recurrent ICH.
Methods: We performed an individual patient data analysis of patients with $\geq$ 2 ICH from twelve European cohorts. Main outcomes were adjICH, defined by CHARTS location and side, and time to recurrence. We performed multivariable regression analyses. We defined probable cerebral amyloid angiopathy (CAA) by Boston 2.0 or simplified Edinburgh criteria.
Results: We included 567 patients with 1277 ICH (567 index and 701 recurrent ICH, range 2–7, median 2) over a median follow-up of 2.49 years (IQR 0.54–5.31). 274 patients (48.2%)

had adjICH and 293 (51.8%) had remICH. Lobar ICH accounted for 328/394 recurrences (85.6%) in patients with adjICH versus 164/307 recurrences in patients with remICH (53.4%, $p < 0.001$). CAA at index ICH was associated with adjICH (aOR 1.95, 95%-CI 1.18–3.24). Median time to recurrence was shorter in patients with adjICH (median 1.15 years, IQR 0.31–3.59 versus 2.34 years, IQR 0.66–5.15; $p < 0.001$) and decreased with each additional event. Among patients with CAA at any timepoint, 175/289 (60.6%) had adjICH and 114/289 (39.4%) had remICH. Median time to recurrence was 1.10 years (IQR 0.28–3.38) in adjICH versus 1.26 years (IQR 0.32–3.75) in remICH ($p = 0.22$).
Conclusions: Half of recurrent ICH were adjacent to prior ICH. This phenomenon was associated with lobar ICH location and a diagnosis of CAA. These findings suggest regional disease burden and activity as a potentially modifiable treatment target in CAA.

O10

Classification of MS-Severity-Subgroups Using Smartphone-Based Motor Tests and Machine Learning

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Aim: Remote monitoring of patients with multiple sclerosis (PwMS) with wearables promises quantitative, objective, and sensitive insights with high temporal resolution and ecological validity [1]. However, thorough clinical validation of potential digital biomarkers is necessary [2]. We aimed to assess the discriminant validity of smartphone-based motor tests in PwMS with mild (expanded disability status scale [EDSS] < 3.5) and moderate/severe disability (EDSS $\geq$ 3.5).
Methods: Patients were included from our ongoing dreaMS validation study 1 (NCT05009160) [3]. After instruction and first performance at the in-clinic baseline visit, they performed up to 8 motor tests at home by themselves on their smartphones ("bring your own device") up to once weekly: 30-s-walk, chair-rising, pronator-drift, screen-to-nose, stair-climbing, static-balance, tandem-walk, and timed-up-and-go. The first up to 10 repetitions were used for each test. Accelerometer signals were sampled at 50 Hz and reoriented to account for differences in orientation. A convolutional neural network (CNN) was used for unbiased feature extraction [4], and 3-fold cross validation (CV) was used to assess performance.
Two logistic regression models with the same CV were used for comparison: one on sex, age and disease duration, and one on timed 25-foot walk (T25FW), which was measured in-clinic at baseline. The outcome measure was the cross-validated mean area under the ROC curve (AUC) with the standard deviation between folds.
Results: N = 169 PwMS were included: 69% female, 46 $\pm$ 13 years old, median disease duration 12 years (IQR 4–19), median EDSS 2.0 (IQR 1.5–3.5, range 0–8.0). N = 121 were labeled PwMS | mild and 48 PwMS | moderate.
The comparison model on sex, age, and disease-duration achieved a classification performance of AUC = 0.70 $\pm$ 0.05 and the model on T25FW of AUC = 0.80 $\pm$ 0.06. The 8 smartphone-based motor tests achieved AUCs of 0.71 $\pm$ 0.02 (tandem-walk), 0.77 $\pm$ 0.08 (screen-to-nose), 0.77 $\pm$ 0.02 (timed-up-and-go), 0.78 $\pm$ 0.08 (static-balance), 0.81 $\pm$ 0.01 (pronator-drift), 0.82 $\pm$ 0.11 (chair-rising), 0.84 $\pm$ 0.08 (30-s-walk) and 0.86 $\pm$ 0.11 (stair-climbing).
Conclusions: All 8 smartphone-based motor tests discriminated better between PwMS | mild and PwMS | moderate than sex, age, and disease-duration and 4 of them even discriminated better than T25FW. This supports the discriminant validity of the dreaMS motor tests as a self-assessment in the patient's natural environment.

O11

Cerebral Amyloid Angiopathy in Dementia with Lewy Body: A Clinical and Brain Morphological Study

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Background: Dementia with Lewy bodies (DLB) is the second cause of neurodegenerative dementia and often associated with Cerebral Amyloid Angiopathy (CAA). However, the prevalence of CAA in DLB patients and its impact on memory performances and hippocampal volumes are poorly studied.
Aims: To determine the prevalence of CAA among DLB patients in a Memory Clinic and compare memory performances and hippocampal volumes between DLB patients with (DLB + CAA) and without (DLB-only) CAA co-pathology.
Methods: In this retrospective case-control study, we included consecutive patients referring to the Leenaards Memory Center (Lausanne University Hospital) with a clinical diagnosis of DLB. We used the MARS (1) scale (microbleed detection/localisation) to rate the MRIs and the Boston Criteria 2.0 (2) for CAA classifications. Memory performances were evaluated with the free and cued selective reminding test or the GERIA-12. The volumes of the hippocampal head, body, tail, and fissure were assessed from T1-weighted MR images segmentation with FreeSurfer(3). Volumes were normalized with respect to age, sex, and total intracranial volume. Memory performances and hippocampal volumes were compared between DLB + CAA and DLB-only groups.
Results: 93 patients were included (age: 76.5 $\pm$ 8.0; 35.5%female): 61 (66%) presented probable or possible CAA (DLB + CAA group) and 32 (34%) presented with no CAA (no-CAA group). There were no age and sex differences between DLB + CAA and no-CAA groups. We found no differences in memory performances and head/body/tail/fissure hippocampal volumes between the two groups (ANOVAs, all p-value > 0.05).
Conclusions: In our DLB patients, CAA does not affect memory performances nor hippocampal volumes. Co-pathologies in DLB are under-diagnosed and require further study for personalized patient care. CAA needs further research especially with the arrival of anti-amyloids and the morbidity associated with devastating brain haemorrhages.

O12

Determined vs. Undetermined Etiologies of Stroke in Young Adults: A Nationwide Swiss Study on Risk Factors, Clinical Profiles, Treatments and Outcomes

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Background: The rising prevalence of stroke in young adults, particularly with undetermined etiology, is a growing health concern. This study aims to bridge the knowledge gap regarding their risk factors, treatment options, and outcomes.

Methods: This retrospective Swiss study analyzed young adults aged 18–55 with acute ischemic stroke (AIS) from January 2014 to September 2022. Stroke etiology was determined using the modified TOAST classification. The study focused on the prevalence of vascular risk factors, acute treatments (recanalization therapies, antiplatelets, anticoagulation), 90-day functional outcomes, and AIS recurrence. Statistical analyses included logistic regression, Fine-Gray proportional hazards models, and group comparisons.
Results: Patients with undetermined etiology showed—compared to those with determined etiology—higher rates of overweight (62% vs. 56%, $p = 0.003$), dyslipidemia (59% vs. 54%, $p = 0.007$) and smoking (43% vs. 37%, $p = 0.001$), but less diabetes (8.6% vs. 11%, $p = 0.05$). Intravenous thrombolysis administration was performed more frequently in the undetermined group (31% vs. 27%, $p = 0.046$), with comparable endovascular treatment rates. Approximately two-thirds of patients attained favorable 90-day functional outcomes, more commonly in the undetermined etiology group (70% vs. 66%, $p = 0.053$), but with a higher 90-day stroke recurrence risk (HR = 1.72, CI = [1.01, 2.94], $p = 0.047$). Comparisons between the undetermined stroke etiology group and other specific etiology groups reveal that the undetermined group falls intermediate across all examined aspects, complicating its characterization.
Conclusions: Young adults with AIS of undetermined etiology show distinct risk factor- and treatment patterns from those with determined etiologies. They have better short-term outcomes despite a higher recurrence risk, underscoring the need for targeted prevention and further research.

O13

What Is an Acute Symptomatic Seizure: The Impact of Seizure Timing on Seizure Recurrence after Stroke

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Purpose: The current practice of categorizing first seizures after stroke as acute (within 7 days post-stroke) or remote (day 8 or later) symptomatic relies on a threshold of a high (>60%) risk of seizure recurrence. Despite the significant diagnostic and therapeutic implications, there is insufficient robust evidence supporting the validity of the 7-day cutoff for defining acute versus remote symptomatic seizures following a stroke.

Method: We analyzed data from a multicenter study on post-stroke seizures, involving 4452 adults from 9 international cohorts with neuroimaging-confirmed acute ischemic stroke (mean age 73 years, 56% male). We used Cox proportional hazards regression to assess the impact of first seizure timing on the risk of recurrent seizures.
Results: Within 24 months of stroke onset, 355 (8%) stroke survivors experienced a first seizure, with 184 (4%) occurring within the initial 7 days and 171 (4%) on day 8 or later. Among those with a first seizure, 141 (40%) had recurrent seizures. Examining the impact of seizure timing, seizures occurring on day 0 had a higher risk of recurrent seizures (29%) compared to seizures on days 1–7 (18%). Subsequently, the risk of recurrent seizures increased following first seizures occurring on days 8–14 (36%) and 15–30 (45%), stabilizing at approximately 60% (57–61%) for first seizures occurring one month or later after stroke.
Conclusions: The risk of recurrent seizures after a first seizure within the first month following ischemic stroke is moderately low (<60%), challenging the current 7-day cutoff for defining acute symptomatic seizures. These findings have practical implications for initial seizure treatment decisions after stroke.

O14

Astrocyte-Produced HB-EGF Limits Autoimmune CNS Pathology

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Central nervous system (CNS) resident cells such as microglia, oligodendrocytes and astrocytes are gaining increasing attention in respect to their contribution to CNS pathologies including Multiple Sclerosis (MS). It has only recently become clear that the underlying heterogeneity of astrocytes and microglia can not only drive inflammation, but also lead to its resolution through direct and indirect mechanisms. Failure of these tissue-protective mechanisms may potentiate disease and increase the risk of conversion to progressive stages of MS, for which currently available therapies are limited.
Aims: We here seek to identify novel astrocyte-derived tissue-protective factors relevant for lesion resolution in the CNS, which fail to exert their beneficial effects during chronic stages of autoimmune CNS inflammation with the goal of discovering novel targets relevant for acute and chronic CNS inflammation
Methods and Results: Using proteomic analyses of cerebrospinal fluid specimens from MS patients in combination with experimental studies, we here identify Heparin-binding EGF-like growth factor (HB-EGF) as a central mediator of tissue-protective and anti-inflammatory effects important for the recovery from acute inflammatory lesions in CNS autoimmunity. Hypoxic conditions drive the rapid upregulation of HB-EGF by astrocytes during early CNS inflammation, while pro-inflammatory conditions suppress trophic HB-EGF signaling through epigenetic modifications. Finally, we demonstrate both anti-inflammatory and tissue-protective effects of HB-EGF in a broad variety of cell types in vitro and use intranasal administration of HB-EGF in acute and post-acute stages of autoimmune neuroinflammation to attenuate disease in a preclinical mouse model of MS.
Conclusions: Altogether, we identify astrocyte-derived HB-EGF and its epigenetic regulation as a novel modulator of autoimmune CNS inflammation and potential therapeutic target in MS.

P01

Retinal Neuroaxonal Loss and Disease Progression in Multiple Sclerosis

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Aim: Progression Independent of Relapse Activity (PIRA) is the main driver of disability in multiple sclerosis (MS). Retinal neuroaxonal loss measured by optical coherence tomography (OCT) is associated with cortical thinning and neurodegeneration. We aimed to evaluate the association between OCT markers and PIRA in patients with MS.
Methods: We included patients from the Swiss MS Cohort Study with $\geq$1 OCT. Peripapillary retinal nerve fiber layer (pRNFL) thickness, ganglion cell inner plexiform layer (GCIPL)-, and inner nuclear layer (INL) volumes were assessed. Eyes with prior optic neuritis were excluded. Neurological examination was performed every 6–12 months including the Expanded Disability Status Scale. PIRA events were defined as previously described (Table 1).
PIRA events were determined by a confirmed EDSS score increase ($\geq$1.5 points, if baseline EDSS = 0, $\geq$1, if baseline EDSS: 1.0–5.5, or $\geq$0.5, if baseline EDSS > 5.5), without an intervening relapse. Annualized PIRA rate was the number of PIRA events divided by years of follow-up, during a period of $\geq$4 years before the OCT. We examined the association of OCT markers with annualized PIRA rate in linear regression models adjusted for disease duration, age at disease onset, sex, body mass index, and disease modifying treatment (DMT).
Results: We included 172 patients (median age 51 years (IQR 42.2–59.7), 64% women, median disease duration 15.9 years (IQR 10.5–23.1), median EDSS score 2.5 (IQR 1.5–4.0), 87.2% with relapsing-remitting course, 84.9% on DMT. A total of 36.6% patients had $\geq$1 PIRA event before OCT. In the adjusted models, both pRNFL and GCIPL were significantly associated with PIRA rate (beta = $-$28.4, p = 0.007 and beta $-$0.53, p = 0.005, respectively). According to the estimates, a lower pRNFL thickness of 28.4 µm and a lower GCIPL volume of 0.53 mm3 were associated with an additional annual PIRA event in our patients. No significant association was found for INL volume.
Conclusions: Our findings show an association between rate of PIRA and retinal neuroaxonal integrity. pRNFL and GCIPL may represent a sensitive measure of disease progression in MS.

P02

Female Sex Is Associated with Higher Risk of Experiencing a Relapse after Fingolimod Cessation

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Background: Data on sex differences in Multiple Sclerosis (MS) therapy safety are limited despite their clinical significance. Fingolimod (FTY), the first-in-class Sphingosine 1-Phosphate Receptor (S1PR) Modulator (S1PRM), is a treatment for MS that targets S1PRs on lymphocyte surface, reducing their exit from lymph nodes. Upon treatment cessation, up to 10% of patients experience relapse activity higher than before treatment, sometimes referred to as rebound disease activity. Our study aims to investigate the sex-specific aspects of safety following FTY cessation.
Methods: To investigate sex differences in disease activity after FTY cessation, we did a systematic literature review (PubMed, 2010 to 2024) using the search terms "Rebound disease activation (or reactivation) Fingolimod". Furthermore, we repeated the analysis based on openly available spontaneously reported adverse event reports (FDA adverse event reporting system (FAERS), EMA EudraVigilance (EudV)), up to February 2023) using the search term "rebound effect", and filtering for MS as the indication of medication and FTY as monotherapy only.
Results: From the literature review, seven cohorts were included, totaling 1'502 patients who discontinued FTY. Among them, 243 patients (194 women, 49 men) experienced disease reactivation. Female sex was associated with a higher risk of reactivation (odds ratio [OR] = 1.63, 95% confidence interval [CI] 1.16–2.28, p-value < 0.01) after treatment cessation. Respectively, FAERS and EudV revealed n = 72'809 reports and n = 21'745 reports when looking for the term "rebound effect" with FTY as monotherapy and indication MS. Both registries displayed a significant association between female sex and disease reactivation (FAERS: OR = 2.09, 95% CI 1.41–3.1, p-value < 0.001; EV: OR = 2.45, 95% CI 1.66–3.62, p-value < 0.001), corroborating the results of the literature search.
Conclusions: Our investigation of different patient cohorts from the literature and open registries for adverse events revealed a significant association between a higher risk of disease reactivation after FTY therapy cessation and female sex. Overall, further research is needed to better understand the underlying mechanisms and potential interventions to minimize rebound risk in patients with multiple sclerosis, particularly among females who discontinue FTY therapy.

P03

Identification of Three Multiple Sclerosis Endophenotypes by High Dimensional Blood Signatures Associated with Distinct Disease Trajectories

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Aims: One of the biggest challenges in multiple sclerosis is its immunological and clinical heterogeneity. Here we aim to be elucidate whether this heterogeneity is reflected by discrete imbalances in peripheral blood immune networks as a surrogate of disease pathophysiology. This may instruct individualized treatment selection based on immunobiological principles.
Methods: We investigated immune cells and serological parameters in two independent multi-centric longitudinal cohorts of early multiple sclerosis patients (n = 309 discovery, n = 232 validation) by high-dimensional flow cytometry and PEA-NGS, respectively. State-of-the-art computational biology methods were used to identify specific immune signatures, which were linked to clinical and para-clinical parameters reflecting distinct inflammatory and degenerative disease trajectories.
Results: We identified three distinct peripheral blood immunological endophenotypes in MS patients. Each MS endophenotype was characterized by immune-cell compartment specific characteristics. Correlation with longitudinal clinical and para-clinical data revealed that the immunological endophenotype 1 was associated with disease trajectories of inflammation whereas endophenotyp 3 was linked to early structural damage. Analysis of the capacity of distinct therapeutic approaches to normalize endophenotype-specific immune signatures showed a limited effect of interferon-beta on endophenotype 3-related immune signatures. Accordingly, treatment of endophenotype 3 patients with interferon-beta resulted in significantly enhanced EDSS progression and MRI activity over a four-year follow-up.
Conclusions: Characterization of a patient's blood immune signature before immunomodulatory treatment initiation may instruct individual prognosis and support personalized treatment decisions based on pathobiological principles.

P04

CoGames: Development of a Smartphone-Based and Gamified Monitoring Tool to Assess Cognitive Function of Patients with Multiple Sclerosis

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Aim: As part of the development of a smartphone-based app for monitoring MS disease activity and progression (dreaMS, NCT05009160), we developed 6 gamified smartphone tests with multiple difficulty levels, as a monitoring tool for cognitive function and dexterity. The CoGames study aimed to investigate reliability and acceptance and demonstrate that gamified digital assessment tools can measure change in performance.
Methods: We included 76 healthy volunteers (51 female, age: 40.3 $\pm$ 13.9 years, range 18–69) via online advertisement and flyers in Basel, Switzerland. Participants were instructed on how to download and use the CoGames app remotely on their personal smartphone over the phone. Participants were instructed to play each game twice per day for 11 consecutive days. Every day the difficulty increased. On 3 days during the study the participants were asked to rate the games on a 5-point Likert scale regarding enjoyment. On day 1,2, 6, and 11, the easiest level ("Beginner") was played to measure potential performance change (training effects). For each game, we collected data on predefined quantifiable measures such as number of correct responses, time needed, and error rate. For the reliability analysis we correlated the measures of the two daily repetitions (test-retest) using spearman's correlation coefficient. The average ratings on the 5-point Likert scale were used to describe perceived enjoyment. We visualized differences between the repetitions of the "Beginner" level over the study duration to assess potential training effects.
Results: Over all difficulty levels of all games spearman's correlation coefficients between the two daily repetitions ranged from 0.66 to 0.94. The games were all rated with a mean scoring of 3.8 (range: 3.2 to 4.2). Performance over time increased linearly or showed an initial steep increase with a gradual flattening of the performance-curve over time.
Conclusions: The CoGames study showed that cognitive games provide reliable measures, are enjoyable to play, and can detect change of performance. These results support the hypothesis that gamified digital cognitive tests can be used as a reliable and well-accepted assessment- and monitoring tool.1–3 Such monitoring tools, might lead to higher adherence and better temporal resolution compared to the current established neuropsychological tests, due to their accessibility and motivational nature.

