

Oral Sessions

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Infectious diseases

O1001

Progressive multifocal leukoencephalopathy associated with lymphopenia and T-cell exhaustion successfully treated with interleukin-7

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Background and aims: Progressive multifocal leukoencephalopathy (PML) is a devastating brain infection caused by the JC polyomavirus (JCPyV). Subjects who are immunocompromised are at risk. Survival depends on immune recovery. We have previously used interleukin-7 (IL-7) with success to treat a patient with PML and idiopathic T-cell lymphopenia (ICL). Here we describe a second case.

Methods: A 78-year-old woman who had been treated with corticosteroids for pulmonary sarcoidosis 25 years earlier developed PML associated with severe ICL characterized by expression of programmed cell death-1 (PD-1) receptors on the majority of her total circulating CD4+ and CD8+ T-cells. This is a potential state of T-cell hypo-responsiveness (loss of effector cytokines), so called T-lymphocyte exhaustion.

Results: Mirtazapine, to block serotonin receptors needed for viral cell entry, was started, but the disease progressed. She was then treated with IL-7, which is a cytokine essential for T-cell proliferation. A month later, signs of recovery were observed. The patient continued to improve remarkably, both clinically and radiologically, and along with increasing peripheral lymphocytes and declining PD-1 expression. Viral clearance of CSF was achieved, and repeated FDG-PET scan showed evidence of re-myelination.

Conclusion: Complementary and tailored treatments to enhance the host defense against JCPyV in PML are promising. IL-7 therapy in PML when lymphopenia is present could be offered. The IL-7 treatment reversed PD-1 up-regulation in our patient suggests also the possibility of combining IL-7 with PD-1 blockade in future research studies.

Disclosure: Nothing to disclose

O1002

Infectious encephalitis and myelitis in a tropical area during 2012-2018: Influence of emerging viral infections and rare causes

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Background and aims: The frequency of infectious encephalitis and the distribution of causative pathogens in the Caribbean are unknown and might be influenced by emerging arbovirus infections.

Methods: Using a hospital database, we retrospectively collected detailed information on a comprehensive series of immunocompetent patients with acute infectious myelitis and encephalitis over the 2012-2018 period.

Results: From 259 suspected cases with acute central nervous system (CNS) infection, we included for analysis 175 cases, comprising 145 encephalitis, 22 myelitis, and 8 encephalomyelitis. The annual incidence peaked at 15.2/100 000 during the Zika 2016 outbreak. Children accounted for 21.7% of cases. Ten adults died during hospital stay, all encephalitis. Infectious agents were identified in 105 cases (60.0%), including 39 confirmed cases (37.1%), 48 probable cases (45.7%), 15 possible cases (14.3%) and 3 clinical cases (2.9%). Among 175 cases, the most frequent etiologic agents were Zika virus in 23 cases (13.1%), herpes simplex in 12 (6.9%), varicella zona virus in 11 (6.3%), dengue virus in 11 (6.3%) and leptospirosis in 11 (6.3%). Pathogens unidentified until then in Guadeloupe were found.

Conclusion: Zika outbreak had a major influence on the annual incidence of acute CNS infection. Acute neuroleptospirosis was over-represented in our series. It is important for clinical practice in tropical areas since neuroleptospirosis has a good prognosis when early treated. Further efforts are mandatory to develop new diagnosis tools for pathogen profiling.

Disclosure: Nothing to disclose

O1003

Retinal changes in cerebral malaria among Sudanese patients in Khartoum state, Sudan

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Background and aims: It is thought that Malaria parasites live in red blood cells and make them stick to the inside of small blood vessels, particularly this causes the unique whitening of eye blood vessels. The light-sensitive tissue in the eye is also affected because the parasites disrupt the supply of oxygen and nutrients. These changes, known as malarial retinopathy, include white, opaque patches, whitening of the infected blood vessels, bleeding into the retina and swelling of the optic nerve.

Objectives: Our study aims to demonstrate malarial retinopathy in patients presented with neurological manifestations of malaria.

Methods: A cross-sectional Hospital based study included all patients with malaria seen during the period between 1-1-2019 and 25-4-2019.

Results: Almost 40 patients with neurological manifestations of malaria were included in the study (29 having cerebral malaria, 3 with post malarial cerebellar ataxia, 2 with post malarial syndrome and abnormal movement, one with peripheral neuropathy, one with proximal myopathy, one had cerebral infarction, one had cerebral haemorrhage, one had sagittal sinus thrombosis and one had six nerve palsy. Out of 29 patients with cerebral malaria 14 were children and 15 were adult. Malarial retinopathy changes were detected only among those with cerebral malaria (7 children and 3 Adult).

Conclusion: The eye can provide a very reliable way of diagnosing cerebral malaria. By looking at the changes to the retina our research demonstrates that the detection of malarial retinopathy is a much needed diagnostic tool in cerebral malaria, and can identify those children at most risk of death.

Disclosure: Nothing to disclose

O1004

Tumor necrosis factor-alpha signaling may contribute to chronic west Nile virus post-infectious proinflammatory state

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Background and aims: West Nile virus (WNV) causes human disease ranging from a febrile illness (WNV fever) to severe neuroinvasive disease (meningitis, encephalitis, acute flaccid paralysis). Since WNV became a global Public Health concern, clinicians caring for WNV survivors have observed persistent neurological symptoms occurring long-after the production of neutralizing antibodies and clearance of the virus. Alternative pathogeneses other than direct viral invasion have been hypothesized to explain these post-infectious symptoms. A dominant hypothesis is that antiviral responses triggered initially to clear WNV may persist to promote a post-infectious proinflammatory state.

Methods: In 4 serologically-confirmed WNV patients with persistent post-infectious symptoms (3 WNV fever, 1 neuroinvasive disease), we ordered a comprehensive cytokine panel at weeks 8, 10, 12 and 36 months post-onset of illness, respectively, to better understand the pathophysiology of the protracted symptoms.

Results: All 4 patients had abnormally elevated tumor necrosis factor alpha (TNF- α), a major molecule triggering antiviral cytokines and chronic inflammation in many human autoimmune diseases, but heretofore not reported to be upregulated in human WNV infection. Three patients also had elevations of other proinflammatory proteins. Major symptoms included fatigue, arthralgias, myalgias, generalized or multifocal pain or weakness, imbalance, headaches, cognitive problems, and symptoms of dysautonomia.

Conclusion: The findings provide support for an extended post-infectious proinflammatory state that may contribute to chronic inflammation and long-term morbidity in some WNV survivors and further suggest that TNF- α may play a pathogenic role in initiating this inflammatory environment. Clinical trials are warranted to determine if TNF- α inhibitors or other immunosuppressive agents can improve patient outcomes.

Disclosure: Dr. Leis receives funding from the Mosquito Illness Alliance (mosquitoillnessalliance.org) and the Wilson Research Foundation, Jackson, MS.

O1005

Impact of brain biopsy on management of nonneoplastic brain disease

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Background and aims: Diagnostic yield of brain biopsy in neoplastic brain disease is high and its clinical impact is well established. In non-neoplastic brain disease with negative conventional investigation, decision to undergo invasive procedures is difficult due to its inherent risk. This study aimed to assess clinical impact of brain biopsy results on management of non-neoplastic brain disease.

Methods: A multidisciplinary team retrospectively reviewed and included all non-neoplastic brain disease cases submitted to biopsy between 2009-2019, in a tertiary hospital in Lisbon. Baseline characteristics were registered, including immunosuppression status, diagnostic workup and treatment prior to biopsy. Diagnostic yield, clinical impact and in-hospital complication rates were assessed.

Results: 64 patients were included, 20 (31.3%) of them immunosuppressed (15 HIV+ patients). 35 (67.7%) were previously treated with corticosteroids or anti-infectious agents, with higher percentage (93.3%) in the immunosuppressed group. Biopsy results were diagnostic in 48 (75%) cases. More frequent diagnosis were infectious diseases in 20 (31.2%), inflammatory diseases in 13 (20.3%) and neoplastic in 12 (20%). Brain biopsy resulted on impact on patient's clinical management in 56 (87.5%), of which 69.8% were submitted to treatment change. In-hospital complications were registered in 4 (6.6%) patients. All cause in-hospital mortality was 3.3%.

Conclusion: Brain biopsy had clinical impact, including a change in treatment, in the majority of patients studied, and may be considered a useful diagnostic option in nonneoplastic brain disease. However, associated complication rate is not negligible, and previous thorough workup, patient selection and risk-benefit assessment are important.

Disclosure: Nothing to disclose

O1006

Recurrent community-acquired bacterial meningitis in adults

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Background and aims: Recurrent episodes of bacterial meningitis have previously been described in 5% of cases and has been associated with a relatively favorable prognosis. Recent changes in epidemiology of bacterial meningitis may have changed the risk factors and characteristics. Furthermore, it is unclear whether vaccines failures occur.

Methods: We analyzed adults with recurrent episodes from a prospective nationwide cohort study of community-acquired bacterial meningitis.

Results: We identified 143 recurrent episodes of community-acquired bacterial meningitis out of 2264 episodes (5%) in 123 patients. The median age was 57 years (IQR 43-66) and 57 episodes (46%) occurred in men. The median duration between the first and the current episode was 5 years (IQR 1-15). For 82/123 patients (67%) it was the first recurrent episode, 30 patients had 2-5 previous episodes (24%), 2 had 6-10 episodes (2%), and 2 had >10 episodes. Predisposing factors were identified in 86/123 patients (70%), most commonly consisted of ear or sinus infections (45/123 [37%]) and cerebrospinal fluid leakage (36/122 [30%]). The most common pathogens were *Streptococcus pneumoniae* (80/123 [65%]) and *Haemophilus influenzae* (16/123[13%]). The outcome was unfavorable (Glasgow outcome scale score<5) in 22 patients with recurrent meningitis (18%) versus 806 (40%) for non-recurrent meningitis patients (p<0.001). Five versus 363 patients died (4% vs. 18%, p<0.001).

Conclusion: Recurrent meningitis frequently occurs due to predisposing factors, most commonly ear or sinus infections and CSF leakage. Recurrent episodes are predominantly caused by *S. pneumoniae* and *H. influenzae*. The disease course is less severe with a lower mortality rate compared with non-recurrent meningitis patients.

Disclosure: Nothing to disclose

O1007

Molecular epidemiology, incidence and mortality of neonatal group B streptococcal meningitis and sepsis in the Netherlands

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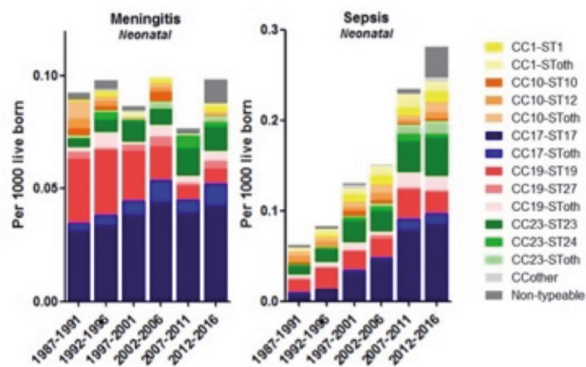
Background and aims: Group B streptococcus (GBS) is the most common cause of neonatal meningitis and sepsis. We assessed the molecular epidemiology, incidence and mortality of invasive neonatal GBS infections in the Netherlands.

Methods: Culture positive GBS cases in patients 0-3 months old between 1987 and 2016 were identified through Netherlands Reference Laboratory for Bacterial Meningitis. Serotyping was performed by latex agglutination. Sequence types (ST) were determined using whole genome sequencing. Outcome data was obtained through the Municipal Personal Records Database.

Results: 1396 episodes in 1386 patients were identified; 177 (13%) were cultured from cerebrospinal fluid (CSF), 344 (25%) from CSF and blood, and 875 (63%) from blood only. The annual incidence of meningitis remained stable, due to a decline in ST19 cases ($b=-0.001$, $p<0.001$) with a concurrent non-significant increase of ST17. The incidence of sepsis increased from 0.06 in 1987 to 0.29 per 1000 livebirths in 2016 ($b=0.009$, $p<0.001$), mainly due to a rise in ST17 ($b=0.003$, $p<0.001$). Serotype III was associated with meningitis, causing 403/508 (79%) of the meningitis and 433/838 (52%) of the sepsis cases ($p<0.001$). Mortality rate was 8% (27/323) in meningitis cases and 6% (39/656) in sepsis cases ($p=0.175$). Serotype Ib was associated with mortality in meningitis (OR 8.78 95%CI 1.92-40.05) compared to serotype III, even after correcting for multiple testing.

Conclusion: The overall incidence of GBS meningitis remained stable. The incidence of sepsis increased mainly due to the rise of ST17.

Disclosure: Nothing to disclose



O1008

Central Nervous System Vasculitis in Whipple Disease: a Case Report

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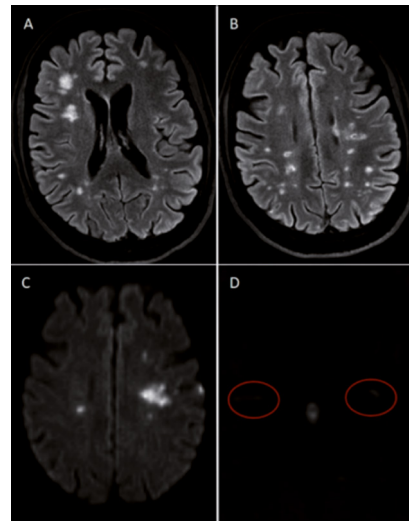
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Background and aims: Whipple disease (WD) is a rare systemic infection with possible involvement of the central nervous system (CNS). The neurological manifestations of the disease are various and can mimic any neurologic condition.

Methods: Case report.

Results: A 46-year-old woman developed acute right-sided hemiparesis and dysarthria. She had a 10-year history of diffuse arthralgias, episodic fever and rash of unclear etiology poorly responsive to different immunotherapies. Brain MRI demonstrated multiple anterior circulation infarctions and stenosis of the bilateral M1 segments of the middle cerebral artery on MR angiography. Black blood sequences revealed contrast enhancement of the vessel walls consistent with vasculitis (Figure 1). Cerebrospinal fluid (CSF) analysis was unrevealing, including PCR for viruses and bacteria. A working diagnosis of primary CNS vasculitis and progressive neurologic deterioration with abnormal behavior and altered mental status prompted the initiation of intravenous (IV) methylprednisolone followed by cyclophosphamide without significant improvement. Re-evaluation of the long-standing history of ill-defined rheumatologic manifestations unresponsive to immunotherapy led to wide-spectrum investigations. PCR for *Tropheryma Whipplei* was positive in stool, urine, blood and CSF, and duodenal mucosal biopsies confirmed the diagnosis. A combination of ceftriaxone, doxycycline, and hydroxychloroquine was initiated. Three days later the patient developed periocular burning pain and cutaneous vesicles consistent with shingles. Varicella-zoster virus DNA was detected in CSF and IV acyclovir was started. At 3 months follow-up neurologic examination was unremarkable except for a slightly fatuous behavior.



Brain MRI FLAIR sequences revealing hyperintense lesions in the subcortical white matter of both hemispheres (A-B). C, DWI sequences showing several recent ischemic lesions bilaterally with prominent involvement of the left frontal lobe. D, black blood sequences documenting enhancement and thickening of the wall vessel of both MCAs (red circles).

Conclusion: Recognition of rare manifestations of WD is important to avoid diagnostic delay and inappropriate, potentially harmful treatments.

Disclosure: Dr. Matteo Tagliapietra receives training grant from Pfizer

Neuromuscular junction diseases; peripheral nerve disorders

O1009

Zilucoplan, an investigational peptide inhibitor of complement component 5, blocked muscle weakness in a humanized passive transfer model of immune-mediated necrotizing myopathy

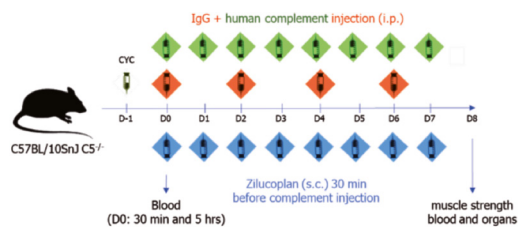
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Background and aims: Immune-mediated necrotizing myopathy (IMNM) is a rare and severe inflammatory myopathy. On biopsy, necrosis of skeletal muscle fibers, prominent complement activation and deposition of C5b-9 membrane attack complex (MAC) is observed. Autoantibodies against signal recognition particle and hydroxy-3-methylglutaryl-CoaA reductase (HMGCR) are associated with IMNM subtypes. Zilucoplan is a convenient, subcutaneously self-administered macrocyclic peptide inhibitor of complement component 5 (C5) developed by Ra Pharma, currently in Phase 2 development for IMNM and in Phase 3 development for acetylcholine receptor-positive generalized myasthenia gravis (gMG).

In this study, we provide preclinical evidence of the protective role for C5 inhibition by Zilucoplan in a humanized murine model of IMNM.

Methods: C5-deficient B10.D2/oSn mice received daily intraperitoneal injections of IgG-depleted human serum as source of human complement. Disease was induced by injection of IgG purified from an anti-HMGCR+ IMNM patient or healthy donor as control every other day. A subgroup was treated with daily subcutaneous injections of zilucoplan (Figure 1). Muscle strength following sciatic nerve electrostimulation of a gastrocnemius and markers of C5 activation in sera and muscle tissue sections were measured at day 8.



To reduce anti-human xenogeneic immune responses, mice received a single dose of 300 mg/kg of cyclophosphamide at day-1. A total of 24 mice for a n=8 per group was used.

Figure 1: Description of dosing-regimen for the IMNM passive transfer model

Results: Administration of zilucoplan completely prevents the decrease in muscle strength observed following co-administration of human complement and anti-HMGCR autoantibodies (Figure 2). C5 activation is inhibited in the sera of animals treated with zilucoplan. Histological data (ongoing) will be provided.

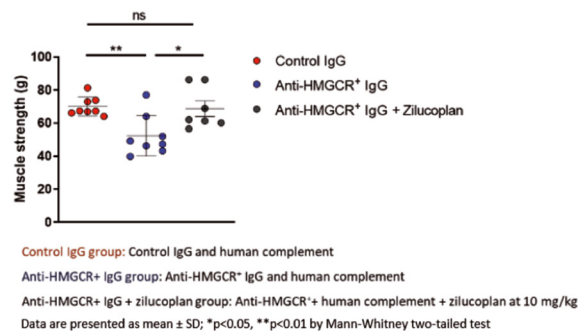


Figure 2: Zilucoplan completely prevents muscle weakness following passive transfer of anti-HMGCR and human complement to C5-deficient B10.D2/oSn mice

Conclusion: Our data establish a central role for C5 activation in a preclinical IMNM model, supporting the therapeutic evaluation of zilucoplan in an ongoing multicenter Phase 2 IMNM clinical trial (NCT04025632).

Disclosure: This work received financial support from Ra Pharmaceuticals. SR, AR, CS, and DV are employees and shareholders of Ra Pharmaceuticals.

O1010

Clinical correlations and progression rate of patients with late-onset dysferlinopathy (≥ 30 years): a French nationwide retrospective study

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Background and aims: Dysferlinopathies are a group of muscle disorders caused by mutations in the DYSF gene. Onset of disease is rarely beyond 30 years. With the advent of NGS technologies, patients with late-onset dysferlinopathy are recognized more frequently, although descriptions as a group are lacking. The aim of this study is to characterize this subgroup of “milder” forms of the disease and to define clinical correlations and progression.

Methods: Nation-wide retrospective study of French neuromuscular network (FILENEMUS) centers. Inclusion criteria are i) symptomatic patients ii) onset ≥ 30 years iii) absent dysferlin on muscle immunoblot/western-blot iv) 2 DYSF gene mutations. Clinical, paraclinical and functional data will be collected (at first and last visits). Patients from the international dysferlinopathy cohort from the JAIN foundation will be ascertained following the same criteria.

Results: 22 patients were ascertained in France and 20 (90.9%) already included. Mean age is 59.8 ± 9.52 SD years and 63.2% are females. Symptom onset was at 39.5 ± 9.1 SD years, 12 between 30-39 years (late-onset) and 8 after 40 years (very-late-onset). Phenotypes at onset encompass Miyoshi myopathy (40%), pseudometabolic (40%) and axial (20%). 73.3% showed proximal lower-limb weakness on follow-up (at 12.9 ± 5.9 SD years). One patient has lost ambulation, and one patient presents respiratory insufficiency. Genetic heterogeneity was noticed. Furthermore, 19 patients fulfilling inclusion criteria from the JAIN international cohort will be added.

Conclusion: We will provide a full characterization of

patients with late-onset dysferlinopathy with the goal of better understanding this subgroup of patients who will influence power and design of clinical trials.

Disclosure: Nothing to disclose

O1011

Role of next generation sequencing in the diagnosis of congenital neuromuscular diseases: the experience of an Italian centre

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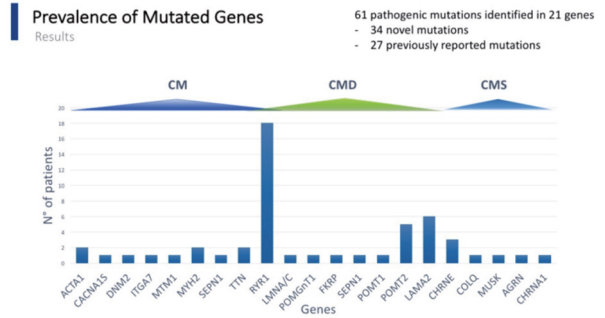
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Background and aims: Congenital myopathy (CM), congenital muscular dystrophies (CMD) and congenital myasthenic syndromes (CMS) are heterogeneous groups of genetic disorders. In last years, genetic techniques developed from Sanger to Next Generation Sequencing (NGS) and Whole Exome/Genome Sequencing allowing the discovery of disease-related genes and a better understanding of molecular disease-basis.

Methods: We analysed our 10-year experience in the diagnosis of congenital neuromuscular diseases from a clinical, histopathologic and genetic point of view. We select a cohort of 90 patients/86 probands with a clinical suspect of congenital neuromuscular disease, which underwent extensive genetic analysis; most of patients underwent muscle biopsy prior to genetic testing.

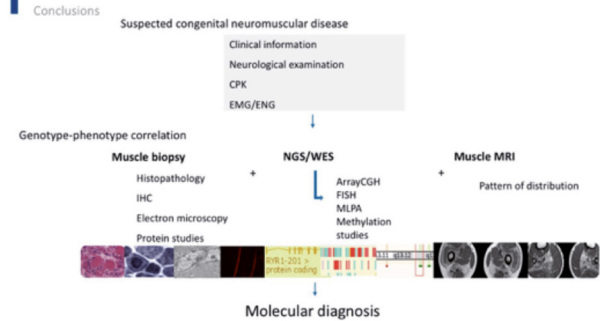
Results: The cohort presented 54 CM (60%), 26 CMD (29%) and 10 CMS (11%). 60% of patients manifested early-onset disease (6±7 m), 6 patients in infantile age (7.3±2.7 y), 33% was adult-onset (42±15 y). A molecular diagnosis was reached in the 59% (53/90): among CM 28 mutations were identified in 9 genes (14 novel mutations); in CMD 24 mutations in 9 genes (15 novel mutations); in CMS 8 novel mutations in 5 genes (6 novel mutations). NGS was applied in 52% (47/90) of patients and was diagnostic in 44%. In undiagnosed group we identified 92 variants of unknown significance in 31 genes.



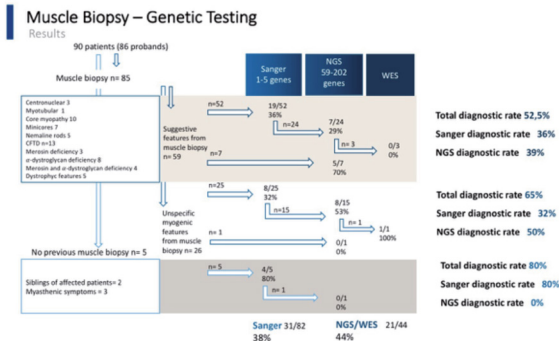
Prevalence of mutated genes and their distribution in CM, CMD and CMS.

Conclusion: NGS panels reached a molecular diagnosis in a higher number of patients and identified overlapping genes and phenotypes; however, many patients remain without a molecular diagnosis: this will be fundamental for patient's selection for treatments under development. Finally, we propose a diagnostic algorithm for congenital neuromuscular diseases.

Diagnostic Algorithm



Disclosure: Nothing to disclose



Flow diagram to visualize the step-wise diagnostic workup and the number of positive genetic results (absolute number and frequency) for all patients. Biopsy findings and clear phenotypic data that guided the targeted testing are mentioned in detail and in their frequency.

O1012

Exploring possible predictors of clinical outcomes following nusinersen treatment of Spinal Muscular Atrophy (SMA): interim results from the Phase 2 NURTURE Study

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Background and aims: NURTURE is an ongoing open-label study (NCT02386553) examining the efficacy and safety of intrathecal nusinersen initiated in presymptomatic infants with 2 or 3 SMN2 copies.

Methods: Enrolled infants were age ≤ 6 weeks at first dose, clinically presymptomatic, and genetically diagnosed with SMA. Primary endpoint is time to death or respiratory intervention (invasive/non-invasive ventilation for ≥ 6 hours/day continuously for ≥ 7 days or tracheostomy). Cerebrospinal fluid (CSF) was drawn prior to nusinersen administration to assess phosphorylated neurofilament heavy chain (pNF-H) levels on Days 1, 15, 29, 64, 183 and every 119 days subsequently. Correlations (Spearman's rho) were determined between pNF-H levels and HINE-2 motor milestone total score and WHO motor milestone walking alone, with additional correlational analyses.

Results: NURTURE enrolled 25 infants (2 copies SMN2, n=15; 3 copies, n=10). As of 29 March 2019 interim analysis, median age at last visit was 34.8 (range 25.7–45.4) months. All infants were alive and none required permanent ventilation. CSF pNF-H levels rapidly declined after initiation of nusinersen before stabilizing at lower plateau levels. CSF pNF-H levels at Baseline and Day 64 in the overall population were significantly correlated with earlier achievement of WHO motor milestone walking alone and HINE-2 total score at Day 302. In participants with 2 SMN2 copies, Day 64 weight for age and CMAP amplitude were correlated with achievement of WHO walking alone and HINE-2 total score at Day 302.

Conclusion: CSF and plasma pNF-H levels following nusinersen loading may predict future motor function in NURTURE participants.

Disclosure: This study was sponsored by Biogen (Cambridge, MA, USA). Writing and editorial support for the preparation of this abstract was provided by Excel Scientific Solutions (Fairfield, CT, US): funding was provided by Biogen.

O1013

Knockdown and replacement of MFN2: a gene therapy to treat dominantly inherited peripheral neuropathy CMT2A

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Background and aims: Charcot-Marie-Tooth type 2A (CMT2A) is an inherited, debilitating sensory-motor neuropathy caused by missense mutations in the MFN2 (Mitofusin2) gene. MFN2 mutations appear to induce the disease with a dominant-negative mechanism, where the expression of the wild-type MFN2 allele is negatively regulated by the mutant protein. Although no effective treatment exists, the molecular silencing of the mutant pathological protein, in combination with the replacement of wild-type activity, represents a possible treatment for this disease.

Methods: We produced an adenovirus associated type 9 co-expressing short hairpin (sh)-RNA targeting MFN2 for degradation and shRNA-resistant MFN2 cDNA. This vector has been tested in in vitro (patient-specific induced pluripotent stem cell (iPSCs)-derived motor neurons (MN)) and in vivo (MitoCharc1 mice) disease models, evaluating the rescue of disease hallmarks previously identified (Rizzo et al., 2016; Cartoni et al., 2010).

Results: We demonstrated the correct silencing of MFN2 endogenous alleles and their replacement with an exogenous copy of the functional wild-type gene. This approach significantly rescues the CMT2A MNs phenotype in vitro, promoting correct mitochondrial axonal transport and mitophagy process. Finally, we demonstrated that this approach allows proper MFN2 therapeutic correction also in vivo in MitoCharc1 transgenic mice.

Conclusion: This study yields proof-of-principle data for the first effective treatment of CMT2A or other dominantly inherited forms of CMT, representing the preclinical basis to move towards clinical translation.

Disclosure: This work is supported by a grant from "Associazione MFN2" and a grant from "Telethon Foundation"

O1014

Small fiber neuropathy in clinical practice: a diagnostics algorithm

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Background and aims: Small fiber neuropathy (SFN) is a subgroup of painful sensory neuropathies which affects A-delta and C nerve fibers. A diagnostic gold standard is missing for SFN.

Methods: We recruited 92 patients with a pain history indicative of SFN and applied six small fiber tests: complete neurological examination, skin punch biopsy for intraepidermal nerve fiber density (IENFD), quantitative sensory testing (QST), corneal confocal microscopy (CCM), pain-related evoked potentials (PREP), and quantitative sudomotor axon reflex test (QSART). SFN was diagnosed if ≥ 2 tests were abnormal.

Results: Distal IENFD 61/92 (66%) and neurological examination 53/92 (53%) most frequently reflected small fiber impairment in patients followed by CCM 20/57 (53%) and PREP 27/57 (47%). Combining neurological examination, distal IENFD, and CCM and/or PREP resulted in 49/57 (86%) patients diagnosed with SFN, while QST and QSART were of low diagnostic impact.

Conclusion: We show that neurological examination and distal IENFD are key, but additional measures of small fiber abnormality enhance the diagnostic yield in SFN. We further propose a new diagnostic algorithm for SFN in clinical practice, which enables to increase the diagnostic yield when adding CCM and/or PREP to the clinical work-up.

Disclosure: Nothing to disclose

O1015

The role of observing corneal whorl-like nerve plexus in evaluating small fiber neuropathy in transthyretin familial amyloid polyneuropathy

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Background and aims: Small fiber nerve is firstly involved in transthyretin familial amyloid polyneuropathy (TTR-FAP). In vivo corneal confocal microscopy (CCM) is a rapid, noninvasive technique to detect small-fiber polyneuropathy (SFN). The whorl-like pattern of the corneal nerve plexus provides a potential static landmark for observation. We evaluated whether CCM images of the whorl-like patterns can sensitively evaluate SFN and monitor disease progression in FAP patients.

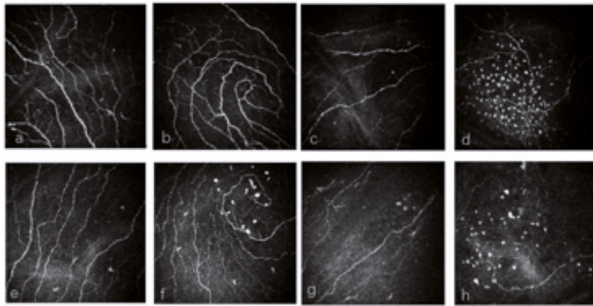
Methods: 15 FAP patients and 15 health controls underwent neurological evaluation and CCM observation. Corneal nerve fiber length (CNFL), density (CNFD), branch density (CNBD) detected by conventional method and inferior whorl length (IWL), branch density (IWBD), fiber density (IWFD) were compared in controls and patients. Langerhans cells (LCs) density in each image was calculated.

Results: CCM parameters were significantly reduced with disease progression (table1). IWL, CNFL, CNBD and CNFD were significantly lower in early phase patients. Only IWL was significantly reduced in preclinical patients ($p=0.008$). LCs density was significantly increased around the whorl area in early phase patients, and was declined in the progressive patients (figure 1). Both IWL and CNFL correlated with severity of neuropathy. IWL was more significantly reduced with disease progression (figure 2). The area under the ROC curve for CNFL and IWL was 88.0% and 89.3%, exceeding other parameters.

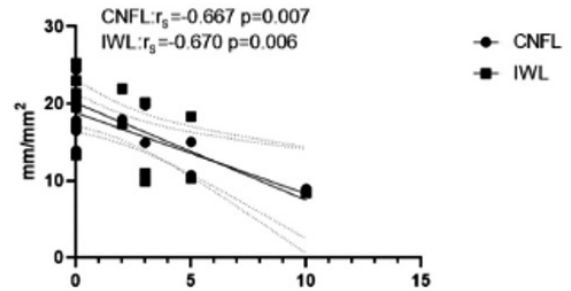
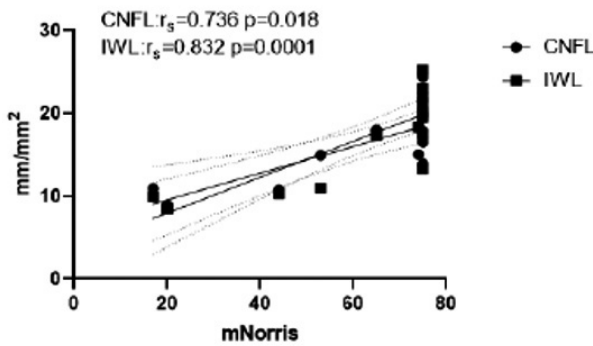
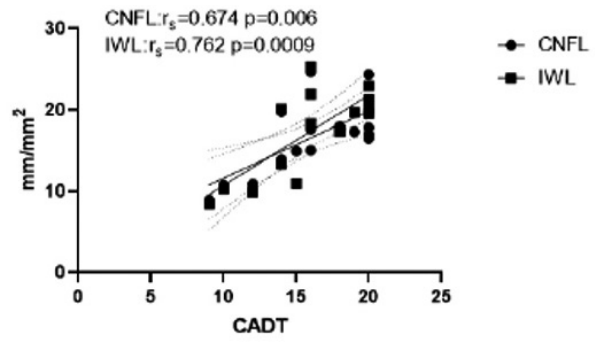
	Control (n=14)	Phase I (n=10)	Phase II (n=5)	P Control vs I	P I vs II
IWL(mm/mm ²)	24.36±3.39	18.26±7.14	11.42±3.47	0.006**	0.001**
IWBD/(mm ²)	87.79±32.71	72.19±14.58	15.42±12.47	0.26	0.001**
IWFD/(mm ²)	39.44±9.61	34.17±11.80	15.83±7.45	0.24	0.008**
CNFL(mm/mm ²)	22.54±3.20	18.42±3.61	11.37±2.53	0.005**	0.04*
CNBD/(mm ²)	68.13±23.36	42.92±14.97	12.08±6.49	0.008**	0.00*
CNFD/(mm ²)	41.13±8.86	32.50±7.62	23.32±11.80	0.014*	0.21
CNFT(°)	141.81±7.02	140.36±6.60	139.20±5.60	0.53	1.00
IW LC(n/mm ²)	86.95±38.93	226.07±175.02	129.20±107.89	0.002*	0.31
LC(conventional)(n/mm ²)	36.83±29.65	35.28±30.58	37.58±17.62	0.68	0.59
IW LC- LC(conventional)	50.05±99.62	190.79 ± 182.19	99.97±96.26		
	(p=0.07)	(p=0.009)	(p=0.19)		

IWL: inferior whorl length; IWBD: inferior whorl branch density; IWFD: inferior whorl fiber density; CNFL: corneal nerve fiber length; CNBD: corneal nerve branch density; CNFD: corneal nerve fiber density; CNFT: corneal nerve fiber tortuosity; LC: Langerhans cells;

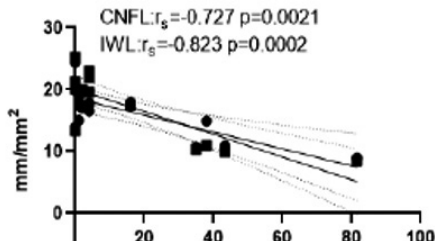
CCM parameters in controls, early phase (phase I) and progressive phase (phase II) of FAP patients.



CCM images of the central cornea and IW in control subject (a and b), preclinical FAP patient (c and d), early phase patient (e and f) and progressive phase patient (g and h). Distinctive whorl-like pattern of the sub-basal nerve plexus could be detected and LC clustered could be noted at preclinical and stage I patient.



Correlation Between Corneal Nerve Length and Neurologic Findings. IWL was more significantly reduced with the progression of disease.



Conclusion: IWL is a more sensitive surrogate to detect SFN in FAP patients and can best discriminate FAP patients from controls. The converge of immature LCs at the whorl area might reflect the inflammation response of small nerve fiber at the very early stage.

Disclosure: Nothing to disclose

Headache and pain

O1016

Cardiovascular safety of erenumab in patients with migraine with or without a history of aura

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Background and aims: Migraine with aura is associated with cardiovascular and cerebrovascular disease. We evaluated cardiovascular safety of erenumab (erenumab-aooe in the US) in patients with migraine with or without a history of aura.

Methods: Safety of erenumab was assessed in a post-hoc analysis of adverse events (AEs) from four double-blind, placebo-controlled studies and their open-label extensions in patients with episodic or chronic migraine with/without a history of aura. Standardised search terms were used to identify cardio/cerebrovascular and hypertension AEs.

Results: Of 2443 patients treated with erenumab (70 mg/140 mg once monthly) or placebo during double-blind treatment phase (DBTP), 1140 (47%) had a history of aura. At baseline, ≥ 2 cardiovascular risk factors were present in more patients with aura than without (35% vs 27%). Vascular disease risk factors were more prominent in the aura subgroup (Table). Cardio/cerebrovascular AE rates were low throughout the erenumab exposure period (up to 256 weeks) with no differences among patients with/without aura (n=6, 0.4/100 patient-years; n=5, 0.3/100 patient-years). Hypertension-related AEs were reported at similar rates in both subgroups (n=30, 2.3/100 patient-years; n=37, 2.2/100 patient-years). Rates of cardio/cerebrovascular and hypertension-related AEs, general AEs, and all serious adverse events were similar between the placebo and erenumab treatment groups during the 12-week DBTP regardless of aura history.

Table. Vascular disease risk factors in the subgroup populations with aura and without aura

Vascular disease risk factors	With aura	Without aura
Diabetes	2.6%	1.0%
History of hypertension	8.2%	6.6%
High blood pressure (systolic ≥ 140 mm Hg or diastolic > 90 mm Hg)	7.5%	6.1%
High lipids (triglyceride > 150 mg/dL)	26.7%	22.5%
BMI > 30 kg/m ²	30.4%	20.6%
Elevated cholesterol (total cholesterol > 200 mg/dL, LDL > 130 mg/dL, or HDL < 40 mg/dL)	47.9%	47.7%

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein

Conclusion: The vascular safety profile of long-term erenumab treatment was similar in patients both with and without a history of aura and was comparable to that of placebo over 12 weeks, with no increased emergence of events over time.

Disclosure: Novartis Pharma AG, Basel, Switzerland, funded this study. Erenumab is co-developed by Amgen and Novartis. A detailed disclosure from each author will be included in the oral/poster presentation. Abstract also submitted to AAN 2020; acceptance outstanding.

O1017

Characteristics of the first head-to-head randomized, double-blind, double-dummy trial of erenumab and topiramate for the prevention of episodic and chronic migraine

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Background and aims: Migraine is one of the most common causes of disability worldwide. In the past, several drug classes with a multitude of mechanisms have been used for prophylactic treatment of migraine, most of which are associated with high treatment discontinuation rates due to poor tolerability or insufficient efficacy. In 2018, the FDA and EMA approved erenumab as the first specifically developed prophylactic migraine treatment. For the first time, erenumab will directly be compared to one of the most commonly prescribed first-line prophylactic drugs.

Methods: HER-MES is the first head-to-head trial comparing the tolerability and efficacy of erenumab to the highest individually tolerated dose of topiramate in a German cohort of 750 episodic and chronic migraine patients who are naive to, not suitable for or have already failed up to three previous prophylactic treatments. HER-MES comprises a 24-week double-blind, double-dummy treatment epoch (DBTE) in which patients receive either 70mg or 140mg erenumab (investigator's choice) and a topiramate-placebo. The control group receives an erenumab-placebo and the maximally tolerated dose of topiramate, titrated within the first six weeks of the DBTE. Patients will complete eDiaries during baseline (4-weeks) and DBTE to evaluate treatment efficacy. As primary endpoint, tolerability will be assessed by the rate of treatment discontinuation due to adverse events.

Results: We will present the detailed study design and an analysis of the population characteristics of the enrolled patients.

Conclusion: This analysis will provide insights into the patient population enrolled in the first head-to-head trial comparing the tolerability and efficacy of erenumab and topiramate.

Disclosure: Nothing to disclose.

O1018

Type of headache at onset and severity of reversible cerebral vasoconstriction syndrome

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Background and aims: In a recent Italian study, 30% of patients with reversible cerebral vasoconstriction syndrome (RCVS) presented without typical thunderclap headache (TCH), and had a tendency to present more severe forms of RCVS than patients with TCH (Caria et al., Cephalalgia 2019). We aimed to analyze the severity of RCVS in patients with and without TCH at onset.

