Oral Sessions

Saturday, 16 June 2018

Neurological manifestations of systemic diseases

O101

EXPLORE: a prospective, multinational natural history study of patients with acute hepatic porphyria with recurrent attacks

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Background and aims: Acute Hepatic Porphyrias (AHPs) are rare, genetic diseases caused by mutations in the heme pathway. Central to AHPs is the upregulation of aminolevulinic acid synthase1 (ALAS1), the first, rate-limiting enzyme which causes accumulation of neurotoxic heme intermediates, aminolevulinic acid (ALA) and porphobilinogen (PBG). This results in life-threatening attacks and chronic, debilitating manifestations due to injury to the nervous systems, including neurovisceral pain, fatigue, and motor weakness.
Methods: EXPLORE is the first observational study characterizing clinical management of patients with AHPs with ≥3 attacks/year, including patients receiving prophylactic treatment to prevent attacks. We will be presenting updated ≥12 month data.
Results: 112 patients enrolled from 13 countries. Patients reported a mean of 9.3 attacks in 12 months prior to the study, with pain (99%), mood/sleep, and digestive (each 96%) symptoms being the most common. Annualized attack rate on study was 4.9 attacks/person, of which 77% required treatment. For those on hemin prophylactically, mean attack rate/person-year=4.0. Chronic symptoms were reported by 65% of patients, with pain (63%), mood/sleep (44%), and digestive (36%) manifestations most frequent. The EQ5D quality of life score was 66 (1-100); 35% had some difficulty walking and 57% had difficulty with usual activities or anxiety/depression. Mean ALA and PBG levels at screening (during non-attack) were increased to 8Xs and 20Xs ULN, respectively.
Conclusion: EXPLORE demonstrates that patients suffer from chronic symptoms in addition to frequent attacks that decrease quality of life. Given morbidity and mortality, there remains an unmet need for novel therapies to prevent attacks and treat chronic symptoms.
Disclosure: This is supported by Alnylam.

O102

Clinical characterisation of Wilson's Disease patients: a retrospective study at a tertiary-care centre in Lisbon

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Background and aims: Wilson's Disease (WD) is an autosomal recessive metabolic disorder caused by ATP7B gene mutations, producing toxic copper accumulation, mainly in the liver and the brain. We aim to characterise the population of patients with WD followed at our centre and to identify possible factors that may correlate with neurological involvement in WD.
Methods: We identified all patients with the diagnosis of WD listed in our centre's database between 2009 and 2017. We reviewed case records and collected clinical, laboratorial, genetic and imaging data.
Results: We identified 24 patients, 17 (81%) of them were females. Median age at diagnosis was 17 years (SD±14). ATP7B gene sequencing result reported c.2123T>C as the most frequent mutation. Mixed hepatic and neurological presentation was the most common form (45.8%, 11 cases). Pure hepatic and neurological presentations were found in 10 (41.7%) and 3 (12.5%) patients, respectively. Patients with neurological involvement were older at diagnosis than patients with only hepatic involvement (29 vs. 17 years). Rigidity, bradykinesia and tremor were the most reported neurological signs, with bradykinesia being more frequent in the younger patients. Normal liver transaminase levels at diagnosis correlated with presence of neurological disease (p=0.000034). Six patients with neurological symptoms presented brain MRI changes compatible with WD. Follow-up reported improvement with treatment in 8/11 (73%) patients with neurological symptoms.
Conclusion: Initial assessment of liver transaminase levels may help to identify WD patients who are more likely to develop in time neurological symptoms, alerting to the need of regular neurological evaluations.
Disclosure: Nothing to disclose

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O103

Impact of Patisiran, an investigational RNAi Therapeutic, on nutritional status in patients with hereditary Transthyretin-Mediated Amyloidosis

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Background and aims: Patients with hereditary transthyretin mediated amyloidosis (hATTR), a multi-systemic, rapidly-progressive, life-threatening disease, often have poor nutritional status and overall weight loss due in part to severe gastrointestinal manifestations as well as cardiac disease. In the phase 3 APOLLO study, Patisiran demonstrated significant improvements in neuropathy (mNIS+7) and quality of life (QOL) compared to placebo in hATTR amyloidosis patients with polyneuropathy, and was generally well-tolerated. We present the impact of Patisiran on nutritional status, as measured by modified body mass index (mBMI) the APOLLO study.

Methods: APOLLO was a multi-center, international, randomized (2:1), double-blind study of Patisiran 0.3mg/kg or placebo IV q3W in hATTR amyloidosis patients with polyneuropathy (NCT01960348). Primary endpoint was change from baseline at 18-months in mNIS+7. One of the secondary endpoints was change in mBMI, defined as the product of BMI and albumin levels.

Results: APOLLO enrolled 225 patients: mean age 60.5 years (24-83), 74% males and 43% V30M. At baseline, mBMI was similar in the Patisiran and placebo groups. In the placebo group, mBMI declined by a LS mean of 119.4 kg/m2 x g/L over 18-months relative to baseline, whereas LS mean decline was only 3.7 with Patisiran. This improvement compared to placebo was seen as early as 3-months of treatment with Patisiran.

Conclusion: Patients treated with Patisiran maintained their nutritional status over 18 months. The favorable effect of Patisiran on mBMI relative to placebo indicates stabilization of mBMI decline in hATTR amyloidosis patients, therefore improving overall nutritional status.

Disclosure: This research was supported by Alnylam Pharmaceuticals.

O104

Impact of prior TTR stabilizer use in patients with hereditary Transthyretin-Mediated Amyloidosis in the APOLLO phase-3 study of Patisiran

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Background and aims: Hereditary transthyretin-mediated (hATTR) amyloidosis is a multi-systemic, life-threatening disease caused by transthyretin (TTR) mutations resulting in TTR protein destabilization forming multi-organ amyloid fibril deposits. TTR tetramer stabilizers have been used in hATTR amyloidosis patients; however, some studies have shown disease progression is still observed. In the APOLLO study, Patisiran, an investigational RNAi therapeutic, resulted in significant improvement in neuropathy (mNIS+7) and Norfolk Quality of Life Diabetic Neuropathy (Norfolk QOL-DN) compared to placebo in hATTR amyloidosis patients and was generally well-tolerated. We evaluated the impact of prior treatment with TTR tetramer stabilizers on Patisiran efficacy from the APOLLO study.