P05

Intranasal Delivery of TGFα—A Novel Therapeutic Approach for Lesion Resolution in Multiple Sclerosis?

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After acute lesions in the central nervous system (CNS) such as in Multiple Sclerosis (MS), the interaction of microglia, astrocytes and infiltrating immune cells defines the inflammatory microenvironment in the CNS, which can either induce resolution of inflammation or lead to its chronification. However, this CNS-compartmentalized cross-talk and their respective contribution to the resolution of tissue damage is poorly characterized. In this context, we have recently identified microglia-derived TGFα as key factor driving recovery in MS and its preclinical animal model experimental autoimmune encephalomyelitis (EAE) [1].
Aims: This study seeks to evaluate the relevance of tissue-protective TGFα as a novel therapeutic target for the resolution of CNS inflammation. We fine-dissect how microglial

TGFα impacts recovery, describe its regulation, and harness its potential to effectively modulate glial cell interactions during autoimmune inflammation in the CNS.
Methods: Utilizing CRISPR–Cas9-based genetic perturbation models, high-dimensional flow cytometry, immunohistochemistry and magnetic resonance imaging (MRI), alongside mechanistic in vitro studies to identify the specific effects and target populations of microglia-derived TGFα during recovery in MS and its preclinical animal model EAE. In a translational therapeutic approach, we target the signaling by intranasal delivery of TGFα to evaluate its therapeutic potential to improve recovery from CNS inflammation.
Results: We show that microglia secrete TGFα in a highly regulated temporospatial manner during autoimmune neuroinflammation. This secretion orchestrates a coordinated response, shifting the immune environment from a pro-inflammatory to an anti-inflammatory and tissue reparative state. TGFα contributes to recovery by decreasing infiltrating T cells, pro-inflammatory myeloid cells, oligodendrocyte loss, demyelination, and axonal damage. In a therapeutic approach, blood-brain barrier penetrating intranasal application of TGFα attenuates pro-inflammatory signaling in astrocytes and CNS infiltrating immune cells, while promoting neuronal survival and lesion resolution, therefore promoting clinical recovery. Moreover, we demonstrate a reduction in TGFα levels in the cerebrospinal fluid (CSF) of MS patients.
Conclusions: Altogether, we identify TGFα as an important mediator of glial-immune crosstalk, highlighting its therapeutic value in resolving acute CNS inflammation.

P06

Pregnancy-Management in Multiple Sclerosis: Analysis of the Swiss Multiple Sclerosis Cohort

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Aims: Therapeutic management during pregnancy and postpartum in MS is challenging. We analysed the different disease modifying treatment (DMT) strategies in the Swiss MS Cohort (SMSC) and their effect on disease activity during pregnancy and postpartum.
Methods: We conducted an analysis of all pregnancies prospectively followed in the multicentric SMSC since 2012. We collected clinical, radiological, and biological data and information on DMT. We defined continuously treated women as being exposed to the effect of DMT during the entire pregnancy and evaluated the effect of different DMTs on disease activity using logistic regression models.
Results: We identified 129 pregnancies in 99 women. Six pregnancies were excluded due to early termination. Thus, we included 123 pregnancies in 93 women (median age at pregnancy start 32.2 years (IQR 29.1–35.8); 95% relapsing-remitting MS; median EDSS before pregnancy 1.5 (IQR 1.0–2.0); disease duration 7.8 years (IQR 4.5–10.8)). Before birth, the last used DMTs were natalizumab in 29/123 (23.6%), anti-CD20-monoclonal antibodies in 25/123 (20.3%), fingolimod in 25/123 (20.3%) and other DMTs in 38/123 (30.9%) pregnancies whereas in 6/123 (4.9%) pregnancies women were untreated. Fingolimod was stopped in all 25 pregnancies after confirmation of pregnancy. Natalizumab was stopped

early in 21 out of 29 cases (2 stopped before pregnancy start, 8 during the first and 11 during the second trimester) but was continued in the 8 remaining cases. Age and disease activity before conception were comparable between the different DMT groups. The probability of a relapse during the pregnancy and the first year post¬partum or new T2w lesions on the first brain MRI postpartum, adjusted for age at disease onset, disease duration, relapse rate and EDSS pre-birth, was lower in patients treated with anti-CD20-antibodies compared to other DMTs (for relapse analysis: n = 106, OR 0.15 [95% CI: 0.02; 0.63], $p = 0.0071$; for MRI activity analysis: n = 113, OR 0.03 [95% CI: 0.0; 0.20], $p < 0.0001$). Continuously treated women had a lower risk of clinical and MRI disease activity during pregnancy and postpartum compared to women who were not continuously exposed to the effect of a DMT during pregnancy.
Conclusions: This study shows the heterogeneity in current pregnancy management in MS in Switzerland. Continuous exposure to DMT during pregnancy was associated with a lower risk of disease activity during pregnancy and pospartum.

P07

Integrative Analysis of Circulating Metabolites, Gut Microbiota, Clinical and Lifestyle Factors in Predicting Multiple Sclerosis Disease Parameters

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Aims: Multiple sclerosis (MS) is a prevalent demyelinating autoimmune neurological disease affecting primarily young individuals. Emerging research suggests that circulating metabolites, gut microbiota, and lifestyle factors play pivotal roles in predicting MS disease course. This study aims to investigate the predictive potential of these factors on key MS disease parameters, including MS-related fatigue, the Expanded Disability Status Scale (EDSS), serum concentrations of neurofilament light chain (sNfL) and glial fibrillary acidic protein (sGFAP).
Methods: 53 persons with MS participated in this observational prospective study. Disability was assessed using the EDSS and MS-related fatigue using the validated EMIF-SEP questionnaire. Fasting blood samples were collected for the measurement of sNfL and sGFAP. sNfL Z-scores were calculated based on controls. Untargeted metabolomics of plasma samples was performed. The least absolute shrinkage and selection operator (LASSO) algorithm with ten-fold cross-validation was used to predict MS-related parameters using serum metabolites, gut microbiota, clinical, lifestyle, and MS data.
Results: Serum metabolites emerged as superior predictors for sNfL Z-score, sGFAP concentration, and MS-related fatigue, while clinical data were better predictors of EDSS. Notably, gluconate and succinate demonstrated strong predictive abilities for sNfL Z-score, sGFAP concentration, and MS-related fatigue. Combining serum metabolites, MS data, lifestyle, and clinical data enhanced the prediction of sNfL Z-score, surpassing the performance of serum metabolites alone. However, the inclusion of gut microbiota analysis diminished the model's efficacy. The optimal model for predicting sGFAP concentration involved combining all datasets. Clinical and lifestyle datasets jointly produced the best prediction for EDSS, while serum metabolites alone were the most effective predictors for MS-related fatigue.
Conclusions: Our study uses the LASSO algorithm to predict various measures of disease activity/severity in MS, revealing that serum metabolites exhibit strong predictive abilities for sNfL Z-score, GFAP concentration, and MS-related fatigue. Addressing MS-related fatigue remains a challenge, and supplementation with metabolites emerges as an innovative approach to ameliorate this aspect of MS management.

P08

Communication, Coordination and Security for People with Multiple Sclerosis (COCOS-MS): A Randomised Phase II Clinical Trial

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Introduction: People with severe multiple sclerosis (PwsMS) have complex needs ranging from organizing one's daily life, monitoring disease-specific therapy, to palliative care (PC). They and their caregivers depend on multiple healthcare providers who are difficult to find and to coordinate.
We investigate effects of a cross-sectoral long-term (12 months) Care and Case Management (CCM) for PwsMS and their caregivers on patients' (1) quality of life (QoL) measured by HALEMS (the German version of the HAQUAMS, Hamburg Quality of Life Questionnaire), (2) PC needs (integrated palliative outcome scale Neuro S8 (IPOS-Neuro S8)) (3), depression and anxiety(Hospital Anxiety and Depression scale (HADS)), (4) health services use (cost diary) and (5) caregivers' QoL (Short Form Health Survey (SF-12)) and (6) caregivers' burden (Zarit Burden Interview (ZBI-12)).
Methods: In this randomized phase II clinical trial PwsMS were randomly assigned to control (standard care) or intervention group (standard care plus CCM). The CCM intervention was carried out along a study specific CCM-manual taking multidimensional needs into account. Blinded researches collected outcome data every 3 months from baseline to month 15 (T1–T5). Our primary outcome of interest was patients' change in QoL from baseline (T0) to month 12 (T4). Secondary outcomes were patients' QoL from baseline to month 3, 6, 9 and 15. Subscales of the HALEMS are to be analyzed as well as further secondary endpoints, including PC, psychological wellbeing caregiver burden and QoL.
Results: Of 81 screened patients 80 were 1:1 randomized. male:female ratio = 1:2, mean age 55.7 years (SD 11), median EDSS 6.5 (IQR: 6, 7.5). Attrition was low (10%, death: 2/8, illness 4/8, at random: 2/8). The HALEMS showed a significant improvement within the intervention group (T0–T4, p= 0.018) but not in the control group (T0–T4, p= 0.119).
Conclusions: PwsMS benefit from the intervention of long-term CCM with an improvement of the QoL over the course of the intervention.

P09

Two Cases of Concurrent Syphilis Infection and MOG Antibody-Associated Disease: Causation or Coincidence?

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Aims: Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is frequently preceded by infections. The underlying pathomechanism, however, remains poorly understood. Here, we present clinical data of two MOGAD patients with concurrent

syphilis infection and investigate the reactivity of patient-derived antibodies to MOG and *Treponema pallidum* (*T. pallidum*).
Methods: Longitudinal serum samples and soluble immunoglobulins in single B cell supernatants were measured for MOG-reactivity by a live cell-based assay. Reactivity against *T. pallidum* was assessed by enzyme-linked immunosorbent assay.
Results: The two patients presented MOGAD and concurrent latent syphilis infection, manifesting as cervical myelitis and unilateral optic neuritis, respectively. The first patient had been living with HIV on antiretroviral therapy, the second was concomitantly diagnosed with chronic hepatitis B infection. Upon screening of B cell supernatants, we identified reactivity to MOG or *T. pallidum*. Notably, one B cell showed reactivity to both antigens.
Conclusions: The co-existence of MOGAD diagnoses and latent syphilis, alongside the identification of antibody reactivity to MOG and *T. pallidum* underscore the potential pathomechanistic link between syphilis infection and subsequent autoimmune neuroinflammation. Cross-reactivity between MOG and *T. pallidum* antibodies remains to be validated on a molecular level, and further characterization of infectious triggers associated with MOGAD is needed.

P10

Dynamic Reshaping of Lymphocyte Repertoires in Multiple Sclerosis Patients Treated with Alemtuzumab: Insights into Secondary Autoimmunity

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Alemtuzumab (ALEM), a recombinant, humanized IgG1 monoclonal antibody targeting the surface molecule CD52 expressed on T- and B-lymphocytes. This study aimed to comprehensively characterize the longitudinal changes in lymphocyte repertoires pre- and post-ALEM treatment, shedding light on both its therapeutic benefits and potential side effects, particularly secondary autoimmunity. Utilizing high-throughput immune repertoire sequencing, we analyzed the CD4+ and CD8+ T cell receptor (TCR) repertoires, as well as the B cell repertoires (BCR), of 12 multiple sclerosis (MS) patients before and at three time points within 40 months after the onset of treatment with ALEM. Additionally, five untreated controls were included for comparative analysis. Our findings reveal distinct patterns in the post-ALEM lymphocyte repertoires. The CD4+ TCR repertoires exhibited a predominant composition of newly generated, low-abundance clones in reconstituted post-ALEM CD4+ TCR repertoires. In stark contrast, the dominant CD8+ T cell clones persisted over the treatment, with post-treatment repertoires largely restored from pre-existing, highly abundant clones. Of particular interest is the dynamics of antigen-specific clones, which showed robust expansion, even at baseline, particularly in MS patients with secondary autoimmune diseases (SAID). These antigen-specific CD8+ T cell clones, identified by comparison with matching TCRβ sequences of known antigen specificity in public databases and patients' HLA haplotypes, demonstrated a greater propensity for expansion in SAID patients compared to those without secondary autoimmunity conditions. This heightened expansion of antigen-specific CD8+ T cell clones in SAID patients, both prior to and during ALEM treatment, underscores a potential predisposition towards secondary autoimmunity. Moreover, this observation possibly suggests an imbalance in B- and T-cell regulatory networks heightening the likelihood of developing secondary

autoimmunity. In conclusion, our study provides valuable insights into the dynamic reshaping of lymphocyte repertoires following ALEM treatment in MS patients. Further investigations with larger SAID patient cohorts are essential to elucidate the underlying mechanisms and develop clinical management strategies aimed at mitigating secondary autoimmunity risks associated with ALEM therapy.

P11

Current Trends in Stroke Events, Mortality and Case Fatality in Switzerland: An Epidemiologic Update

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Background: Stroke is a major cardiovascular disease. The last epidemiologic update of stroke events, mortality, and case fatalities (CF) in Switzerland dates back to 2004. During the last two decades', traditional- and non-traditional cardiovascular risk factors (cvrf) have changed, life expectancy increased, Stroke-Units were built, and stroke treatment improved. Therefore, we present an update of stroke epidemiology in Switzerland.
Methods: Data was obtained from two databases, namely the Federal Hospital Discharge Statistics (HOST) and the Cause of Death database (CoD), to analyze stroke diagnoses coded according to I60–I64 (ICD 10) for the year 2017. Age- and sex-specific discharge- and event rates for stroke, in- and out-of-hospital CF, and mortality were calculated.
Results: A total of 26,032 hospital discharges from stroke (2004: 13,996) were recorded (11,744 women (45%), 14,288 men (55%)) in the HOST database. The age-standardised event rate was 265.1/100,000 for women and 396.7/100,000 for men (2004: 119.7/100,000 vs. 178.7/100,000). A total of 2816 deaths due to stroke (2004: 3568 deaths) were reported (1660 women (59%), 1156 men (41%)) in the CoD database. The age-standardised mortality rate was 32.2/100,000 for women and 35.1/100,000 for men. The overall CF rate was notably higher in women compared to men (13.4%, 95% CI 12.8–14.0 vs. 8%, 95% CI 7.5–8.4). Out-of-hospital deaths due to stroke accounted for 30.1% of all deaths (2004: 48.7%).
Conclusions: Compared to 2004, the rates of stroke events and discharges have increased. However, the overall CF rate has halved, and the number of out-of-hospital deaths due to stroke is now a third of what it was in 2004. This suggests increased recognition and better treatments for stroke.

P12

Temporal Characteristics of Diffusion-Weighted Imaging Lesions in the Acute and Post-Acute Phase of Small Vessel Disease-Related Intracerebral Haemorrhage

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Background and aims: Diffusion-weighted imaging (DWI) lesions in patients with intracerebral haemorrhage (ICH) are associated with poor outcomes. Whether they are associated with the underlying small vessel disease (SVD), consequences of acute treatment or secondary brain damage is unknown.
Methods: This study in the Swiss Stroke Registry analyzed patients with SVD-associated ICH who underwent MRI within 14 days after the index ICH. The primary outcome was presence of DWI lesions on the first available MRI. We measured cerebral amyloid angiopathy (CAA) and SVD severity using total MRI marker burden scores. We performed multivariable regression analyses. Timing of MRI was used as continuous variable and dichotomized to hyperacute (=first imaging on admission prior to any treatment) versus subacute (=after admission up to day 14).
Results: We included 645 patients (median age 73 years, IQR 64–79, 46.5% female), 103 (16.0%) had hyperacute and 542 (84.0%) subacute MRI. Overall, 166 patients (25.7%) had DWI lesions. In multivariable analysis, hyperacute (vs subacute) MRI was not associated with presence of DWI lesions, but timing was associated with presence of DWI lesions as continuous variable (aOR 1.06, 95%CI 1.00–1.12 per day, $p = 0.040$). Higher CAA (aOR 1.99, 95%CI 1.40–2.81) and SVD burden scores (aOR 1.64, 95%CI 1.16–2.33) were independently associated with presence of DWI lesions.
Conclusions: DWI lesions in patients with ICH were associated with timing of MRI acquisition and burden of small vessel disease, suggesting that acute treatments, secondary damage and underlying SVD play a role in their pathogenesis.

P13

Gender and Age-Related Differences in Cardiovascular Risk Factors, Stroke Etiology and Outcomes among Stroke Patients Aged 18–55 Years in Switzerland

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Background: Stroke in young adults is an increasingly recognized health concern, yet gender and age-related disparities in occurrence rates, cardiovascular risk factors (CVRFs), and outcomes remain underexplored.
Methods: This study analyzed 3978 young adults aged 18–55 who were hospitalized in a Stroke Unit or -Center with a first-ever stroke, utilizing Quasi-Poisson models to investigate gender-specific differences in stroke occurrence rates (calculated per 100,000 person-years), risk factors, etiologies, and functional outcomes.
Results: Stroke occurrence rates were similar in males and females until the mid-thirties, after which rates increased exponentially, more so in males. At the average age of 45.8, males had a 95% higher stroke occurrence rate than females. Additionally, the annual increase in stroke rates was more pronounced in patients with at least two CVRFs and those with a BMI $\geq$ 25, regardless of gender. Males also showed higher prevalence of cardiovascular risk factors (CVRFs) like hyperlipidemia, smoking, and hypertension at

younger ages. Stroke etiologies shifted with age, with stroke due to undetermined etiology, small vessel disease and large artery atherosclerosis becoming more common in older patients, particularly males. Functional outcomes deteriorated with age but remained similar between genders.
Conclusions: The study highlights significant gender disparities in stroke occurrence rates, influenced by CVRFs and BMI, with males at a higher risk, particularly as they age. These findings emphasize the need for gender-specific preventive strategies and interventions targeting modifiable risk factors in young adults to reduce stroke risk.