Methods: In a cohort of 173 French patients with RCVS, we compared patients with and without TCH at onset regarding rates of any brain lesions on imaging and any neurological complications (namely persistent focal deficit, seizures, dissections and brain lesions); and severity of RCVS defined as mild (absence of brain lesions, mRS 0 at 3 months) vs. moderate/severe (presence of brain lesions, mRS ≥ 1 at 3 months).

Results: As compared to the 142 patients with TCH at onset, the 31 patients without TCH had significantly more brain lesions (52% versus 30%, $p=0.035$, OR 2.5 [1.1-5.4]), neurological complications (64.5% versus 34%, $p=0.002$, OR 3.6 [CI 1.6-8.0]), and a higher risk of having a moderate/severe form of RCVS (52% versus 30%, $p=0.035$, RR 1.7 [CI 1.1-2.6]).

Conclusion: Absence of TCH at onset might predict a higher risk of severe RCVS. Our results warrant further studies in order to provide better pathophysiological understanding and clinical management of patients with RCVS.

Disclosure: Nothing to disclose

O1019

BRAIN NETWORKS IN MIGRAINE: a pilot study using advanced fMRI techniques in experimentally-induced attacks

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Background and aims: Resting state functional magnetic resonance imaging (rs-fMRI) studies have depicted cyclical functional connectivity changes during the ictal and inter-ictal phase of the migraine attack.

In this pilot study, FC changes during nitroglycerin (NTG) induced migraine attacks versus pain-free state were assessed on 5 subjects with episodic migraine (EM) without aura (3M-2F, 33±6.5 years). NTG-triggered a spontaneous-like migraine attack in all the 5 EM subjects without aura.

Methods: All subjects underwent 4 rs-fMRI repetitions during different phases of the attack (baseline, prodromal, full blown, recovery phase) using a 3T MRI-scanner.

Subjects' rs-fMRI data were processed with a seed-based correlation analysis (SCA), selecting different brain areas as seeds, according to literature in the pain field.

Results: In EM, results showed that the brainstem elements involved in the pain circuits (such as the spinal trigeminal nucleus, periaqueductal grey and dorsal raphe nuclei) and the thalamus exhibit an altered functional coupling within themselves and the hypothalamus, particularly during the prodromal phase. The whole brain activity coupled with the left thalamus instead, showed greater involvement during the full-blown phase.

Conclusion: These findings reveal that during the NTG-induced migraine attack the whole brain FC changes systematically, involving areas well known for their roles in pain modulation and migraine generation. Therefore, this study with the NTG model applied to advanced fMRI approach promotes the idea of migraine as a cyclical functional disorder in which brainstem pain-modulating circuitry and hypothalamus have a leading role in the premonitory phase, while the thalamus plays a more relevant role in the full-blown phase.

Disclosure: Nothing to disclose

O1020

Prevention of post-dural puncture headache – a randomized controlled trial

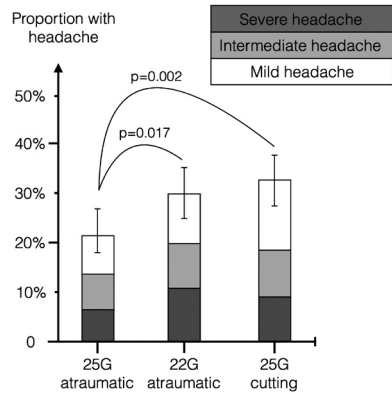
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Background and aims: The objectives were to investigate the effects of needle size, needle design and stylet reinsertion on the risk for post-dural puncture headache (PDPH). To this end, we investigated n=952 subjects undergoing diagnostic LP.

Methods: This randomized double-blind study was performed at Umeå University Hospital in Sweden during 2013–2018. Subjects were randomly assigned one of three needles (22 Gauge (G) atraumatic, 25G atraumatic and 25G cutting); and stylet reinsertion before needle withdrawal or not. The main outcome measure was PDPH assessed by standardized telephone interview(s) 5 days after the LP, repeated until headache cessation. We used logistic regression to calculate odds ratios (ORs) with 95% CIs for PDPH.

Results: Mean (SD) age was 51.1 (16.7) years and 53.6% were females. The smaller bore (25G) atraumatic needle incurred a lower risk for headache, 22.0% (69/314), compared with the larger bore (22G) atraumatic needle, 30.2% (98/324), OR (95% CI) = 0.65 (0.45–0.93); and compared with the cutting needle, 32.8% (103/314), OR (95% CI) = 0.58 (0.40–0.82). Reinserting the stylet before needle withdrawal did not reduce the risk for headache, 26.3% (125/475) vs. 30.4% (145/477), OR (95% CI) = 0.82 (0.62–1.1).



No. of subjects with post lumbar puncture headache	69/314	98/324	103/314
Odds ratio (OR) and 95% confidence interval (CI) for any headache	0.65 (0.45–0.93)	Reference	– (size)
Odds ratio (OR) and 95% confidence interval (CI) for any headache	0.58 (0.40–0.82)	–	Reference (design)

Proportion of subjects within each needle arm reporting post-dural puncture headache (PDPH). The PDPH was graded as mild (not needing intervention), intermediate (exceeding the previous grade but not meeting the criteria for severe headache), and severe (preventing daily activities such as studies, work etc.).

Conclusion: This study provides class 1 evidence that a 25G atraumatic needle is superior to a larger atraumatic needle, and to a same sized cutting needle, to prevent PDPH after diagnostic LP; and that stylet reinsertion does not prevent PDPH.

Disclosure: This study was funded by a research grant from the Department of Clinical Science, Neurosciences at Umeå University.

Movement disorders 1

O1021

Clinical and genetic findings in a multigenerational Austrian family harbouring a SCA40 mutation

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Background and aims: We report clinical features and genetic findings of the first Austrian and third reported family worldwide with Spinocerebellar Ataxia Type 40 (SCA40). SCA40 is an autosomal dominant disease. Clinical symptoms include ataxia, spastic paraparesis, and parkinsonian symptoms. It is caused by mutations in the CCDC88C gene on chromosome 14, which activates the c-Jun terminal kinase (JNK) pathway and triggers apoptosis. To date only two families (China, Poland) with SCA40 have been reported.

Methods: We identified a family with six affected patients from three generations. Clinical follow-up is available in three patients for up to nine years. Genetic workup, repeated neurological examinations, and cerebral imaging were performed in affected family members. Interestingly, two affected patients suffer from haemochromatosis, diabetes mellitus and one of non-Hodgkin lymphoma. We undertook further genetic and functional testing to elaborate the pathogenicity of the mutation and its impact on downstream pathways.

Results: First clinical symptom was gait disturbance in their mid-thirties. All patients subsequently developed a slowly progressive pure cerebellar syndrome. MR imaging displayed cerebellar atrophy. SARA-scores range from 10.5 to 14/40 points. Genetic testing revealed a new missense mutation (c.956G>A;p.Arg319Gln) in the conserved hook domain of the CCDC88C gene. It was classified as Variant of unknown Significance. Functional testing in fibroblasts revealed hyperphosphorylation of JNK.

Conclusion: We hereby present the third reported family with SCA40. Our patients presented with an adult onset slowly progressive cerebellar syndrome. Genetic and functional testing indicated pathogenicity of the mutation. Functional testing on the impact on downstream pathways is under way.

Disclosure: Nothing to disclose

O1022

Disruption of white matter tracts and cognitive decline after deep brain stimulation in Parkinson's disease

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Background and aims: Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a well established treatment with marked motor benefits for patients with Parkinson's disease (PD). However, adverse cognitive effects have been described and their mechanisms are still poorly understood. It has been suggested that it may be related to a microlesion effect due to the electrodes trajectories. We evaluated the lesions of white matter tracts as a possible reason for cognitive side effects of STN-DBS.

Methods: A consecutive group of 51 PD-patients underwent neuropsychological assessment before DBS and 6 months after in on-drug/on-stimulation condition. It included a global cognitive evaluation and selective cognitive investigation comprising attentional-executive functions, verbal memory, phonemic and semantic verbal fluency tasks. Pre-operative brain MRI and post-operative CT were acquired. We segmented the trajectories of the electrodes and after normalization we used a white matter tract atlas (Tractotron Software) to obtain probability and proportion of fibers disconnection.

Results: We found a decline six months after surgery in global cognitive evaluation and in selective cognitive domains including episodic verbal memory, executive functions and phonemic and semantic verbal fluency. The tract atlas analysis revealed that the electrodes intersected with the frontal aslant tract, arcuate tract, superior longitudinal fasciculus, anterior thalamic radiation and fronto-striatal tract. We found a correlation between decline in cued recall in verbal memory and proportion of lesion of superior longitudinal fasciculus.

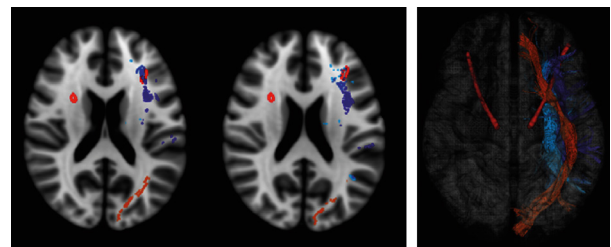


Figure. Axial slices and 3D reconstruction of Superior Longitudinal Fasciculus (blue) and Inferior Longitudinal Fasciculus (orange). In red : electrodes trajectory.

Axial slices and 3D reconstruction of Superior Longitudinal Fasciculus (blue) and Inferior Longitudinal Fasciculus (orange). In red : electrodes trajectory.

Conclusion: The trajectories of electrodes in STN-DBS intersect with tracts involved in different cognitive domains. Our study provides further support for a micro-lesion effect in cognitive decline after surgery.

Disclosure: Nothing to disclose

O1023

A prediction model for functional movement disorders based on associated features

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Background and aims: Functional movement disorders (FMD) pose a diagnostic challenge for clinicians. Over the years several associated features showed to be suggestive for FMD. We examined which of the associated features mentioned in literature are discriminative between functional and organic movement disorders. Secondly, we developed a prediction model for FMD based on these differences.

Methods: We reviewed the medical records of all consecutive patients who visited the hyperkinetic outpatient clinic from 2012 till 2019 and compared 12 different clinical characteristics and associated features in patients with functional versus organic movement disorders. We performed an independent t-test for the continuous variable age of onset and Pearson Chi-square analyses for all other categorical variables. Multivariate logistic regression analysis was applied to develop a model for the prediction of FMD.

Results: A total of 874 patients were eligible for inclusion in the study of which 554 (63%) had an organic and 320 had a functional movement disorder. The features that significantly differed between these groups were sex, age of onset, more than one movement disorder, psychiatric history, family history, pain, fatigue, abrupt onset, waxing and waning over long term, and fluctuations during the day. Based on these we computed a predictive model with a discriminative value of 91%.

Conclusion: The good to excellent discriminatory capacity of the model could be used to assist physicians identify patients with FMD. When there is a high predicted chance of FMD, the physician can be alert for testing positive signs at neurologic examination.

Disclosure: Nothing to disclose

O1024

Patient characteristics, treatment patterns and disease burden in people with Parkinson's disease: insights from the Parkinson's disease real-world impact assessment (PRISM) study

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Background and aims: PRISM was a European survey of the burden of Parkinson's disease (PD), medication use, healthcare resource utilisation and health-related quality of life (HRQoL) in people with PD (PwP) and their care-partners. Data on patient characteristics, treatment patterns and burden of disease in PwP are presented.

Methods: PRISM was a descriptive, exploratory, observational study with cross-sectional design. The survey was designed in collaboration with The Cure Parkinson's Trust (a UK-based advocacy group) and an international scientific committee. Data were collected using an online survey completed by PwP and their care-partners as matched samples. Multivariate analysis was used to explore drivers of Parkinson's Disease Questionnaire-39 (PDQ-39) summary score.

Results: Between April-July 2019, data were collected from 861 PwP (599 complete responses; 262 partial responses) from six European countries (characteristics in Table 1). Levodopa was used by 84% of PwP in the previous 12 months and as monotherapy in 22% of all PwP (Table 2). In 67% of PwP (544/812), levodopa was the first prescribed anti-PD medication. PwP had impaired HRQoL (mean±standard deviation PDQ-39 score, 32.1±18.3), a wide range of non-motor symptoms (mean±standard deviation Non-Motor Symptoms Questionnaire score, 12.8±6.0) and frequent issues with sexual functioning (Table 3). Higher numbers of comorbidities and non-motor symptoms were associated with worse HRQoL (Table 3).

Conclusion: Two-thirds of PRISM respondents have been levodopa users since PD treatment start, in contrast to previous prescription patterns [1], and experienced decreased HRQoL in relation to more comorbidities and non-motor symptoms.

1. Fargel et al. Clin Drug Invest 2007;27(3):207-218.

Disclosure: Study supported by Bial - Portela & C^a, S.A.

Table 1. Patient characteristics of PwP

Characteristic	N=861
Country, n (%)	
France	63 (7.3)
Germany	92 (10.7)
Italy	264 (30.7)
Portugal	80 (9.3)
Spain	149 (17.3)
UK	213 (24.7)
Male gender	
N	851
Male, n (%)	433 (50.9)
Age, years	
N	855
Mean (SD)	65.0 (10.2)
Age at diagnosis, years	
N	827
Mean (SD)	57.7 (11.3)
Disease duration, years	
N	813
Mean (SD)	7.7 (6.3)
Most frequently reported ^a comorbidities	
N	845
Hypertension, n (%)	217 (25.7)
Depression, n (%)	188 (22.2)
Anxiety, n (%)	136 (16.1)
Rheumatic diseases, n (%)	91 (10.8)

^a>=10% of PwP. PwP, people with Parkinson's disease; SD, standard deviation

Table 2. Medication use in PwP

Parameter	
Current use ^a by agent ^b , %	
L-dopa/DDCI, n/N (%)	659/788 (83.6)
DA, n/N (%)	397/779 (51.0)
MAO-Bi, n/N (%)	318/779 (40.8)
COMTi, n/N (%)	114/778 (14.7)
Amantadine, n/N (%)	75/775 (9.7)
Rivastigmine, n/N (%)	33/774 (4.3)
Anticholinergics, n/N (%)	16/773 (2.1)
Current use ^a by therapeutic combinations ^c	
N	800
L-dopa monotherapy, n (%)	175 (21.9)
L-dopa + COMTi, n (%)	21 (2.6)
L-dopa + DA, n (%)	111 (13.9)
L-dopa + MAO-Bi, n (%)	71 (8.9)
L-dopa + COMTi + DA, n (%)	26 (3.3)
L-dopa + DA + MAO-Bi, n (%)	115 (14.4)
L-dopa + COMTi + MAO-Bi + DA, n (%)	30 (3.8)
DA monotherapy, n (%)	31 (3.9)
DA + MAO-Bi, n (%)	28 (3.5)
MAO-Bi monotherapy, n (%)	17 (2.1)
No therapy, n (%)	46 (5.8)

^aWithin previous 12 months; ^bn/N, affected subjects/total number of replies; ^ccombinations with >=2% of use. COMTi, catechol-O-methyltransferase inhibitor; DA, dopamine agonist; DDCl, dopa decarboxylase inhibitor; L-dopa, levodopa; MAO-Bi, monoamine oxidase-B inhibitor; PD, Parkinson's disease; PwP, people with Parkinson's Disease

Table 3. Current health-related quality of life in PwP

Parameter	
PDQ-39 score	
N	859
Mean (SD)	32.1 (18.3)
NMSQuest score	
N	591
Mean (SD)	12.8 (6.0)
Problems with sexual functioning ^{a,b}	
Erection (men), n/N (%)	121/205 (59.0)
Orgasm (women), n/N (%)	51/142 (35.9)
Enjoyment, n/N (%)	117/335 (34.9)
Arousal, n/N (%)	115/343 (33.5)
Interest, n/N (%)	111/348 (31.9)
Current variables associated with worsened PDQ-39 summary score, mean (95% CI) increase in score	
One additional comorbidity	3.1 (1.6-4.6)
One additional non-motor symptom ^c	2.1 (1.7-2.4)

^aPatients reporting 'Very much of a problem' or 'Somewhat of a problem'; ^bn/N, affected subjects/total number of replies; ^cOne unit increase in NMSQuest score. CI, confidence interval; NMSQuest, Non-Motor Symptoms Questionnaire; PD, Parkinson's disease; PDQ-39, Parkinson's Disease Questionnaire-39; PwP, people with Parkinson's Disease; SD, standard deviation

O1025

Cerebellar rTMS theta burst for postural instability in progressive supranuclear palsy: a double blind cross-over sham-controlled study using wearing sensors technology

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Background and aims: There are no medical effective treatments for progressive supranuclear palsy (PSP). Imaging, neurophysiology and pathology studies have been suggesting the cerebellum as a promising target for tbrain stimulation to reduce postural instability. The objective of this pilot study was therefore to test the efficacy of TTS on postural instability in PSP patients using a cross-over design.

Methods: Probable PSP patients with no dementia and able to walk were included. Each patient underwent a single session of sham TBS or cerebellar TBS with a wash out period of ≥14 days. Each participant was evaluated before and after stimulation with the Berg Balance Scale (BBS), Tinetti scale, PSP-rating scale (PSP-RS), and 30-seconds-trials in semitandem and tandem positions with eyes open and closed measured with validated digital mobile technology.

Results: 20 PSP patients (mean age 74.3 years, disease duration 3.8 years, PSP-RS 29.4 + 9.6 points) entered the study. No differences in clinical scales and clinically assessed gait parameters in sham vs real stimulation sessions were detected. In static balance tests with digital technology endpoint, active stimulation was associated with increase in time without falls in tandem/semitandem tasks (p=0.04). Rehgait-extracted parameters revealed significant improvement in volume of perturbation (p=0.007), 3D-acceleration compensatory movements (p=0.005) and anterior-posterior speed (p=0.008) in real vs sham trials.

Conclusion: Repetitive cerebellar TBS showed a significant effect on stability in PSP patients, when assessed with mobile digital technology, in a double-blind design. These results of this pilot study should motivate larger and more intensive trials using TBS for stability improvement in PSP patients.

Disclosure: Nothing to disclose

O1026

The role of LRP10 mutations in Parkinson's disease and dementia with lewy bodies

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Background and aims: Parkinson's disease (PD) and Dementia with Lewy Bodies (DLB) belong to a continuum spectrum of neurodegenerative diseases characterized by alpha-synuclein accumulation in neurons, whose etiopathogenesis remains largely uncovered. Recently, a new candidate gene (LRP10) for alpha-synucleinopathies has been identified by linkage analysis and positional cloning on an Italian family with late-onset PD. After the first characterization of a LRP10 pathogenic variant, other eight mutations have been detected in an international series of 660 PD and DLB patients. The aim of our study was to test LRP10 in an Italian cohort of clinically diagnosed PD patients.

Methods: A cohort of 511 PD patients was analysed by NGS panel approach. LRP10 variants identified were subsequently confirmed by Sanger sequencing. All variants were searched in in-house exomes from 3500 healthy subjects.

Results: 8 variants (MAF<1%) were identified in fifteen patients: one was synonymous (c. 1923G>A) and predicted to generate a potential splice site change; one was detected in an intronic region (c. 80-23G>A); seven (c.334G>A, c.415A>G, c.643T>C, c.1105T>C, c.1646G>A, c.1685G>A and c.1991C>T) led to a missense change at protein level, respectively V112I, M139V, S215P, S369F, R549Q, R562H and R661C. The M139V and R562H were detected also in 3500 Italian controls, respectively 17 and 26.

Conclusion: We reported several rare LRP10 variants in patients with PD and DLB. Considering prediction tools and the low prevalence among general population, some of them are possible pathogenic. Further investigations are warranted to define their precise role in alpha-synucleinopathies.

Disclosure: This work was supported by ADF's funds, from Intesa San Paolo and Fresco Institute.

Cerebrovascular diseases 1

O1027

Decompressive neurosurgery for patients with cerebral venous thrombosis. A prospective multicenter registry (DECOMPRESS2)

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Background and aims: Decompressive neurosurgery (DN) may be life-saving in patients with cerebral venous thrombosis (CVT) with large lesions and impending brain herniation. The ESO-EAN Guidelines made a strong recommendation for this intervention, supported by a low level of evidence (retrospective studies, small sample sizes), which could overestimate the treatment effect. We aimed to report the outcomes of CVT patients treated by DN in a large multicenter cohort.

Methods: We included consecutive CVT patients treated by DN at the participating centres. Outcomes were evaluated at discharge and 6 months. The primary outcome was modified Rankin Scale (mRS) 0-4 vs. 5-6. Secondary outcomes were complete recovery (mRS 0-1), independence (mRS 0-2), severe dependence (mRS 4-5) and death.

Results: 118 patients (80 women, median age 38 years) were included from 14 centers in Europe, Asia, and America. DN (115 craniectomies, 36 hematoma evacuations) was performed a median of 1 day after diagnosis. 71 (60.2%) patients were comatose before surgery. Pupillary reflexes were absent unilaterally in 27 (22.9%) and bilaterally in 9 (7.6%). 65 (55.1%) patients had a mRS 0-4 at discharge and 61.9% at 6 months. Mortality during hospital admission was 24.6% and 31.4% at 6 months. Complete recovery (1.7 to 11.4%) and independence (6.8 to 29.5%) increased between discharge and 6 months, while severe dependence decreased (from 49.1 to 13.3%).

Conclusion: Mortality and functional dependence were higher than those reported in previous studies of DN in CVT. Still, 2/3rd of patients were alive and 1/3rd independent by 6 months.

Disclosure: Nothing to disclose

O1028

The reliability of serum glial fibrillary acidic protein testing in differentiating between ischemic and hemorrhagic strokes: a meta analysis of diagnostic accuracy studies

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Background and aims: The aim of this meta analysis is to assess the reliability of serum glial fibrillary acidic protein (GFAP) testing in differentiating between ischemic and hemorrhagic stroke patients within the first 6 hours of onset of symptoms.

Methods: Data sources were extracted from literature search in MEDLINE, EMBASE, Cochrane library and other sources. QUADAS-2 quality grading tool was used to include the most appropriate studies relevant to our review topic. Due to the absence of heterogeneity, a fixed effect model was applied to calculate the pooled sensitivity (SN), specificity (SP), positive likelihood ratio (PLR), negative likelihood ratio (NLR), summary receiver operating characteristics curve (SROC), and diagnostic odds ratio (DOR) with their 95% confidence intervals (CI).

Results: Four studies were included in the review, all studies were observational and prospectively enrolled the total number of 584 patients (441 ischemic stroke patients and 143 hemorrhagic stroke patients). The pooled SN, SP, PLR, NLR and DOR of serum GFAP testing in diagnosing patients with hemorrhagic stroke were 0.79 (95% CI 0.69-0.86), 0.95 (95% CI 0.093-0.97), 16.56 (95% CI 10.53-26.03), 0.22 (95% CI 0.16-0.33) and 71.75 (95% CI 37.94-135.71), respectively. The area under the curve (AUC of the SROC) was 0.95.

Conclusion: Serum GFAP testing showed a high diagnostic accuracy in confirming the presence of hemorrhagic strokes within the first 6 hours of onset of symptoms.

Disclosure: Nothing to disclose

O1029

Intracranial pulsatility index on transcranial Doppler sonography: a marker of microangiopathic white matter hyperintensities?

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Background and aims: Previous studies suggested an association between increased intracranial arterial pulsatility and the severity of microangiopathic white matter hyperintensities (WMH). However, possible confounders such as age and hypertension were rarely considered and longitudinal data are lacking. We here hypothesize that in community-dwelling stroke-free subjects an increased middle cerebral artery (MCA) pulsatility index (PI) measured by transcranial Doppler sonography (TCD) relates to WMH severity and progression over 5 years follow-up.

Methods: The study population consisted of elderly participants without stroke and dementia from the community-based Austrian Stroke Prevention Study. Baseline and follow-up assessment comprised TCD, brain MRI and clinical/laboratory examination of cerebrovascular risk factors. Individuals TCD PI was averaged from baseline PIs of both MCAs and was correlated with baseline WMH severity and WMH progression over a median follow-up of 5 years. WMH severity was rated by the Fazekas scale and quantified by semi-automated volumetric assessment.

Results: The final study cohort comprised 491 participants (mean age: 60.7±6.9 years; female: 48.5%). TCD PI was related to more severe WMH at baseline ($p<0.001$) and tended to be associated with WMH progression during follow-up ($p=0.099$). However, in multivariable analyses only age ($p<0.001$) and arterial hypertension ($p<0.05$) remained significantly associated with baseline severity and progression of WMH, while TCD PI was not predictive ($p>0.1$, respectively).

Conclusion: In this large community-based cohort, MCA PI on TCD was neither associated with microangiopathic WMH severity at baseline nor predictive of WMH progression during follow-up after adjustment for important co-variables.

Disclosure: Nothing to disclose

O1030

Long-term functional decline in spontaneous intracerebral haemorrhage survivors

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Background and aims: To identify clinical characteristics and cerebral small-vessel disease (SVD) markers associated with long-term functional decline in 6-month survivors of spontaneous intracerebral haemorrhage (ICH).

Methods: We included consecutive spontaneous ICH patients with a modified Rankin scale (mRS) score between 0 and 3 six months after the index event. Long-term functional decline was defined by a transition to a mRS score of 4 or 5 during the follow-up. We evaluated clinical and radiological characteristics associated with long-term functional decline using univariate and multivariable cause-specific Cox' proportional hazard regression models.

Results: Of 560 patients with spontaneous ICH, 174 (31%) were alive and had a mRS score of 0 to 3 at 6 months. During a median follow-up of 9 years (interquartile range [IQR] 8.1-9.5), 49 patients (28%) died and 40 patients (23%) reached a mRS score of 4 or 5. Age (cause specific hazard ratio [CSHR] per 10-year increase: 1.08; 95% confidence interval (95%CI): 1.04-1.11), male sex (CSHR: 0.47; 95%CI: 0.24-0.92), diabetes (CSHR: 2.81, 95%CI: 1.31-6.01), and baseline ICH volume (HR per 1ml increase: 1.03; CI: 1.01-1.06) were independently associated with functional decline. In the subgroup of 144 patients who underwent a magnetic resonance imaging (MRI)-scan, cerebral atrophy (CSHR: 2.31; 95%CI: 1.44-3.69) and presence of strictly-lobar cerebral microbleeds (CMBs; CSHR: 3.55, CI 1.22-10.37) and mixed-CMBs (HR: 4.70; CI 1.77-12.42) were also independently associated with long-term functional decline.

Conclusion: Besides age, male sex, diabetes and baseline ICH volume, MRI markers of SVD are associated with long-term functional decline.

Disclosure: Nothing to disclose

O1031

Prospective observational study of safety of early treatment with Edoxaban in patients with ischemic stroke and atrial fibrillation (SATES STUDY)

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Background and aims: New direct oral anticoagulants are recommended for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). However, no data is available for the optimal timing for starting oral anticoagulation after a stroke or TIA. We conducted this observational perspective study to evaluate the safety of early initiation (within 72 hours) of full dose of edoxaban in patients with acute ischemic stroke.

Methods: The primary objective was to evaluate any major bleeding (MB) in the first 3 months of treatment. The secondary endpoints were to evaluate the incidence of MB, hemorrhagic transformation (HT) and symptomatic hemorrhagic transformation rate, 3±2 days after the start of Edoxaban treatment. We included patients with CT/MRI signs of <1/3 MCA infarction, NVAF, no previous treatment with any other anticoagulant, preserved swallowing function. Patients with eGFR <50ml/min, body weight <60kg, receiving ciclosporin, dronedaron, eritromicine, ketoconazole were excluded.

Results: We enrolled 50 patients, the average age was 77 years and the mean NIHSS 7.8. After 3 months we observed only one MB (gastrointestinal bleeding) which comported a temporally suspension of edoxaban and 8 minor bleeding, without stroke recurrence. Evaluating the secondary objectives, we did not observe any MB or symptomatic hemorrhagic transformation; the incidence of HT was 12% for HI-1 (small petechiae) and 8% for HI-2 (confluent petechiae) without neurological deterioration. After 3 months no patient stopped the treatment.

Conclusion: According to our data the early initiation of Edoxaban seems to be safe in patients after a cardioembolic stroke. However, further studies are needed.

Disclosure: Nothing to disclose

Sunday, May 24 2020
Epilepsy 1

O2001

The connectivity epileptogenicity index: a new method for estimating the seizure onset zone from SEEG signals

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Background and aims: The main diagnostic challenge of drug resistant epilepsies is to find epileptogenic zone, which will be enough to remove to reach seizure freedom. Most of the existing machine methods focus on seizures with fast activity in the onset (FSO). Our aim was to create a new tool that helps recognize epileptogenic zone through all types of seizure onset patterns from stereo-EEG signals.

Methods: We studied seizures from 51 patients, suffering from focal drug-resistant epilepsy associated with malformation of cortical development. We separated seizure onset patterns to slow and fast. We quantified combined epileptogenicity index (cEI), based on a directed connectivity measure in beta-gamma (“out-degree”) and the classical epileptogenicity index (EI). The results were compared with seizure onset zone (SOZ), detected visually. The quality of the detector was quantified by the area under the precision-recall curve. To test differences between measures was used the Friedman test with Bonferroni correction.

Results: cEI showed the best concordance with visual SOZ in both slow (SSO) and fast (FSO) groups (figure 1). Median AUC whatever seizure onset type 0.73; (range 0.4-1, p<0.05). For fast seizure onset difference between out-degree and cEI is significant (p≤0.05). For slow seizure onset difference between EI and cEI is very significant (p≤0.01).

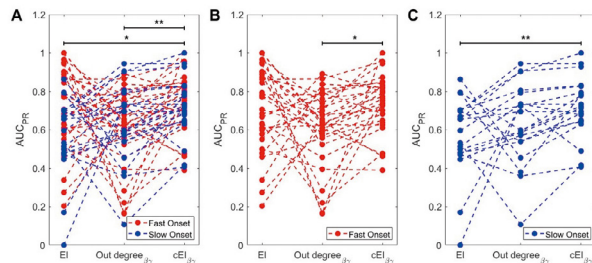


Figure 1. AUC (precision-recall) values according to the fast (FSO) and slow (SSO) seizure-onset patterns. A/ results in the whole population B/ Results in FSO C/ Results in SSO.

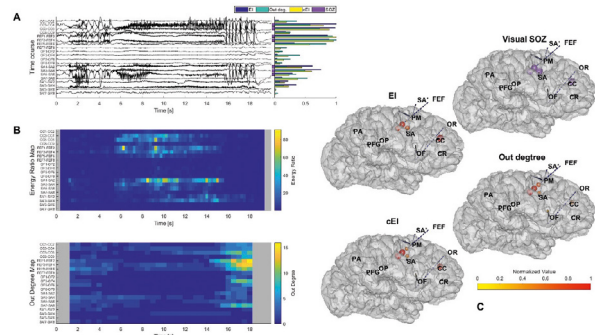


Figure 2. Fast seizure onset example (patient 21). Comparison of EI, Out-degree, cEI in and vSOZ. A/ SEEG time series B/EI energy ratio map and out-degree map. C/3D MRI –electrode map estimation of EI, out-degree, cEI and vSOZ.

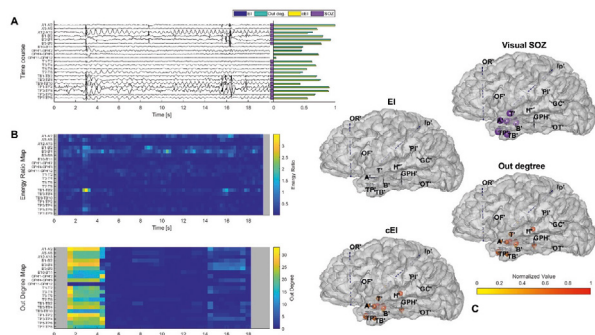


Figure 3. Slow seizure onset (slow waves) example (patient 10). Comparison of out-degree, EI, cEI and vSOZ. A/SEEG time series map. B/EI energy ratio map and out-degree map. C/3D MRI –electrode map estimation of EI, out-degree, cEI and vSOZ.

Conclusion: cEI may help epileptologist to delineate SOZ in a complex epileptogenic network. As cEI include the very beginning of fast activity during seizure onset and ictal changes in the epileptogenic network.

Disclosure: This research has been supported by the European Academy of Neurology MD/PhD fellowship program 2019.

O2002

Long-term safety and efficacy of Cannabidiol (CBD) treatment in Lennox Gastaut syndrome: results overall and for patients completing 1–3 years of an open-label extension (GWPCARE5)

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Background and aims: We assessed the long-term safety and efficacy of add-on CBD in patients with Lennox-Gastaut syndrome (LGS) in the 3rd interim analysis of the open-label extension (OLE; GWPCARE5; NCT0224573) of two randomised controlled trials (RCTs; GWPCARE3, GWPCARE4).

Methods: Patients who completed either RCT could enter this OLE, in which they received plant-derived highly purified CBD medicine (Epidyolex[®]; 100mg/mL oral solution). Primary endpoint: safety (n=366). Secondary endpoints: median percentage change from baseline in drop and total seizure frequency overall (n=364) and patients completing 1, 2, and 3 years (n=299, 236, and 200).

Results: 99% (366/368) of eligible patients with LGS enrolled. Median follow-up was 150 weeks (3 days–179 weeks) overall. Mean age was 16 years; 33% ≥18 years; 54% male. Patients were taking a median of 3 concomitant antiepileptic drugs at baseline; 54% were on clobazam and 39% valproate. Mean modal CBD dose was 24mg/kg/day overall and ranged from 21–25mg/kg/day over follow-up for 3-year completers. 33% (119/366) of patients withdrew. Adverse events (AE) occurred in 96% of patients and serious AEs in 42%; 12% discontinued due to AEs. Aspartate/alanine aminotransferase levels >3× upper-limit-of normal occurred in 13% of patients. There were 11 deaths; none deemed treatment-related by the investigator(s). Median percentage reduction in drop seizure frequency during 12-week visit windows over 156 weeks was 48–71% overall; and 55–61%, 58–71%, and 55–71% for 1-, 2-, and 3-year completers.

Conclusion: Long-term treatment with add-on CBD in patients with LGS produced sustained seizure reductions, with no new safety concerns.

Disclosure: This trial was sponsored by GW Pharmaceuticals.

O2003

Epilepsy phenotype in patients with rare de novo DYNC1H1 variants

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Background and aims: Dynein, cytoplasmic1-heavy-chain1 (DYNC1H1) encodes subunit of the cytoplasmic dynein complex, which traffics cargo along microtubules. Dominant DYNC1H1 mutations are implicated in neural diseases, including spinal muscular atrophy with lower extremity dominance (SMA-LED), intellectual disability with neuronal migration defects, malformations of cortical development, Charcot-Marie-Tooth disease. Epilepsy has been described in sporadic reports. Our purpose was to study the epilepsy features of patients bearing rare de novo DYNC1H1 variants collected through an international collaboration

Methods: Genetic, clinical, neurological and epilepsy features, electroencephalography's (EEG), therapy and brainMRI data have been collected

Results: 14 patients (8M, 6F); median age 19,7 years old (1-37); 13 had a missense variant (11 denovo, one unknown and one inherited) and 1 had a stop-codon denovo variant. Mean age at onset was 5.9 years old (range 5 months-18 years old). 6 patients had infantile spasms (IS) with onset at 5-7 months; 4 had hypsarrhythmia. 7 had a severe epilepsy with polymorphic seizures and multifocal EEG abnormalities (3 of them were consistent with Lennox-Gastaut Syndrome-LGS). 1 patient had a drug-resistant generalized myoclonic epilepsy; interestingly he has no intellectual disability. 3 patients were seizures free at last follow-up. 8 patients had mild brain atrophy; 6 had brain malformations (4 lissencephaly, 1 heterotopia, 1 cortical dysplasia). None had spinal muscular atrophy or Charcot-Marie-Tooth disease.

Conclusion: DYNC1H1 de novo rare variants might manifest with severe drug resistant epilepsy including IS

and LGS. Less than half of these patients have an associated cortical malformation, while none had a motoneuron or a peripheral nerve condition. A broader cohort will help elucidate the genotype-phenotype correlations.

Disclosure: Nothing to disclose

O2004

The maternal effect in epilepsy – findings from a Danish population-based study

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Background and aims: Many previous studies have found a higher risk of epilepsy in offspring of affected mothers than in offspring of affected fathers. We examined whether this maternal effect was present in a large-scale population-based sample.

Methods: We considered all singletons born in Denmark between 1981 and 2016. Using diagnostic information from the Danish registers, we identified diagnoses of epilepsy and other neuropsychiatric disorders in all cohort members and their family members.

Results: We included 1.754.742 individuals contributing with >30 million person-years of follow-up. The incidence rate (IR) of epilepsy in offspring of unaffected parents was 78.8 (95% CI: 77.8-79.8) per 100.000 person-years, while the corresponding rate was 172 (95% CI: 156-187) in offspring with an affected father, and 260 (95% CI: 243-277) in offspring with an affected mother. Thus, having an affected mother was associated with a 1.45-fold (95% CI: 1.30-1.65) higher risk of epilepsy in the offspring, compared to having an affected father. This maternal effect was found both in male (adjusted hazard ratio (aHR) =1.39, 95% CI: 1.19-1.61) and female offspring (aHR=1.53, 95% CI: 1.31-1.79), across various ages at onset in the offspring (0-4, 5-9, 10-14, 15-19, 20-24 and 25-29 years), and in familial epilepsies, where the affected parent had an affected sibling (aHR=1.50, 95% CI: 1.07-2.12). The maternal effect was stronger in epilepsy, than in other neuropsychiatric disorders (e.g. schizophrenia aHR: 1.19, 95% CI: 1.04-1.37).

Conclusion: We found a clear maternal effect on offspring risk of epilepsy in this nationwide cohort study.

Disclosure: This study was supported by Novo Nordisk Foundation grant NNF16OC0019126, the Central Denmark Region, the Danish Epilepsy Association, and NINDS grant NS106104-01A1

MS and related disorders 1

O2005

Assessing the immune cell subtype reconstitution profile using deconvolution algorithms in patients treated with cladribine in the CLARITY study: findings at the 96-week timepoint

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Background and aims: Following treatment with cladribine tablets (CT) there are transient reductions in total lymphocyte cell counts and B-cells and potentially long-lasting reductions in memory B-cells according to flow cytometry findings. The aim was to assess immune cell subtypes in peripheral blood of patients with relapsing-remitting multiple sclerosis (RRMS) in the CLARITY study using advanced computational algorithms.

Methods: In CLARITY, patients received CT 3.5mg/kg (cumulative licensed dose), CT 5.25mg/kg or placebo administered as two short oral courses over 2 years. Gene expression profiling was undertaken using Human Array U133 Plus 2.0 of whole blood collected at week 96 post-baseline from 189 patients (62 on CT 3.5mg/kg, 70 on CT 5.25mg/kg and 57 on placebo). The CIBERSORT5 deconvolution algorithm and xCell6 signature-based method were used to estimate absolute fractions of 22 immune cell subtypes and cell type enrichment analysis for 43 immune cell subtypes in the samples, respectively. A Wilcoxon Rank Sum test was used to compare the arms with a P-value of less than 0.05 considered nominally significant.

Results: At 96 weeks, the relative abundance of naïve B-cells was significantly higher and memory B-cells and plasma cells were significantly lower with CT versus placebo (Figure 1). There were significant reductions in the abundance of naïve and memory CD4+, CD8+ and TH2 T cells (Figure 2) and enhancement of the M2 macrophage signature (Figure 3).

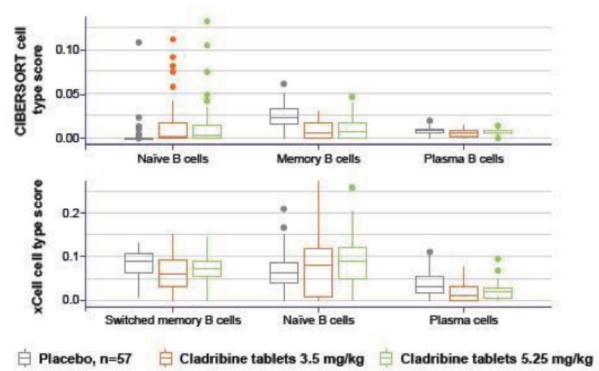


Figure 1: B cell abundance

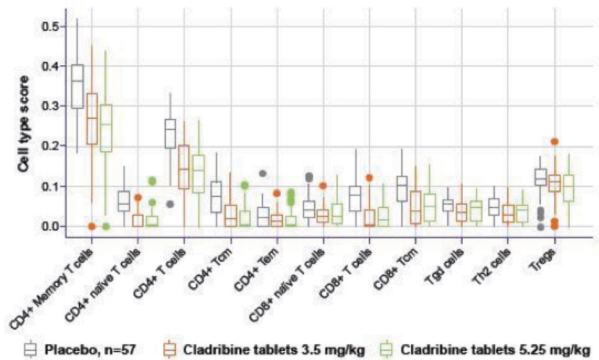


Figure 2: CD4+ and CD8+ T cell abundance

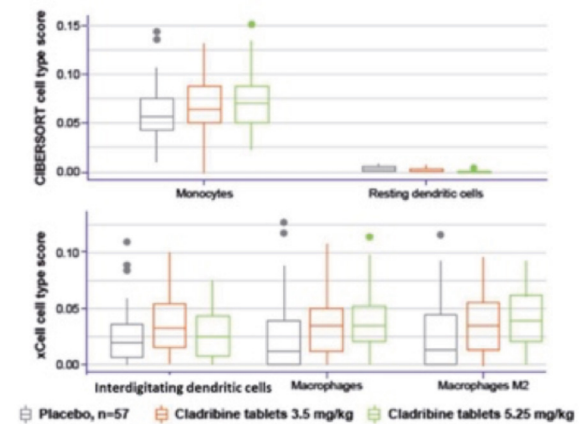


Figure 3: Monocyte and macrophage abundance

Conclusion: These findings suggest that there is a shift towards an anti-inflammatory phenotype at 96 weeks following CT treatment in Year 2.