Methods: APOLLO was a Phase 3, randomized (2:1), double-blind, study of patisiran 0.3mg/kg or placebo IV q3W (NCT01960348) in hATTR amyloidosis patients with polyneuropathy. Primary endpoint was change from baseline at 18-months in mNIS+7. TTR tetramer stabilizer discontinuation was required 14 or 3 days prior to study entry for tafamidis or diflunisal, respectively.

Results: APOLLO enrolled 225 patients: mean age 60.5 years (24-83); 74% males; 43% V30M. Prior to study entry, 53% of patients had previously received a TTR stabilizer (Tafamidis: n=74(33%); Diflunisal; n=45(20%). An

improvement in mNIS+7 and Norfolk QOL-DN was seen in patients with or without prior stabilizer use (Table 1) at 18-months. Additional efficacy and safety data to be presented.

Analysis	Patient Population	Placebo Patients (n)	Patisiran Patients (n)	LS Mean Treatment Difference (Patisiran-Placebo)	95% Confidence Interval
mNIS+7	Overall	77	148	-34.0	-39.9,-28.1
	Previous Stabilizer Use	25	76	-38.3	-46.1,-30.5
	No Previous Stabilizer Use	26	61	-29.9	-39.1,-20.8
Norfolk QOL-DN	Overall	77	148	-21.1	-27.2,-15.0
	Previous Stabilizer Use	41	78	-17.6	-25.7,-9.4
	No Previous Stabilizer Use	36	70	-25.9	-36.2,-15.6

Table 1. mNIS+7 and Norfolk QOL-DN Results

Conclusion: Patisiran demonstrated significant benefit relative to placebo in mNIS+7 and Norfolk QOL-DN in patients with or without prior TTR tetramer stabilizer use, thus providing evidence that hATTR amyloidosis patients with prior stabilizer use may benefit from Patisiran.

Disclosure: This research was supported by Alnylam Pharmaceuticals.

O105

Phase 1/2, randomized, placebo controlled and open-label extension studies of Givosiran an investigational RNA interference (RNAi) therapeutic, in patients with Acute Intermittent Porphyria

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Background and aims: Acute hepatic porphyrias (AHPs) are rare genetic diseases resulting from loss-of-function mutations that cause upregulation of Aminolevulinic Acid Synthase 1 (ALAS1), the first and rate-limiting enzyme in the heme pathway. The resulting accumulation of neurotoxic intermediates Aminolevulinic Acid (ALA) and porphobilinogen (PBG) leads to neurovisceral attacks and chronic symptoms. Common neurological symptoms include pain, fatigue, muscle weakness, peripheral neuropathy, and neuropsychological manifestations. Givosiran acts via RNA interference (RNAi) to inhibit liver ALAS1 synthesis.

Methods: A Phase 1/2 (ClinicalTrials.gov Identifier: NCT02452372), multinational study evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of subcutaneously administered Givosiran (2.5mg/kg monthly). Impact on clinical activity, including chronic symptoms, annualized attack rates, and hemin use were explored. Patients completing the study were eligible for the open label extension (OLE) study (NCT0294983).

Results: Givosiran was generally well tolerated with no clinically significant laboratory abnormalities related to study drug. One unexpected serious adverse event (SAE; hypersensitivity) related to Givosiran occurred. Urinary ALA and PBG were reduced by 77% and 76% versus baseline, respectively. Additionally, Givosiran decreased mean annualized attack rate versus placebo by 73% and decreased annualized hemin doses versus run-in period by 73%. The OLE (n=8) data showed maintenance of clinical activity as observed in Phase 1.

Conclusion: Givosiran was generally well-tolerated and resulted in rapid and durable lowering of neurotoxic intermediates. ALA and PBG lowering were associated with marked reductions in both the annualised attack rate and hemin use. Complete Phase 1/2 and interim OLE data will be presented.

Disclosure: This was supported by Alnylam Pharmaceuticals

Movement disorders 1

O107

Glucose dysregulation in advanced Parkinson's Disease: too much glucose or not enough insulin?

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Background and aims: Glucose metabolism has recently been reported to be altered in Parkinson's Disease (PD) as a non-motor consequence of the disease. Since insulin pancreatic production and secretion is modulated by the autonomic nervous system, the severity of dysautonomia in PD could be linked with blood glucose dysregulation. We aimed to detect changes in glucose regulation in PD patients compared to healthy controls in response to oral glucose intake.
Methods: Blood glucose and insulin kinetics during a 75-g Oral Glucose Tolerance Test were compared between 50 PD patients and 50 healthy controls (CT) matched for Body Mass Index (BMI), age and sex. Potential relationships between changes in glucose kinetics and clinical parameters were analyzed including PD severity and autonomic function using SCOPA-AUT (Scales for Outcomes in Parkinson's disease, Autonomic dysfunction).
Results: Blood glucose was significantly higher at T90 ($p=0.04$) and T150 ($p=0.01$) in PD patients compared to CT. Moreover, the total area under time curve for blood glucose was significantly higher in PD patients compared to healthy controls (1187±229 vs 1101±201 mmol.min.l-1; $p=0.05$). Simultaneously, no significant increase of insulin levels was observed in PD patients compared to controls. Higher blood glucose levels were associated with higher BMI ($p<0.001$), female gender ($p<0.033$), longer duration of PD ($p=0.001$), lower dose of dopaminergic treatment ($p=0.023$), and higher score of dysautonomia ($p=0.017$).
Conclusion: Glucose control is impaired in advanced non-diabetic PD patients, due to impaired adaptive insulin response which may be a novel non-motor consequence of PD associated dysautonomia.
Disclosure: Nothing to disclose

O108

Skin nerve phosphorylated α-synuclein deposits in Parkinson's disease with orthostatic hypotension