P14

ALDH4A1 Blood Levels and Atherosclerotic Disease among Patients with Ischemic Stroke

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Background and Aims: The role of Aldehyde Dehydrogenase 4 Family Member A1 (ALDH4A1) in patients with atherosclerotic diseases remains unclear. We explored the association of circulating ALDH4A1 with atherosclerotic disease outcomes in stroke patients.
Methods: Multicenter study using data from the prospective BIOSIGNAL cohort, including patients with acute ischemic stroke between 2014 and 2017. ALDH4A1 plasma levels were measured in stored samples collected within 24 h after stroke onset. Primary outcome was large artery atherosclerotic stroke (LAAS) origin. Secondary outcomes were atherosclerotic disease outcomes such as the maximum intima-media-thickness (IMT), the degree of stenosis on ultrasound, and a composite for atherosclerotic disease burden (large artery atherosclerotic index stroke, history of myocardial infarction, coronary artery disease, or peripheral artery disease). Logistic regression analyses were performed to examine the association between ALDH4A1 plasma levels (absolute and log-transformed) and the primary and secondary outcomes.
Results: Of 1759 stroke patients, 84.5% had available ALDH4A1 measurements. We found no consistent association between circulating ALDH4A1 levels and LAAS (logALDH4A1 aOR 0.97, 95%CI 0.79–1.21, p = 0.81) nor the secondary outcome measures including the maximum IMT, stenosis degree or the composite for atherosclerotic disease burden. Sensitivity analysis using inverse probability of treatment weighting were in line with the main findings.
Conclusions: In acute stroke patients, no association was found between clinically relevant atherosclerotic disease outcomes and circulating ALDH4A1 levels. In addition, the maximum IMT—as a subclinical marker of atherosclerosis—was also not associated with elevated ALDH4H1 levels.

P15

Influence of Time from Symptom-Onset on D-Dimer Levels in Acute Ischemic Stroke

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Aims: Elevated D-dimer levels are frequently found in acute ischemic stroke (AIS) and TIA. The factors influencing D-dimer levels in code stroke patients including the time dynamics after symptom onset, as well as potential further influencing factors are poorly understood. This study aimed to investigate the influence of time from symptom-onset and other factors on D-dimer levels in AIS and TIA patients.
Methods: Consecutive AIS and TIA patients treated at our tertiary stroke center between January 2015 and December 2020 were identified for this retrospective analysis. Inclusion criteria were: (1) D-dimer levels available within 7 days after symptom-onset, (2) known time from symptom-onset to D-dimer measurement and (3) absence of factors known to interfere with D-dimer levels (e.g., venous thromboembolism, active cancer, and treatment with intravenous thrombolysis and thrombectomy before D-dimer measurement). Non-linear models with restricted cubic spline were created. Time-specific knots were set based on the visual interpretation of the distribution of D-dimer levels throughout the time from symptom-onset in AIS-patients. Multivariable non-linear regression analyses were performed and resulting standardized coefficients of regression (β) and their corresponding 95% confidence intervals (CI) were reported with adjustments for potential confounders.
Results: In total, 2467 AIS-patients and 708 TIA-patients were included. In AIS, an early increase in D-dimer levels was shown in the first 6 h after symptom-onset (β 0.728; 95% CI 0.324–1.121) followed by a decrease between 6 h and 35 h (β −13.022; 95% CI −20.401−−5.643) and a second late increase after 35 h (β 11.750; 95% CI 4.71–18.791). Besides factors already known to be associated with elevated D-dimers such as older age, reduced kidney function and higher admission stroke severity, we demonstrated an association between intake of anticoagulation and lower D-dimer levels (β −0.096; 95% CI −0.154−−0.038). In TIA-patients, no significant time-dependent increase in D-dimer levels was demonstrated.
Conclusions: The time from symptom onset and the intake of anticoagulation might be taken into account in the interpretation of D-dimer levels in AIS. Further studies confirming those findings and validating time-specific knots are needed to reliably use D-dimer levels to rule out concomitant thrombotic complications.

P16

Patients with Progression Independent of Relapse Activity Show Increased White Matter Degeneration on Diffusion Tensor Imaging Maps of Major White Matter Tracts

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Aims: To compare tissue integrity alterations by analyzing diffusion tensor imaging (DTI) metrics [1,2] in patients who experienced PIRA or not over a 4-year follow-up (FU) using a protocol compatible with clinical practice.
Introduction: Patients with multiple sclerosis (MS) may acquire disability through progression independent of relapse activity (PIRA) [3,4], which has been associated with increased atrophy rates in multiple brain regions [5] and spinal cord. The association between PIRA and increased degeneration of major white matter (WM) tracts is yet unknown.
Methods: We selected 258 patients with relapsing-remitting MS from the Swiss MS Cohort [6] study with 3T MRI including MPRAGE, FLAIR, single-shell diffusion MRI (20 b-value = 1000 s/mm^2 and 10 b-value = 0 s/mm^2) and a 4-year clinical FU. Based on the clinical evolution during the FU, we identified patients with PIRA (presenting at least one episode

of Expanded Disability Status Scale (EDSS) increase $\geq$1.5 if baseline EDSS = 0, $\geq$1.0 if 1.0–5.5; $\geq$0.5 if >5.5, confirmed after $\geq$6 months, in absence of a relapse [7]).
We computed fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) of normal-appearing WM. We used the JHU DTI-based WM atlas [8] to assess the corpus callosum (CC) and motor tracts (MT). We compared DTI metrics between two groups of patients with PIRA (74% female; 50.3 $\pm$ 12.0 y, mean $\pm$ SD) and without PIRA(63% female; 48.0 $\pm$ 11.2 y) with a linear model including propensity-score weights (using age, sex, disease duration, lesion volume, relapses in the last 2 years, and treatment in the propensity-score model); *p*-values were adjusted for multiple comparisons with the false-discovery rate.
Results: In patients with PIRA (n = 39), we observed a reduction of FA in the genu of CC ($p < 0.01$) and an increase of MD ($p < 0.01$) and RD ($p < 0.01$) compared to patients without PIRA (n = 219). We also observed an increase of MD ($p < < 0.01$) and RD ($p < 0.01$) in the splenium. In MT, we observed a trend towards a decrease of FA and an increase of RD and MD; MD was increased in the left ($p = 0.01$) and right ($p = 0.01$) corticospinal tract and in the left superior corona radiata ($p = 0.03$).
Conclusions: Patients with PIRA showed alterations compatible with increased degeneration in CC and in MT compared to patients without PIRA, hereby suggesting Wallerian degeneration [9] as a possible contributor to the development of disability accumulation independent of acute clinical activity.

P17

Anti-Amyloid Drugs for Patients with Idiopathic Normal Pressure Hydrocephalus and Comorbid Alzheimer's Disease?

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Aim: Alzheimer's disease (AD) is a frequent comorbidity in patients with idiopathic normal pressure hydrocephalus (iNPH) 1. Since anti-amyloid drugs will soon be available for patients with AD in Switzerland 2, we aimed to identify the prevalence of NPH with comorbid AD eligible for anti-amyloid drugs among consecutive NPH patients evaluated in a Memory clinic setting.
Methods: We identified patients suffering from NPH evaluated at the Leenaards Memory Center (CHUV) according to Relkin criteria 3 between 2019 and 2023. AD patients were biologically defined on cerebrospinal fluid (CSF) Ab42/Ab40 ratio inferior to 0.051 and/or Ab42 inferior to 599 ng/L plus pTau over 56.5 ng/L5. For these patients we verified eligibility criteria: (i) a mild dementia stage as defined by the Clinical Dementia Rating (CDR) equal or inferior to 1, and the absence of risk factors for intracerebral hemorrhage, as anticoagulant treatment and presence of cerebral amyloid angiopathy (CAA) according to Boston criteria 6. ApoE status was not available for these patients.
Results: Sixty-one patients were included in this study (age:79.4 $\pm$ 5.3; 51% female). The prevalence of AD was 19.6% (12/61); Out of these 11 patients, 1 was under anticoagulant treatment, 2 presented with more than 4 microhemorrhages and another one had a CDR of 2. Therefore, 58.3% (7/12) of iNPH patients with comorbid AD are eligible for anti-amyloid drugs.
Conclusions: Our findings confirm the frequent association between NPH and AD in patients evaluated in a Memory clinic and highlight the frequent association with CAA among these patients. These results open the question of the therapeutical strategy among NPH patients with AD eligible for anti-amyloid drugs: if and when anti-amyloid drugs should be delivered.

P18

Gut Bacteria from a Human APOE2 Donor Induce Neuroinflammation and Protects against AD Pathology in a 3xTg AD Mouse Model

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Aims: In this study we evaluate the effect of the transplantation of gut bacteria isolated from donor "resistant" to Alzheimer's disease (AD) pathology to 3xTgAD mice, with or without antibiotic pre-treatment (ABT), and tested the effect of microbiota perturbation on AD pathology.
Methods: 15-month-old 3xTg mice (APPSWE, PS1M146V and TauP301L) received microbiota transplantation twice a week for 2 months. The transplanted microbiota was isolated from an amyloid negative cognitively healthy subject with protective APOEε2 genotype (e2-FMT) or untreated 3xTg mice (M-FMT). When administered, ABT consisted of 14 days of broad-spectrum antibiotic administration prior the first FMT. AD pathology assessment in the hippocampus and colon was performed at the end of the treatment.
Results: e2-FMT reduced amyloid, pTau pathology as well as increased neuroinflammation in the hippocampus as compared with M-FMT ($p < 0.05$). The combination of e2-FMT with ABT enhanced the reduction of the amyloid markers and strongly increased the negative association of neuroinflammation with amyloid and tau. Finally, e2-FMT induced the production of the soluble form of amyloid 42 in the colon of e2-FMT but the effect was fully reversed by ABT.
Conclusions: Bacteria from a human APOE2 donor reduced AD pathology and increased neuroinflammation suggesting that the gut microbiota may be a novel mediator of the protective effect of APOE2.

P19

Association of Blood Pressure Mean and Variability with Hippocampal Subfield Volumes in Cerebral Amyloid Angiopathy with Mild Cognitive Symptoms

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Introduction: The interaction between Alzheimer's pathology and cerebral amyloid angiopathy (CAA), a common cerebral small vessel disease, plays a crucial role in cognitive impairment development in older adults. Recent studies suggest that increased blood pressure (BP) variability may affect subclinical vascular disease and cognitive decline. However, it is currently unknown whether a particular BP profile is linked to hippocampal subfield volumes, which are a significant feature of cognitive decline in neurodegenerative diseases.

Therefore, we conducted a study to investigate the relationship between BP profile and hippocampal subfields in nondemented subjects with CAA.
Methods: We investigated the relation between BP mean and variability and hippocampal neurodegeneration in a memory clinic cohort of non-demented participants with possible and probable cerebral amyloid angiopathy (CAA), diagnosed using the modified Boston criteria v1.5. Linear regression models were used to assess the associations between BP profile and hippocampal volumes. The subfield volumes were measured using an automated method on T-1 weighted sequence using FreeSurfer v6.0. The BP profile was defined using serial outpatient BP measurements five years prior to 3T research MRI. The BP variability was calculated using the coefficient of variation (standard deviation/mean).
Results: We have included 59 participants (74.3 $\pm$ 6.8 y, 9/50 F/M) who underwent a median of 12 (IQR 26) outpatient BP measurements five years prior to index MRI. We found a significant association between mean BP and all measured hippocampal subfields, notably the CA1: b = -032, $p = 0.008$, CA3: b = -0.24, $p = 0.049$, CA4: b = -0.34, $p = 0.003$, and the subiculum: b = -0.29, $p = 0.006$), adjusted for age and brain volume normalized for total intracranial volume. However, we found no significant association with long-term BP variability.
Conclusions: We found an association between mean BP and hippocampal volume in all subfields. Our results suggest that elevated BP, but not its variability, is a modifiable risk factor for preventing hippocampal degeneration in the context of CAA-related cognitive impairment. Further pre-planned analyses will evaluate associations in a subgroup of participants with mild dementia and non-CAA participants.

P20

Does Focal Remyelination in White Matter Influence Myelin-Weighted Network Properties in Patients with Multiple Sclerosis?

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Focal repair activity can be measured in Multiple Sclerosis (MS) patients (1–3). Myelin Streamlines Decomposition (MySD), a quantitative tractography method (4) adapted to focal lesions (5), can be applied to reconstruct myelin-weighted brain networks. We examined the association between remyelinated lesions along fiber tracts and brain network properties. We included 129 MS patients that underwent 3T MRI. Remyelinated lesions were considered as hypo- and isointense on quantitative susceptibility maps (QSM). QSM map was registered to diffusion image space and lesions were mapped to the reconstructed tractogram. dMRI were pre-processed, and 3M of streamlines were reconstructed using anatomically constrained tractography MRtrix3 algorithm. In the extended model of MySD, both intracellular and lesion compartment were integrated to evaluate contribution of the streamline and of axonal damage concerning the estimated signal in the myelin volume fraction map. To account for sensitivity to axonal damage, the model utilizes its estimated contribution to adjust the weight of streamlines accordingly. From each connectome, global

network measures (mean strength, modularity, clustering coefficient and global efficiency) were extracted.
We assessed linear robust models to explore the effect of network metrics on the remyelinated patient group accounting for Age, Age2, density and gender as confounders.
Patients were divided based on their remyelination load (50th percentile) along white matter tracts. Patients with more remyelinated lesions were significantly older, had higher EDSS, and longer disease duration. Patients with more remyelinated lesions showed more segregated and less efficient brain networks than patients with lesser remyelinated lesions ($p < 0.05$, adj. $R2 > 0.35$). Patients with larger volume of remyelinated lesions showed decreased global efficiency, clustering coefficient and increased modularity ($p < 0.01$, adj. $R2 > 0.37$) and a tendency towards decreased mean strength ($p = 0.055$, adj. $R2 > 0.31$).
The presence of focal remyelination along the tracts constituting brain connectomes is not associated with compensatory changes in myelin-weighted network properties. The second group was older with longer disease duration, which might explain the accumulation of irreversible damage. Future work will extend these findings to larger MS cohorts and consider the imbalance between damage and repair along the tracts.

P21

Systematic Review of the Diagnostic Accuracy of a Graded Gait and Truncal Instability Rating in Acutely Dizzy and Ataxic Patients

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Aims: In patients with acute prolonged vertigo/dizziness and/or gait imbalance, distinguishing peripheral from central causes is essential. Whereas subtle oculomotor bedside examinations (e.g., HINTS [Head-Impulse Nystagmus Test-of-Skew]) have excellent diagnostic accuracy, their application may be limited by lack of training of frontline providers and absence of vertigo/dizziness and nystagmus. Alternatively, a graded gait/truncal instability (GTI, grade 0–3) rating may provide useful.
Methods: We searched MEDLINE/Embase for studies reporting on diagnostic accuracy of bedside examinations in acute vertigo/dizziness. Results were stratified by GTI-ratings used and stroke location.
Results: We included 17 articles (n = 904 patients), with ischemic strokes (n = 613) and acute-unilateral vestibulopathy (n = 237) being most frequent. Grade 2/3 GTI had moderate sensitivity (66.6% [95% confidence-interval = 62.4–70.8%]) and specificity (79.2% [73.8–84.6%]) for predicting a central cause, whereas grade 3 GTI had a lower sensitivity (45.9% [42.1–49.7%]) and higher specificity (97.6% [95.7–99.5%]). In comparison, diagnostic accuracy of HINTS (sensitivity = 96.8% [94.7–98.9%]; specificity = 95.3% [92.2–98.5%]) was higher. When combining central-nystagmus patterns and grade 2/3 GTI, sensitivity was increased to 74.4% [68.8–79.9%] and specificity to 98.5% [95.5–100.0%]. Sensitivity for detecting stroke (GTI 2/3) was not significantly different for AICA and PICA strokes (74.1% [62.9–85.4%] vs. 80.5% [75.2–85.7%]). Sensitivity was higher in studies using the GTI-rating (grade 2/3) by Lee compared to Moon (71.7% [66.7–76.6%] vs. 57.4% [49.6–65.2%]).
Conclusions: Compared to HINTS, the diagnostic accuracy of the GTI-rating was inferior. When combined with central nystagmus-patterns, GTI-diagnostic accuracy could be improved. Furthermore, the GTI-rating can be readily applied in the ED-setting and also in patients with acute imbalance syndrome.

P22

Vestibular Perceptual Thresholds in Patients with Persistent Postural Perceptual Dizziness (PPPD)

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Aims: Persistent postural perceptual dizziness (PPPD) is a common functional disorder. It is characterized by a chronic sensation of dizziness which is exacerbated by upright posture. PPPD usually evolves as a consequence of a vestibular or other illness. As standard vestibular testing is usually normal in patients with PPPD we studied whether there are changes in vestibular perception.
Methods: 12 patients with PPPD were assessed, 10 males, 2 females (mean age 60 years). The diagnosis of PPPD was established according to the criteria of the Bárány Society from 2017. 23 healthy controls were also assessed,11 males, 12 females (mean age 42.3 years). Vestibular perceptual thresholds were determined for yaw-plane rotations with randomly presented half cosine stimuli. Patients were assessed for handedness, Dizziness Handicap Inventory (DHI), Ten-item personality inventory (TIPI) and Hospital Anxiety and Depression scale (HADS). History of migraine was obtained. Last migraine attack or ongoing symptoms were noted.
Results: Vestibular perceptual thresholds in PPPD patients did not significantly differ from those of normal controls. There was no correlation between age and elevated thresholds. The number of trials needed to determine the respective threshold was not related to lower threshold values. Handedness was not correlated with direction errors when indicating motion perception. There was no correlation between DHI values and high or low thresholds.
Conclusions: Patients with PPPD did not differ from normal controls regarding vestibular perceptual threshold values for yaw-plane rotations. There was no correlation between age and threshold value.

P23

Antiseizure Medication Effects on EEG Microstates

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Evidence of the impact of Antiseizure Medications (ASMs) on brain electrical activity is limited, and which variations are associated with improved or worsened therapeutic outcomes remains unsolved. In this context, the support of visual interpretation of the electroencephalogram (EEG) is scarce and more advanced methods should be considered as potential alternatives. EEG microstates represent brief, quasi-stable scalp potential topographies derived from the synchronous activation of different cortical areas, reflecting the alternating dynamics within resting-state networks. In our study we investigated the impact of ASM introduction on EEG microstate dynamics and evaluated the potential of first EEG recording in predicting seizure recurrence compared to follow-up EEGs.
In our retrospective study, we included 42 patients with newly diagnosed epilepsy (30 focal structural, 5 IGE, 7 focal of unknown etiology) who underwent a first routine EEG before ASM prescription (6 CBZ, 1 LCM, 11 LEV, 8 LTG, 2 PHT, 14 VPA). All patients performed a follow-up EEG after an average of 96 days (range 17–272) from ASM introduction. We then identified 11 patients who had seizure relapse in the 6 months following treatment initiation. EEG-microstate parameters (Classes A-D) were compared between the initial and follow-up EEGs, with a sub-analysis conducted on relapsers (R) and non-relapsers (NR).