Disclosure: The trial is sponsored by Merck KGaA, Darmstadt, Germany.

O2006

MEsenchymal StEm cells for Multiple Sclerosis (MESEMS) study: results from a multi-center, randomized, double blind, cross-over phase 2 clinical trial with autologous Mesenchymal Stem Cells (MSC) for the therapy of multiple sclerosis

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Background and aims: Prevention of disability accumulation and protection of the nervous tissue by detrimental effects of inflammation are still unmet needs in the treatment of multiple sclerosis (MS). Bone marrow-derived mesenchymal stromal cells (MSC) are multipotent cells with anti-inflammatory and neuroprotective potential, as demonstrated in EAE.

Methods: MESEMS was an international, multi-center phase II double-blind, randomized, cross-over, placebo-controlled trial lasting 56 weeks. Active relapsing remitting, secondary progressive or primary progressive patients were randomized to receive intravenously either autologous MSC (1-2 x 10.6/Kg) or sham MSC infusion (placebo). At 24 weeks, treatments were switched. Primary endpoints were safety, as measured by the number and severity of adverse events (AE) and efficacy in terms of reduction, as compared to placebo, in the total number of contrast-enhancing lesions (CEL) on MRI over 24 weeks. Secondary efficacy outcomes included evaluation of treatment on other MRI, clinical and neuropsychological measures.

Results: 144 subjects were randomized in the MESEMS trial. Demographic measures and disease characteristics were similar among the 2 randomization arms. The number of AE and serious AE was not higher in subjects treated with MSC compared to control group. Mean number of CEL at 24 weeks did not differ among 2 treatment groups.

Conclusion: Treatment with MSC is safe but did not decrease the number of CEL at 24 weeks compared to placebo. Analysis of secondary and exploratory outcomes is ongoing to reveal whether MSC are effective on other MRI and/or clinical parameters in MS, as well as on any defined metrics suggesting repair.

Disclosure: Funders: Fondazione Italiana Sclerosi Multipla (FISM), European Committee for Multiple Sclerosis, Multiple Sclerosis International Foundation, The Danish Multiple Sclerosis Society, The Toyota Foundation, Danish Blood Donors' Research Foundation, Spinal Cord Injury and Tissue Regeneration Center Salzburg, Paracelsus Medical University, Salzburg, Austria, ARSEP Foundation, AFM (France), UK MS Society, the NIHR Biomedical Research Centre funding scheme to Imperial College, the NIHR Imperial Clinical Research Facility, The Multiple Sclerosis Society of Canada and the Multiple Sclerosis Scientific Research Foundation.

O2007

Patterns of grey matter atrophy in patients with MS: a multivariate analysis using source-based morphometry

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Background and aims: Grey matter (GM) involvement is crucial in multiple sclerosis (MS). Here, we used source-based morphometry (SBM) to characterize GM atrophy and its 1-year follow-up evolution across different MS stages.

Methods: MRI/clinical data were obtained at 8 European sites from 170 healthy controls (HC) and 398 MS patients (34 clinically isolated syndromes [CIS], 226 relapsing-remitting [RR], 95 secondary progressive [SP] and 43 primary progressive [PP] MS). 57 HC and 144 MS underwent 1-year follow-up. Baseline GM loss, GM atrophy progression and correlations with disability and 1-year clinical worsening were assessed.

Results: SBM identified 26 cerebellar, subcortical, sensorimotor, visual, temporal, default-mode, fronto-parietal, hippocampal, executive and salience GM components. GM reduction was found in MS vs HC in almost all components ($p=\text{range}<0.001-0.04$). CIS patients showed circumscribed subcortical, cerebellar, temporal and salience GM loss vs HC, while RRMS patients exhibited widespread GM atrophy. Cerebellar, subcortical, sensorimotor, salience and fronto-parietal GM loss was found in PPMS patients vs HC, and in SPMS vs RRMS. At 1-year, 21 (15%) MS patients had clinically worsened. GM atrophy progressed over time in MS in subcortical, cerebellar, sensorimotor, and fronto-temporo-parietal

regions. Baseline higher disability was associated ($R^2=0.65$) with lower normalised brain volume ($\text{beta}=-0.13$, $p=0.001$), higher sensorimotor GM loss ($\text{beta}=-0.12$, $p=0.002$) and longer disease duration ($\text{beta}=0.09$, $p=0.04$). Normalised GM volume (odds ratio=0.98, $p=0.008$) and cerebellar GM atrophy (odds ratio=0.40, $p=0.01$) independently predicted clinical worsening (area-under-the-curve=0.83).

Conclusion: GM involvement differed across disease stages and progressed at 1-year in MS. Sensorimotor and cerebellar GM atrophy explained baseline disability and clinical worsening.

Disclosure: Nothing to disclose

O2008

Clinical relevance of multiparametric MRI assessment of spinal cord damage in multiple sclerosis

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Background and aims: We aimed to explore the pathophysiology of cervical spinal cord (cSC) damage in multiple sclerosis (MS) patients and to identify MRI predictors of disability and disease course, using a multiparametric MRI approach.

Methods: 111 MS patients, 57 with relapsing-remitting (RR) and 54 with progressive MS (PMS), and 32 age- and sex-matched healthy controls (HC) underwent brain and cSC 3 Tesla MRI with pulse sequences for assessing lesions, atrophy and microstructural damage (with diffusion-tensor metrics), and a complete neurological assessment. Age-, sex- and phenotype-adjusted linear models were built.

Results: MS patients had cSC lesions, higher brain T2-lesion volume (LV), brain and cSC atrophy and microstructural damage, compared to HC. In MS patients, multivariable analysis identified brain grey matter (GM) volume, cSC lateral funiculi fractional anisotropy (FA) and lateral funiculi T2-LV as independent predictors of EDSS score. The independent predictors of EDSS score were cSC lateral funiculi FA, brain T2-LV and cSC lateral funiculi T2-LV in RRMS ($R^2=0.48$); and cSC lateral funiculi FA and cSC GM atrophy in PMS ($R^2=0.52$). Similar results were confirmed for limb function tests. Logistic regression analysis identified cSC GM atrophy and cSC T2-LV as independent predictors of clinical phenotype ($AUC=0.964$).

Conclusion: cSC involvement has a central role in explaining disability in MS. The processes contributing to disability differ according to the stage of the disease. In RRMS, lesions and microstructural damage to cSC tracts have a prominent role, whereas in PMS, cSC GM atrophy becomes clinically meaningful.

Disclosure: Nothing to disclose

Sleep disorders 1

O2009

Skin biopsy: a sensitive and specific biomarker for idiopathic REM sleep behavior disorder versus subtypes of secondary RBD and versus periodic limb movement disorder

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Background and aims: Isolated RBD (iRBD) has been linked to an underlined synucleinopathy. The pathophysiology of secondary RBD (as for example: RBD within narcolepsy, RBD within obstructive sleep apnea syndrome – OSAS) or of periodic limb movement disorder – PLMs- is instead a vexing issue.

We aimed at comparing results of skin biopsy looking for alpha-synuclein (p-alpha-syn) deposits in patients with iRBD, RBD due to narcolepsy and OSAS and in patients with PLMs.

Methods: The population included 50 patients with iRBD, 10 patients with RBD and OSAS, 17 patients with RBD and narcolepsy and 20 patients with PLMs. All groups underwent neurological examinations, neuropsychological investigations, video-polysomnography, neuroimaging, and skin biopsy looking for phosphorylated p-alpha-syn deposits.

Results: Analysis of data shows that skin biopsy can discriminate between iRBD and RBD due to narcolepsy or PLMs. Indeed, skin biopsy was positive in up to 70% of patients with iRBD and in none of RBD due to narcolepsy or of PLMs patients. Few patient with RBD and OSAS have instead positive skin biopsy. Within this group, positive skin biopsy correlated with abnormal muscle tone during REM sleep (i.e. with atonia Index).

Conclusion: Skin biopsy confirms to be a sensitive a specific marker of iRBD.

Disclosure: Nothing to disclose

O2010

Altered resting state functional connectivity of lateral hypothalamus and amygdala in childhood narcolepsy type-1

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Background and aims: Narcolepsy type 1 (NT1) is a chronic sleep disorder characterized by the loss of hypocretinergic neurons in dorsolateral hypothalamus. Functional and structural neuroimaging results are controversial, but compatible with dysfunction of the hypocretinergic system. The aim of the present study was to investigate the functional connectivity of hypothalamus and amygdala in childhood NT1 during rs-fMRI.

Methods: Fifteen drug naïve children with NT1 (9 males; mean age 11.7+3 years) and fifteen healthy children (9 males; mean age 12.4+2.8 years) participated in an EEG-fMRI study. Functional images were acquired on a 3T Philips Achieva system. Seed-based functional connectivity analyses were performed using SPM12. Regions of Interest were lateral hypothalamus (2mm radius spheres, x=+6, y=-10, z=-10) and amygdala (intersection between the healthy controls' hypothalamic functional connectivity map and the AAL Atlas). The BOLD signal time course was extracted by means of MarsBaR toolbox. Second-level group analyses were conducted using 2x2 full-factorial design.

Results: When comparing to controls, NT1 patients showed decreased functional connectivity between lateral hypothalamus and left superior parietal lobule, hippocampus and parahippocampal gyrus. Decreased functional connectivity was detected between amygdala and post-central gyrus and several occipital regions, whereas it was increased between amygdala and right pre- and post-central gyrus, inferior frontal gyrus and claustrum, bilateral insula and putamen.

Conclusion: Alteration of hypothalamus and amygdala functional connectivity in NT1 patients, suggests that the loss of hypocretin containing neurons in NT1 causes abnormal connectivity between the hypothalamus and brain regions involved in arousal and emotional processing.

Disclosure: Nothing to disclose

O2011

CSF and serum ferritin levels in narcolepsy type 1 comorbid with restless legs syndrome

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Background and aims: To investigate whether cerebrospinal fluid (CSF) and serum ferritin levels differ between patients with narcolepsy type 1 (NT1) comorbid with restless legs syndrome (RLS) or periodic leg movements during sleep (PLMS), and patients with NT1 or controls without comorbid RLS or PLMS.

Methods: 66 drug-free patients with NT1 (44 males, age 38.5 years[14-81]) were enrolled, including 20 with RLS, 18 with PLMS index ≥ 15 /hour (6 with both RLS and PLMS). 38 drug-free patients (12 males, age 22.5 years [12-61]) without central hypersomnia, RLS, PLMS were included as controls. Clinical, electrophysiological and biological (CSF ferritin, orexin, and serum ferritin) data were quantified.

Results: NT1 patients with and without RLS did not differ for age, gender and BMI. No between-group differences were found for CSF ferritin, orexin, and serum ferritin levels. No CSF ferritin, orexin, and serum ferritin level differences were found between NT1 patients with and without PLMS, or with RLS or PLMS vs not. CSF-ferritin levels were not different between NT1 and controls in adjusted analyses. CSF-ferritin levels in the whole population correlated positively with age, serum-ferritin, BMI, negatively with orexin, but not with PLMS index. In NT1, CSF-ferritin levels correlated with age and serum-ferritin but not with PLMS.

Conclusion: The absence of CSF ferritin deficiency in NT1 with comorbid RLS or PLMS indicates normal brain iron levels in that condition. This result suggests that the frequent association between RLS, PLMS and NT1 is not based on alterations in brain iron metabolism, a pathophysiological mechanism involved in primary RLS.

Disclosure: Nothing to disclose

O2012

A continuous model of sleep depth to evaluate age-related sleep changes

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Background and aims: In traditional sleep scoring, a 30-s epoch is classified discretely as either wakefulness (W), REM sleep, or a non-REM sleep stage (N1, N2 and N3). With ageing, wakefulness increases and deep sleep decreases. We hypothesized that a continuous model of sleep depth better reflects these changes than traditional scoring of discrete epochs.

Methods: 97 healthy subjects (44.7 \pm 15.2 years, range 19-77 years, 38 males) underwent video-polysomnography. Sleep stages were scored manually. 15 time and frequency features were extracted from non-overlapping 3-s mini-epochs of C4-M1, F4-M1 and O2-M1 electroencephalographic channels. The mini-epochs included in manually scored W and N3 sleep of 15 participants (age <40 years) were used to train a model of sleep depth, which returned as output the sleep depth probability (Pdepth) for each mini-epoch. A mini-epoch was classified as vigilance (V) if Pdepth \leq tv and as deep sleep (DS) if Pdepth \geq td (the thresholds tv and td were optimized during training). For the remaining 82 participants, the percentages of manually scored W (%W) and N3 sleep (%N3) and of estimated V (%V) and DS (%DS) were obtained. Pearson's correlation coefficients were calculated between age and percentages.

Results: High accuracies were obtained when comparing V to W and DS to N3 (Table 1). The proposed model achieved higher correlation between age and the known ageing-related sleep changes than traditional sleep scoring (Table 2).

	W - V	N3 - DS
Training data	0.93 \pm 0.04	0.90 \pm 0.05
Test data	0.89 \pm 0.08	0.92 \pm 0.04

Table 1: Accuracy values in training and test data when manually scored wakefulness (W) and N3 sleep were compared to the automatic identified vigilance (V) and deep sleep (DS).

	Continuous model of sleep depth		Traditional discrete sleep scoring		
	Coefficient	p-value	Coefficient	p-value	
% _v - age	0.34	0.002	% _w - age	0.22	0.048
% _{ds} - age	-0.37	<0.001	% _{n3} - age	-0.33	0.003

Table 2: Pearson's correlation coefficients and relative p-values between age and the calculated percentages. %V: percentage of estimated vigilance; %W: percentage of manual scored wakefulness; %DS: percentage of estimated deep sleep; %N3: percentage of manually scored N3 sleep.

Conclusion: Our continuous model of sleep depth is better suited for individuating age-related sleep changes than traditional sleep scoring and might be applied to evaluation of neurodegeneration-related sleep changes.

Disclosure: Nothing to disclose

O2013

Sleep-wake disturbances after acute stroke predict a higher risk of subsequent cardio-cerebro-vascular events

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Background and aims: Sleep-wake disturbances (SWD) are frequent in stroke patients and may have a detrimental effect on its outcome. The aim of this study is to assess prospectively and systematically whether the presence of one or multiple SWD's are linked with outcome after acute stroke.

Methods: Stroke characteristics, cardiovascular risk profile and sleep disordered breathing (SDB) were recorded during the acute phase by interview, standardized questionnaires and respirography. After 1, 3, 12 and 24 months, we also assessed the presence of several SWD (insomnia, RLS, excessive daytime sleepiness and fatigue). In addition, neurological outcome (modified Rankin score) and occurrence of new cardio-cerebrovascular events (CCVE) were scored. We calculated a "sleep burden index" from the combined severity of different SWD up to 3 months post-stroke as a predictor for subsequent CCVE in multiple regression models.

Results: We recruited 438 acute stroke patients (85% with ischemic stroke, 15% with TIA, mean age 65 years [21-86], 64 % male). The mean NIHSS-score was 3.5 (SD 4.5, range 0-40) at admission and 1.2 (SD 2.1, range 0-18) at discharge. The Sleep Burden Index shows a twofold higher risk for CCVE (Odds Ratio = 2.07 [95% CI: 1.30-3.29, p = 0.002], adjusted for gender, age and baseline NIHSS). Baseline AHI and the combination of other SWDs demonstrates independent predictivity predictive value.

Conclusion: Preliminary results of this ongoing study suggest that the presence of multiple SWDs after stroke represent an independent risk for new, subsequent CCVE in the first 2 years after stroke.

Disclosure: This project was funded by the Swiss National Science Foundation

O2014

The impact of DBS-STN on restless legs syndrome (RLS) and periodic limb movements of sleep (PLMS) – clinical and polysomnography (PSG) study

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Background and aims: RLS and PLMS are common in Parkinson's disease (PD) and have negative impact on sleep quality, which is one of the key determinants of quality of life. We present results of the study on the impact of subthalamic deep brain stimulation (DBS-STN) on RLS and PLMS in PD.

Methods: 36 patients with advanced PD, who fulfilled the CAPSIT criteria and were qualified for routine DBS-STN, were interviewed for RLS symptoms. Those, who met criteria for the diagnosis of RLS were assessed with International RLS Study Group Rating Scale (IRLS). The evaluations were repeated at 6 and 12 months, additionally 24 patients were assessed with 2-night PSG before and at 6 months after surgery.

Results: DBS-STN resulted in the resolution of RLS symptoms in 40% of patients compared to the baseline, both at 6 and 12 months after surgery. Patients who reported RLS symptoms noted significant improvement (median IRLS score 23.5, 18.0 and 19.5, before, at 6 and at 12 months after surgery, respectively). The leg movement arousal index improved significantly after DBS-STN (median value of 0.9 before and 0.2 at 6 months after surgery), however, the improvement in PLM index was not statistically relevant. There were differences in UPDRS II, however no differences in UPDRS III score, among patients with and without RLS.

Conclusion: DBS-STN significantly improved RLS but not PLM in PD patients. Patient with RLS differed in terms of activities of daily living.

Disclosure: Nothing to disclose

Autonomic nervous system disorders

O2015

Validation of the new index of baroreflex function to identify neurogenic orthostatic hypotension

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Background and aims: Blood pressure (BP) overshoot after Valsalva manoeuvre (VM) is the gold standard to differentiate orthostatic hypotension (OH) due to autonomic failure (neurogenic), from non-neurogenic OH. Recently, an increase in heart rate (Δ HR) <15 or 17 bpm upon standing and Δ HR/ Δ BP ratio at 3rd minute of tilt test ≤ 0.49 were proposed as discriminators of neurogenic OH. Our aim was to evaluate the accuracy of these new HR indexes to differentiate neurogenic from non-neurogenic OH.

Methods: We retrospectively applied the HR indexes to all cardiovascular reflex tests performed at our Institution from 1989 to 2019 who fulfilled the following criteria: (1) presence of classical OH at tilt test, (2) reliable VM, (3) absence of heart disease. We classified OH according to VM, Δ HR/ Δ SBP (≤ 0.49 neurogenic) and Δ HR (≤ 17 and ≤ 15 neurogenic). Lastly, we identified tests with neurogenic OH (defined by VM) belonging to patients with multiple system atrophy (MSA) or pure autonomic failure (PAF).

Results: We identified 370 tests with OH. Based on VM, 349 were neurogenic. The Δ HR/ Δ SBP ≤ 0.49 correctly identified neurogenic OH in 314/349 tests (sensitivity 90%) and non-neurogenic OH in 17/21 tests (specificity 81%). The Δ HR ≤ 15 bpm had 83% sensitivity and 67% specificity. The Δ HR ≤ 17 bpm had 88% sensitivity and 52% specificity. The Δ HR/ Δ SBP had a higher sensitivity in detecting neurogenic OH in PAF than MSA (100% and 88% respectively).

Conclusion: The Δ HR/ Δ SBP was a good index to identify neurogenic OH in our cohort, especially in cases with PAF.

Disclosure: Nothing to disclose

O2016

Transient orthostatic blood pressure changes in Parkinson's disease: impact on falls, syncope and orthostatic intolerance

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Background and aims: Transient orthostatic blood pressure (BP) changes within the first minute upon standing influence morbidity and mortality in the aging population. Their prevalence and impact on major clinical outcomes in Parkinson's disease (PD) is however unknown. Here we assessed the prevalence of transient orthostatic BP changes and their influence on falls, syncope and orthostatic intolerance in PD.

Methods: 167 parkinsonian patients, who underwent cardiovascular autonomic function testing under continuous non-invasive heart rate and BP monitoring at the Medical University of Innsbruck between 2007 and 2016 were retrospectively studied.

Results: Transient orthostatic BP changes (systolic BP fall ≥ 20 mmHg or diastolic ≥ 10 mmHg resolving within the 1st minute upon standing) were detected in 16% of PD patients, classic orthostatic hypotension (OH) in 13% and a combination of both in 4%. Beyond postural instability and gait impairment, falls were associated with syncope (OR: 72.461, $p < 0.001$), which mainly occurred upon standing in PD patients. Under continuous heart rate and BP monitoring patients with history of syncope and orthostatic intolerance had a more severe systolic BP fall, lower systolic BP values and a smaller diastolic BP increase during the first minute upon standing.

Conclusion: Transient orthostatic BP falls are more frequent than OH in PD, cause orthostatic intolerance and increase the risk of falls by increasing the risk of orthostatic syncope. A standing test under continuous BP monitoring may therefore help identifying modifiable risk factors for syncope and falls in PD.

Disclosure: Nothing to disclose

O2017

Small fiber pathology in patients with progressive supranuclear palsy

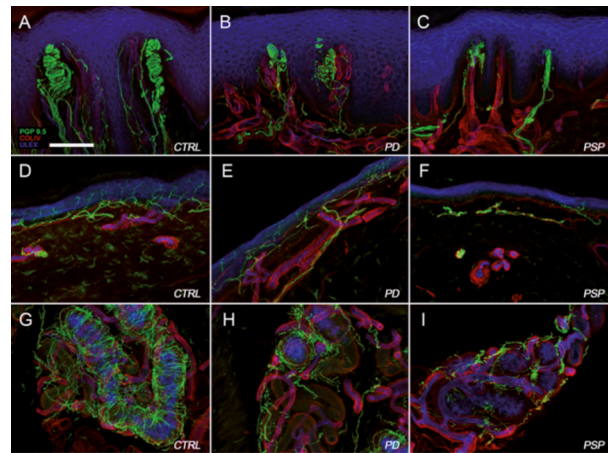
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Background and aims: In the early phase of disease, it can be challenging to differentiate Supranuclear Progressive Palsy (PSP) from idiopathic Parkinson's disease (PD). Small fiber (SF) nerve pathology, involving sensory and autonomic component, is a consistent early feature, that parallels disease progression and sometimes precedes motor impairment in PD. SF involvement is unknown in PSP. Aims of this study were (i) to assess a possible SF involvement in PSP, (ii) to evaluate a possible correlation of SF loss with disease's severity, (iii) to assess possible differences in functional and morphological SF pathology compared to PD.

Methods: We studied 27 PSP and 33 PD patients without electrophysiologic signs of neuropathy, and 33 healthy controls (HC). In addition to motor impairment, assessed by means of UPDRS-III, all patients underwent clinical, functional, and morphologic assessment of sensory-autonomic nerves through dedicated questionnaires, sympathetic skin response, dynamic sweat test, and skin biopsies. Immunohistochemical analysis of cutaneous sensory and autonomic innervation was performed using specific antibodies and confocal microscopy.

Results: PSP patients, compared to HC, displayed a severe length-dependent loss of sensory-autonomic nerve fibers associated to functional impairment (all $p < 0.001$). Motor impairment correlated with autonomic and sensory symptoms and with the loss of intraepidermal nerve fiber density (all $p < 0.01$). Morphological (Figure 1) and functional impairment of SF pathology was more severe in PSP respect to PD (all $p < 0.05$).



Confocal images of immunostained cutaneous nerves. A severe loss of Meissner Corpuscles is evident in PSP patients (C) and a moderate loss in PD patients (B) compared to healthy controls (A). Also in hairy skin of PSP is more evident the epidermal (F) and sudomotor denervation (I) compared to PD (E, H) and healthy controls (D, G).

Conclusion: We demonstrated for the first time a severe length-dependent SF pathology in PSP, paralleling motor severity with peculiar features compared to SF involvement in PD.

Disclosure: Nothing to disclose

O2018

Why does the heart stop? A novel approach to identify the trigger of cardioinhibition in vasovagal syncope.

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Background and aims: Cardioinhibition (CI) is an intriguing phenomenon in vasovagal syncope (VVS). CI causes a decrease in heart rate (HR) including asystole at some point in the process of VVS, but the trigger of CI is still unknown. We developed a novel method for identification of CI and searched for a trigger of CI among haemodynamic variables.

Methods: We included 163 subjects with complete VVS during tilt table testing. All subjects had video and EEG registration and continuous measurements of blood pressure (BP), HR, stroke volume (SV) and total peripheral resistance (TPR). For each subject the start of CI was determined as a downward turn of HR in the minutes before syncope by a 4 person consensus. We evaluated absolute values and variability of BP, HR, SV, TPR three minutes before and at the start of CI.

Results: Our novel approach revealed CI in 149 (91%) of the subjects. The median time from CI to syncope was 58sec (range 12-200 sec). Before the start of CI, BP and SV were already decreasing, HR was increasing and TPR remained stable (fig 1). After the start of CI BP decreased steeply. None of the variables exhibited less variability at the start of CI than before it (fig 2).

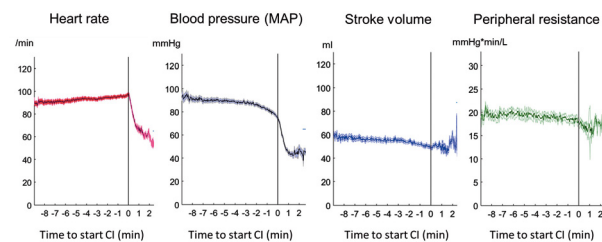


Figure 1. Mean values of heart rate, blood pressure, stroke volume and total peripheral resistance around the start of cardioinhibition

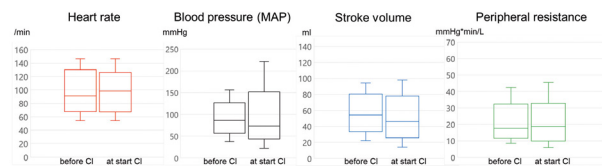


Figure 2. Median values and range of distribution of heart rate, blood pressure, stroke volume and total peripheral resistance at the start of cardioinhibition and 3 minutes before

Conclusion: CI occurred in the majority of subjects with VVS and significantly contributed to the BP lowering in VVS. The start of CI cannot be attributed to a consistent threshold effect of BP, HR, SV or TPR.

Disclosure: Nothing to disclose

O2019

Open-label phase 2 study to explore durability of effect and safety of once-daily oral amprelosetine (TD-9855), a norepinephrine reuptake inhibitor, for symptomatic treatment of neurogenic orthostatic hypotension in subjects with synucleinopathies

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Background and aims: Inadequate norepinephrine (NE) release in neurogenic orthostatic hypotension (nOH) causes fall in standing blood pressure. Amprelosetine, a novel, long-acting NE reuptake inhibitor may improve symptoms of nOH. The objective of this study was to explore durability of effect and safety of once-daily oral amprelosetine for symptomatic treatment of nOH.

Methods: In an open-label, phase 2, exploratory study, subjects received amprelosetine (3-20mg) once-daily for up to 20 weeks, with 4-week follow-up after amprelosetine withdrawal and restarting alternative pressor agents. Assessments included Orthostatic Hypotension Symptom Assessment Item 1 (OHS#1; dizziness, lightheadedness, feeling faint), OHS#1/Orthostatic Hypotension Daily Activities Scale (OHDAS) composite scores, and change in Patient Global Impression of Severity (PGI-S).

Results: Seventeen symptomatic subjects (baseline OHS#1 score >4) were enrolled (mean age, 65 years). At Weeks 4 and 20, mean (SD) improvement on OHS#1 was -3.8 (3.1) and -3.1 (3.0) point, and ~77% and ~86% of subjects reported ≥1-point improvement, respectively. Improvement, seen as early as Week 1, was sustained throughout the study. Deterioration to baseline severity was observed after amprelosetine withdrawal. Similar trends were seen in OHS#1/OHDAS composite scores, and change in PGI-S. Most common adverse events (AEs) were urinary tract infection (24%), hypertension (19%) and headache (14%), with no study-drug-related serious AEs.

Amprelosetine showed durable symptom improvement over 20 weeks, with return to baseline severity after amprelosetine withdrawal. Amprelosetine was well tolerated.

Conclusion: These encouraging findings of durable symptom improvement with open-label amprelosetine treatment are being evaluated in ongoing Phase 3, double-blind, confirmatory studies in subjects with nOH.

Disclosure: R Vickery is an employee of Theravance Biopharma Ireland Limited and stockholder of Theravance Biopharma, US, Inc.

O2020

Impairment of autonomic cardiovascular modulation is more pronounced in focal epilepsy patients with than without limbic system lesions

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Background and aims: Interictal autonomic dysfunction is common in epilepsy patients. Patients with focal epilepsy (FE) frequently have lesions involving the limbic system which closely interacts with central autonomic modulation. Therefore, autonomic dysfunction might be more prominent in FE-patients with limbic-system lesions (LSL+) than in FE-patients with lesions not involving limbic structures (LSL-). We aimed to assess possible autonomic differences between LSL+ and LSL- patients.

Methods: In 36 FE-patients (20 LSL+, 16 LSL-; mean age 34.8±9.0 years, 15 males) and 30 gender- and age-matched healthy controls, we recorded RR-intervals (RRI), beat-to-beat systolic blood pressure (BPsys), and respiratory frequency during 5 minutes at supine rest. We calculated parameters of total cardiac autonomic modulation [RRI-standard-deviation (RRI-SD), RRI-coefficient-of-variation (RRI-CV), RRI-total-powers (RRI-TP)], sympathetic [low-frequency-powers (LF) of RRI and BPsys] and parasympathetic cardiac modulation [root-mean-square-of-successive-RRI-differences (RMSSD), RRI-high-frequency- (RRI-HF)-powers], and baroreflex sensitivity (BRS). We compared autonomic parameters in LSL+ patients, LSL- patients, and controls (Kruskal-Wallis test and post-hoc Mann-Whitney-U-tests; significance: p<0.05). Data are presented as median and interquartile ranges.

Results: In the patients, all autonomic parameters were significantly lower than in the controls. In LS+ patients, only LF-BPsys (2.5 [1.73-3.38] vs. 5.2 [2.68-6.95] mmHg²; p=0.012) and LF-RRI (234 [172-378] vs. 501 [276-744] msec²; p=0.004) were lower than in LS- patients.

Conclusion: Sympathetic and parasympathetic modulation was reduced interictally in our FE-patients. In FE-patients with limbic system lesions, the decrease in sympathetic heart rate- and blood pressure-modulation was more pronounced than in LSL- patients, probably because limbic lesions more severely compromise the function of the central autonomic network.

Disclosure: Nothing to disclose

O2021

Autonomic response during endotracheal suctioning episodes in subarachnoid hemorrhage patients

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Background and aims: Endotracheal suctioning (ES) provokes a cumulative hemodynamic response by activation of sympathetic and parasympathetic circuits. In this study, we aimed to analyse hemodynamic changes during ES in ventilated subarachnoid hemorrhage (SAH) patients and investigated whether the associated activation relates to the time to arousal and functional outcome.

Methods: For the observational study, 191 SAH patients requiring mechanical ventilation were included. 1080 ES episodes during the first 72 hours of admission were analysed. Baseline median heart rate (HR) was calculated 30-10 minutes before ES and compared to HR during ES (DHR). Multivariable analysis to assess associations between DHR and time to arousal (Richmond Agitation Sedation Scale, RASS≥0) and poor 3-month functional outcome (modified Rankin Scale, mRS>2) was performed using generalized estimating equations.

Results: Patients were 59 (IQR, 50-70) years old and presented with an admission H&H grade of 4 (IQR, 3-5). Median time to arousal was 13 (IQR, 4-21) days. HR increased by 2.2±0.2 beats per minute (bpm) from 75.1±0.5 bpm at baseline. Poor-grade patients (H&H 4-5) showed a significantly lower DHR during suctioning compared to good-grade patients (1.5±0.3 bpm vs 3.3±0.3 bpm, p<0.001). In multivariable analysis, DHR (p<0.001) was significantly lower in patients who aroused later and in patients with poor outcome independently of sedation depth (Table 1).

Table 1: Association between increase of heart rate during suctioning and poor functional 3-month outcome

Variable	Adjusted for midazolam dose		Adjusted for RASS*	
	AdjOR, 95%-CI	p-value	AdjOR, 95%-CI	p-value
ΔHR	0.96; 0.94-0.98	<0.001	0.96; 0.93-0.98	<0.001
Age, years	1.05; 1.04-1.06	<0.001	1.06; 1.04-1.07	<0.001
H&H grade	1.83; 1.64-2.06	<0.001	1.90; 1.68-2.16	<0.001
Absolute HR	1.01; 1.00-1.02	0.01	1.02; 1.01-1.03	0.001
Daily cumulative midazolam dose, mg	1.00; 0.99-1.00	0.475	-	-
RASS	-	-	0.75; 0.54-1.03	0.076

*179 patients were included due to missing RASS recordings
 ΔHR=delta heart rate during suctioning, H&H=Hunt&Hess, RASS= Richmond Agitation Sedation Scale, adjOR=adjusted odds ratio, CI=confidence interval

Conclusion: Augmentation in HR may quantify the hemodynamic response during endotracheal suctioning in brain injured patients. The value as a biomarker to early discriminate the time to arousal and functional outcome needs prospective confirmation.

Disclosure: Nothing to disclose

Cognitive neurology/neuropsychology; ageing and dementia 1

O2022

Accelerometer speech recording: technical aspects, reliability, clinical and intraoperative utility

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Background and aims: Speech disorders are usually just clinically characterized and in the specific situation of intraoperative mapping with electrostimulation, there is a high risk of seizures. Here, we have investigated the feasibility of accelerometer (ACC) recording of glottis vibration during speech through intraoperative testing of brain tumor patients (BTP) and on dysphonic patients (DP). We aimed to identify technical caveats, to test its reliability and applicability during a picture naming task (PNT).

Methods: A uniaxial ACC was used to record surface infraglottic vibration. We first tested the influence of position and filter bandwidth on recorded parameters such as amplitude, baseline level, burst artefacts and repeatability. Using a scoring scale for artefact contamination, amplitude and reproducibility, 6 evaluators ranked each condition. With the selected settings, we recorded baseline data during PNT in 25 healthy volunteers and compared it with 15 BTP and 7 DP data.

Results: The highest scores were given to the suprasternal notch site and 20-200 Hz filter bandwidth. A intrasubject reliability of 0.92 (range of 0.88-0.95, CI 95%) was found for each parameter. Lower amplitudes and frequencies were identified in DP. We detected mainly a speech arrest with brain stimulation in patients (57% vs 16% in healthy subjects). In intraoperative language testing, 11% of the evoked errors were detected by evaluating parameters' deviation from ACC baseline recordings. In these cases, the brain site was re-stimulated (after increasing 20% of the intensity) and evoked clinical language disturbances.

Conclusion: ACC speech recording was found reliable and allowed to identify language disturbances during PNT.

Disclosure: Nothing to disclose

O2023

Predictive factors for recurrent transient global amnesia

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Background and aims: Transient global amnesia (TGA) is a clinical syndrome characterized by sudden anterograde amnesia of less than 24 hours in duration, in the absence of other neurological symptoms. The risk of recurrence ranges between 2.9-26.9%. The predictive factors for recurrent TGA have not yet been identified.

Methods: Retrospective analysis to identify recurrence predictors in a cohort of 69 TGA patients from a single center in Portugal, diagnosed between January 2012 and June 2019. Clinical features and complementary studies performed during the acute phase were analyzed.

Results: Mean age at presentation was 64.8 years (37-84), 69.1% were female; mean follow-up was 16.5 months (6-36); co-morbidities more frequent: hypertension (50.7%), dyslipidemia (39.1%), diabetes (20.2%), depression (20.2%), migraine (14.5%), and cerebrovascular disease (8.7%). Average episode duration lasting 6 hours and 50.7% had an identifiable trigger – emotional stress (24.6%), physical effort (11.6%), and sexual intercourse (2.9%). In the acute phase, 20 (29.8%) patients performed brain-MRI - 5.8% with hippocampus DWI restriction; 18 patients (26.1%) had TGA recurrence. The following features had a positive association with the risk of recurrence: female sex (p=0.038), depression (p=0.039), shorter duration (p=0.037) and hippocampus signal alteration on brain-MRI (p=0.008). Accompanying symptoms, precipitating events, other coexisting conditions and altered EEG or ultrasound did not show any correlation with recurrent TGA

Conclusion: We present a cohort of TGA patients with a considerable recurrent rate (26%), alerting for the possibility of recurrence of this clinical entity. The following predictive factors were identified: female sex, depression, shorter episode duration, and hippocampal hyperintensity on brain-MRI. Additionally, to its diagnostic value, brain-MRI performed in the acute phase could have prognostic value

Disclosure: Nothing to disclose

O2024

Distinct white matter tract changes associated with apathy in cerebrovascular small vessel disease

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Background and aims: Clinical apathy is a poorly understood neuropsychiatric syndrome characterised by a significant decrease in goal-directed and motivated behaviour 1,2. It occurs in ~30% of patients with cerebrovascular small vessel disease (SVD). With the aim of improving our mechanistic understanding of apathy, we conducted a multimodal investigation combining validated behavioural paradigms and magnetic resonance imaging (MRI) techniques.

Methods: 83 patients with MRI evidence of SVD were recruited from the Oxford Vascular Study (OXVASC) and Oxford neurology clinics. They were investigated using a novel effort-based decision making task³ and the Apathy Evaluation Scale (AES). Structural and diffusion weighted MRI was conducted to measure white matter lesion load (WMLL) and tract integrity, indexed by Fractional anisotropy (FA).

Results: Patients with apathy demonstrated a significant reduction in motivated behaviour and were significantly less incentivised by low levels of reward (Fig 1). Diffusion weighted imaging demonstrated that apathy was characterised by focal changes to limbic association tracts including the uncinate fasciculus and cingulum bundle, as well as fronto-striatal white matter tracts (Fig 2). Importantly, global measures of disease severity did not independently associate with apathy.

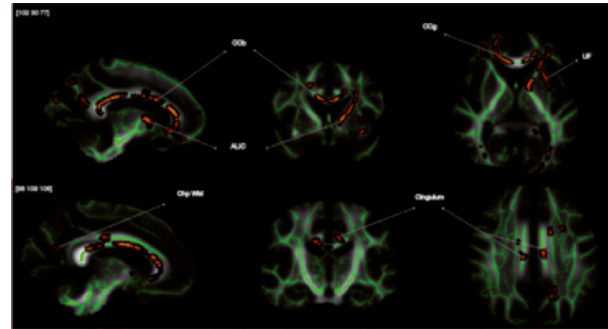
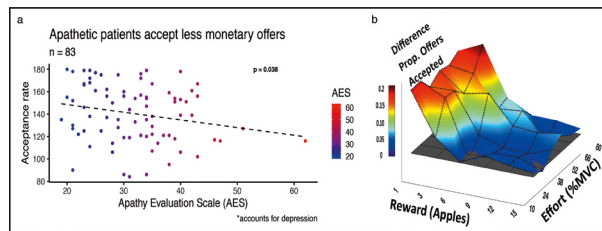


Figure 2. Apathy in SVD characterised by reduced Fractional anisotropy in white matter tracts.

Conclusion: Reduced incentivisation by low reward characterised apathy in SVD, as previously reported in Parkinson’s disease, suggesting a common mechanism underlying apathy across diseases. At the network level, the association of apathy with focal white matter tract changes is consistent with disruption to key frontostriatal circuits (linking medial frontal regions to each other and to the basal ganglia) which previously have been implicated in effort-based decision-making for rewards.

Disclosure: Nothing to disclose



Apathy is related to performance on effort-based decision making task
 a) Severity of apathy predicts motivated behaviour in SVD. b) The greatest differences between motivated and apathetic subjects are shown by the red peaks and occur when the reward levels on offer are low. In other words, apathetic subjects are less incentivised by low reward.

O2025

Linguistic cognitive reserve may influence post-stroke aphasia recovery and rehabilitation: the “QuALiCoMe” study

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Background and aims: Aphasia is a disabling consequence for 30% of ischemic stroke patients. The wide variability of recovery among post-stroke aphasic patients despite similar baseline stroke severity and clinical characteristics could be in part explained by the involvement of a sort of ‘Linguistic Cognitive Reserve’. Therefore, an informant-based questionnaire named “QuALiCoMe”, was developed by an interdisciplinary work based on various branches of linguistics, cognitive psychology, educational research and neurology, with the aim of estimating the pre-morbid linguistic abilities in patients with post-stroke aphasia.