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Background and aims: We aimed to investigate phosphorylated α-synuclein (p-syn) deposits in skin nerves and clinical characteristics in patients with Parkinson's Disease (PD) and Orthostatic Hypotension (OH) vs PD patients without dysautonomia (PD-OH) to clarify the peripheral nerves involvement in these two conditions.
Methods: We enrolled 28 idiopathic PD patients with abnormal nigro-striatal DatScan and cardiac MIBG: 1) 14 PD+OH; and 2) 14 disease duration matched PD-OH; 7 of them were re-evaluated over a long follow-up (4±2 years). Corrected Mini-Mental State Examination (MMSEc) was normal in all recruited patients. All patients underwent skin biopsy in proximal (i.e. C7 paravertebral spine region) and distal (i.e. thigh and leg) sites.
Results: PD+OH patients showed a higher incidence of REM sleep behavior disorder (RBD) than PD-OH. PD+OH showed a higher p-syn deposition than PD-OH with a widespread autonomic cholinergic and adrenergic skin nerves involvement. Over the follow-up PD-OH patients showed a marked increase in motor dysfunctions scores without autonomic symptoms and a slight increase of skin p-syn deposition but still lower than PD+OH.
Conclusion: 1) PD+OH showed a wide involvement of p-syn deposits in autonomic cholinergic and adrenergic skin nerves and higher incidence of RBD compared to PD-OH; 2) skin p-syn in PD-OH was mainly restricted to adrenergic fibers of skin vessels. A slight increase of skin p-syn deposition was found over a follow-up but still lower than PD+OH. These data supported a different pathogenesis between PD+OH and PD-OH and may help to identify a specific diagnostic trait for PD+OH patients.
Disclosure: Nothing to disclose

O109

Clinical predictors of screen-defined dementia in early Parkinson's disease

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Background and aims: Predicting early dementia in Parkinson's disease (PD) has important implications for individual prognosis, designing clinical trials and targeting novel treatments, but there remains a lack of evidence in this area. This study examined which clinical factors predicted early dementia in a large cohort of early PD subjects.

Methods: Parkinson's patients assessed within 3.5 years of diagnosis were recruited between 2010-2015 (the Discovery cohort, UK) and then re-assessed after 18 months. The Montreal cognitive assessment was used to assess cognition, using a score of <23 for screen-defined dementia. A broad spectrum of other motor and non-motor symptoms were also assessed. A logistic regression model with a backward stepwise selection was used to determine which baseline clinical assessments were independent predictors of dementia at 18 months.

Results: 61 of the 488 included PD patients developed new dementia at 18 month follow-up. Older age at diagnosis with poor performance on phonemic fluency, cube copying, and the Purdue assembly task were all included in the final model as independent predictors of dementia (figure 1).
The area under the ROC curve for this model is estimated at 0.81 (95% CI 0.74-0.89) (figure 2).

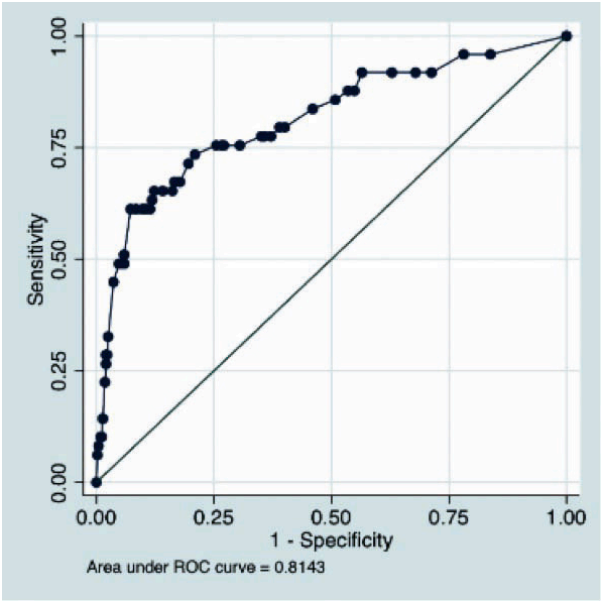

Figure 1 - Odds ratios of model for factors predicting dementia, with their 95% confidence intervals. Age at diagnosis was analysed as a 5 level ordinal variable, cube copying errors was analysed as a 3 level ordinal variable, and both phonemic fluency and purdue assembly were analysed as a dichotomous variables (poor performers <20th centile).

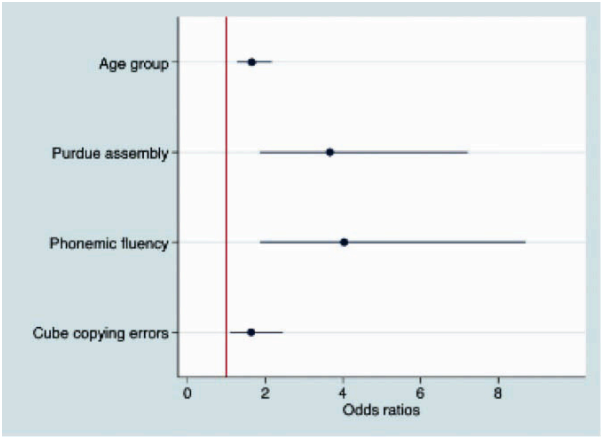

Figure 2 - ROC curve depicting model of factors predicting dementia including age at diagnosis, Purdue assembly task, phonemic fluency and cube copying connection errors.

Conclusion: Poor performance on three simple clinical tests performed early in PD (the Purdue assembly task, phonemic fluency and cube copying) can be used to predict early dementia. This has implications for both clinical practice and clinical trials.

Disclosure: This study was funded by the Monument Trust Discovery Award from Parkinson's UK and supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre based at Oxford University Hospitals NHS Trust and University of Oxford, and the NIHR Clinical Research Network: Thames Valley and South Midlands.

O110

Temporal evolution of biomarkers in isolated REM sleep behavior disorder and early Parkinson's disease

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Background and aims: We aimed to study the temporal evolution of biomarkers of various modalities in healthy ageing controls (HC), the prodromal condition of idiopathic REM sleep behavior disorder (iRBD) and in Parkinson's disease (PD).
Methods: We investigated previously identified biomarkers for early PD in 34 iRBD subjects and compared these to 88 HC and 91 PD patients. We stratified the PD group into 31 patients with RBD (PD+RBD) and 60 patients without (PD-RBD). Baseline and follow-up investigations after 24 months covered questionnaires On Non-Motor signs (NMS), cognitive testing, video-polysomnography (PSG), ECG, olfactory testing, magnetic resonance imaging with Voxel Based Morphometry (VBM) and Cerebrospinal Fluid (CSF) measures.
Results: Most biomarkers in the iRBD group lay between HC and the PD groups. ECG frequency, that was elevated in PD, was normal in iRBD and HC ($p<0.01$). Other biomarkers already showed abnormalities similar to PD: a high NMS burden ($p<0.01$) and a non-significant decrease of β-amyloid 1-42 and total tau protein in CSF. There was also a trend towards more abnormalities in iRBD patients compared to the PD group, but did not reach statistical significance: more severe hippocampal atrophy by VBM, more pronounced cognitive decline. The CSF levels of α-synuclein were lower in the iRBD compared to the PD+RBD group ($p=0.03$)
Conclusion: In prodromal PD abnormalities in NMS, imaging and fluidic markers are already obviously pointing towards the development of overt disease. Based on these results iRBD represents a prodromal state of various α-synuclein aggregation disorders and may develop into a specific, motor phenotype.
Disclosure: The study was supported by unrestricted research grants from the Paracelsus-Elena-Klinik, Kassel, TEVA Pharma/Lundbeck, GE Healthcare and the Parkinson Fonds Deutschland.