In the overall analysis, a significant decrease in duration (F (288.7, 1) = F_12.54; $p < 0.0001$) and increase in occurrence (F (289.5, 1) = F_6.12; $p = 0.013$) of all microstate maps (A–D) was identified after ASM introduction compared to baseline EEG. We found significant differences in the first EEG between R and NR (χ^2 (1) = 4.03, $p = 0.04$). Posthoc decomposition (FDR corrected) showed that NR patients had significantly higher global explained variances (GEV) for Map A (z = 2.7; $p = 0.03$) and higher GEV for Map D (z = 2.15; $p = 0.07$) compared to R. No differences were found in follow-up EEG between R and NR.
Our study shows that ASM introduction induces a modification in EEG microstate dynamics, which does not exhibit significant differences between relapsers and seizure-free patients. Conversely, relevant discrepancies in microstate parameters between the two groups were observed only in the first EEG, suggesting that initial, drug-naive recordings hold greater potential for predicting seizure recurrence compared to follow-up EEGs, where brain activity is influenced by ASM effects.

P24

Connectivity Profile of Anterior, Centromedian, Pulvinar and Dorsomedial Thalamic Nuclei to Seizure Onset Areas for Target Selection in Neuromodulation

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Different thalamic nuclei may be targeted for neuromodulation in pharmacoresistant epilepsy. The anterior (ANT), centromedian (CM), pulvinar (PLV) and dorsomedial (DM) nuclei have been mostly proposed due to their anatomical connections to different regions, but determining which nucleus is the best target for individual patients is unclear. We propose that this lack of certainty is partly due to limited knowledge of specific functional connectivity with epileptogenic zones (SOZ) and of how electrophysiological properties of the nuclei may differ based on where the SOZ is located.
We studied real-time interactions between these nuclei and seizure onset zones (SOZ+) in 40 drug-resistant epilepsy patients (ANT = 12, PLV = 15, CM = 28, DM = 14) using stereoelectroencephalography in pre-surgical evaluation in NREM, REM and AWAKE periods. We analyzed interictal connectivity (weighted phase lag index) to SOZ in different brain regions.
We firstly confirmed varying connectivity patterns between the nuclei and different brain regions, as known by anatomical connectivity, but more intriguingly, we found significant fluctuations within SOZ+ and non-epileptogenic (SOZ-) contacts belonging to the same area. We indeed observed heightened SOZ+ than SOZ- connectivity ($p < 0.001$) only for mesial temporal in ANT, posterior in PLV, broad areas except temporal ones in CM, frontal in MD. Interestingly, we noticed state-specific fluctuations based on the closeness to the next seizure, finding significant correlations that could pave the way for predictive biomarkers. We finally were able to confirm our hypotheses on a sub-cohort of CM patients implanted with Responsive Neuromodulation, showing how responsiveness to therapy is strongly correlated to specific SOZ+/SOZ- differences in connectivity in specific areas.
Our study proposes an unprecedented view on complex thalamic neuromodulation dynamics in epilepsy, suggesting that therapeutic efficacy is strongly related to specific SOZ connectivity of the implanted nucleus. We argue that the thalamus may play a permissive role in seizure initiation based on how the interaction with the SOZ changes in relationship to seizures, setting the ground for further investigation that could have profound therapeutic impact.

P25

Three Heterozygous GAA Cases Mimicking Late-Onset Pompe Disease

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Background: Late-onset Pompe disease (LOPD) is a recessive disorder caused by acid αglucosidase (GAA) deficiency. Carriers of one GAA pathogenic variant are asymptomatic. There are several cases reported, where only one pathogenic GAA variant has been identified. Here, we present three unrelated cases with suspected LOPD carrying one pathogenic GAA variant together with other heterozygous variant(s) related to glycogen storage or structural muscle protein.
Methods: All patients were examined by a neurologist and underwent WGS (60x, PCR-free, PE150). The GAA enzyme activity was measured in dried blood spot, leukocytes and/or in fibroblasts (also used for total RNA sequencing, PE75).
Results: The phenotype of all three patients included adolescent to adult disease onset, proximal weakness and myalgia. GAA was decreased, and creatine kinase was normal to mildly elevated. WGS revealed following heterozygous phenotype-related variants: Patient 1 maternal GAA c.-32-13T>G (pathogenic), paternal PHKB (VUS) and AMPD1 (VUS); Patient 2 GAA c.-32-13T>G and AMPD1 (VUS; same variant as in Patient 1); Patient 3 GAA c.1082C>T p.(Pro361Leu) (pathogenic) and FHL1 (VUS). In fibroblasts of Patient 1, the activity of GAA was 0.83 (NR 6.04–17.06) nmol/min/mg protein and RNA sequencing confirmed abnormal transcripts due to c.-32-13T>G but no other splicing defects in GAA.
Conclusions: There may be a small cohort of LOPD-like cases where a symptomatic heterozygosity or digenic/oligogenic inheritance can be considered.

P26

Efficacy, Tolerability, and Safety of Onabotulinumtoxina Treatment for Chronic Migraine in Patients with Acute Medication Overuse: Analysis of the PREEMPT and COMPEL Trials

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Aim: To evaluate the efficacy, tolerability, and safety of onabotulinumtoxinA (onabotA) [BOTOX®] in patients treated for chronic migraine (CM) with or without acute medication overuse (MO).
Material and Methods: Data analyzed from patients with CM treated with onabotA with or without MO across COMPEL, a phase 4, single-arm trial (NCT01516892) and PREEMPT, a phase 3, placebo (PBO)-controlled trial (NCT00156910, NCT00168428). Per ICHD, MO was defined as taking acute medication $\geq$ 2 times per week in any week (depending on the medication category) during screening. Patients received onabotA every 12 wks for 108 wks (COMPEL) or 56 wks (PREEMPT). In PREEMPT, PBO patients received onabotA starting at week 24. Efficacy was reported as mean headache days (MHD), 6-item Headache Impact Test (6-HIT) score, and MSQ (Role Function Restrictive) score. Tolerability and safety were reported as adverse events (AEs).
Results: MO criteria was met by 65% (n = 904/1384) of patients in PREEMPT (onabotulinumtoxinA: n = 445, PBO: 459) and 64% (n = 456/715) of patients in COMPEL (MO: n = 456, no MO: n = 259). In PREEMPT, onabotA reduced MHD vs. PBO at 24 wks in patients with MO (mean: −8.2 vs. −6.2, $p < 0.001$) and without (−8.8 vs. –7.3, $p = 0.019$). OnabotA reduced moderate/severe MHD with MO ($p < 0.001$) and without ($p = 0.008$). Se-

vere impact via HIT-6 was reported by fewer patients with MO vs. PBO at 24 wks ($p < 0.001$) and without MO ($p = 0.027$). MSQ score was improved vs. PBO at 24 wks ($p < 0.001$) and without ($p < 0.001$). In COMPEL, the improvements were no different between patients with or without MO: MHD (mean: −10.6 vs. −11.0, $p = 0.397$), moderate/severe MHD ($p = 0.573$) and HIT-6 score ($p = 0.644$) at 108 wks. Treatment related AEs were of similar frequencies in patients with MO (27%) or without (26%) and were consistent with onabotA safety profile for CM.
Conclusions: In this post-hoc-analysis, patients with CM and MO treated with onabotA responded in similar frequency to patients with CM without MO and displayed a similar safety profile.

P27

Real-World Data on Efgartigimod and C5 Complement Inhibition Therapies in Myasthenia Gravis

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Aims: Myasthenia gravis (MG) is the most common autoimmune disorder affecting the neuromuscular junction, characterized by antibody-mediated destruction of the postsynaptic membrane. While the majority of MG patients can be effectively treated with standard immunosuppression, a relevant number of patients continue to suffer from a significant disease burden. Therefore, novel approaches such as terminal complement inhibition (C5IT) and the reduction of pathogenic IgG autoantibody levels through neonatal Fc receptor antagonism are gaining increasing consideration as treatment options for refractory MG. This study aims to provide real-world data on the efficacy as well as safety of C5IT and efgartigimod, and to compare the outcomes of both treatment strategies in MG.
Methods: In a retrospective cohort analysis, we evaluated the clinical course and safety outcomes of 21 patients receiving C5IT and 12 patients undergoing efgartigimod treatment. Changes in quantitative myasthenia gravis (QMG) score, MG activities of daily living (ADL) score, and prednisolone as well as pyridostigmine doses were analysed at months 1, 3, and 6 after baseline using Analysis of Covariance. A two-sided Student's *t*-test was used for statistical analysis of baseline characteristics and the safety profile.
Results: Baseline characteristics were comparable between both groups. Concerning clinical outcome parameters, no substantial differences were found between the groups in terms of the QMG change (month 1: −2.76 [C5IT] vs. −2.25 [efgartigimod], ns; month 3: −4.52 vs. −4.08, ns; month 6: −4.95 vs. −4.22, ns). Additionally, comparable improvements were observed in both groups with regard to MG-ADL and prednisolone as well as pyridostigmine dosing. Adverse events (AEs) were experienced by 38.1% of C5IT and 41.7% of efgartigimod patients (ns), with headache (19.0% vs. 25.0%, ns) and nausea (23.8% vs. 25.0%, ns) being the most frequent. Notably, no severe AEs were reported apart from myasthenic exacerbations.
Conclusions: In conclusion, no substantial differences in efficacy were observed between patients receiving C5IT and efgartigimod during the first 6 months of treatment. However, further longitudinal data is necessary to guide treatment strategies in terms of therapy escalation. Of note, additional longitudinal data from our cohort will be available at the time of presentation. Finally, both treatment cohorts showed a favorable and overall comparable safety profile

P28

Differential Spike Detection Patterns in Idiopathic Generalized Epilepsy and Focal Epilepsy: Insights from Routine and Overnight EEG

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Aim: This study aimed to compare the incidence of interictal epileptiform discharges (IEDs) detected on routine and overnight EEG recordings between patients diagnosed with Idiopathic Generalized Epilepsy (IGE) and those with focal epilepsy.
Method: We conducted a retrospective analysis of EEG recordings from patients diagnosed with IGE (n = 35), focal lesional epilepsy (n = 389), and focal non-lesional epilepsy (n = 62). Routine EEG and overnight EEG recordings were analyzed for the presence of IEDs. Statistical analysis was performed using Chi-square tests to compare spike detection rates among the different epilepsy groups.
Results: In routine EEG recordings, a significantly higher proportion of patients with IGE exhibited IEDs (80%) compared to those with focal lesional epilepsy (21.9%, $p < 0.001$) and focal non-lesional epilepsy (22.6%, $p < 0.001$). In overnight EEG recordings, IGE patients showed a markedly higher incidence of spikes (94.4%) compared to focal lesional epilepsy (38%, $p < 0.001$) and a strong tendency compared to non-lesional epilepsy (64.1%, $p = 0.069$). The difference between lesional and non-lesional epilepsy groups was marginally significant in overnight EEG (p 0.077) and non-significant in routine EEGs recordings ($p = 1$).
Conclusions: Our study reveals distinct spike detection patterns among epilepsy syndromes. While IGE is predominantly diagnosed via routine EEG, overnight EEG detects IEDs, especially crucial in focal epilepsy. This highlights the diagnostic utility of overnight EEG in capturing interictal epileptiform abnormalities, particularly in focal epilepsy. Nevertheless, further research is essential to optimize EEG monitoring protocols for enhanced epilepsy diagnosis and management.

P29

iSPHYNCS: A Multi-Omics Approach towards Novel Biomarkers for Narcolepsy and Its Borderland

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Introduction: The international Swiss Primary Hypersomnolence and Narcolepsy Cohort Study (iSPHYNCS) aims at providing new data to improve the management of primary central disorders of hypersomnolence (CDH). The three main specific aims of iSPHYNCS are: (1) discovery of new biomarkers, and assessment of (2) treatment adherence, and (3) patients' related outcome. This abstract presents initial data related to the first objective.
Patients and Methods: The study is ongoing at 11 study sites in Switzerland, Germany and the Netherlands and plans to prospectively include 500 CDH patients and 60 healthy controls (HC) by the end of 2026. Initial evaluations comprise a set of assessments: questionnaires, video-polysomnography, the Multiple Sleep Latency Test (MSLT), the Sustained Attention Response Task (SART), and actigraphy. Additionally, for every patient, we con-

duct further analyses using a wearable Fitbit device, as well as examining the microbiome, peptidomics/proteomics, and genetics. This comprehensive approach includes the collection of bio-samples such as plasma, serum, DNA, stool samples, and cerebrospinal fluid and Fitbit recordings over 1 year. AI-driven analyses, including unsupervised clustering, will be used for data-driven patient phenotyping, followed by a multimodal approach that combines various data types after domain-specific analyses.
Results: 194 participants have been recruited, including 7 children. This group comprises 37 individuals with narcolepsy type 1 (NT1), 134 with other primary CDH, such as narcoleptic borderland (NBL), and 23 HC. Initial analyses reveal notable differences among NT1, NBL, and HC groups across various domains, including questionnaire responses, neuropsychiatric profiles, microbiome, and Fitbit data.
Conclusions: Following an initial three-year phase in Switzerland, the internationalization of iSPHYNCS in 2023 was successful. Preliminary results suggest novel and promising clinical, biological and digital markers of CDH.

P30

Transfer Learning for Automatic Detection of Hypothalamic Hamartomas

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Introduction: Transfer Learning (TL) is used in deep learning applications, where a pretrained Convolutional Neural Network (CNN) is modified and adapted for a new task. Compared to training from scratch, training times are shorter and less training data is required. This is advantageous for radiological applications, where typically only limited data is available.
Aims: Exemplarily, TL was applied and tested for the automatic detection of hypothalamic hamartomas (HH) in T1-weighted MRI scans.
Methods: 82 patients (1–71 years; mean 24.9 +/− 15.5 years) with HH (Valdueza 1a-2b: 6, 5, 23 & 48, including 18 HH overlooked in previous MRIs) and native 3D T1 images from 11 different 1.5T & 3T scanners across 3 epilepsy centers were included. A comparison group consisted of 150 healthy control datasets (15–77 years, mean 31 +/− 9.6 years) from 5 different 1.5/3T MRI scanners. After normalizing the 3D T1 datasets to MNI space using SPM12, 9 axial slices of 60 × 60 pixels each, centered on the floor of the third ventricle, were extracted per case. A pretrained version of a CNN (GoogLeNet, 22 layers) provided by MATLAB® was modified to distinguish between images showing HH and those that did not. Retaining the trained state in the lower layers, the upper layers of this CNN were retrained with the aforementioned slices. Validation for distinguishing HH patients and controls was done through leave-one-out cross-validation, requiring evidence of HH in at least 2 of the 9 slices extracted per case for classification as patient.
Results: Cross-validation yielded a sensitivity of 97.6% for HH with a specificity of 96.7%. Overall, 97.0% of cases were correctly classified. All previously overlooked HH cases were automatically detected.
Conclusions: Automatic detection of HH using CNN together with TL achieved excellent detection rates, even for previously overlooked lesions. Remarkably, the method was applied to MRIs from different scanners with varying field strengths without requiring scanner-specific training. These results suggest that TL is a promising approach for training CNNs in radiology, especially with limited numbers of training cases. This is facilitated by utilizing pretrained networks that have already learned basic image features such as edges, corners, and other simple structures. The method might also be useful for detecting other potentially epileptogenic lesions with clear boundaries and typical brain locations, such as periventricular nodular heterotopias.

P31

Paramagnetic Rim Lesions are Associated with Enhanced Microstructural Damage and Diffuse Neurodegeneration in People with Multiple Sclerosis

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Background: Paramagnetic rim lesions (PRLs), a subset of chronic active lesions identifiable through susceptibility-based imaging, are associated with worse clinical outcomes in people with MS (PwMS) [1,2]. However, data regarding pathological changes linked to PRLs are limited.

Objectives: To explore brain structural alterations associated to PRLs in a cross-sectional setting: (1) at the microstructural level, assessing changes within lesions and perilesional tissue using advanced quantitative MRI (qMRI); (2) at the macroscopic level, measuring regional/diffuse brain atrophy.

Methods: Microstructural changes were explored in a cohort of 175 PwMS (60% female, age 46.5 $\pm$ 14.1, median EDSS 3.0), utilizing qMRI maps sensitive to myelin, neuro-axonal, and iron content (including quantitative-T1, magnetization transfer saturation, myelin water fraction, intracellular volume fraction, and QSM maps). Comparison of qMRI changes between PRLs and other lesion types ("non-PRLs") was conducted using mixed-effect models, with reference values obtained from a group of 104 healthy subjects.

Additionally, we investigated the association between brain volumes (including normalized whole brain, cortex, thalamus, and deep gray matter volumes) and PRL count in a cohort of 518 PwMS (65% female, age 48.2 $\pm$ 11.9, median EDSS 2.5), adjusting for age, sex, disease duration, treatment, and T2-lesion volume.

PRLs, defined as T2-lesions surrounded by a paramagnetic signal rim, were identified by consensus.

Results: PRLs exhibited more severe damage in all qMRI metrics compared to non-PRLs, indicating enhanced demyelination, neuro-axonal loss, and iron accumulation (all $p < 0.0001$). These differences were most pronounced within the lesions and gradually diminished, albeit remaining statistically significant, within the perilesional tissue.

In the multivariable regression models, PRL count was negatively associated with all considered brain volumes (all $p < 0.0001$).
Conclusions: PRLs demonstrate enhanced microstructural tissue damage, extending beyond lesion boundaries to affect normal-appearing perilesional tissue. The burden of PRLs is associated with regional and diffuse brain atrophy, also independently of the general T2-lesion load.
Collectively, these findings strengthen PRLs as reliable biomarkers for lesions with smoldering degenerative activity and offer insights into their association with a more severe disease course.

P32

Single-Cell Transcriptomics of Cerebrospinal Fluid Cells in Progressive Multiple Sclerosis Reveals Disease-Associated Microglia/Macrophages as Shared Feature with Alzheimer's Disease

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Aims: The pathophysiological understanding of progression independently from clinical relapses in multiple sclerosis (MS) remains still limited. Nevertheless, the accumulation of disability via silent progression significantly contributes to individual disease burden and therapeutic options remain scarce. While inflammatory processes dominate in relapsing-remitting MS (RRMS), self-sustaining neurodegenerative processes are more relevant in secondary progressive MS (SPMS) and primary progressive MS (PPMS). Here we aim to deeper investigate cellular and transcriptional differences between RRMS and progressive forms of MS (PMS) thereby approaching potential therapeutic targets for the latter.
Methods: Initially, we investigated cellular changes in the cerebrospinal fluid via retrospective flow cytometric analysis of 77 non-inflammatory control patients, 174 RRMS and 50 SPMS patients. Subsequently, we performed unbiased single-cell RNA-sequencing (scRNA-seq) of a new cohort of six SPMS/PPMS samples and compared our findings to single-cell data from RRMS and control patients.
Results: The direct comparison of cellular changes between RRMS and PMS revealed an increase of plasma cells, B cells, T cells and total cell count in RRMS. This observation is in line with previously identified pan neuro-inflammatory markers of CNS diseases [1]. Monocytes were more abundant in the flow cytometric analysis in PMS. Via scRNA-seq we found a trend to an increase of border-associated macrophages (BAM). In our deeper transcriptomic characterization, we identified shared features of these BAM with TREM2-/APOE-dependent disease-associated microglia/macrophages (DAM).
Conclusions: Our data support the preponderance of neurodegenerative processes in PMS. TREM2-/APOE-dependent DAM are known from Alzheimer's disease and are assumed to have a disease-slowing effect [2]. TREM2 expression in microglia attenuates neuroinflammation by downregulation of pro-inflammatory pathways [3], contributes to phagocytosis of myelin debris and enhances remyelination [4]. Thus, the identification of TREM2-dependent DAM in PMS may represent a potential therapeutic target.