Methods: Validation of QuALiCoMe questionnaire on 182 healthy subjects (HS) and 82 respective caregiver/cohabitant (CC). Pilot study: Frenchay Aphasia Screening Test (FAST) was administered within 48 hours after stroke onset (baseline) and after 6-month follow-up, and QuALiCoMe was administered to aphasic patient’s CC. As explanatory variable for aphasia recovery, we used delta-FAST score (baseline – follow-up).

Results: QuALiCoMe demonstrated a good informativeness and reliability (high concordance between HS and CC), applicability, internal consistency and external validity. Sixty stroke patients (29 female, mean NIHSS±DS=14.30±7.11, mean FAST±DS=10.02±9.61) fulfilled inclusion criteria. In a multivariate analysis, corrected for age, baseline-NIHSS, education, speech and language therapy, and thrombolysis, QuALiCoMe score showed a trend for significance in predicting recovery from aphasia (p=0.062).

Conclusion: This result represents the first clinical evidence of the role of Linguistic Cognitive Reserve as an outcome predictor in post-stroke aphasia. QuALiCoMe demonstrates a valid and promising tool to estimate pre-morbid linguistic reserve in post-stroke aphasic patients. Its potential utility needs to be confirmed in larger cohorts of patients.

Disclosure: This research has been granted by “Ente Cassa di Risparmio di Firenze”.

O2026

The association between cognitive impairment and structural and functional brain organization in amyotrophic lateral sclerosis

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Background and aims: The aim of this study was to evaluate the association between cognitive impairment and structural and functional brain organization in patients with amyotrophic lateral sclerosis (ALS).

Methods: 54 ALS patients with pure motor impairment (ALS-pure), 20 with cognitive and/or behavioural deficits (ALS-plus), and 61 age- and sex-matched controls underwent clinical, cognitive and MRI evaluations. Graph analysis and connectomics assessed structural and functional topological network properties. The relationship between structural/functional brain properties and clinical/neuropsychological data was also investigated.

Results: Both ALS-pure and ALS-plus demonstrated lower structural clustering coefficient within the sensorimotor network relative to controls. In addition, ALS-plus patients showed higher functional mean nodal strength, local efficiency and clustering coefficient in sensorimotor regions. Regarding the connection-wise analysis, ALS-pure showed significant structural changes relative to controls involving connections within and among sensorimotor and basal ganglia regions, whereas ALS-plus patients showed increased functional connectivity within the sensorimotor, anterior frontal, temporal and parieto-occipital areas. Global structural nodal strength positively correlated with verbal fluency in ALS-pure patients. Functional connectivity within the temporal network connections positively correlated with language tests in ALS-plus group, while ALS-pure showed a negative correlation between functional connectivity within the fronto-striatal network connections and scores in verbal fluency test.

Conclusion: Whereas structural disruptions of the sensorimotor network are a common signature of ALS, the occurrence of cognitive impairment is characterized by further functional connectivity changes involving extra-motor brain areas. Graph analysis and connectomics are suitable tools to better characterize ALS phenotypes.

Disclosure: Supported by: Italian Ministry of Health (#RF-2011-02351193) and AriSLA (ConnectALS).

O2027

Hippocampal atrophy in vascular MCI as biomarker of subclinical memory impairment

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Background and aims: Vascular mild cognitive impairment (VMCI) is a transitional condition that may evolve to vascular dementia (VaD). Deeper understanding of the mechanisms of cognitive impairment in VMCI is crucial to develop biomarkers of disease progression. Studies have suggested hippocampal atrophy as a putative MRI-based biomarker in early VaD. To assess whether hippocampal atrophy occurs in VMCI and to what extent correlates with cognitive impairment and is influenced by vascular risk factors (VRF).

Methods: In this multicentre study, 108 VMCI patients underwent brain MRI and were scored on cognitive tests (Table-1). Hippocampal volume was calculated using FIRST (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki>) and compared with appropriate normative values (cohort of 5139 healthy controls). Linear regression models were used to assess differences in MRI measures and their association with cognitive tests and VRF.

Total n. of patients	108
Sex (male/female)	60/48
Mean (±SD) age, years	74.3 (±6.6)
Mean (±SD) education, years	8.3 (±4.2)
N. patients with vascular risk factors (y/n)	
<i>Hypertension</i>	86/22
<i>Hypercholesterolemia</i>	65/43
<i>Smoking</i>	51/57
<i>History of stroke</i>	33/75
<i>No physical activity</i>	30/78
<i>Diabetes</i>	17/ 91
Global cognition	
<i>MMSE (range 0-30)*</i>	27.2 ± 2.7
<i>MoCA (range 0-30)*</i>	21.2 ± 4.4
Memory	
<i>RAVL immediate recall (range 0-75)*</i>	32.4 ± 8.6
<i>RAVL delayed recall (range 0-15)*</i>	6.1 ± 2.8
<i>Short Story (range 0-28)*</i>	11.7 ± 4.1
<i>ROCF recall (range 0-36)*</i>	12 ± 5.6
Attention and executive functions	
<i>TMT-A (time to complete, secs)**</i>	67.3 ± 50.1
<i>Visual Search (range 0-50)*</i>	31.8 ± 9
<i>SDMT (correct answers in 90 secs)*</i>	34.4 ± 10.4
<i>Stroop test (time to complete, secs)**</i>	36.6 ± 31.2
<i>TMT-B (time to complete, secs)**</i>	104.4 ± 60
Language	
<i>Phonemic verbal fluency (words in 3 mins)*</i>	28.1 ± 9.6
<i>Semantic verbal fluency (words in 3 mins)*</i>	34.3 ± 7.7
<i>Constructional praxis ROCF copy (range 0-36)*</i>	23.8 ± 9.1
MRI Field strength	
1.5T/3T	90/18

Table 1. Demographic, clinical and MRI characteristics of the VMCI patients

Footnotes: All cognitive tests were corrected by age and education.

* Higher scores correspond to better performance.

** Lower scores correspond to a better performance.

Demographic, clinical and MRI characteristics of the VMCI patients

Results: After comparison with normative values, VMCI were stratified in subjects with no (n=70/108, Group I), mild (n=25/108, II) and moderate (n=13/108, III) hippocampal atrophy (Fig. 1). In patients with hippocampal atrophy there was an association between lower hippocampal volume and worse verbal memory tests scores such Rey-Auditory-Verbal-Learning Test immediate and delayed recall (both $p < 0.001$) and Short-Story ($p = 0.05$). When comparing the groups for each VRF, they differed only for smoking ($p = 0.02$; Fig. 2). There was no association between the number of VRF and hippocampal volume.

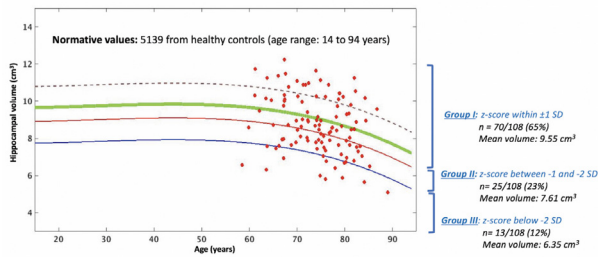


Figure 1: Comparison of hippocampal volumes between patients and normative values. The graph shows the distribution of hippocampal volume in our patients with VMCI (red dots), compared with the average of predictive normative values from a cohort of healthy controls (green line)

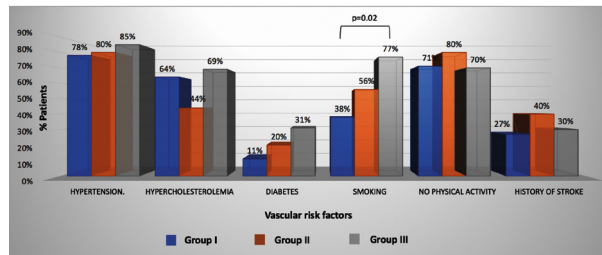


Figure 2: Differences between groups for each vascular risk factor. The graphs show the distribution of patients from the three groups for each vascular risk factor.

Conclusion: Hippocampal atrophy can be detected in patients with VMCI and seems to be closely related to subclinical memory impairment. Presence of hippocampal atrophy may be an unfavourable marker of disease outcome in patients with VMCI.

Disclosure: Nothing to disclose

MS and related disorders 2

O2028

Effectiveness and safety of ocrelizumab in patients with relapsing-remitting multiple sclerosis who had a suboptimal response with prior disease-modifying therapy: 2-year findings from CHORDS

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Background and aims: Ocrelizumab is an anti-CD20-directed monoclonal antibody that showed superior efficacy vs interferon β -1a treatment in pivotal trials of patients with relapsing multiple sclerosis (MS). The Phase IIIb CHORDS study (NCT02637856) examined the effects of ocrelizumab in patients with relapsing-remitting MS (RRMS) who experienced a suboptimal response to previous disease-modifying therapy (DMT).

Methods: The CHORDS study enrolled 608 patients with RRMS who experienced ≥ 1 relapse, ≥ 1 T1 gadolinium-enhancing lesion or ≥ 2 new/enlarging T2 lesions while receiving another DMT for ≥ 6 months. Patients received ocrelizumab 600mg every 24 weeks for ≤ 96 weeks. The primary endpoint was the proportion of patients free of protocol-defined clinical or MRI activity (event), evaluated in a modified ITT population for which patients who terminated early for lack of efficacy or death were imputed as having had an event and patients without an event who discontinued for other reasons were excluded. Secondary endpoints included annualised relapse rate (ARR) and Expanded Disability Status Scale (EDSS) change from baseline.

Results: Among the 555 patients who completed treatment, 48.1% were free of protocol-defined events at Week 96. Most patients did not experience protocol-defined relapse (89.6%), T1 gadolinium-enhancing lesions (95.5%), new/enlarging T2 lesions (59.5%) or 24-week confirmed disability progression (89.6%). 71 relapses were observed (ARR, 0.046). Most patients had stable (61.5%) or improved (22.7%) EDSS. Safety findings were consistent with the overall ocrelizumab safety profile.

Conclusion: This analysis demonstrated the benefits of ocrelizumab over 2 years in patients with RRMS who experienced suboptimal response to another DMT.

Disclosure: Sponsored by F. Hoffmann-La Roche Ltd; writing and editorial assistance was provided by Health Interactions, USA.

O2029

MRI-based clustering of multiple sclerosis patients in the perspective of personalized Medicine

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Background and aims: We aimed to find clusters of multiple sclerosis (MS) patients with homogeneous underlying pathophysiology, by using advanced MRI techniques.

Methods: 115 MS (57 relapsing-remitting, 12 primary- and 46 secondary-progressive) patients, and 44 age- and sex-matched healthy controls (HC) underwent brain and cervical cord 3T MRI for assessing lesions, atrophy, and microstructural damage (with diffusion-tensor metrics), and a complete neurological assessment. Clusters of MS patients were identified with hierarchical clustering on age- and sex-adjusted MRI variables.

Results: 5 clusters of MS patients were identified: “early”; “intermediate-cord”, “intermediate-cortical”, “intermediate-late-lesion”; and “late”. “Early” patients showed similar MRI metrics vs HC (except lesions), lower Expanded Disability Status Scale (EDSS) and shorter disease duration (DD) compared to other patients’ groups ($p < 0.01$). Compared to “early” and other “intermediate” groups, “intermediate-cord” patients had higher cord T2-lesion volume (LV) ($p < 0.001$), “intermediate-cortical” had lower cortical thickness ($p < 0.001$), and “intermediate-late-lesion” had higher brain T2-LV, higher deep grey matter (GM) atrophy and longer DD ($p < 0.01$). “Late” patients had higher EDSS and DD, compared to “intermediate” groups ($p < 0.01$), and worst diffusion-tensor metrics and cord/brain atrophy ($p < 0.01$ vs all). “Intermediate-cord” patients could be divided into 2 groups characterized by different cord GM atrophy and cortical thickness ($p < 0.01$), with similar DD; the impaired one including mostly progressive phenotypes and higher EDSS.

Conclusion: MRI-based clustering of MS patients is feasible. It contributes to better characterize disease heterogeneity and in the future it may be useful for personalized medicine. “Intermediate-cord” patients may be the best target to study neuroprotective and regenerative strategies.

Disclosure: Partially supported by Fondazione Italiana Sclerosi Multipla (grant FISM/2018/R/16).

O2030

Challenges of initiating anti-CD20 monoclonal antibodies in RR MS

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Background and aims: Anti-CD20 monoclonal antibodies have demonstrated their efficacy in the treatment of active relapsing-remitting multiple sclerosis (RR-MS). While its drastic efficacy on disease activity has been reported in many studies, none of them have investigated the management of its initiation after another disease modifying therapy (DMT). The aim of this study was to assess the frequency and the predictive factors of disease activity during the wash-out period (WP) between cessation of last DMT and initiation of anti-CD20 monoclonal antibodies in RR-MS.

Methods: All RR-MS patients who initiated a treatment with Rituximab or Ocrelizumab between 2016 and 2019 have been included in this retrospective monocentric study. Univariate and multivariate analysis were conducted to identify predictive factors of disease activity during WP.

Results: 72 RR-MS patients (73.6 % female, mean age 35.4 years) were included, with a mean number of previous DMTs per patient of 3.2 (1-7). The most frequent previous DMT was Fingolimod (Fg, 44.4%). 20 patients experienced disease activity during the WP. The only predictive factor was previous treatment by Fg ($p < 0.001$). After cessation of Fg (32 patients), a WP duration over 1 month was also predictive of disease activity ($p = 0.02$).

Conclusion: Cautious monitoring of disease activity is necessary when switching from another DMT to anti-CD20 monoclonal antibodies, especially after treatment with Fg and according to WP duration. Reduction of WP duration could be enabled by monitoring of immune repertoire reconstitution and the acceptance of a lower threshold of lymphocytes for treatment initiation.

Disclosure: Nothing to disclose

O2031

Serum neurofilament light correlates with reduced grey matter volume in advanced multiple sclerosis

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Background and aims: Grey matter (GM) pathology is associated with physical and cognitive impairment in patients with multiple sclerosis (MS). Increased levels of serum Neurofilament light (sNfL), indicating neuro-axonal damage, have been described in MS and were related to the development of global and regional brain atrophy. However, its relation to MRI-based measures of distinct brain volumes is still poorly investigated.

Methods: We measured sNfL by an ultrasensitive Single Molecule Array (Simoa[®]) in 109 MS patients (mean age 38.1, SD±11.7 years, 63.3% female (16 clinically isolated syndrome (CIS), 72 relapsing-remitting MS (RRMS) and 21 progressive MS (PMS)) and 17 gender- and age-matched non-inflammatory neurological controls (NC). We recorded clinical data and performed 3T MRI to assess global and cortical normalised brain volumes and T2 lesion load.

Results: sNfL correlated with age in the entire cohort (N=126, r=0.329, p<0.001). We found elevated sNfL levels in RRMS and PMS compared to NC (Figure 1). Decreased total and cortical GM volume was found in MS patients compared to CIS (p<0.001). Only in patients with PMS we found sNfL to be correlated with volumes of total GM (r=-0.475, p=0.034), cortical GM (r=-0.508, p=0.001) (Figure 2) and lesion load (r=0.513, p=0.017; data not shown). No such correlation was present when analysing CIS and RRMS patients.

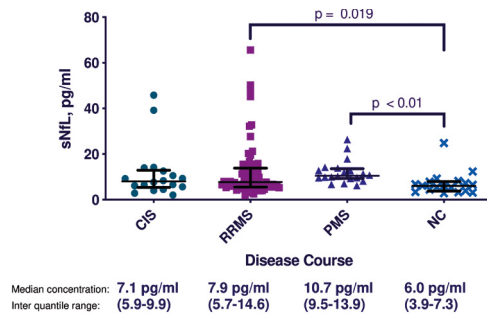


Figure 1 Comparison of sNfL in different stages of MS. sNfL levels are elevated in RRMS and PMS compared to NC (Mann-Whitney-U test, Bonferroni corrected).

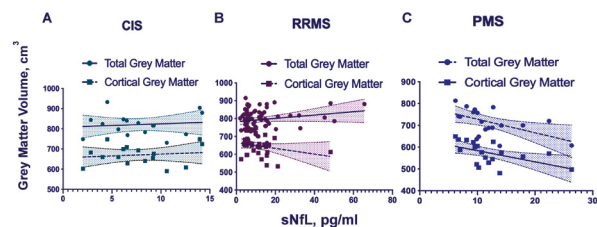


Figure 2 A-C Correlations of sNfL and GM in different stages of MS. 95% confidence bands are shown. Only in PMS we found sNfL to be correlated with volumes of total GM (r=-0.475, p=0.034) and cortical GM (r=-0.508, p=0.001) (C). No such correlation was present when analysing CIS (A) and RRMS (B) patients.

Conclusion: Although sNfL is already increased in earlier phases of MS, its relation to brain tissue damage, in particular GM pathology, becomes only apparent in more advanced, progressive forms of the disease. Further analysis of longitudinal data is ongoing to confirm and extend our results.

Disclosure: Nothing to disclose

O2032

TERIKIDS Study: teriflunomide efficacy and safety in paediatric patients with relapsing forms of MS

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Background and aims: Additional therapeutic options are needed for paediatric MS patients. Teriflunomide is approved for adults with relapsing forms of MS (RMS) in >80 countries; the TERIKIDS study (NCT02201108) assessed efficacy and safety in paediatric RMS patients.

Methods: TERIKIDS is a 96-week, randomised, double-blind, placebo-controlled, parallel-group phase 3 study of teriflunomide in paediatric RMS patients, with a 96-week, open-label extension; earlier extension entry is possible for clinical relapse or high MRI activity above protocol-defined thresholds. Patients receive placebo or teriflunomide (based on body weight equivalent to 14mg in adults). Eligible patients had $\geq 1/\geq 2$ relapses within 12/24 months. Primary endpoint is the time to first confirmed relapse, with sensitivity analysis including high MRI activity as relapse equivalent; secondary endpoints include proportion relapse-free, MRI lesion number and volume, brain volume loss, cognition outcomes, and safety/tolerability.

Results: Target enrolment was met (N=166). At baseline, mean age was 14.6 years (67% female). Time since first MS symptoms/diagnosis was 2.3/1.4 years. Mean number of relapses in the past year was 1.5 (42% experienced ≥ 2 relapses); average time since most recent relapse was 5.2 months. Mean (median) EDSS score and gadolinium-enhancing lesion number were 1.3 (1.5) and 3.8 (1.0), respectively. In the previous 2 years, 23% received disease-modifying therapy. Efficacy and safety results will be presented.

Conclusion: At baseline, patients enrolled in TERIKIDS had high relapse and MRI lesion activity, and relatively short disease duration. Results of this study will provide insight into the efficacy, safety, and tolerability of teriflunomide, and may help further understanding RMS in the paediatric population.

Disclosure: STUDY SUPPORT: Sanofi.

O2033

Efficacy and safety results of the phase 3 SPI2 study of MD1003 (high dose Pharmaceutical grade Biotin) in progressive MS

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Background and aims: An unmet need exists for treating progressive forms of multiple sclerosis (MS): primary or secondary progressive (PPMS, SPMS). Biotin is a coenzyme for carboxylases involved in energy metabolism and fatty acid synthesis. MS-SPI, the first study of MD1003 (high dose Pharmaceutical grade Biotin) in progressive MS, demonstrated a significant sustained improvement in disability with treatment vs placebo. SPI2 is a phase 3 study of MD1003 in progressive MS (EudraCT:2016-000700-29).

Objective: Evaluate the efficacy and safety of MD1003 in progressive MS.

Methods: SPI2 inclusion required documented, relapse-free, disability progression in EDSS over the 2 years before entry and an EDSS score between 3.5 and 6.5. Patients were randomized (1:1) to MD1003 100mg tid or placebo. The primary endpoint was the proportion of patients with improvement – decreased EDSS (0.5 or 1.0) or decreased timed 25-foot walk (T25FW) of $\geq 20\%$ – from baseline to month (M) 12, confirmed at M15. Secondary endpoints were time to 12-week confirmed EDSS progression, clinical global impression (CGI/SGI), and T25FW mean change.

Results: Overall, 642 patients were randomized: Europe/North America/Australia (n=338/290/14). At submission, baseline demographics and disease characteristics were: mean age 52.7 years; 53.7% female; 64.6% SPMS; mean time since diagnosis 12.6 years; mean time since SPMS conversion 5.0 years; mean EDSS 5.4; mean T25FW 11.6 seconds. Last patient last visit occurred in November 2019; database lock will be in early 2020.

Conclusion: Efficacy and safety results of the phase 3 SPI2 study of MD1003 in progressive MS will be presented.

Disclosure: This study was sponsored by MedDay Pharmaceuticals. MD1003 is a not approved, investigational product.

O2034

Effect of ofatumumab treatment on disability progression independent of relapse activity in patients with relapsing multiple sclerosis

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Background and aims: Ofatumumab, the first fully human anti-CD20 monoclonal antibody with a monthly 20mg subcutaneous (s.c.) regimen, demonstrated superior efficacy versus teriflunomide in the Phase 3 ASCLEPIOS I/II trials in relapsing multiple sclerosis (RMS) patients. Here, we present data on the treatment effect of ofatumumab versus teriflunomide on progression independent of relapse activity (PIRA).

Methods: In the ASCLEPIOS I/II pooled analysis, the risk of confirmed disability progression at 3/6 months (3mCDP/6mCDP; Expanded Disability Status Scale [EDSS] score increase of ≥ 1.0 if baseline EDSS score < 6.0 , or ≥ 0.5 if baseline EDSS score ≥ 6.0) was evaluated in three subsets of patients: (A) without confirmed relapses during the study, (B) without confirmed relapses during the study or prior to a 3mCDP/6mCDP event, and (C) with secondary progressive multiple sclerosis diagnosis at study-entry and without confirmed relapses during the study. Hazard ratios (HRs) and p-values were calculated by a Cox-regression model adjusted for study as stratum, for treatment, region, and baseline EDSS score as covariates. An inverse probability censoring weighted (IPCW) analysis, censoring patients with confirmed relapses prior to a 3mCDP/6mCDP event, was also performed.

Results: Ofatumumab significantly reduced the risk of 3mCDP and 6mCDP versus teriflunomide in all subsets analysed, except for 6mCDP in the small Subset-C (Table). IPCW estimation of PIRA confirmed a risk reduction of 46.0% for 3mCDP (HR [95%CI]: 0.540 [0.396-0.738], $p < 0.001$) and 42.5% for 6mCDP (0.575 [0.409-0.808], $p = 0.001$) versus teriflunomide.

Disability-related outcomes	Ofatumumab 20 mg n/N	Teriflunomide 14 mg n/N	HR (95% CI)	Risk reduction	p-value
3mCDP					
Subset-A	50/793	67/661	0.587 (0.407–0.848)	41.3%	0.004
Subset-B	53/796	82/676	0.516 (0.365–0.729)	48.4%	<0.001
Subset-C	6/46	11/37	0.312 (0.114–0.859)	68.8%	0.024
6mCDP					
Subset-A	42/793	53/661	0.632 (0.421–0.947)	36.8%	0.026
Subset-B	45/796	66/674	0.551 (0.377–0.805)	44.9%	0.002
Subset-C	6/46	8/37	0.463 (0.158–1.355)	53.7%	0.160

Results of treatment comparison obtained from a Cox-regression model adjusted for study as stratum, for treatment, region, and baseline EDSS score as covariates.

Subset-A: Patients without confirmed relapses during the study; Subset-B: Patients without confirmed relapses during the study or prior to a 3mCDP/6mCDP event; Subset-C: Patients with a SPMS diagnosis at study entry and without confirmed relapses during the study
3mCDP, disability progression confirmed at 3 months; 6mCDP, disability progression confirmed at 6 months; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; N, total number of patients included in the analysis; n, number of patients with the specified event; SPMS, secondary progressive multiple sclerosis

Table. Risk of 3mCDP and 6mCDP by patient subsets

Conclusion: Ofatumumab 20mg s.c. monthly dosing regimen markedly reduced disability progression independent of relapses versus teriflunomide in RMS patients.

Disclosure: This study was funded by Novartis Pharma AG, Basel, Switzerland. A detailed disclosure from each author will be included in the oral/poster presentation. Abstract also submitted to AAN 2020; acceptance pending.

Cerebrovascular diseases 2

O2035

Intended bridging therapy or intravenous thrombolysis in minor stroke with large vessel occlusion

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Background and aims: Whether bridging therapy (intravenous thrombolysis [IVT] followed by endovascular treatment) is superior to IVT alone in minor stroke with large vessel occlusion (LVO) is unknown.

Methods: Multicentric retrospective observational study including, in intention-to-treat, consecutive IVT-treated minor strokes (NIHSS \leq 5) with LVO, with or without additional mechanical thrombectomy. Propensity-score (inverse probability of treatment weighting) was used to reduce baseline between-groups differences. The primary outcome was excellent outcome, i.e., modified Rankin score 0-1 at 3 months follow-up.

Results: Overall, 598 patients were included (214 and 384 in the bridging therapy and IVT groups, respectively). Following propensity-score weighting, the distribution of baseline clinical and radiological variables was similar across the 2 patient groups. Compared with IVT alone, bridging therapy was not associated with excellent outcome (OR=0.96; 95%CI=0.75-1.24; p=0.76), but was associated with symptomatic intracranial haemorrhage (OR=3.01; 95%CI=1.77-5.11; p<0.0001). Occlusion site was a strong modifier of the effect of bridging therapy on outcome (Pinteraction<0.0001), with bridging therapy associated with higher odds of excellent outcome in proximal M1 (OR=3.26; 95%CI=1.67-6.35; p=0.0006) and distal M1 (OR=1.69; 95%CI=1.01-2.82; p=0.04) occlusions, but with lower odds of excellent outcome for M2 (OR=0.53; 95%CI=0.38-0.75; p=0.0003) occlusions. Bridging therapy was associated with higher rates of symptomatic intracranial hemorrhage in M2 occlusions only (OR=4.40; 95%CI=2.20-8.83; p<0.0001).

Conclusion: Although overall outcomes were similar in intended bridging therapy as compared to intended IVT alone in minor strokes with LVO, our results suggest that intended bridging therapy may be beneficial in M1 occlusions, while the benefit-risk profile may favor IVT alone in M2 occlusions.

Disclosure: Nothing to disclose

O2036

Post-thrombolysis early neurological deterioration in minor strokes with large vessel occlusion

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Background and aims: Whether endovascular therapy added on intravenous thrombolysis (IVT), as compared to IVT alone, is beneficial in minor strokes with large vessel occlusion (LVO) is unknown. To identify predictors of early neurological deterioration (END) following IVT alone may help to select the best candidates for additional endovascular therapy.

Methods: Multicentric retrospective observational study including IVT-treated minor strokes (NIHSS \leq 5) with LVO intended for IVT alone, i.e., including those who eventually received endovascular therapy because of END. END was defined as a \geq 4 points on NIHSS within 24hrs following admission. Thrombus length was measured centrally either on T2*-MRI or CT/CTA.

Results: 721 patients were included: mean age 70years, median NIHSS 3, occlusion located in internal carotid artery [ICA] -T/L, tandem cervical ICA+MCA, proximal M1, distal M1, M2, and basilar artery, in 3%, 10%, 7%, 21%, 54% and 4%, respectively. The thrombus was visible in 85% of patients. END occurred in 12% of patients and was associated with poor 3-month outcome. In multivariable analysis, a more proximal occlusion site (p<0.001) and a longer thrombus (p=0.002) were independently associated with END. END occurred in 55%, 23%, 19%, 13%, 5% and 27% of patients with ICA-T/L, tandem, proximal M1, distal M1, M2, and basilar artery occlusion, respectively, and in 5%, 7%, 15% and 23% of patients with thrombus length of <6, [6-9[, [9-12[and \geq 12mm, respectively.

Conclusion: Our study suggests that thrombus location and length are strong predictors of END in minor strokes with LVO. This may help to select the best candidates for additional endovascular therapy.

Disclosure: Nothing to disclose

O2037

Net water uptake overestimates cerebral edema volumes in thrombolysed patients at 24-hours compared to anatomical distortion

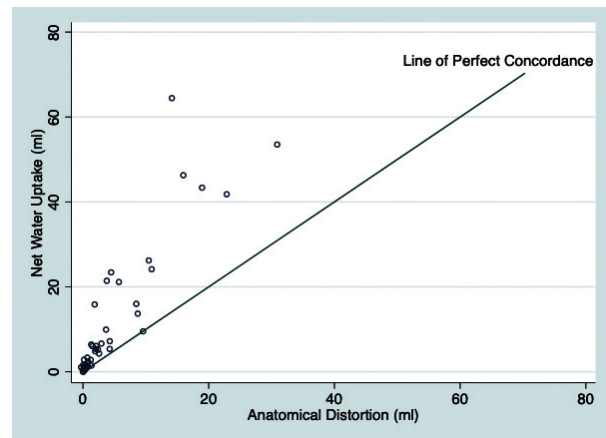
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Background and aims: Following the GAMES-RP trial, there is an increased interest in the measurement of cerebral edema [Net Water Uptake (NWU) Broocks et al. Invest Radiol 2016; Anatomical Distortion (AD): Harston et al. Stroke 2018]. This study uses data from the MAGIC Study [Inzitari et al. Stroke 2013] to explore the agreement between these two methods.

Methods: All patients with a CT Scan available at baseline and at 18-36 hours following symptom onset were included in the analysis. Lesion masks on follow-up imaging were defined and agreed. The volumes of edema (ml) were generated according to the NWU and AD methods. Appropriate statistical tests were used to explore the agreement between these volumes.

Results: On follow-up imaging, 102 patients had scans available for analysis: 28 (27.2%) had no lesion; 23 (22.5%) had evidence of hemorrhage, precluding the use of the NWU method. The mean (SD) volumes of edema were: NWU 10.2ml (15.2); AD 4.0ml (6.5). The Lin Concordance Correlation Coefficient was 0.57 (95% CI 0.47-0.66) with all values above the line of perfect concordance (see figure). The Bland-Altman metrics showed a mean difference in values of 6.2ml (9.8) with 95% CI level of agreement of -13.0ml to 25.4ml. Regression metrics estimated a relationship of $NWU = 1.8 + 2.1 \cdot AD$.



Conclusion: Volumes of cerebral edema generated by NWU and AD methods demonstrated poor concordance and levels of agreement, with NWU volumes typically twice those of those measured by AD. This may influence future trial design where volume is an outcome measure.

Disclosure: Nothing to disclose

O2038

Association between β blocker or statin drug use and hemorrhage from cerebral cavernous malformations

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Background and aims: To determine the association between β blocker or statin drug use and the risk of symptomatic intracranial haemorrhage or persistent/progressive focal neurological deficit in adults with cerebral cavernous malformations.

Methods: The population-based Scottish Intracranial Vascular Malformation Study prospectively identified adults resident in Scotland who were first diagnosed with a cerebral cavernous malformation during 1999-2003 or 2006-2010. We compared the association between β blocker or statin drug use for at least 90 days at any time after first presentation and the occurrence of intracranial hemorrhage or persistent/progressive focal neurological deficit due to the cerebral cavernous malformation for up to 15 years of prospective follow-up.

Results: Of 300 adults in the Scottish Intracranial Vascular Malformation Study, 63 (21%) used β blocker medication (27/63 [43%] used propranolol) and 73 (24%) used statin medication. β blocker medication use was associated with a lower risk of intracranial hemorrhage or persistent/progressive focal neurological deficit (1/63 [1.6%] versus 29/237 [12.2%], adjusted hazard ratio 0.09, 95% confidence interval 0.012-0.68, $p=0.019$) during 15 years of follow-up. Statin medication use was associated with a non-significant reduction of intracranial hemorrhage or persistent/progressive focal neurological deficit (4/73 [5.4%] versus 26/227 [11.5%], adjusted hazard ratio 0.37, 95% confidence interval 0.013-1.07, $p=0.067$) during 15 years of follow-up.

Conclusion: The associations between β blocker and statin drug use and the risk of intracranial hemorrhage or persistent/progressive focal neurological deficit in patients with cerebral cavernous malformations justify the investigation of the effects of these drugs in randomized trials.

Disclosure: Nothing to disclose

O2039

Serum neurofilament light chain levels differentiate spinal cord infarction from inflammatory myelopathies

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Background and aims: To investigate whether serum neurofilament light chain (NfL) levels differentiate spinal cord infarction (SCI) from acute inflammatory myelopathies.

Methods: We retrospectively identified Mayo Clinic patients (January 1, 2000-December 31, 2019) with: 1) SCI; 2) aquaporin-4 (AQP4)-IgG or myelin oligodendrocyte glycoprotein (MOG)-IgG-associated myelitis at disease clinical presentation; or 3) idiopathic transverse myelitis (ITM) from a previously identified population-based cohort seronegative for both AQP4-IgG and MOG-IgG. Serum NfL levels were assessed on available stored samples obtained ≤ 3 months from myelopathy onset at the Verona University Neuropathology laboratory (SIMOA Quanterix) in a blinded fashion. Representative spinal cord MRI T2-lesion areas were manually measured on sagittal images (Figure 1).



Figure 1 - Example of manual measurement of spinal cord lesion area on MRI

Results: 48 patients were included: SCI, 20 (definite, 11; probable, 6; possible, 3); AQP4-IgG-associated myelitis, 17; MOG-IgG-associated myelitis, 5; ITM, 6. Median (range) serum NfL levels (pg/mL) in patients with SCI (188 [14.3-2793.4]) were significantly higher than those of patients with AQP4-IgG-associated myelitis (37 [0.8-6942.9]), MOG-IgG-associated myelitis (45.8 [4-283.8]), and ITM (15.6 [0.9-217.8]); $p=0.01$. The NfL levels to MRI T2-lesion Area Ratio (NAR) showed the highest accuracy for identification of SCI vs inflammatory myelopathies, with values greater than 0.4 yielding 88% specificity and

95% sensitivity, respectively (AUC=0.95; Figure 2). NAR remained independently associated with SCI after adjusting for age, gender, immunotherapy before sampling, and days from myelopathy symptoms onset to sampling ($p<0.0001$).

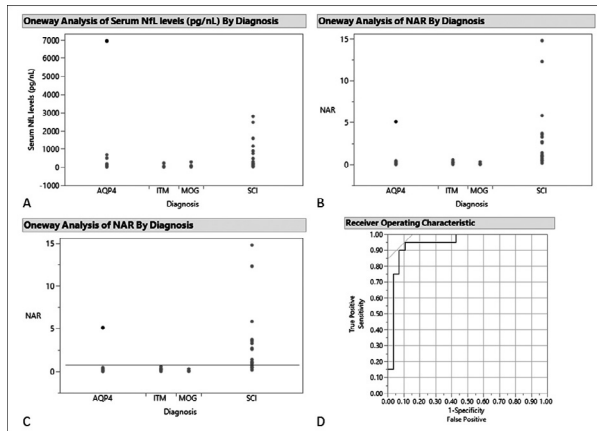


Figure 2 - Scatterplots showing the distribution of NfL levels, spinal cord lesion areas, and NAR in the different groups of myelopathies

Conclusion: In the acute setting, serum NfL and NAR might be a reliable, and easily accessible biomarker to differentiate SCI from acute inflammatory myelopathies.

Disclosure: Nothing to disclose

Clinical neurophysiology

O2040

Interobserver variation of routine EEG vs high value (2000s/mm²) DWI MRI findings in TGA: a prospective study

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Background and aims: Transient global amnesia (TGA) is characterized by the acute inability to form new memories, lasting up to 24 hours. Vascular, epileptic and migrainous events have been proposed as responsible pathophysiologic mechanisms. The value of electroencephalography (EEG) has not been proved, and studies so far have shown EEG to be normal during and after the attack. However, EEG should be performed when transient epileptic amnesia (TEA) is considered likely, as an alternative diagnosis.

Methods: To assess the efficacy of routine EEG at the early phase of TGA, blindly assessed by 2 neurologists, and compare these findings with high-value DWI MRI.

Results: 15 patients were included (male/females:4/11). Mean age was 65 years [SD±4.4]. Mean time from TGA onset to routine EEG (21 electrodes, 10/20 system) was one day [±0.4], mean time to brain MRI was 3 days [SD±2.5]. High-value DWI-MRI was normal in 2 patients, and 2 revealed hippocampal sulcus remnant cysts. Bilateral high 2000-DWI hyperintense hippocampal lesions were noted in 2 patients. In the rest, a unilateral left hippocampal lesion was depicted. Mean PDR was 10c/s [SD±1]. Intermittent slow theta wave activity was recorded in 6/15 EEGs, and was assessed as frequent in 5/6 and occasional in 1 (8-49%). Slow activity was mostly noted in the frontotemporal/anterior-temporal areas. A left predominance of slow activity was noted in the majority of the patients (5/6). Only in 1 patient 2000-DWI MRI findings matched EEG findings, while another had abnormal EEG without concurrent MRI findings.

Conclusion: Routine EEG cannot substitute 2000-DWI MRI in detecting hippocampal involvement in patients with TGA.

Disclosure: Nothing to disclose

O2041

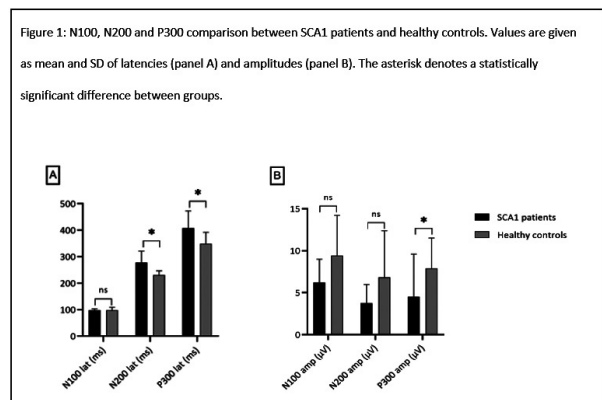
Electrophysiological evaluation of cognition and neuropsychological assessment in Spinocerebellar Ataxia Type 1 patients

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Background and aims: Spinocerebellar Ataxia Type 1 (SCA1) is an autosomal dominant disorder caused by an unstable expansion of CAG repeats. Many studies have provided evidence that cognitive decline is also present along with motor deterioration. In this context, event-related potentials (ERPs) may provide valuable insight into attentive processes

Methods: 10 SCA1 patients (8 females, 2 males) were enrolled in this study. Neuropsychological test battery included: Frontal Assessment Battery, FAS fluency test, Trail Making Test, Raven Progressive Matrices, Stroop Color and Word Test, Rey complex figure, Babcock's short tale, Emotion Attribution Task and VATA-m for anosognosia. Auditory ERPs were assessed through an auditory oddball paradigm by using standard (80% of presenting probability, 2000Hz frequency) and target (20% of presenting probability, 1500Hz frequency) stimuli, presented in a pseudo-randomized manner. EEG signals were recorded from the scalp at the sites of Fz, Cz, Pz with auricular reference. N100, N200 and P300 were detected and analyzed in 9 patients. 11 healthy subjects were chosen to match patients on sex, age and educational level

Results: Neuropsychological tests evaluating frontal, attentive, visuospatial and affective abilities showed significant correlation with SARA score. With regard to ERPs, pathologically longer latencies of N200 and P300 ($p=0.006$; $p=0.012$) and smaller P300 amplitudes ($p=0.02$) were observed in SCA1 patients (Fig.1). Additionally, we found strong correlations between N200 latency and P300 amplitude and scores assessing cerebellar motor symptoms and attentive-affective functions (Fig.2)



Conclusion: This study suggests usefulness of ERPs, providing for the first time electrophysiological evaluation of cognition in SCA1 patients

Disclosure: Nothing to disclose

Figure 2: Spearman's rank correlations between ERP components (N200 latency and P300 amplitude) and clinical and neuropsychological scores. Only significant correlations are reported.

Clinical and neuropsychological features	N200 latency		P300 amplitude	
	r	p	r	p
SARA	0.828	0.006*	-0.765	0.016*
Trail Making Test A	0.820	0.007*	-0.678	0.045*
Emotion Attribution Task	-0.807	0.015*	n.s.	n.s.

O2042

Cortical plasticity after bionic hand prostheses: is the “invasion” hypothesis of deafferented cortex always true?

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Background and aims: Upper limb amputation provokes changes in the cerebral motor and somatosensory cortex that governs the amputated limb and this mechanism is related to Phantom Limb Pain (PLP). Not much is known about the potential reversibility of these changes.

Methods: We tested with TMS motor maps at baseline and after a period of training with a new hand bidirectional prosthesis in three left trans-radial amputees, correlating these changes with the modification of PLP in the same period.