O111

Brain Lewy body density is associated with a lower prevalence of artherosclerotic cardiovascular disease risk factors in patients with Parkinson's disease

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Background and aims: Epidemiological studies suggest that Atherosclerotic Cardiovascular Disease (ASCVD) risk factors increase the risk of developing Parkinson's disease (PD). However, conflicting data suggest lower rates of ASCVD in PD. The objective of this study is to determine, with data from a longitudinal clinicopathological study, whether ASCVD risk factors are associated with a PD diagnosis and/or brain alpha-synuclein pathology load.
Methods: All subjects were enrolled in the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND). Multivariable logistic regression models, including age, gender, and smoking history, were used to investigate the association of a PD diagnosis or brain alpha-synuclein pathology load with ASCVD risk factors
Results: 150 subjects were included (PD n=60, controls n=90). The regression models showed significant inverse associations. The multivariable Odds Ratio (OR) of brain alpha-synuclein pathology load for carotid artery disease was 0.93 (95% CI: .86 to .98; $p=0.02$), for anticoagulant use .95 (95% CI: .90 to .99; $p=0.04$) and for lower heart weight .96 (95% CI: .92 to .99; $p=0.01$).
Conclusion: This study shows a significant association of higher brain alpha-synuclein pathology load with a lower prevalence of both clinical and pathologic indices of ASCVD in PD subjects versus age-similar controls. We hypothesize this is due to alpha-synuclein pathology-induced sympathetic denervation in PD.
Disclosure: Nothing to disclose

O112

Multimodal MRI markers modifications in Multiple System Atrophy: a longitudinal study

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Background and aims: Multimodal MRI (mMRI) approach is based on combination of MRI parameters sensitive to different tissue characteristics (e.g. volume atrophy, iron deposition, and microstructural damage). The combination of different MR biomarkers could help to discriminate different pathologies with parkinsonian syndrome (Péran et al. Mov Disord.; 2018). Using mMRI, the aim of the study was to evaluate brain changes due to disease progression in Multiple System Atrophy (MSA) patients.
Methods: 19 MSA patients underwent 3-T MRI exam twice at time of inclusion and after one year of follow-up. This MRI comprised: T2*-weighted, T1-weighted and diffusion tensor imaging scans. We used the same method as in the previous work (Péran et al., Brain, 2010) to extract MRI markers (grey density, R2* value, mean diffusity (MD) and fractional anisotropy). The GD, R2*, MD, and FA maps were compared using non-parametric paired t-tests. Statistical significance threshold was set to $p<.05$ corrected for family wise error.
Results: Figure 1 shows changes due to disease progression from voxel-based analysis in R2* (red), MD (green) and FA (blue) maps. The main results showed significant increase of MD in brainstem and in cerebellum. MSA patients showed also lower FA mainly in left inferior longitudinal fasciculus. Additionally, MSA patients showed a decrease of R2* mainly in cerebellum and in fusiform gyrus. We did not find significant modifications for GD maps.

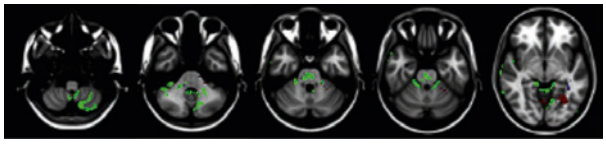

Figure 1

Conclusion: This study demonstrates that mMRI is able to detect longitudinal modifications after one year of MSA progression. Further analyses are on-going to determine the relationships between clinical and MRI markers.
Disclosure: Nothing to disclose

MS and related disorders 1

O113

Spinal cord area is a stronger predictor of physical disability than brain volume in secondary progressive Multiple Sclerosis

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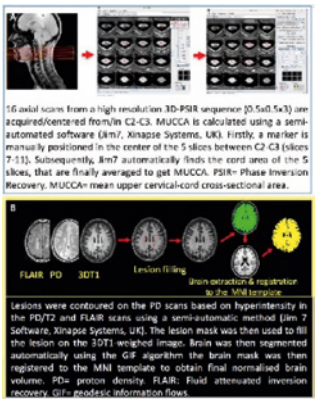
Background and aims: Spinal cord atrophy may be a more sensitive measure of disability worsening than brain atrophy in Multiple Sclerosis (MS).

We aimed at investigate the contribution of spinal cord area and brain volume to disability in people with secondary progressive MS (SPMS).

Methods: A group of SPMS patients randomised in a phase 2 clinical trial (MS-SMART) were included in this study. Patients underwent neurological assessments, brain and cervical cord MRI. We measured the following MRI and clinical parameters: Mean Upper Cervical-Cord Cross-Sectional Area (Mucca), Normalised Brain Volume (Nbv), Expanded Disability Status Scale (Edss), Ms Functional composite (MSFC), and Symbol Digit Modalities Test (SDMT). We analysed associations of MRI variables with clinical scores using multivariable linear regression models adjusting for age and gender. Fig.1A-B shows the MRI analysis pipelines.

Fig. 1A-B MRI analysis pipeline A: cross-sectional area of the cervical cord at C2-C3 level. B: normalised brain volume analysis.

Results: Sixty subjects were analysed. The baseline characteristics are shown in Table 1. Multivariable linear regression analyses (Fig.2) showed that MUCCA (standardised-beta= -0.35, standard-error [SE]=0.12, p=0.005) and NBV (standardised-beta= -0.32, SE=0.14; p=0.02) were independently associated with EDSS. MUCCA, but not NBV, was significantly associated with MSFC (standardised-beta=0.28 SE=0.13; p=0.031). Both MUCCA (standardised-beta=0.3 SE=0.12; p=0.013) and NBV (standardised-beta=0.42, SE=0.14; p=0.006) were independently associated with SDMT.