P33

Modelling Brain Aging Effect in Multiple Sclerosis: A Multi-Parameter Quantitative MRI Study

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Introduction: Quantitative MRI (qMRI) can reveal microstructural properties and pathology in MS. Considering the interaction between aging and pathology, it is essential to explore the aging impact on diverse qMRI metrics to enhance our understanding of MS pathophysiology behind these alterations.
Aims: To model how aging affects the qMRI parameters in individuals with MS, and further investigate the patterns of age-related changes across various metrics.
Methods: We recruited 131 MS patients (18–70 years, mean $\pm$ SD: 43.22 $\pm$ 13.08) and investigated the aging effects on multiple metrics in normal-appearing white matter (NAWM) and cortex grey matter (NAcGM) using polynomial regression models, considering sex, disease duration, disability, and their interaction with age. All patients underwent an MRI protocol including (i) MP2RAGE for T1 (R1) (TR/TE/TI1/TI2/resolution = 5000/2.98/700/2500 ms/1 mm^3); (ii) FAST-T2 for myelin water fraction (MWF): TR/TE/T2prep times/resolution = 7.5/0.5/0, 7.5, 17.5, 67.5, 147.5, 307.5 ms/1.25 $\times$ 1.25 $\times$ 5 mm^3; (iii) Magnetization transfer saturation (MTsat): 3D RF single gradient echo: TE = 4.92 ms, 1 mm^3) with MT-weighted (MTw: TR/α = 25 ms/5°), PD-weighted (PDw: TR/α = 25 ms/5°) and T1-weighted (T1w: TR/α = 11 ms/15°); (iv) ME-GRE for T2* (R2*) (TR/DTE/TI1/resolution = 49/4.06/6.69 ms/0.8 $\times$ 0.8 $\times$ 3 mm^3).
Results: Our study found significant age-related associations with R1, R2*, MWF, and MTsat in NAWM and NAcGM. In NAWM, age had a quadratic effect on R1 (Age: $\beta = 0.005$, $p < 0.0001$; Age^2: $\beta < -0.001$, $p < 0.001$), R2* (Age: $\beta = 0.197$, $p < 0.001$; Age^2: $\beta = -0.002$, $p < 0.001$) and MWF (Age: $\beta = 0.061$, $p < 0.05$; Age^2: $\beta = -0.001$, $p < 0.05$), and also had a linear age dependency in MTsat ($\beta = -0.003$, $p < 0.05$). In NAcGM, age had a quadratic effect on R1 (Age: $\beta = 0.003$, $p < 0.001$; Age^2: $\beta < 0.001$, $p < 0.001$), R2* (Age: $\beta = 0.268$, $p < 0.001$; Age^2: $\beta = -0.003$, $p < 0.001$), MWF (Age: $\beta = 0.102$, $p < 0.001$; Age^2: $\beta = -0.001$, $p < 0.001$), and MTsat (Age: $\beta = 0.102$, $p < 0.001$; Age^2: $\beta = -0.001$, $p < 0.001$). The adjusted R^2 values indicate that polynomial regression models have the strongest age dependency with R2* in NAWM ($R^2 = 0.16$) and with R1 in NAcGM ($R^2 = 0.51$).
Conclusions: The model reveals age-related variations in qMRI metrics in MS across various tissue segments. Differences in modeling the aging effect exist among the qMRI parameters, with the polynomial regression models for R2* in NAWM and R1 in NAcGM exhibiting the strongest age dependency.

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LGI1-/CASPR2-Autoimmune Encephalitis Is Associated with Loss of Regulatory MAIT Cells

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Introduction: Anti-leucine-rich glioma inactivated 1 (LGI1) encephalitis and contactin-associated protein 2 (CASPR2) autoimmunity are two rare autoantibody-defined subgroups of autoimmune encephalitis (AIE). However, the drivers of its CNS- specific and systemic autoantibody immunity are still unknown. We here performed a deep and unbiased characterization of CASPR2/LGI1-AIE.
Methods: We recruited three independent cohorts of treatment naïve CASPR2-AIE and LGI1-AIE patients. We performed scRNA-seq (CASPR2/LGI1-AIE, CSF: n = 13, blood: n = 10), retrospective CSF (CASPR2/LGI1-AIE, n = 14) and blood flow cytometry analysis (CASPR2/LGI1-AIE, n = 25) whom we compared to non-inflammatory controls respectively. We additionally developed the first murine active CASPR2/LGI1 immunization model.

Results: We performed a large scale multi-omic profiling of treatment naive CASPR2-/LGI1-AIE patients. Next to a CSF specific clonal B cell expansion, we transcriptionally identified a reduction of innate-like T cells, such as γδT cells and MAIT, in the CSF of AIE patients. Confirmatory flow cytometry analysis in the blood showed a cross compartment reduction of MAIT cells in blood. We then attempted to functionally confirm the role of MAIT cells in anti-LGI1-/CASPR2- autoimmunity in a MR1- deficient mice, that lack MAIT cells. MR1 deficient mice expressed a higher rate of antineuronal serum antibodies than an immunized C57BL/6 control cohort.
Conclusions: A peripheral loss of mucosa-associated invariant T (MAIT) cells has been consistently described across autoimmune diseases, while select studies show an increase of MAIT cells in the targeted tissue, suggesting a compartment-specific function of MAIT cells. MAIT cells may lose their regulatory capacity in LGI1-/CASPR2-AIE in direct or indirect contact with danger signals in peripheral barrier-tissue, e.g., the gut. This link between innate-like T cells and autoantibody-mediated encephalitis variants might identify exploitable therapeutic targets early in the pathogenic cascade of antibody-driven CNS autoimmunity.

P35

Dura Fibroblasts are Heterogeneous and Respond with Fibrosis to Chronic Multiple Sclerosis

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Aims: The central nervous system (CNS) is ensheathed by meninges, and especially the dura mater was shown to home a high diversity of different immune cells. Whether the dura mater plays an important role in the debilitating human CNS autoimmune disease multiple sclerosis (MS) and its animal model EAE (experimental autoimmune encephalomyelitis) remains controversial as the dura microenvironment has not been deeply characterized so far.
Methods: We performed single-nuclei RNA sequencing of the dura from 4 donors with chronic MS and 4 controls without neuro-inflammatory disease. Using spatial transcriptomics, we performed a localizational analysis of previously identified cell types.
Results: Based on single-nuclei sequencing, we here identified specialized dural and arachnoidal fibroblast subtypes. Using spatial transcriptomics, we found a highly organized layering of fibroblasts and endothelial cells within the dura and identified defining markers. Under neuroinflammation, the stromal landscape changed, with the most prominent changes in the endothelial and fibroblast cell lineages. MS induced transcriptional signs of fibrosis and arachnoid barrier breakdown.
Conclusions: All in all, our data show that the dura microenvironment is unique and that MS affects the dura layer of the meninges causing a local stromal cell re-organization.

P36

Treg Suppressive Capacity and B Cell Responsiveness to Suppressive Signals Are Reduced in Multiple Sclerosis

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Background: Self-reactive B cells play a multi-factorial role in driving pathophysiological processes in multiple sclerosis (MS), since they can escape checkpoints responsible for maintaining self-tolerance and may only be partially suppressed by dysfunctional regulatory T cells (Tregs). Additionally, B cell fate is largely regulated by B cell receptor (BCR) stimulation-induced Ca^{2+} signals with downstream activation of distinct transcriptional programs resulting in either apoptosis, or survival/expansion.

Aims: Here we assess whether single cell Ca^{2+} responses and resultant proliferation differed between healthy and MS-derived B cells, and the influence of MS patient-derived Tregs.
Methods: We immunomagnetically isolated total CD19+ B cells, Tregs and conventional CD4+ T cells (Tcons) from blood samples of patients with MS and healthy donors and used an in-house single cell life Ca^{2+} imaging system to determine Ca^{2+} influx patterns in total B cells following stimulation with anti-IgM and/or anti-CD40 alone or together with either Tregs or Tcons. In addition, we performed in vitro proliferation assays with freshly isolated B cells and Tregs (or Tcons) obtained from MS patients and healthy donors.
Results: In both healthy and MS-derived CD19+ B cells, BCR stimulation and co-stimulation with anti-CD40 resulted in significant increases in intracellular Ca^{2+} and subsequent cell cycle progression. Healthy donor-derived Tregs significantly suppressed activation-induced cell cycle entry in a cell contact-dependent manner, but had little effect on B cell Ca^{2+} signals. Additionally, MS patient-derived Tregs exhibited a decreased suppressive effect compared to their healthy counterparts. This MS-associated Treg-dysfunction was at least partially exacerbated by a reduced sensitivity of MS-derived B cells towards Treg-mediated inhibition.
Conclusions: Overall, although MS-derived B cells displayed unaltered Ca^{2+} responses to BCR:CD40 co-stimulation, their sensitivity to suppressive signals is decreased, which may be further compounded by the reduced suppressive capacity of Tregs in MS.

P37

Role of Astrocyte Metabolism during Acute and Chronic Neuroinflammation

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Aims: Multiple Sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system (CNS) characterized by immune cell infiltration, demyelination and neuronal cell loss. Glial cells such as oligodendrocytes, microglia, and astrocytes are of key interest in the development and progression of neuroinflammation. In this context, astrocytes have been shown to play a crucial role in maintaining CNS homeostasis and in supporting neuronal metabolism in particular. However, numerous studies have demonstrated impaired astrocyte function in chronic inflammation and disease progression. In this context, the metabolic support of neurons by astrocyte-derived lactate is impaired in chronic inflammation for yet unknown reasons.
We here seek to unravel metabolic changes in astrocytes during acute and chronic CNS inflammation, and to understand the underlying molecular mechanisms contributing to a loss of neurotrophic support in progressive disease stages.
Methods: Using ex vivo analyses of metabolic dependencies, high-dimensional flow cytometry, and RNA-seq analyses of astrocytes in experimental autoimmune encephalomyelitis, an animal model of MS, as well as in vitro model systems of chronic inflammatory activation of astrocytes, we are investigating the underlying alterations of astrocyte metabolism related to dysregulation of CNS homeostasis and disease progression.
Results: We were able to detect a metabolic shift of chronically as opposed to acutely activated astrocytes in their expressional profile, as well as in their metabolic dependencies. Furthermore, we observed a spatial regulation of the metabolism of pre-primed astrocytes in the adult murine CNS with a shift towards mitochondrial dependency. Finally, chronic activation leads to increased histone acetyltransferase activity, suggesting epigenetic alterations of relevance to this metabolic reprogramming as well as a potential new treatment target for chronic CNS inflammation.
Conclusions: Together, we here unravel novel mechanisms how chronic neuroinflammation alters astrocyte metabolism, and point to potential therapeutic strategies for progressive stages of MS where current treatment strategies are limited.

P38

Immunoregulatory Properties of MIF in the Context of Autoimmune CNS Inflammation

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Aim: Multiple sclerosis is a chronic autoimmune disease of the central nervous system (CNS). After acute lesions, the resolution or chronification of tissue damage is mainly determined by the interplay between CNS-resident cells and infiltrating immune cells shaping either an anti- or a pro-inflammatory microenvironment. In recent years, inflammation-modulating factors governed by glia cells, such as astrocytes and microglia, have been demonstrated to promote or attenuate disease progression. One cytokine recently shown to be involved in the crosstalk of glia cells is the macrophage migration inhibitory factor (MIF). As MIF is highly expressed in human active MS lesions, the cytokine may evoke an inflammatory response in MIF-sensing cells due to the expression of CD74, the receptor of MIF. Our aim is to determine MIF-responsive cell populations, MIF-provoked effects and their associated impact on autoimmune CNS inflammation. In that way, we possibly decipher a potential novel druggable target for acute and chronic stages of neuroinflammation, for which current therapies are limited.
Methods: High-dimensional flow cytometry, immunohistochemistry and in vitro assays are used to uncover the effects of MIF on responder cells. The impact of MIF in an animal model of MS, experimental autoimmune encephalomyelitis (EAE), is examined using CRISPR-Cas9-mediated gene editing as well as intranasal treatment approaches.
Results: Microglia, myeloid and endothelial cells respond to MIF signaling and their MIF receptor expression is tightly regulated over the course of autoimmune CNS inflammation as exemplified by our findings in EAE. Astrocyte-specific ablation of MIF as well as its pharmacological blockade ameliorate EAE severity by reducing the number of pro-inflammatory T cells and blood-brain barrier leakage.
Conclusions: MIF evokes a pro-inflammatory response in MIF-sensing cells such as microglia, myeloid and endothelial cells and thereby promotes disease-exacerbating pathways in autoimmune CNS inflammation. Therefore, an inhibition of MIF may serve as a promising therapeutic approach for neuroinflammatory diseases.

P39

Escalating to Medium- vs. High-Efficacy Disease Modifying Therapy after Low-Efficacy Treatment in Relapsing Remitting Multiple Sclerosis

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Background: In patients with relapsing remitting multiple sclerosis (RRMS) on low-efficacy disease modifying therapies (DMT), the optimal strategy on how to escalate treatment once needed, remains unknown.
Methods: We studied RRMS patients on low-efficacy DMTs listed in the Swiss National Treatment Registry, who underwent escalation to either medium- or high-efficacy DMTs. Propensity score-based matching was applied using 12 clinically relevant variables. Both groups were also separately matched with control subjects who did not escalate therapy. Time to relapse and to disability worsening were evaluated using Cox-proportional hazard models.

Results: Of 1037 eligible patients, we 1:1-matched 450 MS patients who switched from low- to medium- (n = 225, 76.0% females, aged 42.4 ± 9.9 years [mean ± SD], median EDSS 3.0[IQR 2–4]) or high-efficacy DMTs (n = 225, 72.4% females, aged 42.2 ± 10.6 years, median EDSS 3.0[IQR2–4]). Escalation to high-efficacy DMTs was associated with lower hazards of relapses than medium-efficacy DMTs (HR = 0.67, 95%-CI 0.47–0.95, $p = 0.027$) or control subjects (HR = 0.61, 95%-CI 0.44–0.84, $p = 0.003$). By contrast, escalation to medium-efficacy DMTs did not alter the hazard for relapses when compared to controls.
Conclusions: Our nationwide registry analysis suggests that, once escalation from a low-efficacy DMT is indicated, switching directly to a high-efficacy treatment is superior to a stepwise escalation starting with a moderate-efficacy treatment.

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Predicting Remyelinated Multiple Sclerosis Lesions Using Deep Learning

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Aims: To develop a deep learning method for predicting lesions on MRI that might undergo remyelination in patients with multiple sclerosis
Introduction: Patients with multiple sclerosis (pwMS) have lesions characterized by different extents of myelin/axonal damage [1]. Remyelinated lesions have been shown to be hypo- or iso-intense on the Quantitative Susceptibility Mapping (QSM) providing iron and myelin content information [2]. However, QSM is not common in the clinical practice, but MPRAGE and FLAIR. To address the lack of QSM, this work explored the potential of deep learning to predict prospective hypo- or iso-intense QSM lesions using clinical MRI.
Methods: MRI data from 82 pwMS, who gave their consent to participate in the Swiss Multiple Sclerosis Cohort (SMSC) [3] and subsequently in the INsIDER studies, were retrospectively retrieved. The two closest visits in SMSC were 5–34 months prior to the visit in INsIDER. The included protocols were 1-mm isotropic MPRAGE and FLAIR in SMSC and in INsIDER, 1-mm isotropic MP2RAGE [4] and FLAIR and 0.67-mm isotropic EPI, from which QSM was reconstructed [5]. Images were co-registered to EPI. Remyelinated lesions were identified by raters if the white matter lesions were hypo- or iso-intense on QSM [2]. We limited the study focus on pwMS having remyelinated and other type of lesions. In total, MRIs from 63 pwMS' with 789 remyelinated and 4089 non-remyelinated lesions were in the dataset. 74% of the remyelinated lesions were of at most 250 voxels. Due to the limited number of pwMS, three-fold cross-validation was performed. Different visits of the same patients were in the same cross-validation fold. Patches of $16 \times 16 \times 16$ voxels were sampled on lesions from MPRAGE and FLAIR. UNETR [6], a deep learning algorithm designed for brain tumor segmentation, was adapted to consider lesion size in prediction of prospective remyelinated lesions. The algorithm performance was measured by the area under the receiver operating characteristic curve (AUC).
Results: The mean AUC, accuracy, true positive and true negative rates were 0.67, 0.62, 0.81 and 0.41, respectively. The performance results indicated that even though the clinical MRI has limited information on the iron and myelin content, the algorithm can still extract relevant information for predicting remyelinated lesions.
Conclusions: This work demonstrated the potential of using deep learning to predict prospective remyelinated lesions with only clinical MRI.

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Safety and Efficacy of Frexalimab in Relapsing Multiple Sclerosis: 48-Week Results from the Phase 2 Open-Label Extension

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Aims: Frexalimab is a second-generation anti-CD40L monoclonal antibody that blocks the costimulatory CD40-CD40L pathway, which is important for activation and function of adaptive and innate immunity. In the 12-week (W) double-blind period (DBP) of a phase 2 trial (NCT04879628) in participants with relapsing multiple sclerosis (RMS), frexalimab demonstrated safety and efficacy with the high-dose treatment showing an 89% reduction (vs placebo) in new gadolinium-enhancing (Gd+) T1-lesions. Over 24 weeks in the open-label extension (OLE) period, frexalimab was well-tolerated, and the number of lesions further decreased. Here, we report safety and efficacy data at W48 in the OLE of the phase 2 trial in participants with RMS.
Methods: In the DBP, participants were randomized to frexalimab-high (N = 52), frexalimab-low (N = 51), or matching placebo arms (placebo-high, N = 12, placebo-low, N = 14). At W12, participants receiving placebos switched to respective frexalimab arms and entered the OLE. Key assessments during the OLE included safety and efficacy (number of Gd+ T1-lesions and new/enlarging T2-lesions).
Results: 125/129 (97%) participants completed the DBP and entered the OLE; 112 (87%) remained in the study at W48 cut-off. At W48, the number of Gd+ T1-lesions (mean [SD]) remained low in participants who continued receiving frexalimab and in those who switched from placebo to frexalimab at W12 (frexalimab-high: 0.0 [0.2]; frexalimab-low: 0.2 [0.5]; placebo-high/frexalimab-high: 0.2 [0.6]; placebo-low/frexalimab-low: 0.1 [0.3]). Furthermore, 96% of participants in frexalimab-high, 87% in frexalimab-low, 90% in placebo-high/frexalimab-high, and 92% in placebo-low/frexalimab-low arms were free of Gd+ T1-lesions at W48. New/enlarging T2-lesion counts, and T2-lesion volume change remained low with frexalimab-high through W48, and lymphocyte counts were stable over 48 weeks. Overall, frexalimab treatment was well-tolerated through W48; the most common adverse events included nasopharyngitis, headache, and COVID-19.
Conclusions: Frexalimab continued to show favorable safety and efficacy in participants with RMS through W48. These data support its further development as a potential high-efficacy, non-lymphocyte-depleting treatment option in MS.