Results: Baseline motor maps showed in all 3 amputees an inter-hemispheric asymmetry of motor cortex with a smaller area of muscles representation of the amputated side compared to contralateral hemisphere. Following training and possibility to re-use again cerebral areas for motor and somatosensory tasks, there was a partial reversal of the asymmetry, with a more symmetrical representation of the forearm muscles on the 2 hemispheres, as in normal subjects. The 2 subjects affected by PLP experienced after training with the prosthesis a statistically significant reduction of pain.

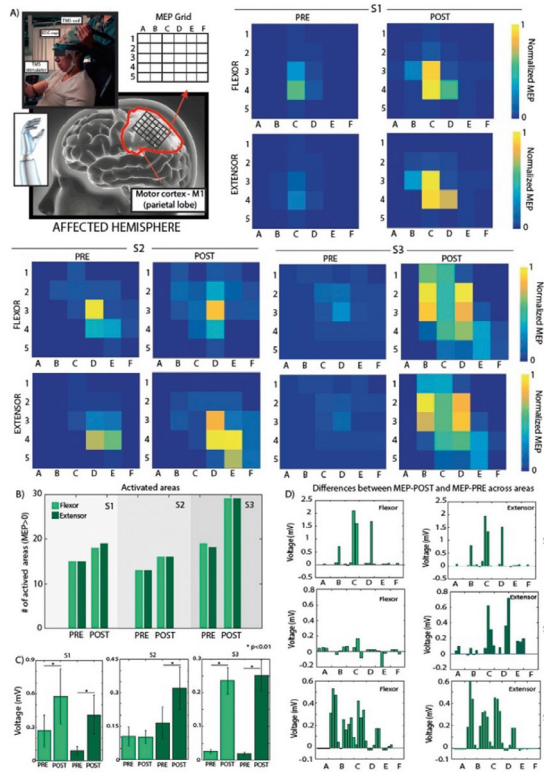


Figure 1: the baseline motor mapping showed that motor area related to the amputee limb was smaller than contralateral

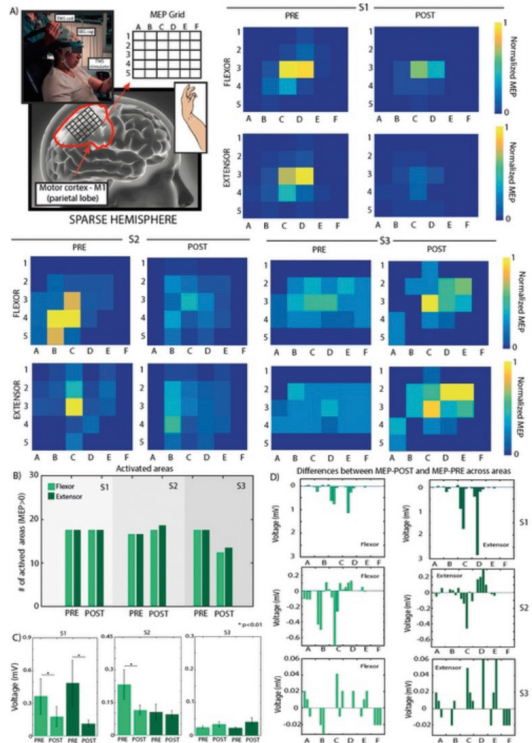


Figure 2: after training with robotic prosthesis able to restore somatosensory feedback, motor area related to stump muscles increased in size

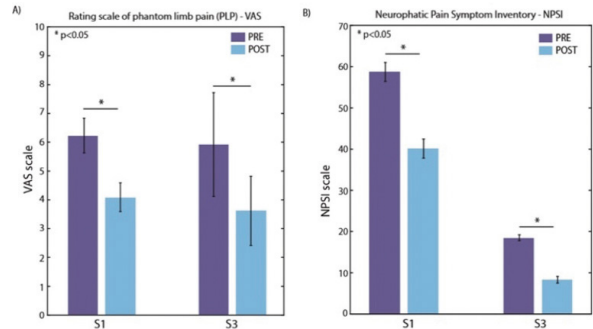


Figure 3: both 2 subjects suffering from Phantom Limb Pain reduced their painful sensations

Conclusion: According to “invasion” hypothesis for plastic brain changes we were supposed to find at baseline a motor cortical area governing the stump increased in size compared with the contralateral, with a rebalancing after the training. Our measurement “in vivo” found opposite results that we can explain as the result of prolonged non-use of the cerebral areas. Motor and somatosensory learning process is partially able to restore symmetry of motor areas and this process correlates with improvement of Phantom Limb Pain.

Disclosure: Nothing to disclose

O2043

Knocking at the brain's door: a direct measure of brain excitability in alternating hemiplegia of childhood

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Background and aims: Alternating hemiplegia of childhood (AHC) is a rare neurodevelopmental syndrome caused by a mutation in ATP1A3, a Na/K-ATPase pump critical to restore membrane excitability, particularly in fast-spiking interneurons. Both paroxysmal and static clinical features of AHC are typically distributed asymmetrically. Transcranial Magnetic Stimulation (TMS) combined with electromyography (EMG) indirectly shows fluctuations in cortical excitability in AHC, with MEP decreasing during a hemiplegic episode.

Our aim was to obtain a direct, bilateral and longitudinal measure of excitability, using hd-EEG as a readout of TMS response (TMS-EEG).

Methods: 5 AHC adults and 5 healthy controls (HC) were tested with TMS-EEG on 2 separate sessions. Primary motor cortex was targeted using neuronavigation and stimulated bilaterally at subthreshold intensity (98% of resting Motor Threshold). A qualitative analysis of TMS evoked potentials was performed. Pearson correlation test was used to evaluate the interhemispheric symmetry. Differences in interhemispheric symmetry between groups and sessions were calculated using Mann-Whitney test.

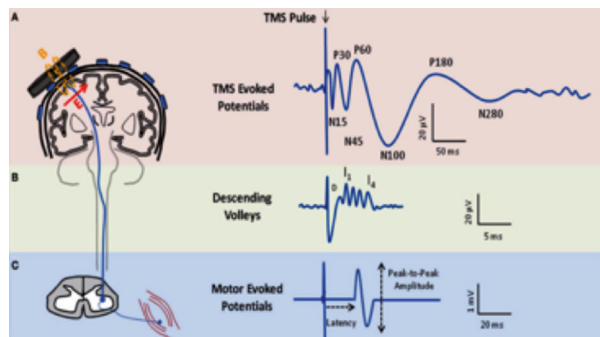


Figure 1: TMS evoked responses at cortical, spinal and muscular level.

Results: In one patient we recorded a baseline condition and a quadriplegic spell, during which the EEG response was abolished. AHC patients exhibited a higher degree of interhemispheric asymmetry compared to HC ($\rho=0.39\pm0.25$ vs. 0.6 ± 0.04 , $p=0.004$). A degree of intersession variability was also observed in patients ($p=0.052$).

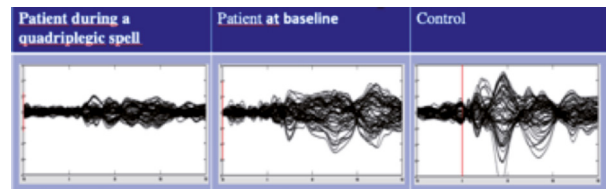


Figure 2: TMS evoked potential during a quadriplegic spell (A), at baseline in AHC patient (B) and in a HC (C)

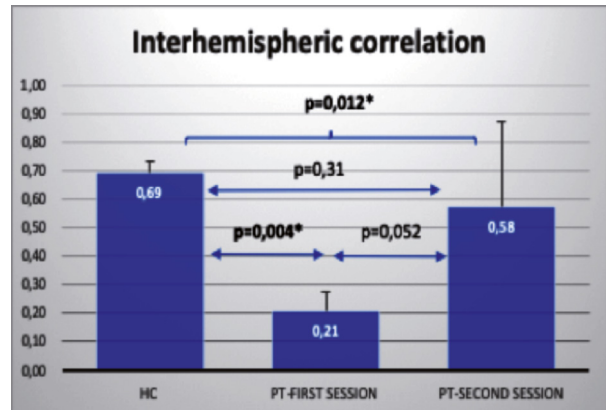


Figure 3: interhemispheric asymmetry in HC and AHC patients

Conclusion: These preliminary data support the central origin of the excitability abnormalities previously described and demonstrate an increased interictal asymmetry in AHC patients. Studies in larger cohorts are needed to further explore the role of TMS as a biomarker and objective outcome measure in interventional trials.

Disclosure: Nothing to disclose

O2044

EEG background patterns correlate with serum neurofilament light after cardiac arrest

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Background and aims: EEG is one of the most commonly used tools for neurological prognostication after cardiac arrest (CA), but the lack of a uniform classification of pathological patterns is a major limitation. A recently proposed classification (Figure 1) based on standardized terminology has high interrater reliability and the proposed patterns predicted 6-month neurological outcome with high specificity but limited sensitivity. Serum neurofilament light (S-NFL) is a novel biochemical marker, potentially superior to other measures of hypoxic brain injury. This study investigated the correlation between S-NFL as a quantitative measure of brain injury and EEG-patterns according to the new classification.

Methods: Retrospective analysis of EEG data and S-NFL from the Targeted Temperature Management (TTM) trial. EEGs were recorded after the temperature intervention was completed (36 hours to 12 days after CA) and classified according to the American Clinical Neurophysiology Society (ACNS) standardized terminology by blinded investigators. The EEG-background and the prevalence of discharges were compared to peak S-NFL-levels at 48 or 72 hours after CA.

Results: We included 262 patients with EEG and S-NFL (Table 1). The classified EEG pattern was significantly related to the peak S-NFL-level (Figure 1). S-NFL-levels increased significantly with increased prevalence of discharges if seen superimposed on a continuous EEG background (Figure 2).

Table 1: Characteristics	
Age, median (IQR), years	65 (58-73)
Male gender, N (%)	214 (81.7)
Time to ROSC, median (IQR), min	27 (20-42)
Peak S-NFL, median (IQR), pg/ml	2316 (158-7673)
Outcome at 6 months, cerebral performance categories scale, N (%)	
1 – Good cerebral performance	56 (21.4)
2 – Moderate cerebral disability	15 (5.7)
3 – Severe cerebral disability	12 (4.6)
4 – Coma or vegetative state	7 (2.7)
5 – Brain death	172 (65.6)
Time to EEG, median (IQR), hours	74 (58-100)
EEG background, N (%)	
Continuous	148 (56.5)
Discontinuous	42 (16.0)
Burst suppression	27 (10.3)
Suppression	45 (17.2)

Table 1 - Patient characteristics

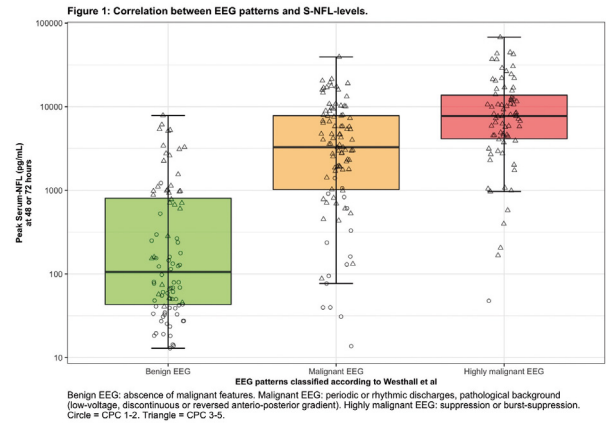


Figure 1 - Correlation between EEG patterns and peak S-NFL-levels

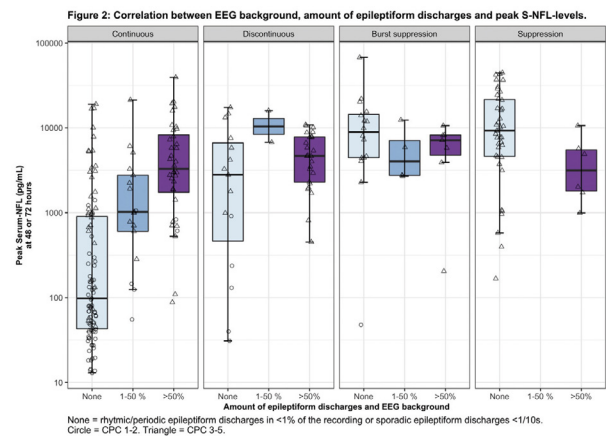


Figure 2 - Correlation between EEG background, amount of epileptiform discharges and peak S-NFL-levels

Conclusion: EEG background is strongly associated with a quantitative biochemical measure of brain injury after cardiac arrest. The amount of epileptiform activity is an additional marker of severity in the subgroup of patients with a more benign EEG background.

Disclosure: This project has received funding from the Swedish National Health System (ALF), the County Council of Skåne and the Skåne University Hospital Foundations.

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Neuro-ophthalmology/neuro-otology

O3001

Retinal axonal degeneration in Niemann Pick type C disease

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Background and aims: Niemann-Pick disease, type C1 (NPC1) is a heterogeneous autosomal-recessive lysosomal storage disorder, presenting at different ages and progressing at different rates. Optical coherence tomography (OCT) is established to detect retinal degeneration in vivo. We examined NPC1 patients (NPC1-P), clinically asymptomatic NPC1 mutation carriers (NPC1-MC), and healthy controls (HC) using OCT in order to (i) identify retinal degeneration in NPC1-disease and (ii) to investigate possible subclinical retinal degeneration in NPC1-MC.

Methods: 14 NPC1-P, 17 NPC1-MC and 31 age-matched HC were examined using spectral-domain OCT. Neurological examinations, clinical scales and video-oculography (VOG) were correlated with OCT data.

Results: Macular retinal nerve fiber layer and volumes of combined ganglion cell and inner plexiform layer were significantly lower in NPC1-P compared to HC (mRNFL(μ m): 0.13 ± 0.01 vs. 0.14 ± 0.02 ; $p=0.01$; GCIPL(mm³): 0.60 ± 0.05 vs. 0.62 ± 0.04 ; $p=0.04$). No significant differences were found in NPC1-MC in comparison to HC. In NPC1-P the decreased amplitude of upward vertical saccades was associated with thinned peripapillary pRNFL ($\rho=0.645$, $p<0.05$), and thinned GCIP ($\rho=0.609$, $p<0.05$), but not in NPC1-MC. In NPC1-P correlations between combined outer plexiform layer and outer nuclear layer (OPONL) with mDRS ($r=-0.617$, $p<0.05$) and GCIP with SARA ($r=-0.622$, $p<0.05$) were observed. Further, in NPC1-MC motor scores were negatively associated with pRNFL ($\rho=-0.677$, $p<0.01$).

Conclusion: We showed retinal degeneration in NPC1-P and significant correlation between retinal neuro-axonal degeneration with clinical measurements. We observed a non-significant trend of retinal degeneration in NPC1-MC correlating with subclinical motor abnormalities. Based on these preliminary data, OCT may be an important marker of neurodegeneration in NPC1 disease after clinical symptoms' onset.

Disclosure: Nothing to disclose

O3003

Prevalence of visual snow syndrome in the UK

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Background and aims: Visual snow syndrome is a recently described condition of unknown prevalence. We investigated the prevalence in a representative population sample from the UK and tested the hypothesis that visual snow syndrome is associated with young age, headache, tinnitus and mood impairment.

Methods: Using a crowdsourcing platform, we recruited a representative sample of 1015 laypeople from the UK, matched for age, gender and ethnicity according to national census data. Participants were unprimed, i.e. were inquired about the "frequency of certain medical conditions" but not "visual snow syndrome".

Results: 38 of 1015 participants reported symptoms compatible with visual snow (3.7%, 95% CI 2.7-5.2), and 22/1015 met criteria for visual snow syndrome (2.2%, 95% CI 1.4-3.3). Female-to-male ratio for visual snow syndrome was 1.6:1. Subjects with visual snow syndrome were older (50.6 ± 14 years) than the population mean (44.8 ± 15 years), albeit not statistically different ($p=0.06$). Of 22 participants with visual snow syndrome, 16 had mood symptoms (72.7%; $p=0.01$), 13 had headache (54.5%, $p=0.06$), including 5 with visual migraine aura (22.7%, $p=0.15$), and 13 had tinnitus (59.1%, $p=0.0001$). No participant had diabetes or a cleft lip (control questions). Following a multivariable regression analysis to adjust for age and gender, only the association between visual snow syndrome and tinnitus remained significant (OR 3.93, 95% CI 1.63-9.9; $p=0.003$).

Conclusion: The UK prevalence of visual snow syndrome is around 2%. We confirmed an association with tinnitus, but unprimed laypeople with visual snow syndrome are on average older than those seeking medical attention.

Disclosure: Nothing to disclose

O3004

Disrupted functional connectivity within the visual, attentional and salience networks in visual snow syndrome

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Background and aims: Visual snow (VS) is a newly defined neurological condition in which patients describe a continuous static-like disturbance present in the entire visual field, and additional symptoms such as palinopsia, photophobia, entoptic phenomena and nyctalopia. The basic neurobiology of visual snow is still mostly unknown, and treatment is challenging.

We performed a brain resting state functional connectivity in patients with VS to understand more about the underlying pathophysiology of the syndrome.

Methods: Subjects with VS (n = 24) and matched healthy volunteers (n = 24) were scanned on a 3T GE MR750 MRI scanner. Whole-brain maps of functional connectivity were acquired under 2 separate conditions: at rest while watching a blank screen and during a visual paradigm consisting of a visual-snow like stimulus.

Results: Subjects with visual snow had increased and reduced connectivity between key visual areas and the rest of the brain, both in the resting state and during a visual stimulation, compared to healthy controls. In particular, we found altered connectivity between visual areas V1 and V5; between the thalamus and both the basal ganglia and lingual gyrus; between the visual motion network and both the default mode and attentional networks.

Conclusion: The data suggest VS is characterized by a widespread disturbance in the functional connectivity of multiple brain systems, particularly of the pre-cortical and cortical visual pathways, the visual motion network, and the attentional networks.

Disclosure: Nothing to disclose

Epilepsy 2

O3005

GABAergic dysfunction mediates motor impairment in Rett syndrome

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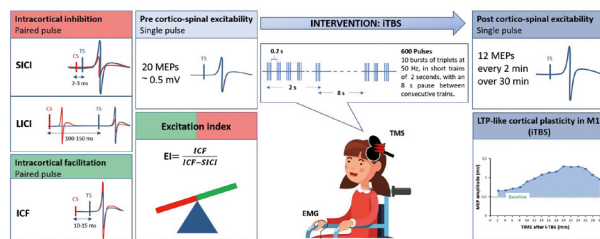
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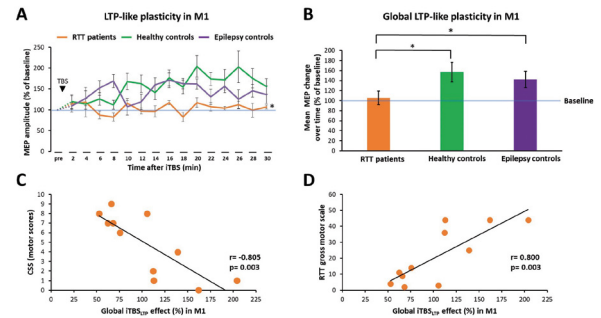
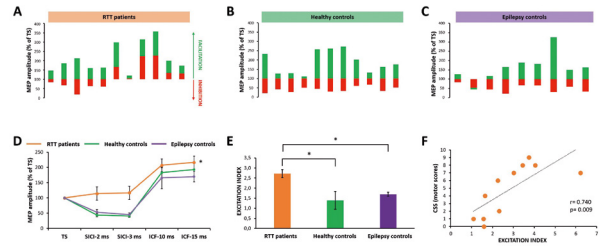
Background and aims: Rett syndrome (RTT) is an X-linked dominant neurodevelopmental disorder due to pathogenic mutations in the MECP2 gene. Motor impairment constitutes the core diagnostic feature of RTT. Preclinical studies have consistently demonstrated alteration of excitation/inhibition (E/I) balance and aberrant synaptic plasticity at cortical level. Herein we aimed at understanding neurobiological mechanisms underlying motor deficit by assessing in "vivo" synaptic plasticity and E/I balance in the primary motor cortex (M1).

Methods: On 14 patients with typical RTT, 9 epilepsy controls patients and 11 healthy controls we applied paired-pulse transcranial magnetic stimulation (TMS) protocols to evaluate the Excitation Index, a biomarker reflecting the contribution of inhibitory and facilitatory circuits in M1. Intermittent TMS-theta burst stimulation was used to probe Long-Term-Potential (LTP)-like plasticity in M1. Motor impairment, assessed by ad hoc clinical scales, was correlated with neurophysiological metrics.



Schematic overview of experiment.

Results: RTT patients displayed a significant increase of the Excitation Index ($p=0.003$), as demonstrated by the reduction of short-interval intracortical inhibition and increase of intra-cortical facilitation, suggesting a shift toward cortical excitation likely due to GABAergic dysfunction. GABAergic impairment was also confirmed by the reduction of long-interval cortical inhibition ($p=0.002$). LTP-like plasticity in M1 was abolished ($p=0.008$) and scaled with motor disability (all $p=0.003$).



Loss of LTP-like plasticity in the primary motor cortex (M1) of RTT patients

Conclusion: TMS is a method that can be used to assess cortical motor function in RTT patients. Our findings support the introduction of TMS measures in clinical and research settings as biomarker to monitor the progression of motor deficit and response to treatment.

Disclosure: Nothing to disclose

O3006

Efficacy and safety of cenobamate as adjunctive therapy in patients with uncontrolled focal seizures: results from two double-blind, placebo-controlled, international studies

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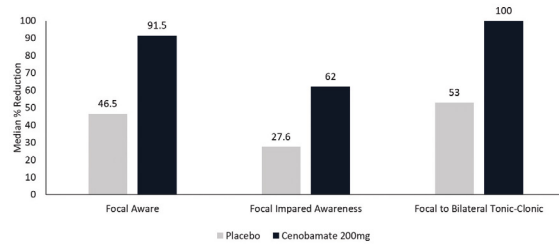
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Background and aims: Cenobamate is a novel antiepileptic drug (AED) recently approved by the Food and Drug Administration. Here we report the safety/efficacy data from 2 international, double-blind, placebo-controlled trials (C013 and C017).

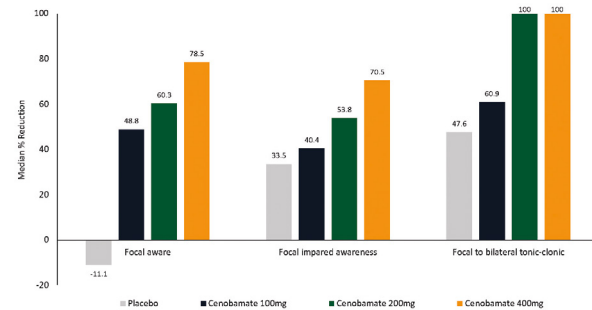
Methods: Adults with uncontrolled focal onset seizures (FOS) with ≥ 3 seizures/month (C013) or ≥ 8 seizures/8 weeks (C017) and treatment with 1-3 concomitant AEDs were enrolled. Patients were randomized to placebo or cenobamate 200mg/day (C013) or placebo vs 100, 200, or 400mg/day cenobamate (C017).

Results: In C013, the responder rate ($\geq 50\%$ reduction in seizure frequency from baseline) in the maintenance phase was significantly greater for cenobamate 200mg vs placebo (62% vs 33%); significantly greater percentages achieved seizure freedom (28% vs placebo 9%). In the C017, $\geq 50\%$ responder rate during maintenance was significantly higher for cenobamate 100, 200, 400mg (40%, 56%, 64%), respectively vs those treated with placebo (26%); significantly greater percentages of patients receiving 200 and 400mg achieved seizure freedom (11% and 21%, respectively vs placebo 1%); In both studies, cenobamate showed a significant reduction across all subtypes of FOS (fig.1, fig.2). Cenobamate was generally well tolerated. Most TEAEs reported in the pivotal studies were mild or moderate in intensity and increased with the dose. The most frequently occurring AEs ($\geq 10\%$) with cenobamate were dizziness, somnolence, headache, fatigue and diplopia.

Conclusion: Consistent, clinically meaningful, and statistically significant response rates ($\geq 50\%$, $\geq 75\%$, $\geq 90\%$, 100%) were observed across the studies.



Percent Reduction in Seizure Frequency by Seizure Type in the maintenance phase (C013 study)



Percent Reduction in Seizure Frequency by Seizure Type in the maintenance phase (C017 study)

Disclosure: Study 017 (NCT01866111) and 013 (NCT01397968) were sponsored by SK Life Science, Inc. and the analyses supported by Arvelle Therapeutics International GmbH.

O3007

Secular trends in adult epilepsy-related and potentially avoidable mortality in Scotland: a nationwide population-based study

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Background and aims: Premature death is common in epilepsy. We aimed to quantify, for the first time, the national burden of avoidable epilepsy-related deaths (EPRDs) in adults (aged ≥ 16 years) in Scotland.

Methods: This retrospective observational study used a sequential cross-sectional design to nationally identify adult EPRDs. We linked death certificates to administrative primary and secondary care datasets. ICD-10 codes (G40-41, R56.8), Read codes (F25.), and antiepileptic drugs (AED) were examined in the linked datasets to identify potential epilepsy patients, using medical records as a diagnostic reference standard to calculate positive predictive values (PPV). EPRDs were determined from death certificates (including post-mortem indicators) and medical records, estimating standardised mortality ratios (SMR) and mortality rates (MR). The Office for National Statistics' Revised Definition of Avoidable Mortality 2016 causes were used to identify potentially avoidable EPRDs.

Results: G40-41-coded causes of death had the highest PPV for epilepsy diagnosis (PPV 93%, 95%CI 89–96%). These codes captured 2,149 epilepsy-related deaths. 1,276 (59%) had ≥ 1 seizure-/epilepsy-related hospital admission during 2009–2016, yet only 516 (24%) were seen in neurology clinic during this period. Age-standardised MR per 100,000 ranged between 6.8 (95%CI 6.0–7.6) in 2009 and 9.1 (95%CI 8.2–9.9) in 2015. SMR was higher in young adults (≤ 55 years), peaking at 6.0 (95%CI 2.3–9.7) between ages 16–24 years. 78% of young adult EPRDs were potentially avoidable. The most common mechanisms of death were SUDEP, aspiration pneumonia, cardiac arrest, alcohol-related, and congenital malformation.

Conclusion: Avoidable epilepsy-related deaths remain common, particularly in young adults, and have not reduced over time despite advances in treatment.

Disclosure: This work was charitably supported by Epilepsy Research UK (R44007) and the Juliet Bergqvist Memorial Fund. The funders played no role in the design or conduct of this review and the authors declare no conflicts of interest.

O3008

Real-world prevalence of autoantibodies in epilepsy

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Background and aims: The prevalence of autoantibodies among people with epilepsy (PWE) is not clear, with widely varying rates of 5–80% reported. Existing studies demonstrate considerable differences regarding participant selection/ascertainment bias, numbers of antibodies tested for (and their clinical relevance), laboratory methods for antibody testing and result interpretation. By determining the prevalence of largely pathogenic antibodies among prospectively recruited outpatients with new-onset focal epilepsy (NOFE), drug-resistant epilepsy (DRE) and seizure-free epilepsy (SFE), we aim to provide a prevalence rate that is generalisable to the broader population of PWE.

Methods: Sera obtained from consecutive adult patients from epilepsy clinics (NOFE patients 2011–2015, DRE and SFE patients 2018–2020) and healthy controls (HC) were screened on live cell-based assays for neuronal-surface antibodies (NSAs) to LGI1, CASPR2, contactin-2, DPPX and the GABAA, GABAB, glycine and NMDA receptors. Radioimmunoprecipitation assays and in-house permeabilised CBAs detected GAD65 antibodies.

Results: Antibodies were detected in 24/232 (10.3%) NOFE, 22/260 (8.5%) DRE, 5/54 (9.3%) SFE and 0/55 HCs. NOFE patients had NSAs only, whereas DRE and SFE cohorts had NSAs and GAD65 antibodies (DRE: 11 NSA, 11 GAD65; SFE: 2 NSA, 3 GAD65).

Conclusion: Overall, 51/546 (9.3%) epilepsy outpatients had autoantibodies detected and the proportion of antibody-positive patients was similar across the three epilepsy groups. Future work should determine any pathophysiological role for antibodies in epilepsy and to explain the striking absence of GAD65 antibodies in NOFE.

Disclosure: Supported by Epilepsy Research UK and Oxford-UCB Alliance.

O3009

Hippocampal epileptogenesis in LGI1, CASPR2 and GABABR antibodies: preliminary findings

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Background and aims: Autoantibody-mediated forms of encephalitis (AE) include neurological disorders characterized by subacute memory loss, movement disorders and, often, frequent, focal epileptic seizures. Yet, the electrophysiological effects of these autoantibodies on neuronal function have received little attention. In this study, we assessed the effects of CSF-containing autoantibodies on intrinsic and extrinsic properties of hippocampal neurons, to define their epileptogenic potential
Methods: We compared the effects of CSF containing leucine-rich glioma inactivated 1 (LGI1), contactin associated protein-like 2 (CASPR2) or γ -aminobutyric acid receptor B (GABABR)-antibodies on ex vivo electrophysiological parameters after stereotactic hippocampal inoculation into mice. Whole-cell patch-clamp and extracellular recordings from CA1 pyramidal neurons and CA3-CA1 field recordings in ex vivo murine brain slices were used to study neuronal function.

Results: By comparison to control CSF, AE CSFs increased the probability of glutamate release from CA3 neurons. In addition, LGI1- and CASPR2-antibody containing CSFs induced epileptiform activity at a population level following Schaffer collateral stimulation. CASPR2-antibody containing CSF was also associated with higher spontaneous firing of CA1 pyramidal neurons. On the contrary, GABABR-antibody containing CSF did not elicit changes in intrinsic neuronal activity and field potentials.

Conclusion: Using patient CSF, we have demonstrated that the AE-associated antibodies against LGI1 and CASPR2 are able to increase hippocampal CA1 neuron excitability, facilitating epileptiform activity. These findings provide in vivo pathogenic insights into neuronal dysfunction in these conditions.

Disclosure: Nothing to disclose

Movement disorders 2

O3010

Longitudinal evolution of white matter damage in Parkinson's disease

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Background and aims: No strong MRI biomarkers were identified to define the Parkinson's Disease (PD) progression. We aimed to investigate the longitudinal evolution of cerebral white matter (WM) micro- and macrostructural damage and its relationship with clinical picture.

Methods: 154 PD patients underwent clinical assessment, cognitive evaluation and MRI scan (including T2-weighted and diffusion tensor [DT] MRI sequences) once a year over a follow-up of 36 months. White matter lesions (WML) were manually identified on T2-weighted scans and the total WML volume was calculated and excluded to define normal appearing white matter (NAWM). Applying tract-based spatial statistics, mean fractional anisotropy (FA), mean (MD), axial (axD) and radial (radD) diffusivity values of the total WM and NAWM skeleton were extracted. Regression models and Pearson's correlation between MRI and clinical/cognitive data were performed.

Results: UPDRS-III score ($p < 0.001$) and WML volume ($p < 0.001$) showed significant progression over follow-up. DTI metrics differed significantly between total and NAWM ($p \leq 0.001$). Longitudinal differences of MD, axD, and radD values significantly correlated with UPDRS-III (r ranging 0.24/0.37, p ranging 0.01/0.04) and Addenbrooke Cognitive Examination total score (r ranging -0.27/-0.29, p ranging 0.01/0.02). WML volume did not correlate with longitudinal alterations of clinical variables. Regression analyses showed a significant interaction between axial diffusivity and MMSE and UPDRSIII score both in total WM and in NAWM.

Conclusion: Our study showed that longitudinal evolution of WM microstructural damage is associated with both motor and global cognitive deterioration in PD and it might provide a sensitive biomarker of disease progression.

Disclosure: Ministry of Education and Science Republic of Serbia (Grant #175090).

O3011

First results for the BeyoND study: A phase 2b, international, open-label study evaluating long-term safety of ND0612 in patients with Parkinson's disease experiencing motor complications

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Background and aims: The primary objective of this phase 2b study was to evaluate the long-term safety and tolerability of a 24-hour regimen and a 16-hour 'waking day' regimen of ND0612. ND0612 is a drug-device combination delivering liquid levodopa/carbidopa via continuous subcutaneous (SC) infusion to reduce motor complications in patients with Parkinson's disease (PD).

Methods: This open-label safety study (NCT02726386) was conducted in PD patients (aged >30 y, H&Y ≤ 3 during ON) taking ≥ 4 levodopa doses/day and ≥ 1 other PD medications, and experiencing ≥ 2 hours of OFF time/day with predictable early-morning OFF periods. Patients were assigned to receive ND0612 for a regimen of either 16-hours/day or 24-hours/day.

Results: 214 patients were enrolled (24-hour regimen: $n=90$; 16-hour regimen: $n=124$) at 46 sites in 8 countries. Over the course of the 1-year treatment period, 66% of patients experienced treatment-related TEAE's with 5.6% of subjects experiencing serious treatment-related TEAE's. Systemic safety is typical for PD patients treated with LD/CD. The most frequent AEs were typical for a continuous subcutaneous mode of drug administration and included infusion-site nodules (30.8%), infusion-site hematoma (25.2%), and infusion-site pain (13.1%). Overall, 17.8% patients discontinued due to AEs.

Conclusion: ND0612 infusion was found to be safe with generally mild to moderate local AEs which were reversible and manageable and no unexpected TEAEs for systemic levodopa treatment. Long-term data will continue to be collected in patients enrolled in the study extension, some of whom are now in their fourth year of ND0612 treatment.

Disclosure: This study was sponsored by NeuroDerm.

O3012

Sensory and autonomic assessment in the differential diagnosis of early parkinsonism

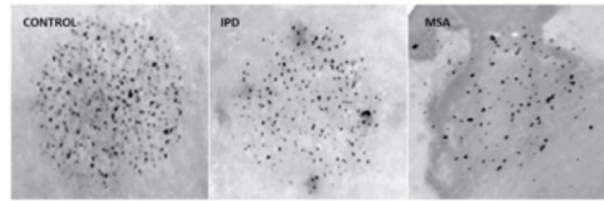
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Background and aims: Parkinsonism such as Parkinson's disease (PD) and multiple system atrophy (MSA) affects 2% of people over 65 years with increased worldwide burden on health system. Diagnosis at early stage of the disease is still challenging in some patients due to the lack of early diagnostic biomarkers. The latter has an implication on effective therapies and to recommend adequate strategies to avoid disease-specific complications.

Aims: To develop biomarkers aiming at improving early diagnosis

Methods: 87 patients with early diagnosis (within 2 years from symptoms onset) of PD or MSA-P (parkinsonian type) (age 62.5±8.7 years; M/F=52/35) and not started on L-dopa treatment, were recruited. Patients underwent a comprehensive functional sensory and autonomic assessment including quantitative sensory testing (QST), the assessment of cardiovascular reflexes (CVR) and sudomotor function (through the dynamic sweat test - DST) and specific questionnaire for sensory and autonomic symptoms at first visit and at 12 months follow up. Patients were recruited from 2 centres (University College London Queen Square, UK and Neurology Division, ICS Maugeri, IRCCS of Telesse Terme, Italy)

Results: Autonomic symptoms scores were greater in MSA compared with IPD patients. In particular, gastrointestinal and genitourinary domains were the ones which better discriminated between the 2 conditions. Also, MSA patients showed a lower density of active sweat glands at distal leg (figure) and a reduced adrenergic cardiovascular response to isometric exercise compared to IPD.



The density of sweat glands activated after pilocarpine by iontophoresis is reduced in patients with parkinsonism compared to controls. In MSA the sweat gland density is significantly lower compared to IPD patients.

Conclusion: Our data support the hypothesis that the functional assessment of sensory and autonomic systems are potential early biomarkers to differentiate MSA versus IPD.

Disclosure: Nothing to disclose

O3013

Disconnected brain in functional movement disorders with anxious & depressive symptoms

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Background and aims: Depression and/or anxiety (DEP/ANX) are common symptoms in functional movement disorders (FMD). However, their neural correlates have not been elucidated.

Methods: Using resting state functional MRI (3T, Siemens, Skyra), we investigated 43 FMD patients (33F, age 45±(SD)9 years, disease duration 8.4±5.6 years) and 44 matched healthy controls (HC). The DEP and ANX symptoms were scored by the Beck depression inventory (BDI-II) and State Trait Anxiety Inventory (STAI). To explore differences in general and selective functional connectivity among FMD-H (n=23; BDI>16, STAI-X2>45), FMD-L (n=17, BDI<16, STAI-X2<45) and HC groups, we used eigenvector centrality (EC) mapping and seed-based connectivity analysis using regions with maximum EC as seeds.

Results: In comparison with the HC group, the FMD-L showed a decrease of general connectivity (EC) in the midcingulate cortex (MCC) (Fig. 1A), while the FMD-H was associated with decreased EC in the inferior occipital gyrus (IOG) (Fig. 1D). Analyzing selective connectivity, the FMD-L<HC comparison revealed decreased connectivity only between the MCC and the motor cortex (Fig. 1B). In contrast, using the FMD-H<HC and FMD-H<FMD-L comparisons, we found that both the MCC and IOG seeds showed decreased connectivity with several cortical and subcortical areas including the frontal, temporal, parietal and occipital cortices, as well the thalamus, the basal ganglia and the cerebellum (Fig. 1C, F-G).

Conclusion: In conclusion, we observed that the brain disconnection pattern differed between the FMD subjects with and without depression and/or anxiety, indicating that these symptoms are in FMD associated with wider disruption of motor and non-motor networks. Supported by the grant AZV 16-29651A.

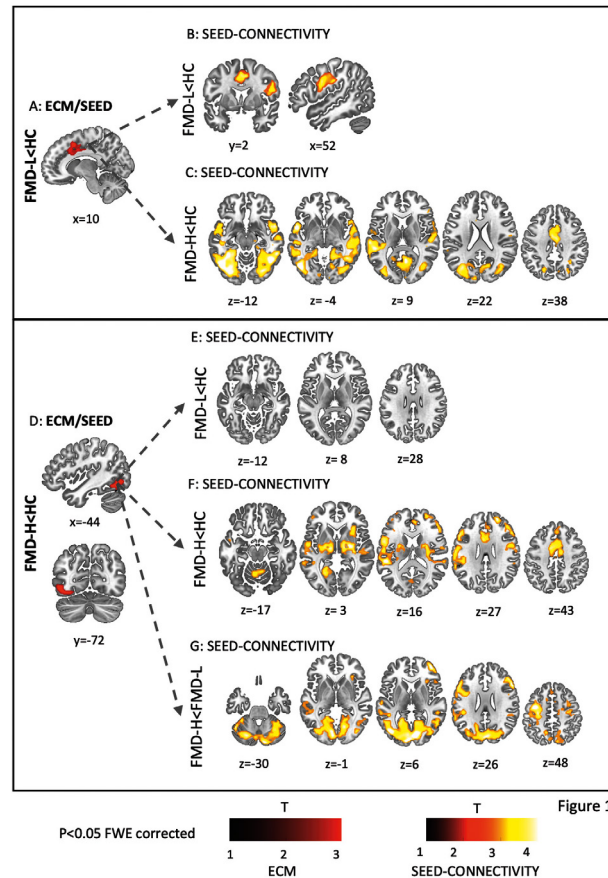


Figure 1

Disclosure: Nothing to disclose

O3014

Directional deep brain stimulation in subthalamic nucleus for Parkinson's disease: results of a multicenter, prospective, blinded, crossover study

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Background and aims: Published reports on directional DBS have been limited to small series from single-center investigations. PROGRESS assessed the safety and clinical efficacy of directional DBS in a large prospective cohort.

Methods: Patients receiving subthalamic nucleus DBS for Parkinson's disease were programmed with omnidirectional stimulation for 3 months, followed by directional stimulation for another 3 months. The primary endpoint was blinded, randomized, off-medication evaluation of TW for directional vs. omnidirectional stimulation at 3 months. Additional endpoints at 3-, 6- and 12-month follow-ups included adverse events, therapeutic current strength (TCS), UPDRS part III motor score, subject and clinician stimulation preference, activity of daily living and quality of life.

Results: A directional DBS system was implanted in 234 subjects. No intracranial hemorrhages or infections occurred. At 3 months, TW was wider using directional stimulation in 90.6% of subjects, satisfying the primary endpoint for superiority. The mean increase in TW with directional stimulation was 41% (2.98±1.38mA, compared to 2.11±1.33mA for omnidirectional). The TCS was decreased by 39% with directional programming. After 6 months, 53% of subjects blinded to stimulation type (102/193) preferred the period with directional stimulation, 26% (50/193) preferred the omnidirectional period and 21% (41/193) had no preference. Additional results including 12-month data will be available.

Conclusion: In this international prospective blinded

crossover study, directional stimulation yielded a wider TW and a lower TCS compared to omnidirectional stimulation and was preferred by subjects blinded to stimulation type.