16 axial scans from a high resolution 3D-PSIR sequence (0.5x0.5x3) are acquired/centered from/in C2-C3. MUCCA is calculated using a semi-automated software (Jim7, Xinapse Systems, UK). Firstly, a marker is manually positioned in the center of the 5 slices between C2-C3 (slices 7-11). Subsequently, Jim7 automatically finds the cord area of the 5 slices, that are finally averaged to get MUCCA. PSIR= Phase Inversion Recovery. MUCCA= mean upper cervical-cord cross-sectional area.

Lesions were contoured on the PD scans based on hyperintensity in the PD/T2 and FLAIR scans using a semi-automatic method (Jim 7 Software, Xinapse Systems, UK). The lesion mask was then used to fill the lesion on the 3DT1-weighed image. Brain was then segmented automatically using the GIF algorithm the brain mask was then registered to the MNI template to obtain final normalised brain volume. PD= proton density. FLAIR: Fluid attenuated inversion recovery. GIF= geodesic information flows.

Table 1. Baseline characteristics of the patients

Variable	All subjects N= 60
Age (years) mean (SD)	53.8 (7)
Gender (female:male)	23:37
Disease duration (years) mean (SD)	23.4 (8.9)
EDSS median (range)	6 (4-6.5)
SDMT (correct answers) median (range)	49 (17-70)
MSFC mean (SD)	0.13 (0.52)
MUCCA (mm^2) mean (SD)	67.4 (10.3)
NBV (ml) mean (SD)	1398.4 (89.2)

SD= standard deviation. EDSS= expanded disability status scale. SDMT= symbol digit modalities test. MSFC= multiple sclerosis functional composite. MUCCA= mean upper cervical-cord cross-sectional area. NBV= normalised brain volume.

Fig.2 Multivariable linear regression plots of the statistically significant associations. Plots are based on raw data (i.e. non-standardised data) for a better understanding of the relationships.

Conclusion: MUCCA was the strongest predictor of EDSS, NBV the strongest predictor of SDMT, and MUCCA the only predictor of MSFC. Our findings demonstrate that spinal cord area shows increasing promise as a marker of disability in progressive disease.

Disclosure: The MS-SMART (NCT01910259) trial is a project funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. It is also supported by the UK and National Multiple Sclerosis Society; the National Institute for Health Research University College London Hospitals Biomedical Research Centre and University College London; NIHR Leeds CRF (DenTCRU). CJW and RP were supported in this work by NHS Lothian via the ECTU. The remaining authors declare no conflict of interests with respect to this work.

O114

Long-term prognosis of disease evolution and evidence for sustained Fingolimod treatment effect by plasma neurofilament light in RRMS patients

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Background and aims: Neurofilament light chain (NfL), an intracellular protein exclusively expressed by neurons, is elevated in the cerebrospinal fluid and blood of patients with multiple sclerosis (MS). We studied the mid- and long-term prognostic potential of plasma NfL for disease evolution and progression and long-term fingolimod effect on plasma NfL levels in patients with relapsing–remitting MS (RRMS).

Methods: Plasma NfL was measured at baseline (N=542), Month (M) 6 (N=467), M12 (N=471), M24 (N=225), and M120 (N=79) using Single Molecule Array (SIMOA) technology in participants from two Phase 3 studies (pooled FREEDOMS, TRANSFORMS) who continued fingolimod treatment in an extension study until M120. The relationship between NfL levels in the initial 12 months (NfL-area under the curve [AUC] classified as low, <30pg/mL; medium, 30–60pg/mL; and high, >60pg/mL) and MS outcomes was assessed using regression models adjusted for age, log[baseline NfL] and baseline characteristics.

Results: At M48, assignment to the high NfL-AUC category compared with low NfL-AUC predicted time to (TT) first relapse, mean cumulative number of new T2 lesions, annual rate of brain atrophy, TT EDSS>=4, TT SPMS and 6M-confirmed disease worsening. NfL levels in patients taking fingolimod were reduced and remained low relative to baseline (from 29.9 to 21.6pg/mL at M24 and from 30.6 to 18.4pg/mL at M120; $p<0.0001$, both).

Conclusion: Our data support the value of plasma NfL as a mid- to long-term prognostic biomarker of disease evolution and progression in RRMS. The reduction of NfL levels achieved by fingolimod treatment was sustained over 10 years.

Disclosure: This study was funded by Novartis Pharma AG, Basel, Switzerland. Detailed disclosure of each author will be included in the poster/oral presentation.

O115

Alemtuzumab provides durable clinical efficacy in patients with active rrms in the absence of continuous treatment: 7-Year follow-up of CARE-MS I (TOPAZ Study)

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Background and aims: In CARE-MS I (NCT00530348), alemtuzumab 12 mg/day (baseline: 5 days; 12 months later: 3 days) significantly improved clinical/MRI outcomes versus SC IFNB-1a over 2 years in treatment-naive RRMS patients. Durable efficacy was observed in a 4-years extension (NCT00930553; 95% of CARE-MS I patients enrolled, 92% completed Y6), in which patients could receive alemtuzumab retreatment as-needed for relapse/MRI activity or receive other DMTs per investigator's discretion. Further evaluation is ongoing (TOPAZ extension; NCT02255656). We present efficacy/safety outcomes over 7 years (2 years core study plus 4 years extension and TOPAZ Y1) in alemtuzumab-treated patients from CARE-MS I.

Methods: Assessments: Annualised relapse rate (ARR); EDSS scores; 6-month confirmed disability worsening (CDW); 6-month confirmed disability improvement (CDI); no evidence of disease activity (NEDA); and AEs.

Results: 299 patients (93%) completed TOPAZ Y1. 59% received neither alemtuzumab retreatment nor other DMT after the initial 2 courses. ARR remained low (Y7: 0.13); 60% were relapse-free in Y3 7. The percentage with stable/improved EDSS scores versus baseline remained high at Y7 (78% [improved, 21%; stable, 57%]). The mean change in EDSS score from baseline to Y7 was 0.09. At Y7, 74% were 6-month CDW-free; 37% achieved 6-month CDI. The majority of patients achieved NEDA each year (Y7: 61%). Overall AE incidence decreased over time.