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Varicella-Zoster-Virus Infection Associated Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM)—A Case Report

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Progressive encephalomyelitis with rigidity and myoclonus (PERM), a variant stiff person syndrome with myoclonus added to the rigidity and painful spasms, is a rare neurological disease in which the pathophysiology is not fully understood. Etiology so far is diverse with associated neoplasms as well as infections.
We present a case of a 80-year old female patient, who presented with extensive extratruncal VZV manifestation in the left-sided dermatome L3 and S2 to S4 for which she was treated with parenteral acyclovir, gabapentin and topic zink oxide paste. Previously, she has not received a VZV vaccination, nor were any other chronic illnesses known. On the fifth day of treatment, she developed tonic spasms of the left leg, which morphed into myoclonus, paresis of the left leg with progressive rigidity and tactile hypoesthesia as well as hyperactive patellar and achilles tendon reflex of the left leg. On the twelfth day myoclonus became stimuli-sensitive, intensified in frequency, and extended to the upper body during periodic fever surges accompanied by other features of brainstem and autonomic dysfunction such as hypertensive derailment, plethora and dysphagia resulting in rattle breathing. High dose levetiracetam and low dose benzodiazepines did not improve the symptoms. Up-titration of clonazepam showed a slight reduction of rigidity. Complete cranial and neuronal axis MRI scans and EEG were normal. CSF showed slight increase of cell count and PCR was positive for VZV but otherwise unremarkable. Upon suspicion of PERM, 5-day IVIG and high dose steroid therapy was initiated and resulted in a decrease of myoclonus and after several weeks stiffness and paresis of the left leg were reduced and ambulation was possible for up to 15 min. Serum analysis was positive for PERM associated anti-glycine receptor antibodies (AGRA), a common denominator of all three other reported cases with association to infectious diseases, suggesting possible similarities of GlyR epitopes with in this case VZV epitopes.
This case and other infection associated PERM cases show improvement after immunoglobulin treatment (IVIG), high dose steroids and Rituximab. In Conclusion even without imaging or EEG findings of encephalitis, PERM should be considered early on, when myoclonus and stiffness and a rapidly changing movement disorder is present so treatment is not delayed.

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Recurrent Meningoencephalitis in a T Cell Dysregulated Patient—A Case Report

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Aim: A case report of a 57-year-old male with recurrent episodes of meningoencephalitis of unknown origin.
Methods: Presentation of a seven-month disease course including clinical features, laboratory and radiological findings, and treatment response.

Results: A 57-year-old male presented to the hospital with fever, cephalgia, and fatigue. First magnetic resonance imaging (MRI) of the brain and spinal cord revealed no abnormalities. Cerebrospinal fluid (CSF) revealed a mononuclear pleocytosis of 95 cells/μL. CSF testing for common infectious triggers yielded negative results. Under empirical antibiotic and antiviral therapy, the symptoms disappeared after a few days. In the following months, the patient repeatedly experienced short episodes of cephalgia and subfebrile temperature; he also reported short-term memory disorders. While clinical examinations did not reveal any neurological deficits, neuropsychological testing uncovered a mild neurocognitive disorder. Serial lumbar punctures showed a mononuclear pleocytosis ranging from 5 to 65 cells/μL. Multiple testing for paraneoplastic and autoimmune antibodies in CSF and serum revealed negative results. Testing for differential diagnosis including infectious, rheumatologic, vascular, metabolic disorders, and neoplastic diseases showed negative results except for one positive polymerase chain reaction result revealing human parechovirus in the CSF three months after first symptom onset. In addition, a dysregulation in the T-cell compartment and elevated autoantibodies against interferon could be observed. Several follow-up MRIs of the brain showed fulminant, bihemispheric hyperintense fluid-attenuated inversion recovery (FLAIR) lesions with a predominance fronto-temporoparietal. Interestingly, the course of clinical symptoms was associated with the extent of MRI-FLAIR lesions. Only one further episode was treated with acyclovir; in the other episodes the headache and fever resolved spontaneously. We are currently awaiting the results of the brain biopsy and of a metagenomics analysis (CSF and brain tissue).
Conclusions: Here, we report a rare case of recurrent febrile meningoencephalitis in an adult patient, suspected to have a viral origin, accompanied by a dysregulation of the immune system. Results of the brain biopsy and the metagenomics analysis will be presented at the conference.

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Steroid-Resistant Clinical and Radiological Findings in a Patient with Progressive Rhombencephalitis—A Case Report

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Aim: Presentation of a 71-year-old woman with bulbar symptoms and ataxia associated with progressive brainstem and cerebellar lesions of unknown origin.
Methods: Detailed description of a disease course of unknown etiology including diagnostics obtained and treatment response.
Results: A 71-year-old woman presented to the hospital with multiple fractures and a subdural hematoma after recurrent falls. The patient's family reported a gradual speech disorder, difficulties in swallowing and deterioration in gait for the past two years.
Initial magnetic resonance imaging (MRI) showed fluid-attenuated inversion recovery (FLAIR) signal alterations of the brainstem and cerebellum with no contrast enhancement. A follow-up image three months later showed additional contrast enhancement in both brainstem and cerebellum.
Cerebrospinal fluid (CSF) analysis showed a slightly altered brain-blood-barrier while the cell count was not increased. After referral to our neurological outpatient clinic a few months later, the patient was admitted to inpatient care.

Follow-up cerebral MRI showed unchanged FLAIR hyperintensities; the MRI of the spinal cord demonstrated T2-hyperintense lesions of the cervical, thoracic and lumbar spinal cord with affection of both lateral funiculi, but no contrast enhancement.
Another CSF analysis showed no abnormalities apart from a still slightly altered brain-blood-barrier; testing for anti-AQP4, anti-MOG and other autoimmune and onconeural antibodies was negative. Further laboratory testing for rheumatological, hematologic and infectious diseases turned out negative except for a monoclonal gammopathy IgG Kappa. A thoraco-abdominal computer tomography showed no signs of a solid tumor or sarcoidosis. In view of a progressive inflammatory process compatible with chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), a high-dose intravenous steroid therapy over ten days with slow tapering was established. A referral three months later demonstrated no response to the steroid therapy; on the contrary the bulbar symptoms had worsened and the MRI showed no signs of disease regression. Concerning the monoclonal gammopathy, we are currently awaiting the results of the bone marrow aspiration and PET-CT.
Conclusions: We report a rare case of progressive brainstem and cerebellar syndrome associated with radiological findings suggestive of an underlying (auto-)inflammatory disease.

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Assessment of a Deep-Learning Tool for the Detection and Segmentation of Contrast-Enhanced Lesions in Multiple Sclerosis Patients

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Aim: The detection of contrast-enhanced lesions (CELs) is fundamental for the diagnosis of multiple sclerosis (MS). CELs are typically small, often infrequent under current treatment regimens, and exhibit heterogeneous shapes. CELs detection in clinical practice is time-consuming and suffers from high inter- and intra-rater variability. To develop a deep-learning tool to automatically detect and segment CELs, which can support clinical radiological practice.
Methods: We studied 157 MS patients with CELs (age = 39.4 $\pm$ 10.8; 73,4% F; median EDSS = 2 [0:8.5]) and 129 patients without CELs (age = 45 $\pm$ 12, 66.9% F; median EDSS = 2.8 [0:8]) who underwent a clinical MRI scan including a T1-weighted image acquired with pre- and post-injection of a gadolinium-based contrast agent, as well as FLAIR images ($1 \times 1 \times 1$ mm^3). White matter lesion (WML) masks were segmented by

an automated algorithm and then corrected manually. 557 CELs were segmented by one experienced neurologist and one neuroradiologist and utilized as ground truth.
For this study, we adapted a UNet-based convolutional neural network that had been previously tested for the detection of cortical lesions, which are notoriously small. To overcome the problem of the low frequency of CELs, we reduced the patch size and the WML mask is used as a sampling region. Moreover, we introduced a new loss function—the weighted sum of Dice loss and focal loss—which accounts for the class imbalance(i.e., the number of samples without CELs is far larger than the number of samples with CELs) and partly also for the heterogeneous shape of CELs. An ablation study was performed to choose the best number of layers and filter dimensions of the network.
Results: The optimized model achieved the highest Dice Score Coefficient (DSC) in positive samples and the lowest number of False Positive (FP) voxels (0.62/16) compared to (a) the original model (0.57/15); (b) the model with more convolutional filters (0.62/483) and (c) the model with more layers (0.59/484). In the test dataset (n = 63 patients), we obtained a DSC of 0.74, a True Positive (TP) rate of 0.94 and a FP rate of 0.0085.
Conclusions: We optimized a deep-learning-based tool for the detection and segmentation of CELs that achieved a high DSC and a low FP rate. Our results were comparable with those obtained in few previous studies performed using larger datasets, more contrast images and larger minimal lesion size. Future work will aim to integrate it into clinical practice.

P46

Cerebral Amyloid Angiopathy Differently Impacts Gray Matter Microstructure in Patients with Lewy Bodies Dementia and Alzheimer's Disease

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Background: Cerebral amyloid angiopathy (CAA) has been reported in patients with dementia with Lewy bodies (DLB) and Alzheimer's disease (AD), with a similar prevalence from pathology studies.1,2 CAA typically affects posterior regions, but amyloid deposits have been observed in the striatum in patients with DLB and with APP duplication.1,3 Here, we postulated that CAA-related amyloid pathology results in a different spatial pattern of damage in DLB with respect to AD, and we tested this hypothesis in vivo, by characterizing gray matter imaging features in patients with DLB and AD with and without CAA (CAApos, CAAneg).
Methods: In this retrospective case-control study, we included patients referring to the Leenaards Memory Center (Lausanne University Hospital), with a biological diagnosis of AD and a clinical diagnosis of DLB. Co-occurrence of CAA was defined according to Boston criteria 2.0. Structural and diffusion-weighted MRI data were processed, deriving volume, average fractional anisotropy (FA) and mean diffusivity (MD) for 13 cortical and subcortical regions.4 Multiple comparison correction was applied to all statistical tests.
Results: Eighty-eight AD patients AD and 87 DLB patients were included (Table 1). Among AD and DLB patients, 15 (17%) and 23 (26.4%) presented with probable CAA, respectively (p= 0.132). MD and FA values of putamen, caudate and thalamus were significantly higher in DLB compared to AD patients (t(173) ranging from 2.05 to 2.91, p values ranging from 0.027 to 0.033 after multiple comparison correction).
When comparing the 4 groups (AD-CAApos, AD-CAAneg, DLB-CAApos, DLB-CAAneg) subcortical microstructure significantly differed, and the ratio of limbic over basal ganglia FA values differentiated DLB-CAApos from DLB-CAAneg, AD-CAAneg or AD-CAApos

(ANOVA F(3,171)= 3.44, p= 0.018, post-hoc test corrected p values ranging from 0.021 to 0.041, Figure 1). No significant differences were found for posterior (occipital and parietal) regions metrics.

Conclusions: As expected, patients with DLB and AD present a similar prevalence of CAA co-pathology. However, in DLB patients, CAA associates with an increased basal ganglia over limbic anisotropy that could reflect higher iron content5 and is not observed in AD and DLB without CAA. These results might suggest that alpha-synuclein and amyloid deposition differently interact with CAA pathogenic mechanism.

P47

Definition of Chronic Secondary Pain Associated with Parkinson Disease

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Aims: Chronic pains can be associated with a given disease by specific symptoms with impact on further diagnostics and treatment. Since this association is less obvious in Parkinson disease (PD), we developed the PD Pain Classification System (PD-PCS) questionnaire defining an association with the disease before allocating to the respective mechanism [1,2]. These criteria defining this association were proposed for chronic secondary musculoskeletal pain associated with PD for the ICD-11 [3], recently. Hence, their relevance has not been analyzed, so far.

Methods: The PD-PCS has been evaluated in 101 non-demented PD patients during the On-phase in three centers in Switzerland (enlarged database from the validation study) [2]. It defines PD-associated pain when 1 out of 4 criteria are met (pain at the beginning or aggravated by the disease, pain aggravated at the Off-phase, pain during choreatic dyskinesia, or/and pains responding to dopaminergic treatment). Then, it hierarchically assigns the pain syndrome to the respective pain category (neuropathic, nociceptive, and nociplastic).

Results: Both, mean pain and mean disease duration were about seven years. 92% of the patients presented with 166 pains (mean number of pains: 1.8). 109 (66%) were PD-related and 57 (34%) were unrelated. Pain improvement with dopaminergic medication and pain at worsening of motor symptoms occurred in 75 and 69%, respectively. 33% of the pains were aggravated by the disease (or occurred at the beginning), while pain during choreatic dyskinesia occurred only in 8%. 43% of the PD-related pains were attributed to the nociceptive, 17% to the nociplastic, and 5% to the neuropathic category.

Conclusions: The improvement with dopaminergic treatment and pain at the off-stage were the most common factors as defined according to experimental observations [4–7]. According to the PD-PCS questionnaire, pain aggravated by the disease and pains during choreatic dyskinesia are less common but should not be neglected. All four criteria reflect different aspects (although off phases and dopaminergic responses are closely related) and their use should facilitate further classification, diagnostics and treatment for PD-associated and not-PD associated pains [3,8].

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Swiss Memory Clinics Recommendations for the Use of Anti-Amyloid Monoclonal Antibodies in Alzheimer's Disease: System Preparedness

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Anti-amyloid MABs for Alzheimer's disease (lecanemab, donanemab) may be approved for clinical use in Switzerland in the near future. These are effective but potentially harmful, and occasionally deadly drugs. We provide recommendations for good clinical practice to specialists who will prescribe, deliver, and provide follow-up to patients with Alzheimer's disease. The paper takes the Appropriate Use Recommendations (AUR) of Cummings et al., 2023 on lecanemab as a template and adapts them to the Swiss health care system. The recommendations are being drafted at the time of the submission of this abstract. By the time of the SSN meeting they will be finalized and the results will be presented to the Swiss neurological community.

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On the Choroid Plexus Volume in Alzheimer's Disease: A Cross-Sectional Analysis of the Alzheimer's Disease Neuroimaging Initiative Cohort

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Background: Animal models and clinical studies strongly suggest that inflammation significantly contributes to Alzheimer's disease (AD) pathogenesis. The choroid plexus (CP) is a structure in the brain ventricles that creates a barrier between the peripheral blood and the cerebrospinal fluid (CSF). Studies of the CSF in aging people and AD patients revealed extensive abnormalities in the CP including signs of inflammation. In AD patients, histopathological studies of the CP exhibited altered structural integrity, with transcriptomic and proteomic profiles that are indicative of inflammation. If this is true, the CP might be enlarged in AD patients compared to HCs.
Methods: We randomly included patients with AD (as defined by a qualified neurologist considering clinical, MRI and liquid biomarkers), early mild cognitive impairment (EMCI, defined as memory complaint with preserved activities of daily living, and a Mini-Mental State Examination [MMSE] score between 24 and 30), late mild cognitive impairment (LMCI, defined as memory complaint with mild impairment in activities of daily living and an MMSE score between 24 and 30) as well as healthy controls (HC) from the Alzheimer's Disease Neuroimaging Initiative Cohort database. MRI were analyzed using Freesurfer. The outputs were quality controlled. We used the CP of the lateral ventricles relative to the intracranial volume to adjust for the head size (relative CPV, rCPV). To compare clinical and MRI characteristics between the groups, we used analysis of variance (ANOVA) and multivariable linear regression models, as appropriate.
Results: We included 151 patients (mean [SD] age 74.3 [8.1] years, 78 females, mean [SD] CPV 2087 [469] μL). The rCPV was largest in patients with AD (n = 44, 0.0013 [0.00032]), followed by LMCI (n = 16, 0.0012 [0.00019]), EMCI (n = 45, 0.0011 [0.00027]), and HCs (n = 47, 0.0010 [0.00025]; $p < 0.001$; ANOVA adjusted for age and sex). The larger rCPV in patients vs. HCs was further confirmed in a multivariate linear regression model adjusted for brain parenchymal fraction (BPF) and lateral ventricle volume (LVV; beta 7.748×10^{-5};

95% CI: 4.209×10^{-5};0; $p < 0.001$). The rCPV was higher in patients with lower MMSE scores (beta: -2.234×10^{-5}, 95% CI: -3.227×10^{-5}; -1.241×10^{-5}; $p < 0.001$; multivariable linear regression adjusted for age, sex, LVV and BPF)
Conclusions: Our findings suggest that in AD, the CPV is enlarged and correlates with the MMSE scores.