Disclosure: This study was funded by Abbott

O3015

[18F]FDG-PET imaging of supraspinal locomotor control in Parkinson's disease

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Background and aims: Hypokinetic gait is a clinical hallmark of advanced Parkinson's disease (PD). The aim of this study was to investigate supraspinal locomotor control in PD using a [18F]FDG-PET-based real locomotion paradigm.

Methods: 20 patients with advanced PD and 25 age-matched healthy controls underwent a detailed neurological examination, falls assessment, and quantitative gait analysis (GAITRite®). Patients and controls performed a well-established locomotion PET paradigm, where they had to walk in a hallway for 10min after injection of [18F]FDG. PET scan started 30min p.i. The regional cerebral glucose metabolism (rCGM) was compared between groups and correlated with disease duration, severity and gait parameters using SPM8.

Results: PD patients had a reduced gait velocity, step length and pathological slowing with cognitive dual task compared to controls. Decrease of gait velocity strongly correlated with the Hoehn and Yahr stage and disease duration. [18F]FDG-PET during locomotion revealed a relatively reduced rCGM in the parietal cortex, caudate nucleus and pontomesencephalic brainstem tegmentum and a higher rCGM in the globus pallidus and primary motor cortex in PD ($p < 0.001$). rCGM decrease in the caudate nucleus and rCGM increase in the globus pallidus correlated with a reduced locomotion velocity and longer disease duration. rCGM decrease in the thalamus was associated with a history of falls.

Conclusion: PD patients show characteristic changes in their supraspinal locomotor network. A reduced input to the basal ganglia (via the caudate nucleus) and disinhibition of the direct basal ganglia loop (via the globus pallidus) correlates with hypokinetic gait features. Postural instability is associated with thalamic pathology.

Disclosure: Nothing to disclose

O3016

The epidemiology of progressive supranuclear palsy in the United Kingdom: evidence from the Clinical Practice Research Datalink GP Online Database (CPRD GOLD)

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Background and aims: PSP is a neurodegenerative disorder with a prevalence of ~6/100,000 in the United Kingdom (UK). Prior UK epidemiologic studies have been small in-depth population samples. The study objectives were to estimate the diagnosed prevalence and incidence of PSP in the UK, using a large population base, and to describe PSP patient characteristics.

Methods: PSP cases and age and sex-matched controls were identified 1987-2018 from CPRD GOLD, a national electronic medical record database of ~1.3M patients. PSP was defined as 1 or more codes for PSP and index date (date of first PSP code) age 40 or older. Prevalence and incidence of PSP were age-adjusted to the UK Census Population. Comorbidities and medications were examined in cases and controls.

Results: Among 704 PSP cases, 55.7% were male and mean age at index date was 73.2 years. Crude and age-adjusted prevalence in 2018 was 4.25 and 4.35/100,000. Crude and age-adjusted incidence in 2018 was 0.96 and 0.97/100,000/year. In PSP cases, the most common recorded comorbidities were central nervous system disorders (97.6%), rheumatism (61.2%), acute respiratory infections (58.9%) and hereditary and degenerative diseases of the central nervous system (54.4%). Major comorbidities related to PSP, such as accidental falls, intracranial injury, and fractures were significantly more frequent in cases than controls. Before index date, 31.1% of PSP cases had a Parkinson's disease diagnosis.

Conclusion: We show that epidemiological studies of PSP can be carried out using a large primary care database. Prevalence, incidence, and patient characteristics in this study are comparable to smaller in-depth patient/record review studies.

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Neurogenetics

O3017

Biodistribution and expression of onasemnogene abeparvovec (AVXS-101) DNA, mRNA, and SMN protein in human tissue

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Background and aims: AVXS-101 is a gene replacement therapy for patients with spinal muscular atrophy type 1 (SMA1) resulting from survival motor neuron 1 (SMN1) deletion/mutation. This study examined the biodistribution and expression of AVXS-101 in human tissues after a single intravenous administration.

Methods: Biodistribution of vector genome, vector mRNA, and SMN protein in the central nervous system (CNS) and peripheral tissues was characterised in 2 infants with SMA1 treated with AVXS-101 in phase 3 studies. Spinal motor neurons were isolated using laser-capture microdissection and vector genome quantified. Both patients died from respiratory illness at 5 weeks and 6 months post-gene therapy. The latter patient demonstrated substantial motor function improvement.

Results: AVXS-101 DNA and mRNA distribution was widespread among peripheral organs, muscles, and all regions of the spinal cord. AVXS-101 vector genomes ranged between 1.5 and 2.7 per diploid genome across spinal segments from both patients. SMN protein expression in motor neurons was detected in all regions of the spinal cord at levels similar to tissue from non-SMA1 controls. Analysis of the motor neuron marker choline acetyltransferase identified motor neurons with morphology similar to non-SMA1 control motor neurons. Expression of SMN protein was detected in cortical and subcortical regions of the motor cortex, medulla, and peripheral tissues, including skeletal muscle.

Conclusion: AVXS-101 traverses the blood–brain barrier following systemic administration with substantial transduction. Expression of SMN protein was detected in the CNS, including motor neurons. AVXS-101 is suited for treating SMA1 by targeting motor neurons and restoring SMN expression in key cellular targets in humans.

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O3018

Spinal cord MRI for early detection of presymptomatic pathology in C9orf72 mutation carriers: a three time-points longitudinal MRI study

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Background and aims: Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal dementia (FTD) are neurodegenerative conditions with a large portion of familial cases due to c9orf72 gene mutations. Brain imaging studies in asymptomatic carriers demonstrated early white (WM) and grey matter (GM) degeneration.

Aim of this study was to investigate whether longitudinal cervical spinal cord (SC) degeneration can be detected in asymptomatic c9orf72 hexanucleotide carriers using multimodal quantitative imaging.

Methods: 72 asymptomatic individuals were enrolled in a prospective study of first-degree relatives of ALS and FTD patients carrying the c9orf72 mutation. 40 (C9+) were carriers. Each subject underwent a 3T cervical SC MRI. Quantitative measures of GM and WM atrophy and DTI parameters were evaluated at baseline, after 18 and 36 months.

Results: At baseline, significant WM atrophy was detected in C9+ subjects older than 40 years of age (p-value<0.05) without associated changes in GM and DTI parameters. At 18 and 36-month follow-up, WM atrophy in C9+ subjects older than 40 years was accompanied by significant progressive corticospinal tract fractional anisotropy (FA) reduction (p-value=0.031). Intriguingly, C9+ subjects with a family history of ALS exhibited significant CST FA reduction already on their baseline scans.

Conclusion: Cervical SC imaging is able to detect WM atrophy in C9+ subjects older than 40. While WM atrophy remains stable over time, progressive pyramidal tract FA reduction can be detected on follow-up acquisitions. SC MRI in c9orf72 related conditions is a powerful tool to characterise presymptomatic pathological changes and to predict phenotypic conversion to ALS versus FTD.

Disclosure: This study was supported by the Assistance Publique – Hôpitaux de Paris, the ANR (Agence nationale

de la recherche), the Centre d'Investigation Clinique, and the Centre pour l'Acquisition et le Traitement des Images (CATI), Paris, France.

O3019

Extraneurological features in Kennedy's disease: data from the Italian SBMA registry

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Background and aims: Spino-Bulbar Muscular Atrophy (SBMA, Kennedy's disease), is a rare, neurodegenerative, X-linked hereditary neuromuscular disease due to a CAG trinucleotide repeat expansion in the androgen receptor gene. Main neurological manifestations are weakness, atrophy and fasciculations of limb and bulbar muscles. A non-neurological involvement is typical and early, and contributes significantly to quality of life deterioration.

Methods: In a cohort of male patient from the Italian SBMA Registry we assessed non-neurological manifestations by collecting: minimal dataset of clinical information; standard and modified ECG for Brugada-like pattern; questionnaires to evaluate sexual function (International Index of Erectile Function, IIEF), urinary dysfunction (International Prostate Symptoms Scale, IPSS), and laboratory tests.

Results: Patients: n:117; mean age: 61.3±11.2 years, range 31-83; CAG repeats: mean 45.2±3.2, range: 39-57; 101 patients had gynecomastia (92 bilateral, 8 unilateral); 25 diabetes or glucose intolerance; 42 hypertension; only 2 had abnormal ECG with Brugada-like pattern; IPSS mean: 6.94±7, range 0-35; IIEF mean: 15.1±10, range: 0-30. Laboratory test: HbA1c (mmol/mol) mean: 36.4±7.3, range: 26-80 (abnormal 10.6%); total cholesterol (mg/dl) mean: 206.16±33.6 range: 124-305 (abnormal 49.5%); SGOT(U/L) mean: 44.34±18.6, range: 17-121 (abnormal 59%); SGPT(U/L): mean: 49.53±22.8, range: 16-126 (abnormal 57.5%); vitamin D (ng/ml): 20.42±11.7, range: 3.2-60.7 (abnormal: 84%); CK(U/L): mean 954.2±689, range: 53-2997.

Conclusion: SBMA is a multisystem disease: beyond motor neurons and muscle there is evidence of frequent metabolic syndrome and liver dysfunction, while the Brugada-like pattern is very rare and clinically non-relevant.

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O3020

Lifetime risk of autosomal recessive mitochondrial disorders calculated from genetic databases

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Background and aims: Mitochondrial disorders are a group of rare diseases, caused by nuclear or mitochondrial DNA mutations. Their marked heterogeneity as well as referral and ascertainment biases render phenotype-based prevalence estimations difficult. We calculated the lifetime risk of all autosomal recessive mitochondrial disorders on basis of genetic data.

Methods: We queried the Genome Aggregation Database (gnomAD) and our in-house exome database for the allele frequency of disease-causing variants in genes associated with recessive mitochondrial disorders. Based on this, we estimated the lifetime risk of 249 mitochondrial disorders. Phenylketonuria served as proof of concept since calculations could be aligned with known birth prevalence data from newborn screening.

Results: The estimated lifetime risk for phenylketonuria (16.0/100,000) correlates well with known birth prevalence data (18.7/100,000), supporting the validity of the approach. The combined estimated lifetime risk of 249 investigated mitochondrial disorders is 31.8 (20.9-50.6)/100,000 in our in-house database, 48.4 (40.3-58.5)/100,000 in the European gnomAD dataset, and 31.1 (26.7-36.3)/100,000 in the global gnomAD dataset. The disorders with the highest lifetime risk (>3/100,000) were, in all datasets, those caused by mutations in the SPG7, ACADM, POLG and SLC22A5 genes.

Conclusion: We provide a population-genetic estimation on the lifetime risk of an entire class of monogenic disorders. Our findings reveal the substantial cumulative prevalence of autosomal recessive mitochondrial disorders, far above previous estimates. These data will be very important for assigning diagnostic a priori probabilities, and for resource allocation in therapy development, public health management and biomedical research.

Disclosure: This work was facilitated by the German Federal Ministry of Education and Research (BMBF, Bonn, Germany) through a grant to the German Network for Mitochondrial Disorders (mitoNET, 01GM1906A to TK and a grant for the E-Rare project GENOMIT (01GM1603 and 01GM1207 to HP and TK).

O3021

The genetic landscape for isolated not-OPA1 autosomal dominant optic atrophy

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Background and aims: Autosomal dominant optic atrophy (DOA) includes a heterogeneous group of inherited diseases in most of the cases due to mitochondrial dysfunction. Besides OPA1 gene, which is responsible of the large majority of DOA, other rare genes are reported in association with DOA.

We aimed at evaluating the presence of mutations in genes other than OPA1 in an Italian cohort of sporadic or familial cases with isolated OA.

Methods: Next generation sequencing (NGS) approaches were used for identifying causative genes in a cohort of 185 Italian cases negative for OPA1 mutations.

Results: Heterozygous mutations with confirmatory in-silico analysis for pathogenicity were identified in ACO2 gene in 12 families, AFG3L2 in 5 families, WFS1 in 4 families, SDHA in 2 families, SSBP1 in 2 families, SPG7 in 2 families and OPA3, DNMI1 and YME1L1 in single cases.

Conclusion: These results highlight the genetic heterogeneity of DOA including SSBP1, ACO2, AFG3L2, SPG7, WFS1, DNMI1, SDHA, OPA3 and YME1L1 as genes responsible for isolated OA. Dominant mutations in SSBP1 gene were already reported in association with nephropathy and retinopathy. Only recessive mutations in ACO2, YME1L1 have been reported in syndromic or isolated OA. AFG3L2, DNMI1 and OPA3 mutations have been already reported in association with isolated or syndromic DOA. WFS1 dominant mutation have been described in association with OA and deafness. Remarkably, the same phenotypic expression can be due to different pathogenic mechanisms including mtDNA maintenance (SSBP1), mitochondrial dynamics (DNMI1 and OPA3), proteolytic control (AFG3L2, SPG7 and YME1L1) and metabolic enzymatic activities (SDHA and ACO2).

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O3022

The MYO-SEQ: beyond the exome. A genotype-phenotype correlation of unsolved LGMD individuals

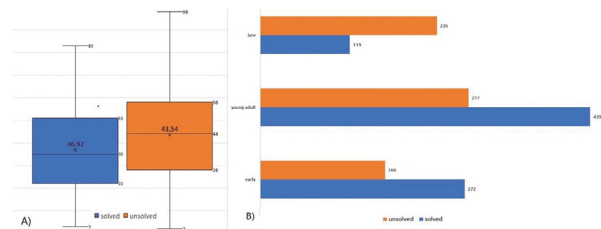
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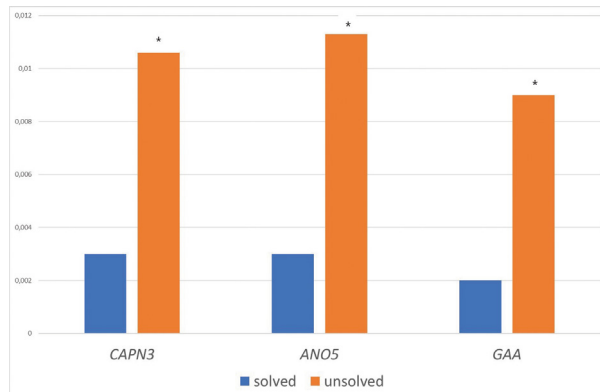
Background and aims: Limb girdle muscular dystrophies (LGMDs) are heterogeneous group of neuromuscular disorders. With whole exome sequencing (WES) diagnostic yield of approximately 25-50% can be reached. Most of the exome sequenced studies concentrate on solved cases analysis. We perform genetic and demographic studies on unsolved LGMD individuals from a large exome sequencing project (the MYO-SEQ).

Methods: We analyzed WES data from 1891 individuals with LGMD. Ethical approval was granted by the NRES Committee North East (reference 08/H0906/28). WES was performed at the Broad Institute of MIT and Harvard's Genomics Platform. Phenotype data collection was performed using the PhenoTips online platform.

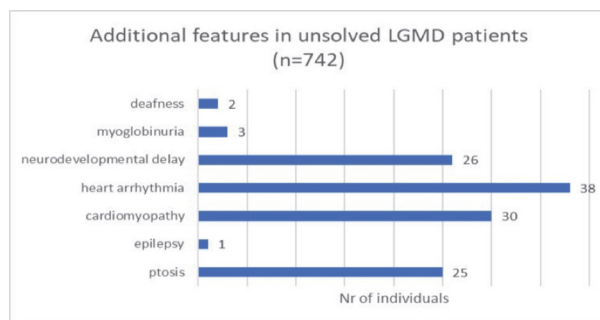
Results: In the MYO-SEQ we reached a diagnostic yield of 52%. The mean age in the unsolved cohort was 43,5 vs. 36,91 yrs in solved (t-test p<0,005). In the unsolved cohort late onset patients represented 36% and early onset 26% of total unsolved vs. 14% and 32% in the solved cohort respectively. Pathogenic variants carrier frequency (solved:unsolved) was for CAPN3 0,003:0,0106; ANO5 0,003:0,0113 and GAA 0,002:0,009. We analyzed WES data for patients sharing a common additional feature (e.g. cardiomyopathy, epilepsy) and identified genetic modifiers (e.g. RYR2 for heart arrhythmia).



A) Age in yrs solved vs. unsolved B) Age structure solved vs. unsolved



Pathogenic single carrier frequency for CAPN3, ANO5 and GAA in solved and unsolved cohort ($p < 0.005$)



Additional features in individuals with unsolved LGMD

Conclusion: Prevalence of late onset LGMD in the unsolved cohort may suggest acquired diseases or polygenic inheritance. Higher pathogenic carrier frequency in unsolved cohort may imply presence of a second deep intronic causative variants. Analysing WES data of individuals sharing an additional feature can identify novel genes or genetic modifiers.

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O3023

Compound heterozygous mutations in ATP10B increase Parkinson's disease risk by compromising lysosomal glucosylceramide export

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Background and aims: Parkinson's disease (PD) causal genes and risk factors provided valuable insights into underlying disease mechanisms and delivered new therapeutic targets.

Methods: We performed whole exome sequencing in 52 unrelated early-onset PD (EOPD) patients (age at onset (AAO) ≤ 50 years) to identify novel genes for PD; targeted resequencing in 617 PD patients (mean AAO 60.0 ± 11.5 years), 226 dementia with Lewy bodies (DLB) patients (mean AAO 70.8 ± 9.8 years) and 597 control individuals (mean age at inclusion (AAI) 70.4 ± 8.0 years); qPCR on mRNA isolated from human brain; and functional assays in in vitro and cellular models.

Results: In 3 EOPD patients with unaffected parents, we identified trans compound heterozygous mutations in ATP10B, compatible with recessive inheritance. Targeted resequencing of ATP10B revealed 3 additional sporadic PD and 1 DLB patient carriers of compound heterozygous mutations. ATP10B mRNA is enriched in the substantia nigra and medulla oblongata, and significantly decreased in patients versus control individuals in these brain regions. We established that ATP10B encodes a late endo-/lysosomal lipid flippase responsible for the export of glucosylceramide and phosphatidylcholine. Mutant ATP10B is catalytically inactive and loss of ATP10B in mouse cortical neurons leads to lysosomal dysfunction and cell death.

Conclusion: We identified recessive loss-of-function mutations in ATP10B increasing risk for PD. Both ATP10B and the PD/DLB risk factor GBA play essential roles in the fate of lysosomal glucosylceramide, and dysfunction of both results in intra-lysosomal accumulation of glucosylceramide.

Disclosure: Nothing to disclose

Neuroimmunology

O3024

Comparison of clinical characterization, risk of relapses and antibody dynamics between children and adults with MOGAD

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Background and aims: Predict the clinical course of myelin oligodendrocyte glycoprotein (MOG)-antibody (Ab)-associated disease (MOGAD) is essential to guide treatment recommendations. We aimed to 1) compare clinical features and disease course, and 2) to evaluate the association of MOG-Ab dynamics and relapses, between children and adults with MOGAD.

Methods: Retrospective study evaluating clinical features of 98 children and 266 adults with MOGAD, between January 2014 and September 2019. To analyse relapses over the whole disease course, Cox regression analysis for recurrent time-to-event data was performed, introducing treatment as time-dependent covariate. To evaluate dynamics, MOG-Ab-delta mean fluorescence intensity ratio signal (MOG-Ab- Δ MFIRatio) was measured in patients with a minimum time elapsed between two samples of 4 months.

Results: Median age at onset of symptoms was 10.9 (interquartile range 5.4-14.3) years in children and 36.2 (27.7-47.6) in adults. Isolated optic neuritis was the most frequent clinical presentation both in children (43.9%) and adults (56.8%). Compared to adults, ADEM-like was more frequent in children (36.7% vs. 5.6%), $p < 0.001$. In multivariate analysis, adults were at higher risk of relapse than children (HR 1.35 CI95%, 1.08-1.67). Among the 124 participants evaluated for MOG-Ab dynamics, 36.3% became seronegative, 60.5% decrease and 3.2% increase the Δ MFIRatio. Relapses occurred in 45/79 patients who

remained persistently seropositive compared to 17/45 who became negative, $p = 0.040$. MOG-Ab- Δ MFIRatio dynamics was similar between age-groups and clinical presentation.

Conclusion: Adults have a higher risk of relapse than children. Although persistent MOG-Ab-positivity is associated with relapses at population level, MOG-Ab dynamics are not useful to predict disease course at individual level.

Disclosure: Nothing to disclose

O3025

Immunological mechanisms for the efficacy of Rituximab in aquaporin-4 autoantibody mediated Neuromyelitis Optica spectrum disorders

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Background and aims: Neuromyelitis Optica Spectrum Disorders (NMOSD) are caused by autoantibodies targeting the astrocyte-expressed water-channel aquaporin-4 (AQP4). Rituximab (RTX), a monoclonal antibody against CD20 expressed on B-cells, is clinically effective despite not reducing overall AQP4-antibody levels. This clinical-serological discrepancy is often attributed to the incomplete depletion of CD20+ B-cells in lymph-nodes. We aimed to investigate the efficacy of RTX on lymph-node resident B-cells with particular reference to AQP4-specific B-cells.

Methods: Cervical lymph-nodes were harvested using ultrasound-guided fine-needle aspirations from NMOSD patients who were RTX-untreated (n=5) or RTX-treated (n=9, including 4 after only 1 RTX infusion). Matched peripheral blood mononuclear cells (PBMCs) were processed in parallel. From 3 patients with detectable lymph-node resident B-cells, CD19+CD3-cells were single-sorted and cultured for 26 days under proliferative conditions with supernatants tested by live cell-based assays for AQP4-antibody reactivity.

Results: We confirmed a significant reduction in the annual relapse rate (ARR) after RTX (p<0.001). Without RTX-treatment, CD19+cells were observed at frequencies of 10% in lymph-nodes, and 5% in PBMCs. Lymph-node aspirates and PBMCs showed AQP4-specific B-cells at frequencies of 0.09% and 0.07%, respectively. CD19+ B-cells in circulation and lymph-node resident B-cells were fully depleted after >1 dose of RTX (p=0.0004).

Conclusion: RTX depletes lymph-node resident B-cells as efficiently as circulating B-cells, suggesting that lymph-nodes do not constitute a RTX-resistant environment in humans. As lymph-nodes contain AQP4-specific B-cells, this depletion may be a mechanism by which RTX shows clinical efficacy without reducing AQP4-antibody levels.

Disclosure: Nothing to disclose

O3026

Cell-based assays for the detection of myelin oligodendrocyte glycoprotein antibodies: a single centre comparative study

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Background and aims: Antibodies against myelin-oligodendrocyte glycoprotein (MOG-Abs) characterize the so-called MOG-Ab-associated disease (MOGAD), in differential diagnosis of multiple sclerosis (MS). Standardization of the cell-based assays (CBAs) for MOG-Ab detection is under progress. Such assays include: a) live-CBA for total IgG with anti-heavy-and-light chain secondary-Ab (LCBA-IgGH+L); b) live-CBA for total IgG with anti-Fc secondary-Ab (LCBA-IgGFc); c) live-CBA for IgG1 (LCBA-IgG1); d) commercial fixed-CBA with anti-Fc secondary-Ab (FCBA-IgGFc). We aimed to define the best strategy for MOG-Ab detection.

Methods: 1557 consecutive sera from patients with demyelinating CNS syndromes were tested by LCBA-IgGH+L. Positive samples (265) were titred and screened by LCBA-IgG1. Seventy-one/265 were also tested with LCBA-IgGFc and FCBA-IgGFc. Patients were classified as “possible MOGAD”, “MS”, or “other neurological disorder” based clinical information, independently of MOG-Ab results.

Results: 204/1557 patients were included. 57/204 samples were MOG-Ab-positive. Sensitivity was 89.1% (confidence interval, CI:77.8-95.9) and specificity 93.3% (CI:88.0-96.7) for LCBA-IgGH+L, and 74.6% (CI:61.0-85.3) and 100% (CI:97.6-100) for LCBA-IgG1. 18/57 samples showed discrepant results, all negative on LCBA-IgG1: 10/18 were low-titre positive for total IgG in non-MOGAD patients, whereas 3/18 medium/high-titre positive, harboring IgG2 subclass, and belonging to the “possible MOGAD” group. In the subgroup analysis, sensitivity was 92.3% (CI:79.1-98.4) and specificity 96.9% (CI:83.8-99.9) for LCBA-IgGFc, and 87.2% (CI:72.6-95.7) and 97.0% (CI:83.8-99.9) for FCBA-IgGFc.

Conclusion: LCBA-IgG1 performed best with regard to specificity. However, MOGAD patients might harbor non-IgG1 high titre MOG-Abs, whose significance warrants further investigations. LCBA-IgGFc yielded the highest accuracy. FCBA-Fc has good specificity, but is at risk of false negative results.

Disclosure: Nothing to disclose

O3027

AMPA autoimmunity: neurological, oncological and serological accompaniments

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Background and aims: Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) autoimmunity is a rare, often paraneoplastic, disorder typically manifesting with encephalitis.

Methods: We retrospectively identified AMPAR-IgG-positive patients (serum and/or cerebrospinal fluid) from the Mayo Clinic Neuroimmunology Laboratory (2004-2019). Clinical information was extracted from records (12) or provided by referring physicians (49).

Results: 61/101 patients (median age 53 years [range 15-81]; 64 female) had available information. Encephalopathy (75%) and seizures (30%) were the most common manifestations. Twelve patients (20%) had - myasthenia gravis and thymoma with AChR (muscle-acetylcholine-receptor) antibodies ; five of them lacked encephalopathy and/or seizures. Brain imaging (9 available) was normal (3) or had T2-hyperintensities (temporal [3], extratemporal [2], both [1]). Neoplasia was detected in 39/61 (64%) patients (46% after symptom onset). The most frequent tumors were thymoma (23, 91% co-existing neural antibodies), small-cell lung carcinoma (3), breast carcinoma (3) and ovarian teratoma (3, 2 co-existing NMDAR [N-methyl-D-aspartate receptor] antibodies). Coexisting neural autoantibodies were detected in 42/61 patients (69%). The most common specificities were muscle AChR, 24; CRMP5 (Collapsin-response-mediator protein-5), 10; voltage-gated calcium channels, 9; striational (titer>7680) 6; NMDAR, 6; and GABABR (γ -aminobutyric acid receptor-B), 5. Other antibody-specificities included: LGI1 (leucine-rich, glioma-inactivated-1 protein), Caspr2 (contactin-associated protein-2), GAD65 (glutamic acid decarboxylase 65-kilodalton-isoform), ANNA1 (antineuronal-nuclear antibody-1), PCA (Purkinje-cell cytoplasmic antibody) 1 and 2.

Conclusion: Encephalopathy is the main manifestation of AMPAR autoimmunity, but some paraneoplastic cases lack CNS manifestations. Thymoma was the most common tumor. Accompanying neural autoantibodies are more frequent than previously reported and the autoantibody profile is a biomarker of the underlying neoplasia.

Disclosure: Nothing to disclose

O3028

Treatment and outcomes in patients with neurosarcoidosis

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Introduction: Neurosarcoidosis is associated with a high degree of morbidity and mortality and its treatments are varied and complex. There is a paucity of information in current literature on patterns of treatment and clinical outcomes in this condition and this is an area of significant unmet need. This study characterises treatment patterns and clinical outcomes in a large cohort of neurosarcoidosis patients.

Methods: We enrolled 85 patients with a diagnosis of neurosarcoidosis based on stringent diagnostic criteria. Prescription patterns were grouped according to first, second and third line regimes. Clinical outcomes before and after treatment were compared using statistical tests.

Results: The most common presentations were cranial neuropathy, pyramidal involvement and headache and the most common treatments were corticosteroids and azathioprine (26.25%), corticosteroids and methotrexate (17.5%), and corticosteroids alone (11.25%). Just over 85% of patients on corticosteroids went on to or started with second or third line treatment. Patients on corticosteroid monotherapy had the worst outcomes and those on a combination of corticosteroids, azathioprine and infliximab showed superior clinical improvements ($p=0.008$).

Conclusions: Patients with cranial mononeuropathy (41.25%) were more likely to be treated with corticosteroids alone than patients with brain parenchymal involvement, hydrocephalus and spinal cord presentations which were more likely to be treated with second and third line treatments. When corticosteroids were given in isolation, patients experienced less favourable outcomes than in all other treatment groups. Patients treated with combination treatments had the best overall outcomes in this study.

Disclosure: Nothing to disclose

Cognitive neurology/neuropsychology; ageing and dementia 2

O3029

Characterization of mixed primary progressive aphasia: language, functional neuroimaging and pathological features

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Background and aims: Current classification identifies three variants of Primary Progressive Aphasia (PPA): Progressive Non-Fluent Aphasia (nfvPPA), Semantic Dementia (svAPP) and Logopenic Aphasia (lvPPA). 10–41% of patients fulfill diagnostic criteria for more than 1 of the variants (mixed-PPA). We aimed to detail language profiles, neuroimaging characteristics and Alzheimer’s disease biomarkers prevalence of a cohort mixed-PPA (mPPA) compared with defined PPA variants.

Methods: We considered 10 nfvPPA, 16 svPPA, 21 lvPPA and 9 mPPA. mPPA subjects were further classified as 4 nf/lvPPA (showing overlapping linguistic features for nfvPPA and lvPPA) and 5 s/lvPPA (showing overlapping linguistic features for svPPA and lvPPA). All patients underwent language evaluation, 18F-FDG-PET brain scan, and Amyloid-PET (Amy-PET) scan or CSF biomarkers measurement. Patients were rated Aβ+ if at least 1 of Amy-PET, CSF Aβ1-42 or Aβ1-42/40 ratio revealed presence of Aβ positivity.

Results: 100% of nf/lvPPA and 40% of s/lvPPA were Aβ+. None of nf/lvPPA patients showed Speech Apraxia but 100% showed Naming impairment and Grammatical Errors. 100% of s/lvPPA patients were impaired in Naming, 80% in Phrases Repetition and 60% in Single-word Comprehension and in Phrases Comprehension (Tab1, Fig.1). SPM group analysis comparing nf/lvPPA to normal FDG-PET, revealed hypometabolism in left parietotemporal junction and superior temporal gyrus. S/lvPPA had significant hypometabolism in left lateral temporal lobe, temporal pole, medial frontal gyrus, orbitofrontal cortex and parahippocampal gyrus compared to normal subjects (Fig.2)

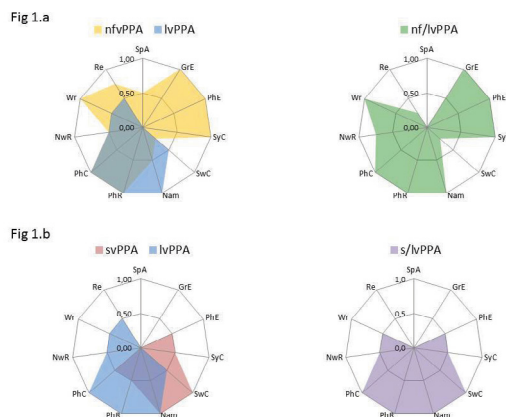


Fig.1. Language profile in each PPA group. SpA=Speech Apraxia; GeE=Grammatical Errors; PhE=Phonologic Errors/Neologism; SyC= Syntactic complexity; SwC=Single-word Comprehension; Nam= Naming; PhR=Phrases Repetition; PhC=Phrases Comprehension; NwR=Non-word Repetition; Wr=Writing; Re=Reading.

	nfvPPA	svPPA	lvPPA	nf/lvPPA	s/lvPPA
Speech Apraxia (SpA)	30%	0%	0%	0%	0%
Grammatical Errors (GeE)	60%	7%	9%	100%	20%
Phonologic Errors/Neologism (PhE)	70%	27%	22%	75%	40%
Syntactic Complexity (SyC)	80%	13%	30%	100%	40%
Single-word Comprehension (SwC)	10%	94%	23%	25%	60%
Naming (Nam)	40%	87%	91%	75%	100%
Phrases Repetition (PhR)	60%	33%	83%	100%	80%
Phrases Comprehension (PhC)	60%	33%	65%	75%	60%
Non-word Repetition (NwR)	30%	14%	10%	50%	40%
Writing (Wr)	60%	47%	48%	75%	40%
Reading (Read)	50%	27%	39%	25%	40%

Tab.1. Prevalence of impaired language domain impairment in each PPA group.

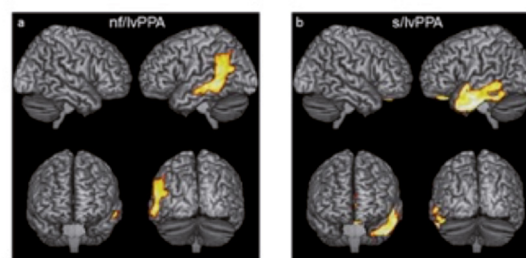


Fig. 2. SPM group analysis comparing nf/lvPPA and s/lvPPA to normal brain FDG-PET.

Conclusion: Even if nf/lvPPA showed grammatical impairment, hypometabolic pattern and pathological biomarkers were consistent with lvPPA. S/lvPPA had lower Aβ prevalence compared to lvPPA and showed typical svPPA hypometabolic pattern.

Disclosure: Nothing to disclose

O3030

Cognitive, neuropsychiatric and quality-of-life sequelae in LGI1-antibody disease demonstrates fatigue as the key determinant of wellbeing

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Background and aims: Despite increasing awareness and early treatment of LGI1-antibody encephalitis, long-term outcomes remain poorly reported. Previous smaller studies have identified multiple deficits in cognitive recovery but few explore psychiatric aspects or quality-of-life (QoL). Here, we delineate long-term follow up of multiple cognitive and neuropsychiatric domains, plus QoL, in a substantial patient cohort.

Methods: 60 patients were recruited at a median of 3.4 years (range 0.3-14.9) post-disease onset. All underwent a detailed interview using validated questionnaires covering several domains our clinical observations had detected to be impaired in this cohort. Clinical, paraclinical and genetic parameters were also collected. Statistical analysis comprised binomial tests, simple and multiple regressions, and a latent variable model, with the LGI1-antibody group's results compared to age-appropriate scores in the literature.

Results: Abnormal scores were observed in 5-52% (median 39%) of patients across disability, cognition, neuropsychiatry, QoL, carer-rated and fatigue measures (Figure). Patients performed significantly worse than controls in episodic and verbal memory, fluency and visuospatial abilities. Significant QoL worsening post-illness was confirmed by 2 separate instruments, which were closely correlated and could be represented by a latent variable model. Multiple regression analysis identified fatigue as an independent predictor of QoL. Fatigue correlated better with QoL than the modified Rankin Scale.

Conclusion: Patients demonstrate widespread difficulties many years after an acute LGI1-antibody episode. Fatigue, independent of depression scores, is the most accurate predictor of long-term QoL. The mechanism by which this occurs and potential treatments need to be further explored in this patient group.

Disclosure: SRI is a co-applicant and receives royalties on patent application WO/2010/046716 (U.K. patent no., PCT/GB2009/051441) entitled 'Neurological Autoimmune Disorders'. The patent has been licensed commercially for the development of assays for LGI1 and other VGKC complex antibodies. SRI and SB are co-applicants on a patent application entitled 'Diagnostic Strategy to improve specificity of CASPR2 antibody detection' (TBA / BB Ref. JA94536P.GBA).

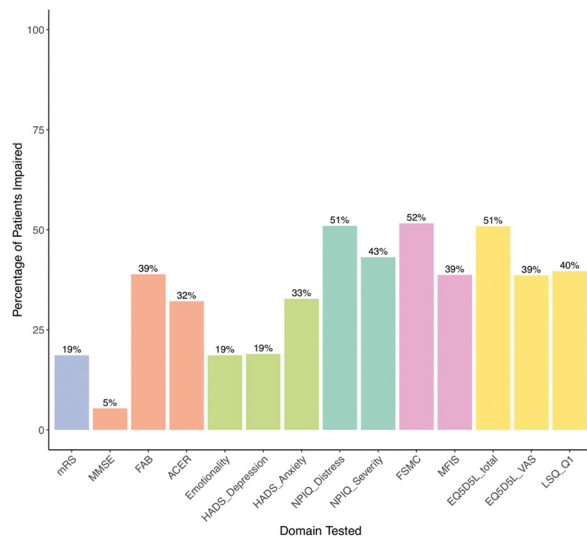


Figure: long-term deficits across multiple domains in LGI1-antibody patients

O3031

Effect of cognitive reserve on structural MR imaging measures in adult healthy subjects

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Background and aims: Early and recurring involvement of cognitive abilities and the exposure to leisure activities during early-life experiences is a requirement to reach a high level of cognitive reserve (CR). However, the impact of this construct on brain measures remains unclear in young-adult population. We investigated the associations between CR and structural MRI measures in young-adult healthy subjects (HS).

Methods: Dual-echo, 3D T1-weighted and diffusion tensor MRI sequences were acquired from 77 HS (40 men; mean age=36 years; range=22-65). A global Cognitive Reserve Index (CRI) and its subdomains (cognitive/social/physical) were assessed including education, leisure activities and IQ. Higher scores reflect higher CR. Regional gray matter (GM) volume was estimated using voxel-based-morphometry (VBM) and white matter (WM) fractional anisotropy (FA) was investigated with tract-based-spatial-statistical (TBSS) analysis. Linear regression analyses were performed.

Results: Higher global-CRI and higher scores in its subdomains were positively associated with higher GM volume of right (R) supplementary motor area. Both higher global and cognitive-CRI were correlated with higher GM volume of left (L) orbital middle frontal gyrus, whereas higher global and physical-CRI were correlated with higher GM volume of L cerebellum. Higher cognitive-CRI was correlated with higher GM volume of L angular gyrus, while higher physical-CRI was correlated with higher GM volume of L medial frontal gyrus and R middle cingulum. TBSS analysis showed no correlations between CRI and WM FA.

Conclusion: These findings suggest that in young adults, higher CRI modulates GM volumes of brain regions involved in motor network, whereas it is likely not to influence WM architecture.

Disclosure: Nothing to disclose

O3032

Defining cognitive phenotypes of multiple sclerosis patients

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Background and aims: Cognitive impairment is one of the most disabling symptoms of multiple sclerosis (MS), affecting about 50% of patients. We aimed to define cognitive phenotypes in a large cohort of MS patients by using a data-driven approach, in order to set the stage for personalized rehabilitative strategies.

Methods: A cohort of 1039 consecutive [925 relapsing-remitting (RR), 40 primary progressive (PP), 74 secondary progressive (SP)] MS patients from 6 Italian MS centers underwent cognitive evaluation with RAO's Brief Repeatable Battery (BRB) and the Stroop Test. Latent profile analysis was used on cognitive domains z-scores (verbal and visuospatial memory, attention, information processing speed, executive functions, language) in order to individuate cognitive profiles.

Results: 5 cognitive phenotypes were identified, characterized by: "preserved cognition" (28%); "mild executive/memory" (13%) impairment with other domains preserved; "mild multi-domain" (36%) impairment with executive function preservation; "severe executive/attention" (19%) impairment with mild impairment of other domains; "severe executive/information-processing" (3%) impairment with preserved memory and mildly impaired attention. "Preserved cognition" patients had shorter disease duration and lower Expanded Disability Status Scale (EDSS) score compared to other groups, but also included PPMS and SPMS patients with high EDSS. Severely-impaired groups had longer disease duration and higher proportion of progressive patients compared to mildly-impaired groups, but were also represented in early MS stages. Interestingly, 47% of PPMS patients had a "mild multi-domain" phenotype.

Conclusion: 5 cognitive profiles of MS patients were identified, pointing at different underlying pathophysiological mechanisms. Future studies will be needed to define personalized rehabilitative strategies for MS patients according to their cognitive phenotype.

Disclosure: Nothing to disclose

O3033

Alzheimer’s disease and cerebral amyloid angiopathy were associated with ABCA7 PTC mutation carriers in a large Belgian AD cohort

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Background and aims: We aimed to delineate the clinicopathological Alzheimer’s disease (AD) phenotype of carriers with a premature termination codon (PTC) in the ATP-Binding Cassette Subfamily A Member 7 (ABCA7) gene. ABCA7 was initially identified as a risk gene in genome wide association studies of large AD patient cohorts. In an extended Belgian AD patient cohort (n=1580), we identified 15 different ABCA7 PTC mutations in 69 carriers with onset ages varying from early- to late-onset AD.

Methods: Medical records of the ABCA7 mutation carriers were reviewed to obtain clinical and neuropathological data.

Results: Brain autopsy was performed in 10 carriers, revealing AD neuropathology and cerebral amyloid angiopathy (CAA) in all carriers. High levels of CAA were present in both the meningeal and capillary blood vessels, and moderate to high levels of CAA in the parenchymal blood vessels. CAA was not limited to the occipital brain region, but extended to the other neocortices and even to the medial temporal region (n=5). There was no correlation between CAA and levels of AD pathology or APOE genotype. Additionally, 3 carriers showed imaging features compatible with CAA, and 3 patients suffered 1 or more lobar hemorrhages. Chronic microvascular lesions were noticed in 43 patients (78,2%, 43/55).