Conclusion: Alemtuzumab efficacy was maintained for 7 years in treatment-naive patients, despite 59% receiving no additional treatment since the initial 2 courses. Alemtuzumab

safety profile remained consistent. Alemtuzumab provides a unique treatment approach for RRMS patients, offering durable efficacy without continuous treatment.
Disclosure: Study supported by Sanofi and Bayer HealthCare Pharmaceuticals.

O116

Effects of Fingolimod on MRI outcomes in patients with paediatric-onset Multiple Sclerosis: results from the Phase-3 PARADIGMS study

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Background and aims: Approximately 3–5% of Multiple Sclerosis (MS) cases manifest in childhood and adolescence, characteristically with highly active inflammatory disease course. Paediatric-onset MS (POMS) has an impact on brain integrity and may increase Brain Volume Loss (BVL) above age-expected rates. This study assessed the effect of oral Fingolimod up to 0.5mg daily versus intramuscular interferon (IFN) beta-1a 30µg once weekly on MRI outcomes in POMS patients.
Methods: In this double-blind, double-dummy, active-controlled, multicentre study, patients with POMS (aged 10–<18 years) received either Fingolimod (dose adjusted for body weight; N=107) or IFN beta-1a (N=107) for up to 2 years. MRI was performed at baseline and every 6 months until the End Of The Study (EOS) core phase. Key MRI outcomes were the number of new/newly enlarging T2 (n/neT2) lesions and Gd-enhancing T1 (Gd+T1) lesions, Annual Rate Of Brain Volume Change (ARBVC), annualised rate of number of new T1 hypointense lesions, change in total T2 Hyperintense Lesion Volume (T2LV) and the number of Combined Unique Active Lesions (CUAL).
Results: At the EOS, compared with IFN beta-1a, fingolimod significantly reduced the annualised rate of n/neT2 lesions (52.6%; $p<0.001$), number of Gd+T1 lesions per scan (66.0%; $p<0.001$), ARBVC (−0.48% vs. −0.80%, $p=0.014$), annualised rate of number of new T1 hypointense lesions (62.8%; $p<0.001$), T2LV (percent change from baseline: 18.4% vs. 32.4%, $p<0.001$) and CUAL per scan (60.7%; $p<0.001$).
Conclusion: Fingolimod significantly reduced MRI activity and slowed BVL for up to 2 years vs. IFN beta-1a in paediatric-onset MS.
Disclosure: This study was funded by Novartis Pharma AG, Basel, Switzerland. Detailed disclosure of each author will be included in the poster.

O117

Characterizing the Slowly Evolving Lesions (SELs) in a cohort of secondary progressive Multiple Sclerosis patients

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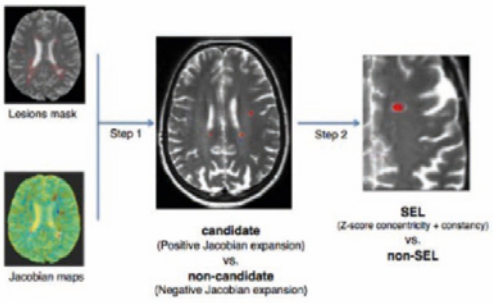
Background and aims: There is a need to develop markers of progression in Multiple Sclerosis (MS). Slowly Evolving Lesions (SELs) on MRI have been recently identified in longitudinal trials of Primary Progressive MS (PP-MS) using non-linear registration-based analysis techniques [1]. Magnetization Transfer Ratio (MTR) highly correlates with demyelination and axonal loss within MS lesions [2].

[1] C. Elliott, J.S. Wolinsky, SL Hauser, L. Kappos et al. "Detection and characterisation of slowly evolving lesions in multiple sclerosis using conventional brain MRI." Presented at the 7th Joint ECTRIMS and ACTRIMS Meeting, Paris 27 Oct 2017.

[2] K. Schmierer, F. Scaravilli, D. R. Altmann, G. J. Barker, and D. H. Miller, "Magnetization transfer ratio and myelin in postmortem multiple sclerosis brain," *Ann. Neurol.*, vol. 56, no. 3, pp. 407–415, Sep. 2004.

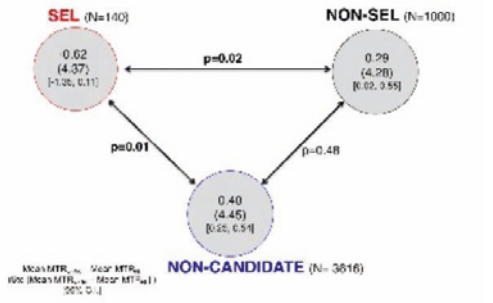
Methods: We included 79 secondary progressive (SP-MS) patients from the MS-SMART trial (NCT01912059) who underwent brain PD/T2, FLAIR and MTR scans at baseline, 24 and 96 weeks. Manually delineated lesions showing Jacobian expansion were selected as "candidates". Final SELs were chosen through a sum score of their concentricity and constancy (figure 1). We calculated baseline MTR values within the different lesion types (SEL, non-SEL and non-candidates) and compared MTR changes from baseline to 96-week.

Figure 1. Two-steps selection of SELs



Results: From 4756 lesions screened, 1140 candidates were identified and ultimately 140 SELs (2.9%) were detected. Baseline MTR within SEL was lower compared to the non-SELs and non-candidates (24.51, 26.26 and 28.89, respectively; p-values<0.001). MTR decrease between baseline and week 96 within SELs was significantly greater compared to non-SELs (p=0.02) and to non-candidates (p=0.01) (Figure 2). In contrast, there were no significant differences in MTR change between non-SEL and non-candidates (p=0.50).

Figure 2. MTR change baseline – week 96



Conclusion: We confirm that, as in PP-MS, there are lesions in SP-MS that can be classified as SELs. Given their more destructive signature on MTR, SELs are promising biomarkers of chronic plaque evolution in progressive MS. Future studies will investigate whether there is a relationship between the occurrence of SELs and clinical disability.