P50

Remyelinating Lesions Are Identified through Advanced MRI Measures of Axon, Myelin and Extracellular Compartment Properties in Multiple Sclerosis

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Introduction: Pathological studies showed that remyelination occurs in multiple sclerosis (MS); however, the characteristics of this process are poorly understood in living patients.
Aims: To identify changes in myelin (MVF), axonal (AVF), and extracellular water (isoVF) volume fractions that are compatible with processes occurring in remyelinating lesions.
Methods: 127 MS patients (mean[SD] age 46.5[14.4] yr, male = 32, median[IQR] Expanded Disability Status Scale score 3[3]; relapsing-remitting-RRMS: 75, progressive-PMS: 52) and 71 healthy controls (HC: mean[SD] age 36.3 [12.9] yr, male = 33) underwent 3T MRI acquisition at baseline (TP1) and 2-years follow-up (TP2), including (a) Magnetization Transfer Saturation maps for MVF calculation (b) multishell diffusion for intracellular volume fraction (icVF) and isoVF; (c) 3D FLAIR and MP2RAGE for white matter lesion (WML) detection; AVFwas calculated as follows: (1-MVF)*(1-isoVF)*icVF. WMLs were segmented at TP1 and registered to TP2. The %-change (PoC) of each parameter (M) is calculated as PoC = (M_TP2-M_TP1)/M_TP1. Age, Age, gender, and disease duration were regressed using a linear model. In MS patients, the AVF, MVF and isoVF PoC were categorized in decreased, normal range, and increased, defining a normal PoC between the 5th and 95th percentile in HC. To test group differences in the frequency of WMLs types, we used a nonparametric bootstrap approach. *p*-values were corrected using False Discovery Rate.
Results: A pattern compatible with focal remyelination (increased MVF, and no changes in AVF and isoVF) was found in 20% WMLs (n = 528). A similar WMLs percentage showed no significant changes in the three parameters (17%, 456 WMLs). Two other combinations (a) decreased MVF, with no changes in AVF and isoVF (b) decreased MVF and AVF, and increased isoVF were found in 15.7% (399 WMLs), and 9.3% (232 WMLs) WMLs, respectively. Remyelinated lesions with/without change over time were prevalent in RRMS ($p = 0.04$, CI: 0.01,0.04; $p = 0.001$, CI:0.02,0.05), while demyelinated/degenerated lesions were more prevalent in PMS($p = 0.001$, CI: -0.03,-0.009).
Conclusions: Advanced measures of axon, myelin, and extracellular compartment properties help to identify remyelination activity in vivo in MS patients. Remyelinating lesions appear most prevalent in RRMS, whereas focal demyelination is most evident in PMS phenotypes.

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The ATN Classification and CSF-Defined Suspected Non-AD Pathology—A Clinical Correlation Study

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Aims: Cerebrospinal fluid (CSF) biomarkers for Alzheimer Disease (AD) including Amyloid-beta (Abeta, A), phospho-Tau (pTau-181, T) and total-Tau (tTau, N) are integrated in the ATN classification framework [1]. The biomarker category "Suspected Non-AD pathologic change" (SNAP; including A-/T+/N-, A-/T-/N+, A-/T+/N+) is incompletely characterized in real-world cohorts, and the clinical relevance of negative CSF biomarkers is unknown. Thus, this study aimed:

1. To describe the relative frequency of ATN biomarker profiles in a Swiss tertiary care center cohort
2. To assess differences in demographics, cognition and CSF biomarkers between SNAP biomarker profiles
3. To correlate cognitive performance with CSF pTau in SNAP biomarker profiles

Methods: We retrospectively assessed cases with suspected neurodegenerative disease that underwent clinically indicated lumbar puncture for AD CSF biomarkers (Fujirebio Lumipulse®) at the University Hospital Zurich from 2020 to June 2023. The cases were classified according to the ATN framework, and differences between groups and correlations with global cognition were evaluated.
Results: Out of 383 internal CSF samples sent for AD biomarker workup, 36% were negative for all three biomarkers, 51% were on the AD continuum. Moreover, 0% were A-/T+/N-, 7% were A-/T-/N+, and 5% were A-/T+/N+. The established correlation between tTau and pTau in A+ cases dissipated in A- contexts. Focusing on patients with SNAP profiles (n = 42), A-/T+/N+ individuals were older (n = 19, $p < 0.005$), scored 4 points worse in the Montreal Cognitive Assessment (MoCA, $p < 0.016$), but had higher absolute CSF Amyloid-beta-42 and -40 levels ($p < 0.001$) than A-/T-/N+ (n = 23). Additionally, a correlation between sub-threshold CSF pTau-181 and MoCA scores was evident in non-Prion A-/T-/N+ individuals ($R = -0.56$, $p < 0.003$).
Conclusions: The ATN classification system was originally intended for research purposes, and selection bias may limit generalizability of longitudinal cohort studies in the AD spectrum. However, our analysis supports the stratification of subjects with SNAP profiles considering the demographic and cognitive differences in a broader population. Despite the heterogeneous nature of the underlying neuropathology of SNAP [2], we identified unexpected correlations between laboratory and clinical measures (i.e., sub-threshold pTau-181 and cognition), particularly when excluding Prion-related samples.

P52

Prediction of Language and Verbal Fluency in Parkinson's Disease Patients Undergoing Deep Brain Stimulation

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Aims: Bilateral deep brain stimulation (DBS) in the subthalamic nucleus (STN) is a commonly performed neurosurgical treatment for the motor manifestations of advanced Parkinson's disease (PD). Despite the well-documented improvement of motor function, some data suggest that DBS may worsen verbal fluency and/or the semantic component of language. We studied the effects of DBS speech capacity of our patients, with special attention to phonematic and semantic fluency, and explored possible predictors for problems in these areas.
Methods: We retrospectively evaluated the pre- and postoperative findings relating to speech and cognition in patients with PD who underwent DBS in our PD-patient's cohort (N = 31, F = 12, M = 19, median age 63.5 $\pm$ 10.06 years, disease duration 12.5 $\pm$ 5.38 years, preoperative UPDRS 20 $\pm$ 13.12 postoperative UPDRS 14 $\pm$ 9.16, preoperative LEDD

1150 ± 536.29, postoperative LEDD 482 ± 336.81). Phonematic and semantic fluency, as well as further aspects of cognitive function, were evaluated before and 6 to 8 months after DBS with a cognitive test battery consisting of a semantic fluency test (animals), a phonematic test (s-words), forward and backward Digit Span, the Wisconsin Card Sorting test, the Mini Mental State Examination (MMSE), and the Trail Making Test. Statistical analysis was performed using a General Linear Mixed Model. As potential confounders we considered age, global cognition—MMSE converted to Montreal Cognitive Assessment (MoCA) and executive function (Wisconsin Card Sorting test and Digit Span).
Results: As previously reported, both phonematic fluency (preoperative 0.056 ± 1.04; postoperative −0.306 ± 0.83, $p = 0.034$) and semantic fluency (preoperative −0.356 ± 1.004; postoperative −0.90 ± 0.73, $p = 0.009$) decreased after DBS. None of the potential confounders had a significant predictive effect on phonematic or semantic fluency. However, pre-, and postoperative phonematic fluency were significantly correlated (r = 0.54, $p < 0.009$), as were pre-and postoperative semantic fluency (r = 0.62, $p < 0.001$). In contrast, pre- and postoperative MoCA scores were not significantly correlated.
Conclusions:

1. In our cohort of patients with PD the best predictors of post-DBS verbal fluency are the pre-operative scores on phonematic and semantic fluency tests, while other published predictors for low verbal fluency after DBS could not be corroborated.
2. Borderline preoperative verbal fluency constitutes a relative contraindication for DBS in patients with DB.

P53

The Impact of Music Making-Therapy on the Quality of Life in Parkinson's Disease Patients: A Pilot Study

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The therapeutic use of music can have positive effects on language-related problems related to Parkinson's disease (PD), it can facilitate and improve movement and gait, enhance the connections between the auditory and motor systems as well as facilitate emotional and motivational processing.
A recent contribution investigated the effects of choral singing therapy on people with stroke or PD 1 using a mixed-method approach, including a battery of questionnaires and an interview aiming to shed light on participant's experience of their music making. In this way, it emerged that participants enjoyed to a significant extent the creative component and the interpersonal interactions promoted by this activity.
Music making can also have a positive impact on motor and non-motor aspects of PD; a mixed methodology study2 focused on the impact on PD patients of a 12-session program of West African drum circle class, taught by local African drumming instructors. Improvements in bradykinesia, activities of daily life and overall quality of life emerged from quantitative data, while qualitative data highlighted positive effects in terms of connections between peers and perceived improvements in mobility during and after the sessions.
Music Park is a project aimed at testing the effect of music-making therapy on the quality of life of PD patients compared to neutral activities (recreational activities such as yoga, tai-chi, bingo…). Initially, 37 subjects with PD were recruited. On the basis of the inclusion and exclusion criteria of the research project, it was possible to actually recruit and randomise (i.e., allocate to the music group or the control group), 34 patients.
Once the two groups were created, it occurred in the control group some drop-outs (patients who withdrew before the end of the study). It was therefore possible to continue and complete the statistical analysis for the Music Park project considering 26 participants: 11 participants from the control group and 15 from the music group.

All participants were assessed at T0 and T1 through PDQ-39 and qualitative interviews aimed at assessing the degree of appreciation of music by the participants.
Despite the reduced numbers, our data showed a trend of improvement in in the PDQ-39 and its subdomains (communication, daily activities, social stigma and physical discomfort), as well as a closer and more heartfelt relationship with music between T0 and T1 in comparison to control group.

P54

The Impact of Sleep Mediated Downscaling Process on Theta Wake Activity in Parkinson's Disease

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The process of slow wave sleep (SWS) is essential in the brain's ability to adapt and change. During SWS, slow wave activity (SWA) plays a significant role in scaling down synaptic strength. The amount of SWA during SWS, which usually occurs in the first part of the night, serves as a primary electrophysiological marker for the homeostatic process.
Previous research has suggested that there is a connection between levodopa-induced dyskinesia (LID) in Parkinson's disease and impairment in this mechanism (1).
However, this association could be due to either an impaired SWA-mediated downscaling mechanism or a lower build-up process. Our previous research favors the former hypothesis. We are currently studying the build-up process during wake to confirm this.
As part of our study, we recruited three different PD groups: de novo (n = 9), advanced (n = 4), and dyskinetic (n = 5), and compared them to healthy volunteers (n= 5).
All participants underwent a physical and neurological examination and received inertial sensors to monitor their sleep-wake cycle for a week before a PSG recording was taken.
On the day of PSG recording, subjects underwent to short waking recordings, during which they also performed a go/no-go task, the first in the morning and the second 9 h later.
Our findings showed changes in theta activity in the morning amount in Parkinsonian patients, indicating an intrinsic alteration in the sleep-mediated mechanism of synaptic downscaling.
Overall, our study is a valuable effort in clarifying the relationship between sleep and the onset of LID. It also opens up possibilities for innovative therapies that enhance SWA in PD.

P55

Adherence to Positive Airway Pressure Therapy after Ischemic Stroke—Data from the Bernese Sleep&Stroke Database

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Aims: Sleep disordered-breathing (SDB) is frequent in stroke patients and has a negative effect on stroke outcome. Positive-airway pressure (PAP) therapy has been shown to improve post-stroke evolution. Data on long-term adherence are however limited. We aimed to determine PAP adherence in stroke patients with SDB over 2 years in a clinical cohort.
Methods: Utilizing data from the Bernese Sleep&Stroke database, we retrospectively identified patients who suffered a stroke between January 2017 and August 2021 and who were diagnosed with SDB during the acute hospital stay. Subsequently, they were referred for positive airway pressure (PAP) therapy. We evaluated anthropometric and stroke-specific parameters, subjective sleepiness, and PAP adherence during the initial week of treatment and at follow-up visits after 3, 6, 12, and 24 months.

Results: 327 patients were assigned to PAP therapy (25% female, mean age 69 ± 11.6 years, BMI 28.1 ± 4.7 kg/m^2). Mean AHI was 34.9 ± 23.2/h, with 50.9% having severe SDB. 80% suffered from OSA, 5% had CSA, 13% mixed SDB and in 2% SDB was not subclassified. The initial stroke severity (NIHSS-score) did not significantly correlate with the severity of SDB (r = 0.02, p = 0.75). Most patients did not report subjective sleepiness (mean Epworth sleepiness scale 6.0 ± 3.8). PAP-treatment was started in 256 patients (78.3% of all patients), predominantly in autoCPAP mode (n= 245, 95.3% of PAP-patients). The number of patients who were treated with PAP-therapy decreased continuously to 242 (94.5%) at 3 months, 192 (75%), 147 (57.4%) and 106 (41.4%) at 6, 12 and 24 months, respectively. Average usage in patients continuing PAP after the visits was 04:39 ± 02:37 h/night after 3 months and remained stable (6 months: 04:54 ± 02:26 h/night; 12 months: 05:04 ± 02:17 h/night; 24 months 05:25 ± 02:13 h/night). At 24 months a PAP usage of >4 h/ night was seen in 82 patients (77.4% of patients continuing PAP/32% of all patients who had started PAP).
Conclusions: Despite satisfactory adherence to PAP-therapy among patients who continued PAP-therapy, long-term discontinuation exceeded 50% among patients and only 32% used PAP for >4 h/night after 2 years. This underlines the necessity for enhanced treatment strategies, improved selection criteria for PAP candidates, and the incorporation of supportive measures within this population.

P56

Association between Lower Extremity Physical Function and Physical Activity after Ischemic Stroke: Longitudinal Findings from the MOBITEC-Stroke Project

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Background: Stroke is a leading cause of disability and mortality, often resulting in physical impairments. Physical activity (PA) is vital in stroke rehabilitation, offering numerous benefits. However, many survivors struggle to engage in regular PA. Understanding the influencing factors is crucial to optimize rehabilitation. This study aims to explore the association between lower extremity physical function and PA.
Methods: The MOBITEC-Stroke Cohort Study included patients with a first incidence of ischemic stroke. Data assessed at 3 and 12 months after stroke were used for the analysis. A linear mixed-effects model adjusted for age, sex, instrumental activities of daily living, fall self-efficacy, modified Rankin Scale and National Institute of Health Stroke Scale (NIHSS) was used to examine the relationship between lower extremity physical function (i.e., Timed Up and Go test, TUG) and PA (i.e., total daily minutes of PA measured with a wrist-worn accelerometer over one week).
Results: Longitudinal data of 49 patients (65% male, mean age 71 (SD 10.1) years) were analyzed. The mean daily PA was 291.6 (SD 96.2) minutes at 3 months and 298.9 (SD 94.4) minutes at 12 months with a change from 3 to 12 months of 7.31 (SD 59.58; 95%-CI −9.38 to 23.99) post-stroke. We observed significant relationships between the baseline TUG performance and the change in total PA over 9 months (p = 0.011), as well as the change of TUG performance over time and the change in total PA over time (p = 0.022).
Conclusions: Our findings indicate that better initial lower extremity physical function, as well as higher improvements in function over time, are associated with a greater increase in physical activity levels after stroke. This suggests that interventions aimed at maintaining

and improving lower extremity physical function may have a positive effect on improving physical activity levels.

P57

Deep Brain Stimulation of the Anterior Nucleus of the Thalamus Reduces the Risk for Status Epilepticus in Focal Drug-Resistant Epilepsy

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Aims: Deep Brain Stimulation (DBS) of the Anterior Nucleus of the Thalamus (ANT) has been established as a novel treatment option for patients with focal refractory epilepsy, with proven efficacy on seizure frequency. However, the effect on recurrent episodes of Status epilepticus (SE) after ANT-DBS has not been substantially reported in the literature. Here, we aimed to assess whether ANT- DBS has a prospective impact on the risk of SE postoperatively.
Method: We performed a retrospective, monocentric analysis of 24 patients who received bilateral DBS lead implantation in the ANT as a treatment for focal, drug-resistant epilepsy. Medical records of the recruited patients were studied to collect the relevant clinical data. We reviewed time periods of 15 years pre- and 5 years post-operatively to identify the total number of provoked and unprovoked Status epileptici in each patient. Statistical cross-over analysis (pre vs. post) was performed using Wilcoxon signed rank tests.
Results: Among the 24 patients, 46% (n = 11) had a total of 20 episodes of confirmed SE prior to DBS, out of which 18 were unprovoked (and 2 were provoked). Post-operatively, only 2 patients developed an episode of SE, one of them being provoked. The normalized relative annual risk for SE (corrected different observational periods) in this cohort was 28.8% preoperatively and 1.9% postoperatively, demonstrating a statistically significant reduction in SE incidence by ANT-DBS ($p = 0.005$).
Conclusions: DBS of the ANT appears to significantly reduce the risk for recurrent SE in patients with focal, drug-resistant epilepsy. In this light, ANT DBS could be considered as a treatment option in particular for drug-resistant patients who suffer from recurrent status epilepticus. Nevertheless, cohort-based, multi-center studies will are required to further validate our findings.

P58

Auditory Reaction Time in Patients with Epilepsy and Healthy Controls

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Aims: Reaction time (RT) to acoustic stimuli is one of the parameters used to assess the fitness to drive in patients with epilepsy. In patients with idiopathic generalized epilepsy (IGE) the identification of subtle seizures during bilateral epileptiform discharges in the EEG is particularly challenging. Recent research demonstrated a prolonged reaction time during bilateral discharges in EEG, though a cut-off value has not yet been defined. Here we aim to find a standardized value of auditory reaction time in the normal population, in order to better recognize prolonged RT during epileptiform discharges in the EEG.
Methods: We analyzed retrospective data from auditory reaction time tests in patients with epilepsy (n = 58) during and without discharges and compared them to an age- und sex-matched control group of the normal population (n = 120). Patients and control subjects were instructed to comfortably sit in a chair and press a handheld button as soon as possible after hearing a beep-tone. Tones were played during 30 min in random intervals ranging between 20 and 60 s.

Results: The control group showed a significantly faster mean RT as compared to the epilepsy patients during discharges but not-significantly faster than the RT in epilepsy patients without discharges. Furthermore, the variability of the reaction time was significantly smaller in the control group than in the epilepsy cohort. Gender, age and daytime did not correlate with the length of RT in the control group.
Conclusions: Our findings indicate that outliers in patients with epilepsy, with small intrapersonal variance in the control group, are a useful parameter for assessing driving ability.

P59

Case Report: Response to Ketogenic Diet in Treatment-Refectory Autoimmune-Associated Epilepsy

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Background: Ketone bodies are endogenously produced molecules through dietary modification that exert physiological effects, including anti-seizure mechanisms. Modified forms of the ketogenic diet are increasingly being used in adult patients with epilepsy.
Case Report: We describe a 37-year-old female admitted to our department with new onset refractory status epilepticus due to seronegative autoimmune encephalitis. Status epilepticus was successfully terminated following a treatment with intravenous sedatives, anti-seizure medication and immune suppression. After discharge, she continued having frequent focal impaired-awareness seizures, confirmed by in-patient Video-EEG, multiple times per week and focal-to-bilateral tonic-clonic seizures that led to falls and injuries. Her seizures were refractory to several anti-seizure medications and she reported tiredness, cerebellar ataxia, moderate cognitive impairment, and poor quality of life.
We initiated a modified Atkins diet with carbohydrates limited to under 15 g/day. Fat constituted 55–60% of daily caloric intake, She reached a beta-hydroxybutyrate (BHB) value of 0.5 mmol/L. Her anti-seizure medications were unchanged apart from reducing Cenobamate by 50 mg/day.
Two months after starting the diet she had only one single seizure. She reported improved alertness, cognition, and quality of life. She returned to playing sports, participated in social events, and took up new responsibilities at work. The diet was well tolerated.
Discussion: Ketogenic diet may improve seizure frequency and quality of life in autoimmune-associated epilepsy and could be considered in adults not responding to anti-seizure medications.