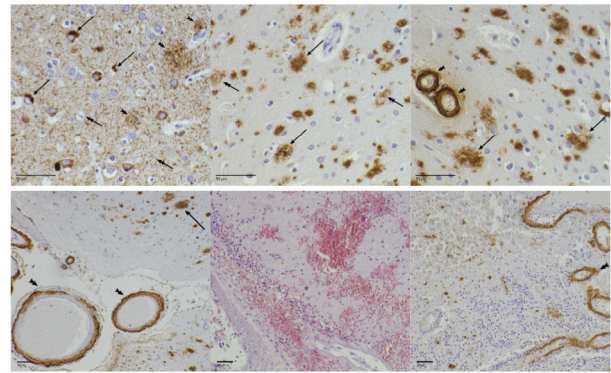


Figure 1 – Neuropathology of ABCA7 PTC mutation carrier DR1317
A. Hippocampus. AT8 stain. Moderate amount of NFTs (arrow) and DN (double arrow head), but many NT (double arrow). **B.** Hippocampus. 4G8 stain showing many SP (classic (arrow) and diffuse (double arrow)). **C.** Frontal cortex. 4G8 stain. There are many SP (arrow) and cerebral amyloid angiopathy (CAA) (double arrow head) is also present. **D.** 4G8 stain. Parietal cortex with many SP (arrow) and severe CAA (double arrow head). **E.** Hematoxylin Eosin stain. Cortical hemorrhage. **F.** 4G8 stain. Cortical hemorrhage with abundant CAA (double arrow head).

Figure 1 – Neuropathology of ABCA7 PTC mutation carrier DR1317

ID	Gender	AAO (y)	AAD (y)	ABCA7 PTC Mutation	gDNA	Protein	APOE	Post-mortem diagnosis	Neuropathology	CAA	Other		
									ABC	Level	Meningeal	Parenchymal	Capillary
DR109	f	90	92	c.2228_2228del	p.E709L	34	Definite AD + CAA	AB3C2-3	Intermediate	2	1	+	Atherosclerosis
DR1211	f	50	55	c.2228_2228del	p.E709L	44	Definite AD + CAA	AB3C2	High	3	2	+	ICH
DR170	f	72	78	c.2228_2228del	p.E709L	33	Definite AD + CAA	AB3C2	High	3	1	+	TDP
DR93	f	83	74	c.2228_2228del	p.E709L	33	Definite AD + CAA	AB3C2	Intermediate	3	3	+	-
DR1229	m	86	88	c.3643G>A	p.W1254*	33	Definite AD + CAA	AB3C2	Intermediate	3	2	+	+
DR1241	f	48	55	c.4088G>A	p.W1288*	34	Definite AD + CAA	AB3C2	High	Moderate CAA	-	-	ICH
DR54	f	61	70	c.4088G>A	p.L1403fs	34	Definite AD + CAA	AB3C2	High	3	2	+	-
DR51	f	59	73	c.4816A>T>C	p.D	34	Definite AD	AB3C2	High	3	3	+	-
DR156	m	Preclinical	75	c.5370G>C	p.D	33	Definite AD + CAA	AB3C2-3	Intermediate	3	3	+	Cortical neurons, meningeal hemorrhages, atherosclerosis
DR1317	f	64	68	c.4735G>A	p.D	34	Definite AD + CAA	AB3C2	High	2	2	+	ICH (2x), ICVA, ICVA

Table 1 – Neuropathology of ABCA7 PTC carriers in Belgian AD patients
 Scoring for meningeal and parenchymal CAA: 0 = no CAA, 1 = scant beta amyloid deposition, 2 = some circumferential beta amyloid, 3 = widespread circumferential beta amyloid. Scoring for capillary CAA: + = present (type 1), * = occasional, ** = TDP-43 coloring found 2 neuronal intranuclear inclusions and neuronal cytoplasmic inclusions in limited places (parahippocampal gyrus and near the superior temporal gyrus).
 Abbreviations: AAO= age at onset, AAD= age at death, y= years, AD = Alzheimer’s disease, CAA= cerebral amyloid angiopathy, ICH = intracerebral hemorrhage, ICVA = ischemic cerebrovascular accident, ICVA = hemorrhagic cerebrovascular accident.

Table 1 – Neuropathology of ABCA7 PTC carriers in Belgian AD patients

Conclusion: Carriers of ABCA7 PTC mutations present with a classical AD phenotype, but with wide onset-age ranges, even for carriers of the same mutation. Additional to the AD hallmarks in pathology, extensive levels of CAA were present in all autopsied brains. These findings have important implications for future research and clinical practice.

Disclosure: Nothing to disclose

Cerebrovascular diseases 3

O3034

TENecteplase in Central Retinal Artery Occlusion (TEN-CRAOS): a prospective, randomized-controlled, double-dummy, double-blind phase 3 multi-centre trial of TNK 0.25mg/kg+placebo vs. ASA+placebo (2 arms with 1:1 block randomization)

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Background and aims: Non-arteritic central retinal artery occlusion (CRAO) is an acute neurovascular-ophthalmological emergency that without swift revascularization bears a high risk of permanent blindness. The consequences of a CRAO are severely disabling and yet there is no evidence-based treatment option. Whether revascularization with thrombolytic agents can improve the outcome in CRAO, as proved in ischemic stroke, remains unanswered. Even though a recent meta-analysis of observational data indicates that systemic thrombolysis might improve outcome, no randomized controlled trial of early systemic thrombolysis for CRAO has so far not been performed. The aim of this study is for the first time to assess the effect of intravenous tenecteplase versus placebo administered within 4.5 hours of CRAO onset.

Methods: The study is a prospective, randomized-controlled, double-dummy, double-blind phase 3 multi-centre trial of TNK 0.25mg/kg+placebo vs. ASA+placebo (2 arms with 1:1 block randomization).

The main endpoint is the proportion of patients with an improvement in visual acuity of at least 15 letters. In addition, we will assess differences in visual field parameters, patient reported outcome measures and adverse events between the groups.

Results: The study is based on a unique collaboration between stroke units and ophthalmologic departments in Norway and selected European centres.

Conclusion: The TEN-CRAO study could be the foundation

for an international change in treatment practice of a sight-threatening disease underrepresented in clinical research by establishing for the first time a novel evidence-based treatment option by means of prompt systemic thrombolysis for these patients.

Disclosure: The study has been funded by the South-Eastern Norway Regional Health Authority, Boehringer Ingelheim and Odd Fellow.

O3035

Association of oral hygiene with occurrence for cerebral aneurysm and subarachnoid hemorrhage: a nationwide population-based cohort study

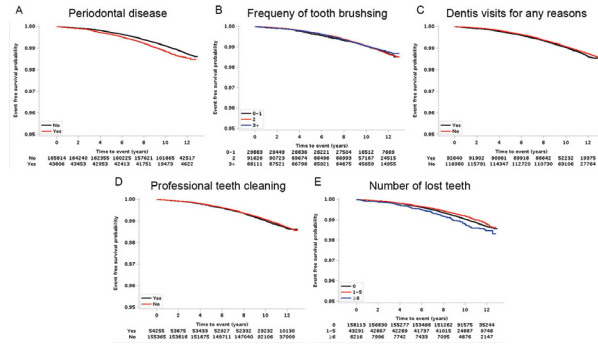
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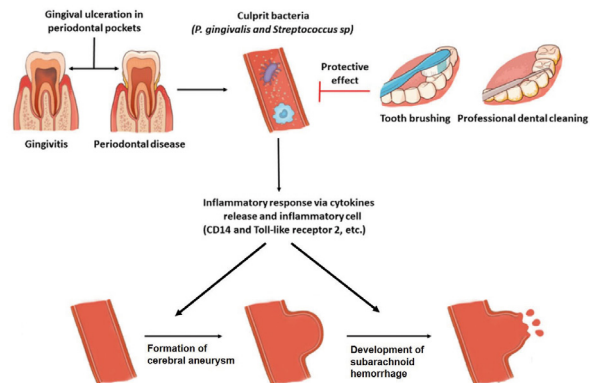
Background and aims: Presence of periodontal disease and poor oral hygiene can provoke systemic inflammatory response, a mediator for the development of cerebral aneurysm and subarachnoid hemorrhage (SAH). Our study hypothesized that presence of periodontal disease and oral hygiene would be associated with occurrence of cerebral aneurysm and SAH.

Methods: Total of 209,620 subjects without missing data including demographic data, medical history, and laboratory findings were analyzed from the Korean National Health Insurance System-Health Screening Cohort. Presence of periodontal disease, frequency of tooth brushing per day, dentist visits for any reason, professional teeth cleaning, and number of lost teeth were investigated as oral hygiene indicators. The occurrence of cerebral aneurysm and SAH were defined as I60 and I67.1, respectively from codes of International Statistical Classification of Diseases Related Health Problems-10.

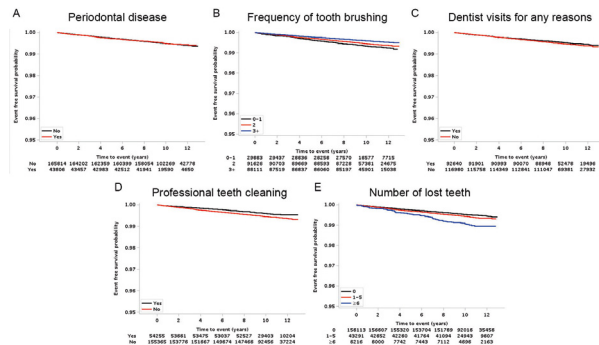
Results: The average age was 53.7±8.7 years, 59.4% were male. Periodontal disease was found in 20.9% of the subjects. During the median follow-up of 10.3 years, 2,160 (1.0%) cases of cerebral aneurysm and 1,097 (0.5%) cases of SAH occurred. Multivariable analysis after adjusting confounding factors showed that the presence of periodontal disease was significantly associated with an increased risk of cerebral aneurysm (hazard ratio [HR]: 1.23, 95% confidence interval [CI] (1.11–1.36), p<0.001). Better oral hygiene behavior was associated with lower occurrence risk of SAH (HR: 0.78, 95% CI: 0.66–0.93, p=0.006).



Conclusion: Poor oral hygiene represented by presence of periodontal disease may be associated with occurrence of cerebral aneurysm.



Disclosure: Nothing to disclose



O3036

Early extubation after stroke thrombectomy is associated with better functional outcome

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Background and aims: We aimed to investigate the clinical impact of the duration of artificial ventilation in stroke patients receiving mechanical thrombectomy (MT) under general anesthesia, which is currently unknown.

Methods: All consecutive ischemic stroke patients who had been treated at our center with MT for anterior circulation large vessel occlusion under general anesthesia were identified over an 8-year period. We analyzed ventilation time as a continuous variable and grouped patients into extubation within 6 hours (“early”), 6–24 hours (“delayed”) and >24 hours (“late”). Favorable outcome was defined as modified Rankin Scale scores of 0–2 at 3-months post-stroke. We also assessed pneumonia rate and reasons for prolonged ventilation.

Results: Among 447 MT patients (mean age 69.1±13.3 years, 50.1% female), median ventilation time was 3 hours. 188 (42.6%) patients had a favorable 3-months outcome, which correlated with shorter ventilation time ($p<0.001$). In patients extubated within 24 hours, early compared to delayed extubation was associated with improved outcome (odds ratio 2.40, 95% CI 1.53–3.76, $p<0.001$). This was confirmed in multivariable analysis ($p=0.007$).

Longer ventilation time was associated with a higher rate of pneumonia during neurointensive care unit/stroke unit stay (early/delayed/late extubation: 9.6%/20.6%/27.7%, $p<0.01$). While stroke-associated complications represented the most common reasons for late extubation, delayed extubation was associated with admission outside of core working hours ($p<0.001$).

Conclusion: Prolonged ventilation time after stroke thrombectomy independently predicts unfavorable outcome at 3 months and is associated with increased pneumonia rates. Therefore, extubation should be performed as early as safely possible.

Disclosure: Nothing to disclose

O3037

Mobile stroke unit for triage of stroke patients: a randomized trial

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Background and aims: Transferring patients with large-vessel occlusion (LVO) or intracranial haemorrhage (ICH) to hospitals not providing interventional treatment options is an unresolved medical problem. Here, we aimed to investigate how management in a Mobile Stroke Unit (MSU) compares with optimized conventional management (OPM) in triaging stroke patients to hospitals providing (comprehensive stroke centre, CSC) or not providing (primary stroke centre, PSC) neurointerventional treatment.

Methods: In this prospective randomized multicentre trial (ClinicalTrials.gov identifier: NCT02465346) with 3-month follow-up, patients were randomly assigned to one of the stroke management pathways. The primary endpoint was the proportion of patients accurately triaged to either CSCs (LVO and ICH) or PSCs (other types of strokes).

Results: A predefined interim analysis was performed after 116 of 232 planned patients had entered the study. The primary endpoint, an accurate triage decision, was reached for 63 (100%) MSU patients and for 37 of 53 (69.8%) patients in OPM (differences, 30.2%; 95% CI, 17.8–42.5; $p<0.0001$). Whereas 7 of 17 (41.2%) optimized conventional group patients with LVO or ICH required secondary transfers from a PSC to a CSC, none of the 11 (0%) MSU patients required such transfers (difference, 41.2%; 95% CI, 17.8–64.6; $p=0.0182$). Stroke management metrics were better in the MSU group, although day 90 outcomes were not different.

Conclusion: Whereas OPM allows correct triage decisions for approximately 70% of patients, MSU-based stroke management enables accurate triage decisions for 100%.

Disclosure: Nothing to disclose

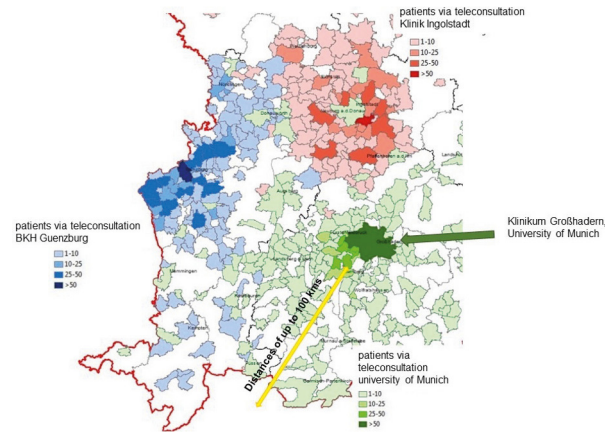
O3038

Inter-hospital transfer for mechanical thrombectomy within the supraregional Neurovascular Network of Southwest Bavaria

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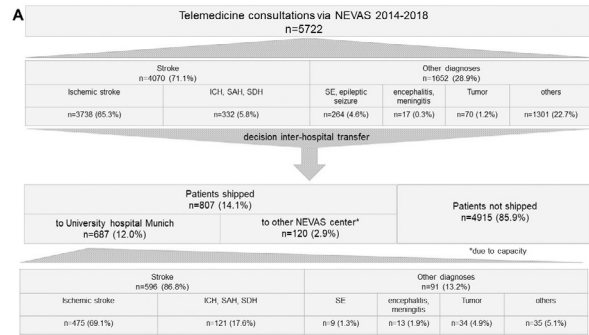
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Background and aims: Telemedicine stroke networks are mandatory to provide inter-hospital transfer for mechanical thrombectomy (MT). We analyzed MT-patients within the supraregional stroke network “Neurovascular Network of Southwest Bavaria” (NEVAS) irrespective of finally MT-treatment.

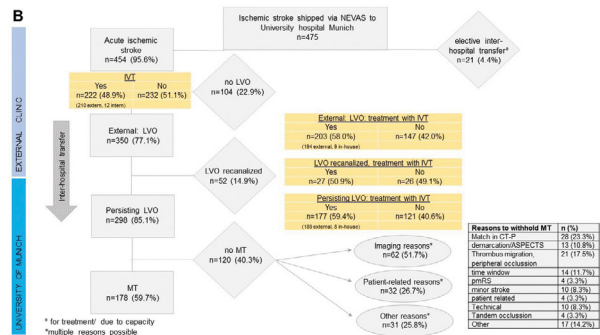


Organization of supraregional stroke network NEVAS

Methods: Consecutive patients from 01/2014-12/2018 who were shipped to our comprehensive stroke center were analyzed. Good outcome at 3 months was defined as modified Rankin Scale of 0-2.



2A: Flow chart of all telemedicine consultations via NEVAS



2B: Flow chart of acute ischemic stroke patients

Results: Out of 5722 telemedicine consultations, n=350 patients presented with large vessel occlusion (LVO). 52 patients (14.9%) spontaneously recanalized before MT (see figure 2). Out of the remaining n=298 patients, n=178 underwent MT and n=120 did not. MT-treated patients had more severe strokes according to the NIHSS (16 vs. 13, p<0.001), higher median ASPECTS (8 vs. 8, p=0.041), were more often treated with intravenous thrombolysis (64.5% vs. 51.7%, p=0.026) and arrived significantly earlier in the comprehensive stroke center (184.5 vs. 228.0, p<0.001). Good outcome (27.5% vs. 30.8%, p=0.35) and mortality (32.6% vs. 23.5%, p=0.79) were comparable in MT-treated vs. no-MT-treated patients at follow-up. In patients with middle cerebral artery occlusion in the M1 segment or carotid artery occlusion good outcome was twice as often in the MT-group (21.8% vs. 12.8%, p=0.184). Independent predictors for performing MT were higher NIHSS (OR 1.096), higher ASPECTS (OR 1.28), and earlier time window (OR 0.99).

Conclusion: Within a telemedicine network stroke care can successfully be organized as only a minority of patients has to be transferred. There are no clear clinical parameters to predict in advance whether MT will be performed or not.

Disclosure: Nothing to disclose

Tuesday, May 26 2020

Neurotraumatology; neurorehabilitation

O4001

IBIA – DoC-SIG multi-centre longitudinal study on clinical and neurophysiological prognostic markers in prolonged disorders of consciousness: a one-year follow-up

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Background and aims: Accurate prognosis in patients with Disorders of Consciousness (DoC) is challenging, but necessary for defining appropriate care pathways 1-3. The present multi-centre, prospective study performed by the Special Interest Group on DoC of the International Brain Injury Association is aimed at identifying predictors for one-year clinical outcome.

Methods: 12 specialized medical institutions enrolled patients in prolonged unresponsive wakefulness syndrome/vegetative state (UWS/Vs) 4 or in minimally conscious state (MCS) 5 with time post-injury (TPI) ≤ 3 months. Demographic, anamnestic, clinical and neurophysiological data were collected at study entry. Clinical follow-up was performed at 12 months post-injury and patients who improved (i.e. recovering from UWS/Vs to MCS, and from

UWS/Vs or MCS to full consciousness) were compared with those who did not (i.e. with unchanged diagnosis or died).

Results: A convenience sample of 147 patients was enrolled (44 women; mean age: 49.4 \pm 19.9 years; mean TPI: 59.6 \pm 25.2 days; UWS/Vs=71, MCS=76; traumatic=55, vascular=56, anoxic=36). At the 12-month evaluation, 71 patients (48%) had improved their diagnosis and 71 (48%) did not (4% dropped out). Logistic and LASSO regression analyses on 134 patients showed that lower age, shorter TPI and presence of EEG reactivity to eye opening and closing at study entry predicted improvement in diagnosis at 12 months post-onset (all $p < .05$).

Conclusion: Multimodal assessment could provide valuable information for prognostication in patients with prolonged DoC. This international project would encourage standardization of diagnostic and prognostic procedures in patients with DoC.

Disclosure: This project was funded by European Union's Horizon 2020 programme (Marie Skłodowska-Curie grant 778234-DoCMA project).

O4002

Pain assessment in non-communicative patients

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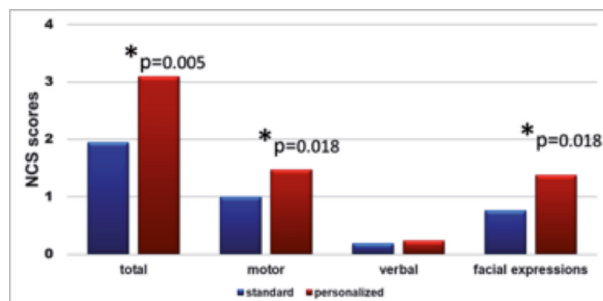
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Background and aims: Recent evidences have shown that covert cognition may be present in around 15% of the patients with DoC. The lack of overt behavioural responsiveness may be due to many clinical confounding factors, including severe spasticity and diffuse pain. Aim of the present study was to compare, in non-communicative patients with DoC, NCS-R scores obtained with the standard pressure on fingernail bed (standard stimulus, SS) versus other personalized painful stimuli (PS), shared with the rehabilitation staff, to verify possible correlation between NCS-R and Coma Recovery Scale-Revised (CRS-R).

Methods: From a population of 66 patients (35 M and 31 F) with a mean age of 42.74 years (range 14-69) diagnosed with DoC, according to the CRS-R enrolled in the study, we selected a subgroup of 22 patients [10 M and 12 F; mean age =40.72 years (range 14-69); etiology: 10 TBI; 3 anoxia; 7 vascular (hemorrhagic or ischemic); 1 encephalitis] were assessed with NCS-R with personalized versus standard painful stimulation.

Results: The personalized painful stimulation (NCS-R-P) reached higher scores as compared to the standard stimulus, both for the total score and for motor and facial expression subscores ($p < 0.05$). Significant correlation with CRS-R were found for both NCS-R-SS ($r = 0.613$, $p = 0.0031$) and NCS-R-PS ($r = 0.539$, $p = 0.0117$).



Bar diagram reporting NCS scores averaged across patients obtained applying both standard (S) and personalized (P) stimuli. We reported the results about the total score and the scores related to the NCS sub-scales. The symbol * highlight a statistically significant difference between S and P painful stimuli (Wilcoxon Matched Pairs Test, $p < 0.05$).

Conclusion: Standard painful stimulation may be affected by sensory deficits (hypoesthesia, anesthesia) of central and peripheral etiology and by the different pain sources. A personalized painful stimulation may be of some support to unveil covert cognition in non-communicative patients, alleviating their possible sufferance and improving their responsiveness and quality of life.

Disclosure: This project was funded by European Union's Horizon 2020 programme (Marie Skłodowska-Curie grant 778234-DoCMA project).

O4003

Coagulopathy and its effect on treatment and mortality in patients with traumatic intracranial haemorrhage

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Background and aims: The role of coagulopathy in patients with traumatic brain injury has remained inconclusively studied. Coagulopathy can be either spontaneous or induced by medication. Our aim was to characterize clinical features of patients presenting with traumatic intracranial haemorrhage and coagulopathy. In addition, we studied the prevalence of coagulopathy and how it affects the treatment and mortality in these patients.

Methods: An observational, retrospective single-centre cohort of 505 consecutive patients with traumatic intracranial haemorrhage treated in Helsinki University Hospital between 01 January and 31 December, 2010 (Figure 1). We compared clinical and radiological parameters in patients with and without coagulopathy – defined as drug- or disease-induced (antiplatelet or anticoagulant medication at a therapeutic dose, thrombocytopenia (platelet count $< 100 \text{ E9/L}$), international normalized ratio (INR) > 1.2 , or thromboplastin time (TT) $< 60\%$). Primary outcome was 30-day all-cause mortality.

Figure 1. Patient selection flowchart

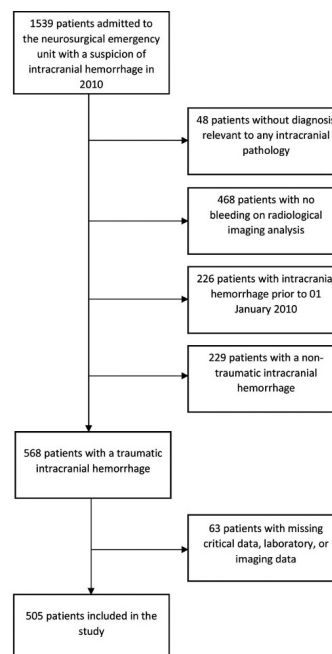


Figure 1

Results: Of our 505 patients, 331 (65.5%) were male and median age was 61 years (IQR 48-75). In total, 206 (40.8%) patients had coagulopathy. Compared to non-coagulopathy patients, coagulopathy patients had larger haemorrhage volumes (121.0ml vs. 82.5ml, $p < 0.001$) (Table 1). Patients with coagulopathy had higher 30-day mortality (18.9% vs.

9.7%, $p=0.002$). In multivariable analysis older age, lower admission GCS, higher haemorrhage volume, and conservative treatment were independently associated with mortality (Table 2).

Variable	Coagulopathy (N=206)	No coagulopathy (N=299)	p
Male gender	137 (66.5%)	194 (64.9%)	0.390
Age, mean (CI)	69.0 (66.8-71.3)	57.5 (55.0-60.0)	<0.001
Age group			<0.001
<50	27 (13.1%)	113 (37.8%)	
50-64	47 (22.8%)	100 (33.4%)	
65-79	82 (39.8%)	53 (17.7%)	
≥80	50 (24.3%)	33 (11.0%)	
Admission GCS, mean (CI)	11.8 (11.2-12.5)	11.3 (10.7-11.9)	0.497
Admission GCS			0.448
13-15	130 (63.1%)	180 (60.2%)	
9-12	26 (12.6%)	32 (10.7%)	
3-8	50 (24.3%)	87 (29.1%)	
Hypertension	90 (43.7%)	73 (24.4%)	<0.001
Atrial fibrillation	64 (31.1%)	6 (2.0%)	<0.001
Coronary heart disease	53 (25.7%)	10 (3.3%)	<0.001
Hematoma evacuation	124 (60.2%)	148 (49.5%)	0.011
Ventriculostomy	6 (2.9%)	8 (2.7%)	0.540
Hemorrhage volume (ml), mean (CI)	140.0 (125.4-154.4)	98.4 (86.4-110.4)	<0.001
Hemorrhage volume (ml)			<0.001
0-50	69 (33.5%)	151 (50.5%)	
51-100	23 (11.2%)	45 (15.1%)	
101-200	67 (32.5%)	60 (20.1%)	
>200	47 (22.8%)	43 (14.4%)	

p = p-value, CI = confidential interval, GCS = Glasgow Coma Scale,

ml = milliliter

Table 1

Variable	Alive	Dead	Multivariate OR (95% CI)	Multivariate p
Male gender	282 (64.5%)	49 (72.1%)	1.712 (0.846-3.467)	0.135
Age group				
<50	128 (29.3%)	12 (17.6%)	Reference	
50-64	128 (29.3%)	19 (27.9%)	1.759 (0.704-4.393)	0.227
65-79	114 (26.1%)	21 (30.9%)	3.213 (1.143-9.028)	0.027
≥80	67 (15.3%)	16 (23.5%)	5.102 (1.566-16.622)	0.007
Admission GCS				
13-15	294 (67.3%)	16 (23.5%)	Reference	
9-12	51 (11.7%)	7 (10.3%)	2.526 (0.873-7.314)	0.087
3-8	92 (21.1%)	45 (66.2%)	14.210 (6.668-30.284)	<0.001
Hypertension	142 (32.5%)	21 (30.9%)	0.798 (0.375-1.699)	0.558
Atrial fibrillation	55 (12.6%)	15 (22.1%)	1.408 (0.567-3.493)	0.461
Coronary heart disease	49 (11.2%)	14 (20.6%)	1.791 (0.711-4.516)	0.217
Coagulopathy	167 (38.2%)	39 (57.4%)	1.534 (0.734-3.206)	0.256
Hematoma evacuation	248 (56.8%)	24 (35.3%)	0.133 (0.059-0.297)	<0.001
Ventriculostomy	11 (2.5%)	3 (4.4%)	2.287 (0.514-10.169)	0.277
Hemorrhage volume (ml)				
0-50	201 (46.0%)	19 (27.9%)	Reference	
51-100	55 (12.6%)	13 (19.1%)	2.782 (1.057-7.323)	0.038
101-200	109 (24.9%)	18 (26.5%)	4.052 (1.526-10.762)	0.005
>200	72 (16.5%)	18 (26.5%)	5.094 (1.807-14.364)	0.002

OR = odds ratio, p = p-value, CI = confidential interval, GCS = Glasgow Coma Scale, ml = milliliter

Table 2

Conclusion: Coagulopathy was frequent in patients with traumatic intracranial haemorrhage and associated with larger haemorrhage volume, but was not associated with higher 30-day mortality. Surgical treatment by hematoma evacuation was associated with lower mortality, regardless of coagulopathy.

Disclosure: The research project has received funding from Maire Tapola Foundation's grant, and from Helsinki and Uusimaa Hospital District's competitive research funding.

O4004

Effect of sex and age on quality-of-life up to ten years after traumatic brain injury

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Background and aims: Traumatic brain injury (TBI) causes lifelong disability and is associated with an increased risk for Alzheimer's or Parkinsonism. Despite its prevalence among the elderly, the influence of age and sex on TBI etiology and health-related quality-of-life (HRQoL) after TBI has not been elucidated. Thus, we conducted a cross-sectional study to assess the effect of age and sex on HRQoL up to ten years after mild, moderate or severe TBI.

Methods: Sex differences (male/ female) were quantified for each TBI severity group (mild, moderate or severe) (%), TBI etiology (traffic accident, fall or others) (%), and the age at TBI (mean±SEM) in 102 male and 33 female TBI patients (18-85 years). The Quality of Life after Brain Injury (QOLIBRI) instrument was used to investigate age- and sex-related HRQoL in this cohort.

Results: TBI etiology differed between males and females in all age groups ($p=0.013$) and in males across ages ($p=0.03$). A shift from traffic accidents to falls was seen between younger (≤ 45 years) and middle-aged males (46-64 years) ($p=0.004$) and between younger and elderly males (≥ 65 years) ($p=0.007$) but was not seen in females. Regarding HRQoL, 69% of males but only 52% of females reported good outcomes with 17% more females than males at risk for one psychiatric disorder ($p=0.01$). This finding was particularly evident in middle-aged females.

Conclusion: Our results show sex- and age-related differences regarding etiology and HRQoL suggesting an increased female brain vulnerability during menopause and emphasizing the need for sex-specific clinical algorithms after TBI.

Disclosure: Nothing to disclose

O4005

Prevalence and prediction of post-concussive symptoms in children and adolescents with mild traumatic brain injury in the CENTER-TBI study

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Background and aims: Mild traumatic brain injury (mTBI) is a frequent injury among children and adolescents from which most fully recover within weeks. However, some patients suffer from persisting post-concussive symptoms. In this study, we aimed to analyze their prevalence, predictive factors, and effects on quality of life using the multi-center, prospectively collected CENTER-TBI database.

Methods: All patients in the CENTER-TBI core study between 5-21 years with available Rivermead Post-Concussion Questionnaire (RPQ) at 6-months were included. Post-concussive syndrome (PCS) was defined according to ICD-10 criteria as having at least 3 of 7 selected symptoms included in the RPQ. Regression analysis using the Lasso method was performed to select a multivariate model with the most important clinical variables predicting PCS. Quality of life was assessed using the Quality of Life after Brain Injury (QOLIBRI) score.

Results: 36% of the 196 included patients reported experiencing at least 1 moderate or severe post-concussive symptom. PCS was present in 13% of patients. Univariate- and multivariate regression analyses identified female gender as significant predictive factor. The final model containing a set of clinical and demographical factors showed reasonable predictive ability but could only explain a small part of the variability in outcome. Pediatric patients with PCS had significantly lower QOLIBRI total scores, indicating a lower quality of life.

Conclusion: Post-concussive symptoms and PCS were present in a considerable proportion of patients and significantly affected patients' quality of life. The developed prediction model displayed reasonable predictive ability, but additional parameters are likely needed for more accurate predictions.

Disclosure: Nothing to disclose

O4006

Therapeutic effects of azithromycin on spinal cord injury in rats: a role for inflammatory pathways

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Background and aims: Inflammatory responses, including macrophages/microglia imbalance, are associated with spinal cord injury (SCI) complications. Accumulating evidence also suggest an anti-inflammatory property for azithromycin (AZM). Thus, we evaluated the therapeutic effects of AZM and its potential anti-inflammatory property on a rat model of SCI.

Methods: Male Wistar rats were subjected to T9 vertebra laminectomy. They were divided into 3 groups: sham-operated group and 2 treatment (normal saline as a vehicle control versus AZM at 180mg/kg/day for 3 days post-surgery) SCI groups. Locomotor scaling and behavioral tests for neuropathic pain were evaluated and compared through a 28-days period. At the end of the study, tissue samples were taken to assess neuroinflammatory changes using the immunohistochemistry, flow cytometry, and ELISA techniques.

Results: Post-SCI AZM (180mg/kg/day for 3 days) treatment significantly improved locomotors ability ($p<0.01$) and decreased sensitivity to mechanical ($p<0.01$) and thermal allodynia ($p<0.001$). Moreover, there was a significant tumor necrosis factor (TNF)- α decline ($p<0.01$) and interleukin (IL)-10 elevation ($p<0.01$) in spinal cord tissue of AZM-treated compared to control groups 28 days post SCI. AZT significantly improved neuroinflammation as evidenced by reduction of expression of M1, elevation of M2 macrophages, and reduction of M1/M2 ratio in both dorsal root ganglion and spinal cord tissue after SCI compared to controls ($p<0.01$).

Conclusion: AZM treatment can be considered as a therapeutic agent for SCI, as it could reduce neuroinflammation as well as SCI sensory/locomotor complications.

Disclosure: The authors declare no conflicts of interest regarding the data presented. This study was funded and supported by a grant (Grant No. 971171, Title: "Evaluation of Azithromycin on Spinal Cord Injury Model in Male Rats") from National Institute for Medical Research Development (NIMAD) in Iran.

MS and related disorders 3

O4007

Development of a circulating microRNA biomarker panel for multiple sclerosis

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Background and aims: Multiple sclerosis (MS) diagnosis is frequently challenging involving clinical examination, imaging and electrophysiological measurements and invasive CSF (cerebrospinal fluid) analysis. Molecules such as antibodies or glycoproteins are used in clinical practice as MS biomarkers with the pitfall of a poor sensitivity and/or specificity. Circulating microRNAs (miRs) are appealing novel disease biomarkers due to the low cost, minimal invasiveness and speed of the analytic process. Several genome-wide studies in both animal models and patients have demonstrated a dysregulation on the miRs profile in MS. Our aim was to analyse the inflammation-associated miR-21, miR-22, miR-146a and miR-155 circulating levels in MS patients and assess its diagnostic performance.

Methods: MiRs serum levels were quantified in 88 patients with definitive MS diagnosis accordingly to McDonald's criteria (87F, 41.8±12.6 years; Mean disease duration: 12.7±9.5years; 75 Relapse Remitting, 9 Progressive MS) and 42 healthy controls. ROC curve, and respective AUC (Area Under the Curve) analysis was performed to assess diagnostic value.

Results: MS patients had lower miR-21 (2 fold, AUC= 0.61) and miR-22 (6 fold, AUC=0.77) and higher miR-146a (2 fold, AUC=0.51) and miR-155 (6 fold, AUC=0.68) circulating levels comparing to controls. The combination of the four studied microRNAs allowed a good diagnostic performance discriminating MS patients from controls, with an AUC of 0.94 (p<0.0001), 90% specificity and 84% sensitivity.

Conclusion: In this study, we report a panel of four circulating microRNAs with promising value as MS biomarker. Our results may contribute to an earlier MS diagnosis and ultimately lead in new directions in MS therapy.

Disclosure: Financial support: BIEM

O4008

Tailoring B-cells depleting therapy in MS according to memory B-cells monitoring: a pilot study

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Background and aims: Phase II and III clinical trials revealed the potent suppressive activity of CD20 directed antibodies in MS. In this study we wanted to evaluate efficacy on inflammatory parameter of rituximab (RTX) personalized reinfusion scheme, using a memory B-cell based reinfusion regimen

Methods: This is an prospective, uncontrolled, open-label, bicentric study including patients with MS treated with RTX in 2 Italian MS units. All patients were treated with rituximab induction, followed by maintenance infusion at the dosage of 375mg/m², according to memory B-cells repopulation (0.05% of PBMC for the first two years, 0.1% for the third year). MS activity was assessed as clinical or MRI activity.

Results: 102 patients were included in the analysis. Mean FU was 2.40 years (range 0.57-7.15 years). ARR was 0.67 in the year before RTX start and decreased to 0.01 in the 3 years after RTX initiation (global ARR). Proportion of patient with MS activity (i.e.: relapse or MRI activity) was 63.16% in the year before RTX start and decreased to 8.7% (0-6 months), 1.3% (6-12), 0% (12-24), and 0% (24-36). Annualized RTX infusion rate was 1.67, 0.76, and 0.78 for the first 3 years after RTX initiation, respectively. Patients were reinfused with a mean infusion interval of 367 days (range 181-839 days).

Conclusion: Results of this study show that memory B-cells based RTX reinfusion protocol is able to reduce mean number of RTX reinfusion with persistent reduction of disease activity.

Disclosure: Nothing to disclose

O4009

Regional outcomes of eculizumab treatment in patients with aquaporin-4 immunoglobulin G-positive neuromyelitis optica spectrum disorder: findings from the phase 3 PREVENT study

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Background and aims: The standard of care in treating aquaporin-4 immunoglobulin G-positive (AQP4-IgG+) neuromyelitis optica spectrum disorder (NMOSD) varies globally. Eculizumab was EMA-approved in August 2019 for this indication. The phase 3, randomized, double-blind PREVENT study (NCT01892345) assessed the efficacy/safety of eculizumab in patient populations of three pre-specified regions: Americas, Asia-Pacific and Europe. We evaluated use of immunosuppressive therapies (ISTs) and impact of eculizumab on rates of relapse-related hospitalization and acute treatment across geographical subpopulations.

Methods: Adult patients with AQP4-IgG+ NMOSD were randomized to eculizumab 900mg/week for 4 weeks, followed by 1200mg/2 weeks (maintenance dose) or placebo. Stable doses of concomitant ISTs were allowed, excluding rituximab and mitoxantrone. Post hoc analysis examined data from patients by region. Annualized rates were defined as total number of events divided by total patient-years in the study.

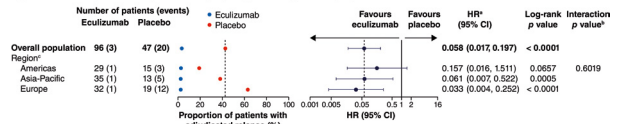
Results: At baseline patient characteristics were similar across all regions, except for IST use (Table 1). Compared with placebo, eculizumab significantly reduced relapse risk, and relapse-related hospitalization and acute relapse treatment rates across all regions (Figure 1, Table 2). In Europe, adjudicated relapses occurred in 1/32 and 12/19 of patients treated with eculizumab and placebo, respectively (p<0.0001); the annualized relapse-related hospitalization rates were 0.05 and 0.43, respectively (p=0.0002), and the annualized relapse-related acute intravenous methylprednisolone (IVMP) treatment rates were 0.11 and 0.47, respectively (p=0.0027).

Table 1. Baseline characteristics and use of ISTs according to pre-specified regional subgroups

Patient characteristic at baseline	Americas (N = 44)		Asia-Pacific (N = 48)		Europe (N = 51)		Overall (N = 143)	
	Eculizumab (n = 29)	Placebo (n = 15)	Eculizumab (n = 35)	Placebo (n = 13)	Eculizumab (n = 32)	Placebo (n = 19)	Eculizumab (n = 96)	Placebo (n = 47)
Female, n (%)	23 (79.3)	14 (93.3)	33 (94.3)	11 (84.6)	32 (100.0)	17 (89.5)	88 (91.7)	42 (89.4)
Age at NMOSD initial clinical presentation, years, mean (SD)	35.8 (17.3)	40.2 (15.6)	35.8 (13.0)	40.8 (15.0)	35.7 (12.2)	35.5 (14.8)	35.8 (14.0)	38.5 (15.0)
Historical annualized relapse rate, mean (SD)*	2.30 (1.04)	1.71 (0.58)	1.84 (0.72)	2.35 (1.48)	1.73 (0.86)	2.17 (0.92)	1.94 (0.90)	2.07 (1.04)
Prior use of rituximab, n (%)†	17 (58.6)	10 (66.7)	3 (8.6)	2 (15.4)	6 (18.8)	8 (42.1)	26 (27.1)	20 (42.6)
No IST	5 (17.2)	5 (33.3)	3 (8.6)	1 (7.7)	13 (40.6)	7 (36.8)	21 (21.9)	13 (27.7)
Corticosteroids only	4 (13.8)	3 (20.0)	8 (22.9)	5 (38.5)	4 (12.5)	3 (15.8)	16 (16.7)	11 (23.4)
Azathioprine ± corticosteroids	6 (20.7)	2 (13.3)	20 (57.1)	4 (30.8)	11 (34.4)	7 (36.8)	37 (38.5)	13 (27.7)
Mycophenolate mofetil ± corticosteroids	13 (44.8)	5 (33.3)	1 (2.9)	2 (15.4)	3 (9.4)	1 (5.3)	17 (17.7)	8 (17.0)
Other ISTs ± corticosteroids	1 (3.4)	0 (0.0)	3 (8.6)	1 (7.7)	1 (3.1)	1 (5.3)	5 (5.2)	2 (4.3)

The Americas: Argentina and the USA; the Asia-Pacific region: Australia, Hong Kong, Japan, Korea, Malaysia, Taiwan and Thailand; Europe: Croatia, Czech Republic, Denmark, Germany, Italy, Russia, Spain, Turkey and the UK.
 *In the 24 months prior to screening.
 †Use of rituximab was not permitted within 3 months of PREVENT start, nor during the trial.
 CI, confidence interval; IST, immunosuppressive therapy; NMOSD, neuromyelitis optica spectrum disorder; SD, standard deviation.