Disclosure: AC, FDA, FP, NJ, AD, JS, DM declare no conflicts of interests. CT acknowledges 2015 ECTRIMS fellowship. OC received research funding from: UK and National MS Society, Rosetrees trust, NIHR UCLH BRC, Biogen, Novartis, Roche, Genzyme, Teva. JC has received support from NIHR, UK MS Society and National MS Society, Receptos, Novartis, Biogen Idec, Roche, Merck, MedDay, Apitope. FB serves as as consultant for Bayer Shering Pharma, Sanofi-Aventis, Biogen-Idec, TEVA, Genzyme, Merck-Serono, Novartis, Roche, Synthon, Jansen Research, Lundbecok, BRC.

O118

Characterizing dynamic functional network connectivity in the main clinical phenotypes of Multiple Sclerosis

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Background and aims: Resting-state (RS) dynamic Functional Network Connectivity (dFNC) in Multiple Sclerosis (MS) has rarely been studied. Here, we investigated dFNC changes occurring in MS patients according to their clinical phenotype.

Methods: RS fMRI data were acquired from 126 MS patients and 40 healthy controls (HC). There were 52 relapsing remitting (RR) MS, 16 benign (B) MS, 34 secondary progressive (SP) MS and 24 primary progressive (PP) MS patients. Between-group dFNC differences in 42 relevant networks were assessed: 1) in MS patients vs HC, and 2) among different clinical MS phenotypes.

Results: Clustering analysis revealed 3 dFNC states in HC and MS patients: State 1 (frequency=57%, low dFNC strength), State 2 (frequency=19%, middle-high dFNC strength), and State 3 (frequency=24%, low FNC strength except for high dFNC strength in the sensorimotor and visual networks). Compared to HC, MS patients showed an overall reduction of dFNC in the main sensorimotor, cognitive and subcortical networks, while increased dFNC was found for the frontal-attention network. The same pattern of dFNC changes was detected when comparing RRMS and PPMS patients vs HC. Compared to RRMS, SPMS showed strong dFNC reductions in most functional networks, mainly in States 2 and 3, and a markedly increased dFNC for the frontal-attention network in States 1 and 2. Conversely, frontal-attention dFNC was significantly decreased in BMS vs RRMS patients.

Conclusion: Significant dFNC changes contribute to explain MS phenotypic heterogeneity. While the prevalent reduction of dFNC might reflect the progressive accumulation of structural damage, compensatory/maladaptative mechanisms may take place in frontal/attentional circuits.

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Peripheral nerve disorders 1

O119

Axonal function predicts response to subcutaneous immunoglobulin in chronic inflammatory demyelinating polyneuropathy: the PATH study

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Background and aims: Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is an immune mediated disease starting with functional impairment and demyelination; in later stages, axonal degeneration may occur.
Methods: PATH was a randomised, double-blind study investigating 0.2 (low) and 0.4 g/kg (high) weekly doses of maintenance SCIG IgPro20 (Hizentra®, CSL Behring) versus placebo (N=172). After Ig dependency testing, and IVIG restabilisation, patients were randomised to SCIG or placebo for 25 weeks or until early termination. Nerve conduction studies (NCS) were performed before study drug administration. Relapse rate (defined as a 1 point increase by adjusted Inflammatory Neuropathy Cause and Treatment score) comparisons were undertaken on patients with assumed non-axonal damage versus assumed axonal damage based on cut-off amplitudes at the distal stimulation site: 1 mV for the foot and 2 mV for the wrist.
Results: Patients with assumed non-axonal damage who received placebo had a 73% relapse rate versus 39% on low-dose and 19% on high-dose SCIG. Patients with assumed axonal damage had relapse rates of 25%, 30% and 19% for placebo, low-dose and high-dose SCIG, respectively.
Conclusion: CIDP patients with assumed non-axonal damage had a high relapse rate when switched from IVIG to placebo that was significantly reduced in patients switched to SCIG therapy. Relapse rates were lower in assumed axonal damage patients and were not influenced by SCIG. These findings could help in redesigning future trials including maintenance regimens based on NCS categorisation of patients.
Disclosure: This study was sponsored by CSL Behring.

O120

Corneal confocal microscopy and skin biopsy in the evaluation of diabetic small fiber neuropathy

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Background and aims: Corneal Confocal Microscopy (CCM) is a comparatively new diagnostic method that enables morphological evaluation of small sensory nerve fibers in the cornea. Currently, Intraepidermal Nerve Fiber Density (IENFD) is considered a gold standard for the diagnosis of Small Fiber Neuropathy (SFN). The aim was to compare sensitivity of CCM and IENFD in the detection of SFN in patients with Diabetic distal symmetrical Polyneuropathy (DPN).
Methods: A group of 81 patients with the diagnosis of definite DPN (mean age 58.2; 50 men, 31 women; 27 patients had painful DPN - pDPN) based on clinical signs and symptoms and nerve conduction studies, and a group of 32 healthy controls (HC) of similar age and gender were assessed using skin biopsy and CCM with evaluation of Corneal Nerve Fiber Density (CNFD), Length (CNFL), Branch Density (CFBD) and Tortuosity (CNFT).
Results: All CCM parameters showed significantly higher proportion of abnormal values not only in DPN group compared to HC ($p<0.001$), but the proportion of abnormalities of all CCM parameters (except CNFT) was significantly higher in pDPN subgroup compared to non-painful cases ($p<0.05$). CCM sensitivity in detection of SFN in DPN group was similar (72%) to that of IENFD (74%). Individual values of CCM parameters, however, showed insignificant correlation with IENFD values ($p<0.05$).
Conclusion: CCM is able to prove significant involvement of small sensory nerve fibers in patients with symptomatic DPN with comparable sensitivity as IENFD obtained via semi-invasive skin biopsy procedure. Higher proportion of CCM abnormalities in pDPN possibly reflects higher severity of neuropathy in painful cases.
Disclosure: Nothing to disclose

O121

Charcot-Marie-Tooth disease type 4B with myelin outfoldings (CMT4B): a multicentre retrospective study

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Background and aims: Charcot-Marie-Tooth neuropathy B1 and B2 (CMT4B1/B2) are characterized by recessive inheritance, early onset, severe course, slowed nerve conduction, myelin outfoldings, loss-of-function mutations in Myotubularin-related protein-2 and -13 (MTMR2, MTMR13/SBF2), respectively, involved in phosphoinositides metabolism. We conducted a multicentre retrospective study to better characterise CMT4B in view of possible clinical trials.