P60

A Patient with Developmental Delay, Autism, Epilepsy and Severe Iron Metbalism Disorder Resulting from PIGA (Phosphatidylinositol Glycan Biosynthesis Class A) Protein Deficiency

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Phosphatidylinositol glycan anchor biosynthesis class A (PIGA) is a key enzyme in glycosylphosphatidylinositol (GPI) anchor biosynthesis. They are critical to normal early central nervous system development. Germline pathogenic variants have been reported in a wide spectrum of clinical syndrome of PIGA, including XLDD (X-linked intellectual developmental disorder, juvenile hemochromatosis, MCAHS2 (multiple congenital anomalies, hypotonia, seizures syndrome-2) and early-onset epileptic encephalopathies. The phenotypic consequences of PIGA variants can be classified into severe and less severe types which correlate with the degree of PIGA activity reduction caused by the variants.

We report on a male 26 year-old patient with a history of developmental delay and epilepsy with absence and focal to bilateral tonic-clonic seizures since the age of 9 months. Autism was diagnosed at the age of 10 years after the start in infancy of stereotypies, perseverations and lacking spoken communication with other persons. Further investigations revealed excessive iron storage disease, and a heterozygous mutation in the HFE gene (C282Y) was found. Cardiopathy required the implantation of a cardioverter defibrillator. In 2019, he suffered from a cardioembolic left hemispheric stroke with subsequent right-sided spastic hemiparesis and focal motor seizures. Since the pharmacoresistant seizures (despite treatment with brivaracetam, cenobamate, clobazam, and perampanel) were extremely sensitive to fever, a comprehensive genetic examination was performed, particularly in order to look after a mutation in the sodium channel 1A or 2A gene.
A de novo novel pathogenic variant c.242G>A in PIGA was identified through exome sequencing in our patient. The single- nucleotide substitution (NC_000023.10:g.15349811C>T (chrX/hg19)) is located in exon 3. The variant was not detected in the healthy parents. We present a male patient with a novel germline PIGA pathogenic variant and his related phenotype, which consist of features belonging to both subtypes. We compare the described pathogenic variant with the variants and clinical aspects in the literature.

P61

Age-Related Variations and Subgroup Differences in Non-Lesional Epilepsy: Implications for Etiology and Treatment

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Aim: This study aims to explore age-related differences in the epidemiology of patients with different epilepsy syndromes.
Method: We conducted a retrospective analysis of patient demographics and EEG data from individuals diagnosed with IGE (n = 35), focal lesional epilepsy (n = 389), and non-lesional epilepsy (n = 62). Statistical analyses, including *t*-tests and chi-square tests, were performed to examine age-related differences and the yield of EEG.
Results: IGE patients were significantly younger (26.8 $\pm$ 11) than those in the focal lesional (58.3 $\pm$ 19.5) and non-lesional epilepsy groups (47 $\pm$ 22.5, $p < 0.001$). The non-lesional epilepsy cohort exhibited two distinct age peaks, i.e., around 25 years old and 65 years old, suggesting the presence of differing etiologies. Regarding routine EEG, there was no significant difference in rates of interictal epileptiform discharges (IEDs) between younger and older non-lesional epilepsy patients ($p = 0.439$). However, among those who underwent a long-term EEG, only 50% (11/22) of the younger subgroup presented IEDs, while 82.4% (14/17) of the older subgroup exhibited interictal epileptiform discharges (IEDs) ($p = 0.08$).
Conclusions: Our findings indicate age-related differences between the three main epilepsy syndromes. Within the group of patients with non-lesional epilepsy, we observed two peaks suggestive of different etiologies, i.e., dysplasia in the younger group vs. a neurodegenerative origin in the elderly. No difference of IEDs were noted as a function of age in routine EEGs, while there was a strong tendency for long-term EEG to pick-up more IEDs in older patients suffering from non lesional epilepsy.

P62

Methylphenidate Markedly Improves Sleepiness in Progressive Myoclonic Epilepsy Type-1 (EPM1)—A Case Report

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Progressive myoclonic epilepsy type-1 (EPM1) is a rare autosomal-recessively inherited genetic disorder caused by various mutations in the cystatin B (CSTB) gene. Clinically,

the disorder starts at age 6–15 years with stimulus-sensitive myoclonus and generalized tonic-clonic seizures. Ataxia, dysarthria, and intentional tremor develop later on. Cognition remains almost normal, but patients suffer from psychiatric comorbidities, like emotional lability and depression. While seizure control by antiseizure medications (ASM) is easy, myoclonias worsen over time becoming action-activated heavily impairing patient's daily life. The disease itself and medication may cause difficult-to-treat sleepiness and fatigue, further lowering quality-of-life. We report a 51 year-old woman with genetically proven EPM1 since age 9 when myoclonias started, followed by seizures at age 13. At age 21, she had to stop studying because of increasing dysarthria, ataxia, atonic falls, and mental slowing. In her thirties she developed severe depression. Her symptoms were controlled by high-dose piracetam, valproic acid, clonazepam, perampanel, zonisamide, duloxetine and vortioxetine. In the last 3 years, she complained of increasing sleepiness (Epworth-Sleeping Scale (ESS): 16 points; Beck depression inventory (BDI): 25 points) and fatigue all while maintaining cognitive abilities (Montreal Cognitive Assessment (MoCA): 30/30). Trials to reduce ASMs failed because the patient did not respond with less sleepiness and she experienced more myoclonias and falls. Eventually, we started with a minimal dose of methylphenidate ((MPH, 5 mg in the morning) while continuing other medications. Within 14 days, the patient became markedly less sleepy (ESS: 3 points), and neither the myoclonias nor the seizures worsened. Three months later, the sleepiness came slightly back; augmentation of methylphenidate to 20 mg resulted in an acceptable wakefulness (ESS: 8 points), though not alike previously achieved. Further increase MPH dose was limited by the appearance of oropharyngeal dyskinesias. The exact mechanism of how MPH led to such a strong effect reducing sleepiness and improving alertness in EPM1 remains unclear. There is no other EPM1-patient treated with MTP in the literature. Given the patient's complex polypharmacy, a pharmacodynamic effect cannot be ruled out. In sum, the use of low-dose MPH in an adult patient with severe EPM1 led to reduced sleepiness without worsening of the classic symptom

P63

EEG Network Dynamics in Photosensitive Epilepsy Depend on Stimulation Frequency and Photosensitivity Type

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Aims: Photosensitive epilepsy (PSE) is a reflex epilepsy, where an abnormal electroencephalogram (EEG) response is induced by photic stimulation. Photosensitivity is classified into four types based on the propagation of the brain's response to visual stimuli. Here, we aim to identify the altered brain networks in PSE patients. To this end, we explored whether spectral properties and EEG connectivity measures differ between PSE patients, non-PSE epilepsy patients and photosensitivity types.
Method: This study analyzes EEG data retrospectively (n = 48, 38 female). The sample includes non-PSE epilepsy patients as Type 0 (n = 20, mean age 42 $\pm$ 15.6) and PSE patients distributed into three groups: Type 2 (n = 8, mean age 25.3 $\pm$ 14.3), Type 3 (n = 10, mean age 31.3 $\pm$ 18.5) and Type 4 (n = 10, mean age 20.9 $\pm$ 10.8). All participants were stimulated with flickering white light with different stimulation frequencies (1–60 Hz) under EEG monitoring (with 19 electrodes, 10–20 montage). Stimulation induced EEG effects were quantified by spectral analysis and EEG connectivity measures (phase locking value).
Results: We observed a significantly higher delta band activity at both occipital and frontal electrodes in Type 4 compared to Type 0 patients, when stimulated with flicker frequencies 15 Hz and 20 Hz, as a correlate for diffuse 3–4/s epileptic activity. This delta activity shows

a trend to vary between all types with the highest values in Type 4 patients. In contrast, the relative occipital EEG power at stimulation frequency (i.e., the direct visual evoked potential) was unchanged between PSE types. This could indicate that the initial processing of the stimuli along the visual pathway is not altered, as suggested by previous studies. However, we observed increased large-scale EEG connectivity between the frontal and occipital electrodes for Type 4 but not Type 0 patients, at stimulation frequencies 10, 15 and 20 Hz. Phase locking value also revealed a trend to vary with PSE type, with highest values for Type 4 patients.
Conclusions: Our results suggest that epileptic activity induced by photic stimulation in PSE patients is maximal at stimulation frequencies 15 and 20 Hz, which is in line with previous findings. In addition, we show a trend that the magnitude of this epileptic activity increases with PSE type severity. The connectivity analysis suggests that PSE response is a network effect, modulated by increased occipital-to-frontal EEG connectivity.

P64

Case Report: Focused Brain Stimulation in Therapy-Resistant Focal Epilepsy

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Case report about a young patient with therapy-refractory structural epilepsy caused by (resected) right frontal astrocytoma. With ongoing seizures under multiple drug-therapy we performed an implantation of a brain stimulator (EASEE®) in july 2023. A so called Laplace electrode is implanted subgaleally and affects brain's surface and deeper structures for seizure therapy. It resembles a non-invasive reversible therapy option for structural epilepsy. After successfull implantation, firstly, we observed shorter and minor seizures, and secondly an overall reduction in seizure frequency.
We would like to present and discuss brain stimulators as an extended therapy option for structural epilepsies.

P65

Design of the Contemporary ProspecTive Understanding of Migraine Real-World Evidence (CAPTURE) Study

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Aim: Insufficient longitudinal evidence is available describing the impact of migraine. This global study will assess how headache/migraine frequency, disability, and treatment patterns change over a 2-year period in individuals being treated for migraine.
Methods: ContemporAry ProspecTive Understanding of Migraine Real-world Evidence Study (CAPTURE) is a 2-year, global, observational, longitudinal, prospective study that will enroll individuals $\geq$ 18 years of age being treated for migraine. Participants will be stratified into 3 baseline monthly headache day (MHD) cohorts: 4–7 days; 8–14 days; $\geq$15 days. Eligibility criteria include men/women diagnosed with migraine for >=1 year, $\leq$50 years of age at migraine onset, taking $\geq$1 migraine medication, and a history of $\geq$4 MHDs in the 3 months prior to screening, which was confirmed prospectively with headache e-diary data in the 30-day screening period. Key study design elements and endpoints are depicted in the Figure and Table.
Results: The target enrolled sample size is approximately 2000 (cohort 1: 30% [n = 600]; cohorts 2–3: 35% [n = 700 each]). Patients will be enrolled from approximately 135 sites in 15 countries. The target for first patient enrollment is early 2023 and the last patient completion is anticipated to be late 2025. The study will collect clinical outcomes, patient-reported outcomes, and changes in the number of patients among the migraine cohorts. Only the methodology of this study will be described.

Conclusions: CAPTURE will provide a better understanding of headache/migraine frequency, disability, and treatment patterns in individuals being treated for migraine and will be one of the first global prospective longitudinal studies of its kind.

P66

Exploring Longitudinal Alterations of the Corpus Callosum Normal-Appearing White Matter in Relapsing-Remitting and Progressive Multiple Sclerosis

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Introduction: Normal-appearing Corpus Callosum tissue (NACCT) is affected in Multiple Sclerosis (MS) patients. The extent of such damage and its temporal evolution have been poorly characterized.
Aims: To investigate the extent of NACCT damage, using axon volume(AVF), myelin volume(MVF), extracellular water volume(isoVF) fractions, g-ratio(GR), and T1 relaxation time in Relapsing Remitting (RRMS) and Progressive (PMS) MS without focal Corpus Callosum lesions in two-time points.
Methods: We included 63 RRMS patients (median [IQR] age: 37.02[18.7]y, males = 27%, EDSS = 2[1.5]); 40 PMS patients (age: 58.76[10]y, males = 40%, EDSS = 4.5[2]); 71 healthy controls (HC, age: 31[16.7]y, males = 46.5%).
3T MRI was performed at baseline and 2-year follow-up, including (a) MTsat maps for MVF; (b) multi-shell diffusion protocol for AVF and isoVF; (c) 3D FLAIR and MP2RAGE for WM lesion (WML) detection and morphometric analyses. MP2RAGE for T1map.
The CC was segmented into Genu (GE), Anterior, Middle and Posterior Body (AB, MB, PB), Splenium (SP). The median was calculated for each measure.
Differences between groups in Rate of temporal change (RoC) were studied with a Linear Mixed Model (LMM) using subjects as random intercept, Group*Time interaction, age at the first visit, gender, and total intracranial volume as covariates. p-values were corrected using a false discovery rate.
The association between each CC microstructure RoC and clinical variables (CVars) (EDSS, WM Lesion Volume (WMLV)) was estimated by introducing the interaction Time*CVars in the LMM.
Results: Time-independent differences between groups were found: MVF: in all CC regions (HC > RRMS > PMS, 1.2E-9 < p < 0.0018); AVF: in MB, PB, SP (HC > RRMS > PMS, 0.0001 < p < 0.04); GR: BP (PMS > RRMS > HC, 0.001 < p < 0.03), and SP (PMS > HC, RRMS > HC, 0.01 < p < 0.02); isoVF: in BM and SP (PMS > RRMS, PMS > HC, 0.001 < p < 0.007); T1: for all CC regions (PMS > RRMS > HC, 8.5E-8 < p < 0.01).
No RoC differences among groups were found for all microstructure variables (p > 0.05).
T1 RoC correlated negatively with WMLV changes in follow-up in GE, AB, PB, SP, 0.01 < p < 0.03.
MVF and AVF were associated negatively with WMLV, 2.6E-8 < p < 0.0008; GR correlated with WMLV in GE, AB, PB, 0.01 < p < 0.03. No associations with EDSS were found.
Conclusions: The NACCT microstructure is affected in PMS more than in RRMS patients, with myelin and axons being the most altered. These alterations are related to the WML load and may reflect distant

P67

Disparities in Neuroimaging Access and Time to Diagnosis among Patients with Unprovoked Seizures and Epilepsy: Implications for Diagnostic Precision

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Aim: This study aims to investigate the critical issue of disparities in neuroimaging access and time to diagnosis among patients presenting with a single unprovoked seizure and patients diagnosed with epilepsy, emphasizing the profound impact on diagnostic precision.
Method: We conducted a retrospective analysis of medical records from patients presenting with a single unprovoked seizure (without epileptogenic lesion on the imaging, n = 135) and patients diagnosed with focal lesional epilepsy (n = 389) and non-lesional epilepsy (n = 62). Data on neuroimaging access (CT and MRI) and time to diagnosis were collected and analyzed. Statistical analyses using Chi-square tests compared neuroimaging access and time to diagnosis among the different patient groups.
Results: We observed a strong tendency for patients with a single unprovoked seizure to receive only CT more often (40.4%) than patients diagnosed with focal epilepsy (30.4%; $p = 0.0581$). Even though median waiting times is longer for the single unprovoked seizure group (14 days) compared to focal epilepsy patients (3 days), the difference did not reach significance ($p = 0.132$). Regarding delay to diagnosis, non-lesional epilepsy patients experienced significantly longer waiting times (median: 40.5 days) compared to focal lesional epilepsy (0 days) ($p < 0.001$).
Conclusions: Our findings underscore the need to address disparities in access to neuroimaging and time to diagnosis among patients with unprovoked seizures and focal epilepsy. These disparities may contribute to more frequent relapses in the group of non-lesional epilepsy and ultimately to a more difficult epilepsy control. Efforts to expedite diagnostic pathways are essential to optimize patient management and outcomes, particularly for individuals at risk of developing epilepsy.

P68

Accuracy of Electrical Source Localization and Dependency on Repetition Count in High-Density EEG-Recorded Medianus Somatosensory Evoked Potentials

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Aim: This study aims to validate the intracerebral localization of Medianus-SEP by means of High-Density EEG and subsequent source localization. In addition, we explore the relationship between the repetition count of stimulations and the dispersion of the resulting electric source localization.
Methods: In a healthy subject, Medianus-SEPs were recorded by High-Density EEG. An individualized head model was computed based on a high-resolution T1 weighted MRI. Electrical source localization (dipole modeling, sLORETA) was calculated using the EEG average of all stimulation epochs. After confirming the anatomically accurate localization, the calculations were repeated with a stepwise reduction in the number of averaged epochs. For each reduction step, the calculations were repeated 15 times with different sets of epochs randomly selected from all available epochs. At each reduction step, the results for the electrical source localization were compared to the original result, and mean distances along with standard deviations were calculated.
Results: Utilizing all epochs, the electrical source of the Medianus-SEPs was accurately localized in the hand knob of the contralateral hemisphere. The dispersion and deviation from the original localization depending on the number of stimulations are presented.
Conclusions: This investigation helps to assess the accuracy of electrical source localization based on High-Density EEG. Furthermore, it allows to estimate a lower threshold of necessary stimulations for a precise localization of SEPs in the utilized system.

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From Renal Cell Carcinoma to Polyradiculopathy: A Case Report

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Introduction: Polyradiculopathies are characterized by damage or dysfunction of multiple nerve roots presenting a variable range of symptoms such as pain, weakness, and sensory disturbances. The signs of polyradiculopathy follow sensory and motor nerve root distribution. Because polyradiculopathy affects multiple nerve roots, it can mimic other syndromes such as plexopathy and polyneuropathy. Causes of polyradiculopathy can be autoimmune, infectious, metabolic, paraprotein-related, paraneoplastic, or neoplastic. For diagnostic workup laboratory analysis, cerebrospinal fluid evaluation, electrodiagnostic testing and magnetic resonance imaging are helpful.

Case: A 73-year-old man was admitted to the Emergency Department due to progressive muscle weakness, paresthesia, and numbness of the left arm for two months and the same symptoms on the right arm for one month with significant exacerbation in the last weeks. He suffers from neck pain spreading out to both arms. In the clinical examination, the patient presented a now rapid progressive, distally and left emphasized paresis of both arms with reduced muscle reflexes and sensory disturbances. Cerebrospinal fluid examinations showed no pleocytosis but increased protein (2.2 g/L) and lactate (3.6 mmol/L) level. Analysis for oligoclonal bands and intrathecal synthesis of immunoglobulins was negative. Type 2 diabetes mellitus could be diagnosed. Studies of other metabolic, infectious, or paraprotein-related causes of the polyradiculopathy were negative. The reason for the bilateral polyradiculopathy was then found in the cervical MRI as a large, in the cervical nerve roots infiltrating mass. By performing biopsy and abdominal CT the large mass could be defined as a metastasis of a renal cell carcinoma and therapy with Dexamethasone, Pembrolizumab and Lenvatinib was initiated. Additionally, radio-oncological treatment is in evaluation.

Discussion: We describe an impressive case of a bilateral neoplastic cervical polyradiculopathy caused by large metastasis of renal cell carcinoma as a rare constellation. The clinical manifestations of polyradiculopathies are very variable and the differentiation from other syndromes such as plexopathies and polyneuropathies can be quite challenging. Therefore, a detailed anamnesis and clinical assessment is crucial for differential diagnostic considerations, determination of further diagnostic workup.