Figure 1. Risk of adjudicated relapse according to pre-specified regional subgroups



Dotted vertical lines show the proportion of patients receiving placebo in the overall population who experienced a relapse (R) and the HR for the overall population (right). The statistical test for interaction assesses whether the treatment effect varies by the different levels of the subgroup variable.
 *Based on a Cox proportional hazards model, with treatment covariate, and Wald CIs.
 †Based on a Cox proportional hazards model, with interaction term.
 The Americas: Argentina and the USA; the Asia-Pacific region: Australia, Hong Kong, Japan, Korea, Malaysia, Taiwan and Thailand; Europe: Croatia, Czech Republic, Denmark, Germany, Italy, Russia, Spain, Turkey and the UK.
 CI, confidence interval; HR, hazard ratio; IST, immunosuppressive therapy.

Table 2. Relapse-related hospitalization and acute treatment rates according to pre-specified regional subgroups

	Americas (N = 44)		Asia-Pacific (N = 48)		Europe (N = 51)		Overall (N = 143)	
	Eculizumab (n = 29)	Placebo (n = 15)	Eculizumab (n = 35)	Placebo (n = 13)	Eculizumab (n = 32)	Placebo (n = 19)	Eculizumab (n = 96)	Placebo (n = 47)
Patients with relapse-related hospitalization, n (%)	0 (0.0)	2 (13.3)	3 (8.6)	5 (38.5)	3 (9.4)	8 (42.1)	6 (6.3)	15 (31.9)
Annualized relapse-related hospitalization rate* (95% CI)	0.00 (NA, NA)	0.12 (0.03, 0.47)	0.05 (0.02, 0.15)	0.35 (0.14, 0.83)	0.05 (0.01, 0.14)	0.43 (0.22, 0.82)	0.04 (0.02, 0.08)	0.31 (0.19, 0.50)
Patients with a relapse requiring acute treatment, n (%)	2 (6.9)	1 (6.7)	2 (5.7)	2 (15.4)	3 (9.4)	3 (15.8)	7 (7.3)	6 (12.8)
High-dose oral steroids	1 (3.4)	6 (40.0)	4 (11.4)	6 (46.2)	7 (21.9)	10 (52.6)	12 (12.5)	22 (46.8)
IV methylprednisolone	0 (0.0)	1 (6.7)	1 (2.9)	3 (23.1)	3 (9.4)	5 (26.3)	4 (4.2)	9 (19.1)
Plasma exchange	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Annualized relapse-related rate (95% CI) of acute treatment	0.05 (0.01, 0.18)	0.06 (0.01, 0.42)	0.03 (0.01, 0.13)	0.14 (0.03, 0.55)	0.05 (0.01, 0.14)	0.14 (0.05, 0.44)	0.04 (0.02, 0.09)	0.11 (0.05, 0.25)
High-dose oral steroids	0.02 (0.00, 0.16)	0.36 (0.16, 0.79)	0.06 (0.02, 0.17)	0.42 (0.19, 0.93)	0.11 (0.05, 0.23)	0.47 (0.25, 0.88)	0.07 (0.04, 0.12)	0.42 (0.28, 0.64)
IV methylprednisolone	0.00 (NA, NA)	0.06 (0.01, 0.42)	0.02 (0.00, 0.11)	0.21 (0.07, 0.65)	0.05 (0.01, 0.14)	0.28 (0.13, 0.63)	0.02 (0.01, 0.06)	0.19 (0.10, 0.35)
Plasma exchange	0.00 (NA, NA)	0.06 (0.01, 0.42)	0.02 (0.00, 0.11)	0.21 (0.07, 0.65)	0.05 (0.01, 0.14)	0.28 (0.13, 0.63)	0.02 (0.01, 0.06)	0.19 (0.10, 0.35)

CI, confidence interval; IST, immunosuppressive therapy; IV, intravenous; Ig, immunoglobulin; NA, not applicable; NMOSD, neuromyelitis optica spectrum disorder.

Conclusion: Eculizumab significantly reduced relapse rates, relapse-related hospitalizations and acute treatment with IVMPs versus placebo in European patient populations, with potential benefits for healthcare resource utilization in these patients experiencing substantial disease burden.

Disclosure: Research funding for this study was provided by Alexion Pharmaceuticals.

O4010

Efficacy and safety outcomes in patients with relapsing forms of MS treated with the CNS-Penetrating BTK inhibitor SAR442168: results from the phase 2b trial

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Background and aims: SAR442168, a central nervous system (CNS)-penetrating Bruton's tyrosine kinase (BTK) inhibitor, has multiple putative modes of action in MS, targeting antigen-induced B-cell activation and CNS microglia-driven neuroinflammation. We evaluated efficacy and safety of SAR442168 in relapsing MS (RMS).

Methods: The DRI15928 phase 2b study (NCT03889639) is a 16-week, dose-finding, double-blind, randomised, placebo-controlled crossover trial testing 4 SAR442168 doses (5, 15, 30, or 60mg daily, administered orally) in patients with RMS. Patients were randomised 1:1 to receive placebo for 4 weeks before or after receiving one of 4 doses of SAR442168 for 12 weeks, enabling all participants to be treated. Primary/secondary endpoints included radiographic outcomes (new gadolinium [Gd] and new/enlarging T2 lesion activity). Exploratory endpoints included additional MRI outcomes, relapse and disability assessments, and evaluation of plasma-based biomarkers. Safety was assessed throughout the study.

Results: 130 patients were enrolled. At baseline, mean age was 37 years, 70% of patients were women, mean time since MS diagnosis was 5.6 years, mean number of relapses in the previous year was 1.2, and median EDSS score was 2.5. Of 79 patients with available MRI data, 52% had active Gd-enhancing lesions at screening.

Conclusion: Baseline characteristics of patients enrolled in the DRI15928 phase 2b study were consistent with those in the general RMS population. Primary and secondary endpoints, including MRI outcomes and safety and tolerability of SAR442168, will be presented. Exploratory relapse and disability endpoints, and the effect of SAR442168 treatment on levels of plasma-based biomarkers will be shown.

Disclosure: STUDY SUPPORT: Sanofi.

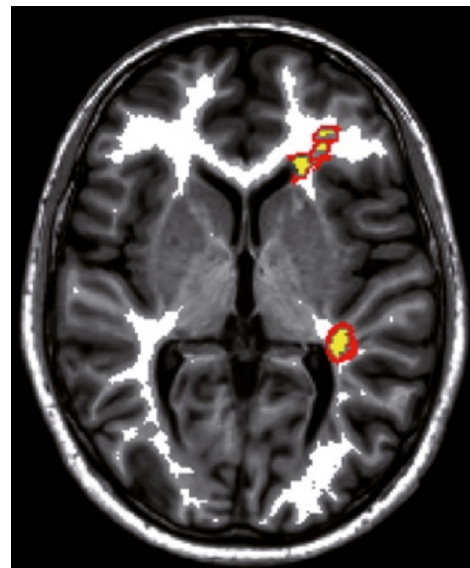
O4011

Exploring the impact of lesional myelin content changes measured with positron emission tomography on perilesional microstructure in multiple sclerosis

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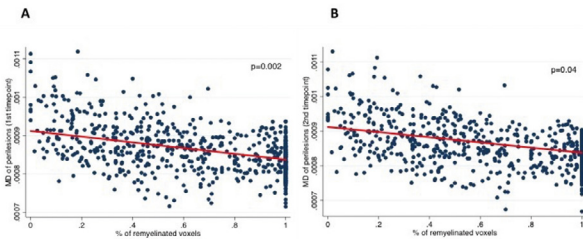
Background and aims: Positron emission tomography (PET) with [11C]PiB allows to explore myelin dynamics in multiple sclerosis (MS). We investigated whether myelin content changes in white matter lesions (WML), measured with [11C]PiB-PET, affect the microstructural integrity in the surrounding normal appearing white matter, as reflected by diffusion tensor imaging (DTI)-derived metrics.

Methods: 19 patients with MS underwent a longitudinal PET/MRI study. Voxel-wise maps of [11C]PiB distribution volume ratio, reflecting myelin content, were employed to calculate for each patient in each non-enhancing WML the percentage of demyelinating voxels at baseline, and the percentage of demyelinating/remyelinating voxels over the follow-up (dynamic indices). After 1mm external lesion erosion to minimize partial volume effects, from each 2mm-thick perilesional area surrounding eroded lesions, mean fractional anisotropy (FA) and mean diffusivity (MD), reflecting microstructural damage, were extracted at both time-points (Fig1). Associations between the 3 PET-derived lesional indices and the DTI-derived perilesional metrics at each time-point were assessed using linear regressions adjusted for age, gender and, for dynamic indices only, baseline demyelination.



Example of 2mm-thick perilesional areas (red) surrounding lesions (yellow) in the white matter of a MS patient on an axial T1-weighted image.

Results: A higher percentage of demyelinated voxels inside lesions at baseline was associated with a more severe tissue damage in perilesions, as reflected by increased MD, at both time-points ($p < 0.0001$). A higher percentage of remyelinating voxels inside lesions correlated with a lower perilesional MD at both time-points, reflecting less severe tissue changes ($p = 0.002$ and $p = 0.04$ at first and second time-point, respectively; adjusted for baseline demyelination, Fig2).



A. Correlation between the normalized percentage of remyelinated voxels inside the lesions and the mean diffusivity (MD) in perilesions at the first (A) and second (B) timepoints. Results were corrected for age, gender and baseline demyelination.

Conclusion: Lesional demyelination, if not compensated by an efficient process of spontaneous myelin repair, results in microstructural damage of perilesional areas.

Disclosure: Nothing to disclose

O4012

Artificial intelligence applied on conventional magnetic resonance images improves the correct diagnosis of CNS diseases mimicking multiple sclerosis

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Background and aims: The diagnostic work-up of patients with suspected multiple sclerosis (MS) may be challenging due to the frequency of brain white matter (WM) hyperintensities on MRI in several neurological conditions. We applied a deep-learning approach for the automated classification of different CNS diseases mimicking MS, comparing the model performance with that of two expert neuroradiologists blinded to diagnosis.

Methods: 268 brain T1-weighted and T2-weighted MRI scans, acquired on 1.5T and 3T MR scanners, were collected from patients with migraine (n=56), MS (n=70), neuromyelitis optica spectrum disorders (NMOSD) (n=91) and CNS vasculitis (n=51). The model architecture, trained on 178 images (Figure 1), was based on a cascade of four 3D convolutional neural network layers followed by a fully dense layer after features extraction. The ability of the final algorithm to correctly classify the diseases in an independent set of 90 MRI was compared with that of 2 expert neuroradiologists.

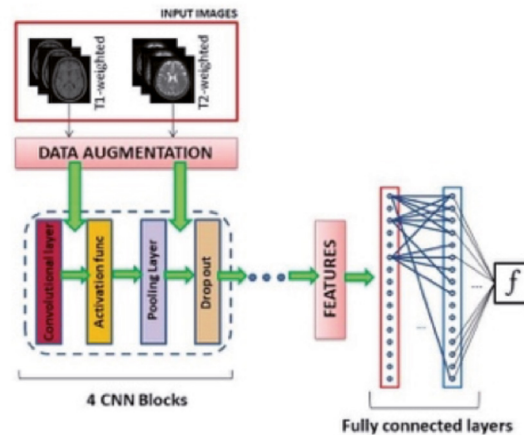


Figure 1. The proposed training architecture for CNS diseases classification. The proposed 4-layer CNN model was trained using multi-sequence 3D images sampled from a subset of training images, where each channel was created from each of the image sequences available and a final model to validate was obtained.

Results: In the test set, the deep-learning algorithm showed higher classification accuracy (92.2% vs 59% for migraine, 98.8% vs 78% for MS, 88.6% vs 4.4% for NMOSD, 92.1% vs 51% for vasculitis) and higher specificity (97.1% vs 88.4% for migraine, 98.4% vs 75.5% for MS, 92.9% vs 92% for NMOSD, 93.2% vs 72.6% for vasculitis) compared with the 2 neuroradiologists ($p=0.01$). The inter-rater agreement was 84.9% (Cohen's kappa=0.78, $p<0.001$, Figure 2).

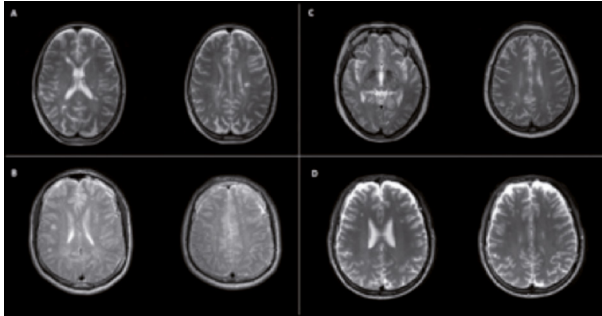


Figure 2. Incorrect diagnoses by human raters. Patients misclassified in agreement by 2 neuroradiologists: A, patient with NMOSD classified as MS; B, patient with migraine classified as CNS vasculitis. Disagreement between the 2 raters: C, patient with NMOSD diagnosed as MS; D, patient with migraine classified as CNS vasculitis.

Conclusion: The classification performance of the deep-learning algorithm exceeded that of 2 expert neuroradiologists, suggesting that artificial intelligence may be a powerful paraclinical tool in the diagnostic work-up of diseases mimicking MS.

Disclosure: Nothing to disclose

Neuro-oncology; neurological manifestations of systemic disease

O4013

Real world clinical features and management of neurotoxicity in CD19 targeted chimeric antigen receptor (CAR) T-cell therapy for high grade lymphoma with off-label use of anakinra

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Background and aims: Immune effector cell-associated neurotoxicity syndrome (ICANS) is a major toxicity complicating CAR T-cell therapy. Presentations and severity are variable, and there remains a clinical need for patients refractory to first line steroid treatment.

Animal models support the use of cytokine targeting therapies such as IL-1 receptor antagonist anakinra. We report our experience of ICANS in a cohort receiving CD19 CAR T-cells, including the first series treated with anakinra.

Methods: Patients with relapsed/refractory B-cell non-Hodgkin lymphoma received axicabtagene ciloleucel (axicel) and tisagenlecleucel (tisagen) between January 2019 and September 2019. Eligibility was determined independently by experts from NHS England and data collected prospectively.

Results: 14 from 43 patients (33%) experienced neurotoxicity, with 7 (16%) having grade 3 or 4. The most common clinical features were dysphasia, delirium, and dyspraxia, while only one patient suffered a self-terminating seizure.

13 patients had neuroimaging, no specific changes were identified. Lumbar puncture performed in 6 patients demonstrated a mild rise in CSF protein (mean 0.96g/L). EEG was performed in 12 patients, almost all (92%) displayed encephalopathic features (generalised rhythmic delta activity) and 2 (17%) had epileptiform foci over the left fronto-temporal region.

Dexamethasone was started for 11 patients, and anakinra administered to 5 patients concurrently for high grade/unresponsive ICANS.

ICANS resolved in all patients surviving to day 30 (n=13), with persistent neurological features in one patient (the sequelae of viral encephalitis) and one sepsis related death.

Conclusion: We describe the clinical features of ICANS in our real-world cohort, and demonstrate feasibility of unresponsive/severe ICANS treatment with anakinra.

Disclosure: Nothing to disclose

O4014

Effects of lentiviral (LV) hematopoietic stem and progenitor cell gene therapy (HSPC-GT) on central and peripheral demyelination and brain atrophy in late-infantile metachromatic leukodystrophy (LI-MLD)

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Background and aims: MLD is a fatal lysosomal disease caused by arylsulfatase A (ARSA) deficiency, leading to accumulation of sulfatides and progressive neurodegeneration, demyelination, and deterioration of motor and cognitive function.

Methods: We have previously reported primary outcomes of 16 LI-MLD patients treated with LV HSPC-GT ("OTL-200", follow-up: 1-7.5 years) compared to a natural history

cohort (NHC) of 19 untreated LI-MLD patients, demonstrating sustained, clinically meaningful benefits in motor function and cognition. Here, we present OTL-200 treatment effects on central and peripheral demyelination and brain atrophy in these 16 LI-MLD patients using brain MRI and nerve conduction velocity (NCV).

Results: ANCOVA modeling showed statistically significant differences in brain MRI total severity scores between OTL-200-treated patients and age-matched NHC patients at year 2 ($p < 0.001$) and year 3 ($p < 0.001$) post-treatment (Figure 1). The score stabilized at lower levels for OTL-200 vs. NHC throughout follow-up ($p < 0.001$, non-linear longitudinal model), suggesting clinically relevant treatment effects on brain demyelination and atrophy. Furthermore, statistically significant differences in NCV Index between OTL-200 vs. NHC at year 2 ($p = 0.004$) and year 3 ($p = 0.010$; Figure 2) were recorded, particularly relevant considering most patients already had signs of PNS impairment at time of treatment. Stabilization or improvement of NCV suggests OTL-200-treated patients may benefit from higher ARSA levels and improved enzyme delivery to the PNS compared to hematopoietic stem cell transplantation (Beerepoot et al. 2019).

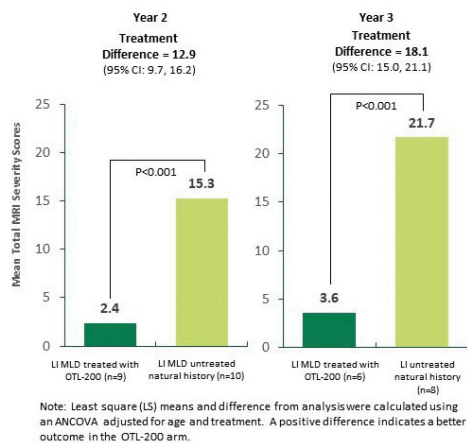


Figure 1: Brain MRI Total Scores at year 2 and year 3, LI-MLD, OTL-200 treated patients with Comparison to Natural History Data (Matched Analysis Set)

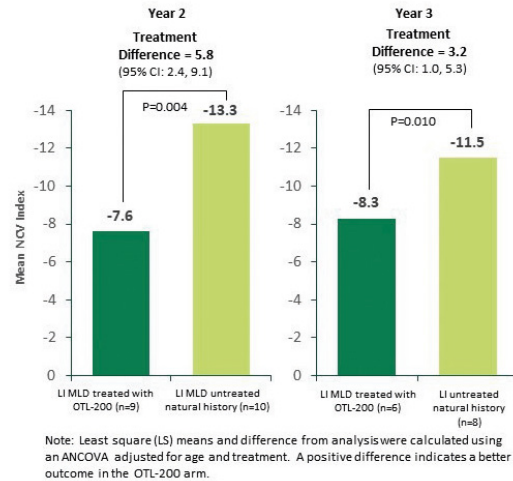


Figure 2: Nerve Conduction Velocity Index at year 2 and year 3, LI-MLD, OTL-200 treated patients with Comparison to Natural History Data (Matched Analysis Set)

Conclusion: Collectively, these results suggest that OTL-200 may prevent, stabilize, or delay the hallmark progressive CNS and PNS damage of LI-MLD, consistent with treatment effects observed on motor function and cognition.

Disclosure: The San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) is a joint venture between Telethon and Ospedale San Raffaele (OSR); MLD gene therapy was licensed to GlaxoSmithKline (GSK) in 2014 and GSK became the clinical trial sponsor; in 2018 MLD development rights were transferred to Orchard Therapeutics (OTL) and OTL became the clinical trial sponsor.

O4015

Reduction in pain during and between attacks in patients with acute hepatic porphyria treated with givosiran: a post-hoc analysis of the phase 3 ENVISION study

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Background and aims: Acute hepatic porphyria (AHP) is a family of rare genetic diseases resulting from enzyme deficiencies in heme biosynthesis. Clinical manifestations include potentially life-threatening neurovisceral attacks and chronic symptoms, with neuropathic pain being the cardinal symptom during and between attacks. In the ENVISION Phase 3 study, givosiran, an RNA interference therapeutic, reduced annualized attack rate ($p < 0.001$), improved daily worse pain (secondary), decreased proportion of days with analgesics use (exploratory) and demonstrated a favorable benefit:risk profile. A post-hoc analysis was conducted to assess reduction in pain and analgesic use during and between attacks.

Methods: ENVISION (NCT03338816), a randomized, double-blind placebo-controlled trial evaluated the efficacy and safety of subcutaneous givosiran in AHP patients (N=94). Daily worst pain, analgesic use (opioid and non-opioid), and the SF-12 health survey were obtained. Analyses are descriptive.

Results: In patients with at least 1 attack, a lower proportion on givosiran (41.7%) compared to placebo (63.2%) had severe pain (median pain score ³7) (Table 1). During attack-free periods, givosiran treatment resulted in reduced daily worst pain scores compared to placebo (Figure 1). This pain reduction was also accompanied by lower analgesic use (Figure 2). The SF-12 Bodily Pain domain demonstrated a greater improvement for givosiran (7.3) versus placebo (2.2) at month 6, suggesting that the reduced pain had a functional impact in patients.

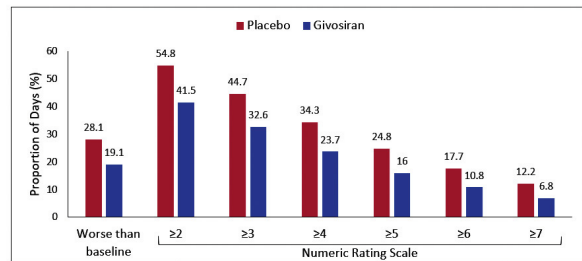
Table 1: Attacks with Median Pain Score ≥ 7 During the 6-Month Double-Blind period in AHP Patients

	Placebo (N=46)	Givosiran (N=48)
Total number of attacks	297	90
Total number of attacks with median pain scores ≥ 7 , n (%)	95 (32.0)	19 (21.1)
Number of patients with at least 1 attack, n (%)	38 (82.6)	24 (50.0)
Number of patients with at least 1 attack with median pain score ≥ 7 , n(%)	24/38 (63.2)	10/24 (41.7)

Attacks included are those requiring hospitalization, urgent care or at home hemin use. Median pain scores of these attacks were calculated based on scores collected during each attack.

Table 1: Attacks with Median Pain Score ≥ 7 During the 6-Month Double-Blind period in AHP Patients

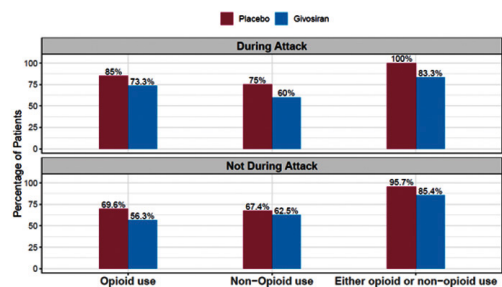
Figure 1. Daily Worst Pain by Numeric Rating Scale on Days Between Attacks During the 6-Month Double-Blind period in AHP Patients



Baseline pain score is the mean score from 4 to 7 days prior to first dose of study drug, when patient not experiencing an attack.

Figure 1. Daily Worst Pain by Numeric Rating Scale on Days Between Attacks During the 6-Month Double-Blind period in AHP Patients

Figure 2. Summary of Analgesic Usage by Attack Status During the 6-Month Double-Blind Period in AHP Patients



All investigator- adjudicated attacks are included.

Figure 2. Summary of Analgesic Usage by Attack Status During the 6-Month Double-Blind Period in AHP Patients

Conclusion: AHP patients on givosiran showed reductions in pain during and between attacks compared to placebo along with decreased analgesic use supporting the potential benefit of givosiran as a disease modifying drug.

Disclosure: This research was funded by Alnylam Pharmaceuticals.

O4016

Neurotoxicity after CAR-T-cell therapy in lymphoma patients: A French neurological multi-center survey

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Background and aims: CAR-T-cell therapy is a promising treatment for haematological malignancies but is frequently associated with cytokine-release syndrome (CRS) and neurotoxicity. The aims of this study are: to follow-up longitudinally patients treated with CAR-T-cell, to exhaustively identify neurological signs, and to describe their occurrence over time.

Methods: During 1 year (July 2018 – June 2019), all patients treated with CD19-targeted CAR-T-cell therapy for relapsing lymphoma were followed-up and monitored for neurotoxicity signs by a neurologist in 4 centres (Paris-Saint-Louis, Lyon, Montpellier, Nantes).

Results: 85 patients, (19-74 years, median 58 years), 28 females/57 males, treated for lymphoma, were included.

Neurotoxicity (presence of at least one neurological sign appearing after treatment infusion) was present in 41% of patients. The median time to onset was 7.7 days after infusion with a median duration of 8.6 days: encephalopathy (43%), cerebellar syndrome (17%), aphasia (23%), headaches (17%), executive syndrome (11%), myoclonus (11%), tremor (11%), agrapahia (9%); meningismus, transverse myelitis, seizure, neglect, dysarthria, neuralgia, dysesthesia: 3%. The severity grade was Grade 1-2: 25 patients, Grade 3-4: 10 patients. CRS was observed in 82% of patients. All patients who developed neurological disorders also had CRS (Grade 1-2: 89%, Grade 3-4: 11%) that preceded neurotoxicity.

Conclusion: The high frequency of neurotoxicity associated with CAR-T therapies underlines the need:

- 1) to neurologically assess all patients before and repeatedly after therapy infusions
- 2) to provide guidelines to improve early recognition of neurotoxicity and its management

Disclosure: Nothing to disclose

O4017

Long-term follow-up of adult neurofibromatosis type 1 patients using whole-body MRI demonstrates dynamic changes in internal neurofibroma size

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Background and aims: Internal neurofibromas (iNFs) affect 40-60% of neurofibromatosis type 1 (NF1) patients and can cause significant morbidity and mortality. They grow more rapidly during childhood and adolescence but adult studies are limited by their retrospective nature and follow-up time <3 years. The long-term natural history of iNFs in adults remains unknown. No guidelines exist on the need and frequency of surveillance imaging. Whole-body MRI (WBMRI) can detect whole-body iNF burden.

Methods: 26 adult NF1 patients who underwent a baseline WBMRI between 2007-2010 underwent follow-up WBMRI between 2018-2019. iNFs were segmented on short tau inversion recovery (STIR) sequences. Tumor volume was calculated using a 3-dimensional tumor quantification software (3DQI). Tumor growth and shrinkage were defined as volume change $\geq 20\%$ over the entire study period.

Results: Median patient age was 42 (baseline) and 52 (follow-up) years. Median time between scans was 9 years. 186 iNFs were assessed (Table 1, Figure 1). 17.7% of tumors grew by a median 68%. 59.1% of tumors spontaneously shrank by a median 59% without treatment. 12 new tumors developed in 10 patients. 18 tumors resolved entirely without intervention. On multivariate analysis, female gender and younger age at baseline were associated with tumor growth ($p < 0.005$).

Number of tumors analysed	186
Median % change in tumor volume	-40.7%
Number of growing tumors (%)	33 (17.7%)
• Median growth (%)	+68%
Number of shrinking tumors (%)	110 (59.1%)
• Median shrinkage (%)	-59%
Number of new tumors (%)	12 (6.5%)
Number of resolved tumors (%)	18 (9.7%)

Table 1. Summary of internal neurofibroma growth behavior in adult NF1 patients

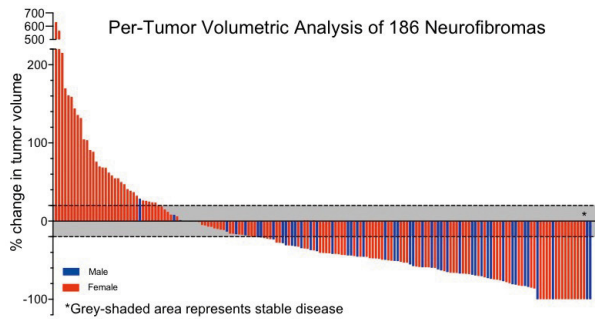


Figure 1. Per-tumor volumetric analysis of 186 neurofibromas summarized as a waterfall plot

Conclusion: A subset of iNFs in adult NF1 patients grow significantly over a long-term period, particularly in female and young adults, suggesting that continued monitoring of high-risk populations is warranted. Surprisingly, more than half of neurofibromas shrink spontaneously without intervention. Continued patient enrollment and correlation of imaging findings with functional outcomes and hormone exposure history are underway.

Disclosure: This research was supported by philanthropic funds to Dr. Scott Plotkin.

O4018

Mechanisms and therapeutic implications of hypermutation in gliomas

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Background and aims: High tumor mutational burden (hypermutation) has been observed in some gliomas; however, its mechanisms of development and whether it predicts immunotherapy response remain poorly understood.

Methods: We comprehensively analyze the molecular determinants of mutational burden and signatures in 10,294 gliomas. We assessed the interactions between DNA damage, repair and the development of hypermutation in patient-derived glioma in vitro and in vivo models. We performed immunohistochemistry, targeted sequencing and single-cell whole genome sequencing to characterize the microenvironment and molecular specificities of hypermutated gliomas. We report the relationship between hypermutation and clinical response to cancer immunotherapy in a pilot cohort.

Results: 2 main pathways to hypermutation were delineated: a de novo pathway associated with constitutional defects in DNA polymerase and mismatch repair (MMR) genes, and a more common post-treatment pathway associated with acquired resistance driven by MMR defects in chemotherapy-sensitive gliomas that recur after temozolomide treatment. Experimentally, the mutational signature of post-treatment hypermutated gliomas was recapitulated by temozolomide-induced damage in cells harboring MMR deficiency. Surprisingly, MMR-deficient gliomas exhibited unique features including the lack of prominent T-cell infiltrates, extensive intratumoral heterogeneity, poor survival and low response rate to PD-1 blockade. Moreover, while microsatellite instability in MMR-deficient gliomas was not detected by bulk analyses, single-cell whole-genome sequencing of post-treatment hypermutated glioma cells demonstrated microsatellite mutations.

Conclusion: This study shows that chemotherapy can drive acquisition of hypermutated populations without promoting response to PD-1 blockade and supports diagnostic use of mutational burden and signatures in cancer.

Disclosure: Nothing to disclose

Sleep disorders 2

O4019

Circadian activity rhythm in isolated REM sleep behavior disorder

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Background and aims: Isolated REM sleep behavior disorder (iRBD) is characterized by abnormal behaviours during REM sleep. Several studies showed that iRBD is a prodromal stage of synucleinopathies. Therefore identifying iRBD in the general population is of utmost importance. In this study we explore whether the assessment of circadian rest-activity rhythm features can distinguish iRBD patients from patients suffering from disorders characterized by other pathological motor activity during sleep and healthy controls.

Methods: 19 subjects with video-polysomnographic (v-PSG) diagnosis of iRBD, 39 subjects with other disorders with motor activity during sleep (19 restless leg syndrome –RLS– and 20 untreated sleep apnea syndrome patients –SAS) and 16 healthy controls underwent 2-week actigraphy, v-PSG, and completed RBD screening questionnaires. Nonparametric analyses were applied to assess rest-activity rhythm features, in addition we computed the I<O index a 24-hours measure that expresses the relationship between nocturnal and diurnal motor activity intensity.

Results: iRBD patients showed lower sleep efficiency, increased WASO and increased frequency of prolonged activity bouts compared to RLS and controls, while no difference emerged with SAS patients. Moreover, iRBD patients presented increased occurrence of estimated nap in comparison to RLS, SAS and controls. The I<O index distinguished iRBD patients from RLS, SAS and controls with an area under the curve greater than that of RBD screening questionnaires.

Conclusion: The I<O index is able to distinguish iRBD patients from patients with other pathological motor activity during sleep and controls, confirming its potential use as an objective measure suitable to screen large at-risk populations.

Disclosure: This study was supported by a grant from the Austrian Science Fund (FWF) to Birgit Högl, I 2120-B27.

O4020

Paroxysmal arousals in Sleep-Related Hypermotor Epilepsy (SHE): the key features to differentiate them from disorders of arousal.

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Background and aims: Sleep-Related Hypermotor Epilepsy (SHE) is a form of focal epilepsy characterized by seizures occurring mostly during sleep ranging from brief paroxysmal arousals (PA) to complex hypermotor seizures and, rarely, ambulatory behaviors. It is difficult to distinguish PA from Disorders of Arousal (DoA), especially from their simplest and shortest episodes called Simple Arousal Movements (SAMs).

Methods: 15 SHE and 30 DoA adult patients and 15 healthy subjects underwent a full-night Video-polysomnography (VPSG). All the sleep-related movements and episodes were analysed by 2 neurologists expert in sleep disorders and epilepsy. For each PA and SAM sleep stage at onset, duration, limbs involvement, progression and semeiology have been identified.

Results: We recorded 121 PA mostly emerging during stage 1-2 NREM sleep, with a median duration of 5 seconds. PA motor pattern at onset was hyperkinetic in 78 episodes (64%), often involving ≥ 3 non-contiguous body parts. A constant progression of movements during PA without any motor arrests was the rule. In DoA patients we recorded 140 SAMs mostly emerging during stage 3 NREM sleep. Their median duration was 12 seconds. In SAMs neither tonic/dystonic nor hypermotor patterns or stereotypy were observed; motor arrest was present in the course of about half of the episodes.

Conclusion: PA in SHE and SAMs in DoA show different semeiological and clinical features. Their recognition could be useful to guide the diagnosis in particular when major episodes are not recorded during VPSG in patients with a clear clinical history of SHE or DoA

Disclosure: Nothing to disclose

O4021

REM sleep behaviour disorder (RBD) and REM sleep without atonia (RWA): a progression marker for Parkinson's disease?

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Background and aims: RBD is associated with neurodegeneration as a diagnostic marker, but there is not enough data about the long-term development of REM Sleep behaviour disorder (RBD) and REM sleep without atonia (RWA) in PD patients. The aim of this study was to investigate the evolution of RWA and RBD in de novo Parkinson's disease (PD) patients prospectively in the DeNoPa cohort Kassel up to 6 years and to detect potential factors influencing this evolution.

Methods: RBD and RWA were analyzed using video-supported polysomnography (vPSG) in a cohort of de novo PD patients (DeNoPa) Kassel. The influence of time, age, gender, levodopa equivalent daily dose (LEDD), MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) ratings and the intake of benzodiazepines on RWA was investigated using mixed-effect models to account for intra-individual correlations.

Results: RBD prevalence increased from 25% at baseline to 56% after 6 years. For 31 PD patients with RBD at 6 years- follow up, vPSG data were available at every visit. In this PD+RBD group, RWA increased from baseline to 6-years follow-up with 0.26 points per 2 years on a logarithmic scale ($p < 0.001$), time was identified as an independent factor ($p < 0.001$) for RWA increase. Age was shown to be an independent factor influencing RWA increase ($p = 0.04$). Gender, LEDD, MDS-UPDRS, and benzodiazepines did not have any statistical significant influence.

Conclusion: RBD and RWA increase significantly over time in PD, so that RBD and RWA may be regarded as progression markers in PD.

Disclosure: This study was supported by unrestricted grants from the University Medical Centre Goettingen, the Paracelsus-Elena-Klinik, Kassel, Germany, the Michael J Fox Foundation for Parkinson's Research (MJFF), ParkinsonFonds Deutschland and from TEVA Pharma.

O4022

Dopaminergic treatment modulates functional brain connectivity in restless legs syndrome

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Background and aims: Functional brain connectivity studies revealed alterations within thalamic, the salience, and default mode network in patients with restless legs syndrome (RLS). Aim of this study was to characterize functional connectivity and network topology in a large cohort of RLS patients compared to healthy controls, and to investigate the modulatory effect of dopaminergic treatment upon connectivity.

Methods: 82 patients with RLS (untreated, $n = 30$; on dopaminergic medication, $n = 42$; on alpha-2-delta ligands as mono- or polytherapy combined with dopaminergic medication, $n = 10$) and 82 age and gender matched healthy controls were studied with resting state functional MRI. We compared connectivity of 12 resting-state networks with independent component analysis, and among 410 brain regions with graph theoretical modeling.

Results: Patients with RLS showed higher connectivity within salience ($p = 0.029$), executive ($p = 0.001$), somatomotor ($p = 0.050$), and cerebellar ($p = 0.041$) networks, as well as lower ($p < 0.05$) cerebello-frontal communication compared to healthy controls. Untreated patients had lower ($p < 0.05$) cerebello-parietal communication compared to healthy controls. Patients on dopaminergic medication showed no significant intra-network connectivity changes, whereas pronounced ($p < 0.05$) between region connectivity was noted between the thalamus and frontal regions compared to untreated patients and healthy controls.

Conclusion: The networks that showed higher intra-network connectivity (i.e. salience, executive, somatomotor, cerebellar) and lower between regions connectivity (i.e. cerebello-frontal, cerebello-parietal) in RLS correspond to regions associated with attention, response inhibitory control, and processing of sensory information. Dopaminergic medication enhances thalamic connectivity to prefrontal brain regions, and hence, might serve as the functional network correlate that mitigates the occurrence of RLS symptoms.

Disclosure: This study was supported by a grant from Translational Research Fund of the government of Tirol, Austria to Dr. Birgit Högl.

O4023

Automated 3D video analysis of lower limb movements during REM sleep: a new diagnostic tool for isolated REM sleep behavior disorder

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Background and aims: The differentiation of isolated REM sleep behavior disorder (iRBD) or its prodromal phase (prodromal RBD) from other disorders with motor activity during sleep is critical for identifying α synucleinopathy in an early stage. Currently, definite RBD diagnosis requires video-polysomnography (vPSG). Aim of this study was to evaluate automated 3D video analysis of leg movements during REM sleep as objective diagnostic tool for iRBD.

Methods: A total of 122 participants (40 iRBD, 18 prodromal RBD, 64 other disorders with motor activity during sleep) were recruited among patients undergoing vPSG at the Sleep Disorders Unit, Department of Neurology, Medical University of Innsbruck. 3D videos synchronous to vPSG were recorded. Lower limb movements rate, duration, extent and intensity were computed using a newly developed software.

Results: The analyzed 3D movement features were significantly increased in subjects with iRBD compared to prodromal RBD and other disorders with motor activity during sleep. Minor leg jerks with a duration <2 seconds discriminated with the highest accuracy (90.4%) iRBD from other motor activity during sleep. Automatic 3D analysis did not differentiate between prodromal RBD and other disorders with motor activity during sleep.

Conclusion: Automated 3D video analysis of leg movements during REM sleep is a promising diagnostic tool for identifying subjects with iRBD in a sleep laboratory population and is able to distinguish iRBD from subjects with other motor activities during sleep. For future application as a screening, further studies should investigate usefulness of this tool when no information about sleep stages from vPSG is available.

Disclosure: This study was funded by the Austrian Science Fund (FWF), Project KLI 677-B31.

O4024

A new incidence peak of childhood narcolepsy type 1 in 2013: a new perspective on the role of influenza virus?

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Background and aims: Increased incidence rates of narcolepsy type 1 (NT1) after the 2009-2010 H1N1 influenza pandemic (pH1N1) have been reported worldwide. While some European countries found an association between the NT1 increase and H1N1 vaccination with Pandemrix, reports from Asian countries suggested the H1N1 virus rather than Pandemrix to be linked with the increase of new NT1 cases. Thus, Pandemrix or the virus itself as potential environmental factor induces NT1, is still not completely understood.

Methods: Using a robust data-driven modelling approach (i.e., locally estimated scatterplot smoothing methods), we analyzed the number of de-novo NT1 cases in the last 2 decades until 2016 using the European Narcolepsy Network (EU-NN) database.

Results: We found the peak of NT1 incidence in both childhood and adulthood NT1 during 2009-2010 pH1N1 in more European countries than we have known before, and identified a new peak in 2013 that is age-specific for

children/adolescents. Most of these de-novo cases showed a subacute disease onset consistent with an immune-mediated type of narcolepsy, which is most likely not related to Pandemrix vaccination that was used in 2009-2010, but may have been triggered by some new epidemiological event in Europe.

Conclusion: Our finding of an unexpected peak in de-novo children narcolepsy in 2013 provides a unique opportunity to develop new hypotheses, such as considering other (influenza) viruses to further investigate the pathophysiology of immune-mediated narcolepsy.

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