Methods: In 16 centres, we collected clinical, genetic, instrumental data from CMT4B subjects.

Results: There were 44 patients (27 CMT4B1, 17 CMT4B2). CMT4B1 patients were younger and with earlier onset than CMT4B2. Onset age: 2.8+/-2.8 years (range 0-13) in CMT4B1, 7.6+/-8.7 (1-36) in CMT4B2; delayed motor milestones in 14/26 CMT4B1 and 4/17 CMT4B2 subjects. Twelve CMT4B1 but only two CMT4B2 patients became chair-bound. Both types are characterised by vocal cord involvement (10/25 CMT4B1, 9/17 CMT4B2); respiratory involvement was seen almost exclusively in CMT4B1 patients (n=8, four NIV, one tracheostomy; one CMT4B2 patient on NIV). Glaucoma (n=6) and buphthalmos (n=3) occurred only in CMT4B2.

CMTNS and CMTES-motor scores were significantly higher in CMT4B1 patients in spite of their younger age, indicating more severe disease: CMT4B1=CMTES mean 17.9+/-5.9 (n=20; range 9-28/28), CMTNS mean 30.1+/-4.7 (n=10; 19-36/36), CMTES-motor mean 13.2+/-2.9 (n=21; 8-16/16); CMT4B2=CMTES mean 15.8+/-4.4 (n=17; 6-24/28), CMTNS mean 23+/-5 (n=16; 13-32/36); CMTES-motor mean 9.2+/-3.9 (n=17; 4-16/16).

Conclusion: CMT4B1 is more severe than CMT4B2. MTMR2, a catalytically active phosphatase, interacts with MTMR13, which is known to increase MTMR2 enzymatic activity but is catalytically inactive. CMT4B2 nerves may have a residual enzymatic activity of MTMR2 which results in less severe phenotype than CMT4B1.

Disclosure: Partly supported by LAM Therapeutics

O122

Cryoglobulinaemia-associated peripheral neuropathies: clinical characteristics and prognosis from 20 years experience of neuromuscular clinic

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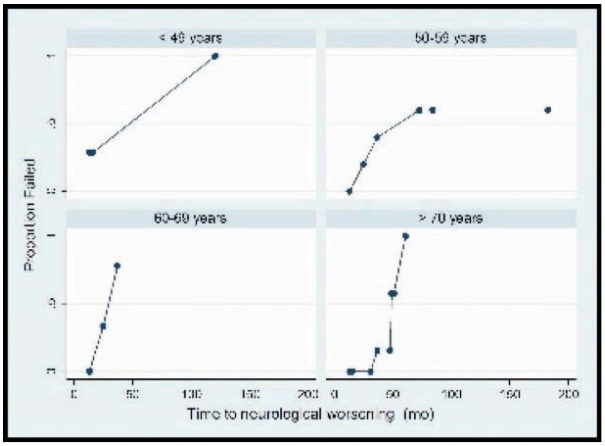
Background and aims: Cryoglobulinaemia is associated with peripheral neuropathies. We assessed prognostic role of clinical and neurophysiological variables among 28 patients over 20 years.

Methods: 28 patients with cryoglobulinaemia-associated neuropathy were enrolled at University of Modena during period 1998-2017. Evaluated independent clinical variables were gender, age at onset, cryoglobulin type, HCV co-infection, type of neuropathy (axonal or demyelinating), copathologies, therapies. Degree of neurological involvement (mild, moderate, severe) was assessed using disability scales (MRC, INCAT, tremor rating scale) and electrophysiological examinations. Probability of death or neurological worsening was estimated from binomial, multinomial, ordered logistic regression, Cox models. P-values <0.05 were considered significant.

Results: 20 patients were female (71%; M:F ratio 1:2.5). Median age was 66 years (range 31-83). Median follow-up time was 33 months. Eighteen patients had type II cryoglobulins (64%), 7 type III (25%), 3 type I (11%). 16 patients had HCV-RNA (57%). Sensorymotor demyelinating neuropathy was prevalent (65%). Neuropathy was mild in 46.3%, moderate in 32.1%, severe in 23% of patients. Cumulative incidence of worsening over time was 39%. None of independent variables had predictive role on neurological worsening or death, except type II cryoglobulin at multivariable ordered logistic regression (OR 12.5, 95% CI 1.24-126, p 0.03). HCV co-infection showed borderline significance (OR 3.93, 95% CI 0.86-17.8, p 0.07). Kaplan-Meyer estimate of worsening in respect of stratified age at onset showed more severe course in subjects above 70 years.



Graph 1

Conclusion: Type II cryoglobulins was associated with more severe peripheral neuropathy especially in aged subjects.
Disclosure: Nothing to disclose

O123

Long-term efficacy and safety of Inotersen in patients with hereditary transthyretin (hATTR) amyloidosis treated in the open-label extension of the phase-3 study NEURO-TTR

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Background and aims: hATTR is a rare, progressive, fatal disease manifested by systemic build-up of TTR protein, resulting in organ failure. The disease causes significant morbidity and progressive decline in Quality of Life (QOL) and robs patients of their independence owing to limitations on activities of daily living. We report results of the Open-Label Extension (OLE) study of NEURO-TTR, highlighting the long-term efficacy and safety of inotersen, an antisense oligonucleotide inhibitor of TTR protein production, in patients with hATTR.
Methods: Patients with hATTR who completed the double-blind, placebo-controlled, phase 3 study NEURO-TTR (NCT01737398) were eligible to receive Inotersen (300-mg weekly subcutaneous doses) for up to 5 years in this OLE. The OLE monitored adverse events and change from baseline in the Norfolk Quality of Life—Diabetic Neuropathy (Norfolk QOL-DN) total score (136 points total, higher scores indicate worse QOL) and modified neuropathy impairment score +7 (mNIS+7) (346 points total, higher scores indicate worse neuropathy).
Results: At the time of the interim analysis, 114 patients had enrolled in the OLE. Most patients were white (95%) and male (70%), and, at OLE baseline, mean age was 61.4 years and 69% of patients had cardiomyopathy. Mean disease duration from time of symptom onset to OLE baseline was 81.8 months. Mean OLE baseline mNIS+7 composite scores and Norfolk QOL-DN total scores were 92.0 and 55.2, respectively. One-year OLE follow-up results will be presented.
Conclusion: Results of the OLE showed continued benefit, as measured by Norfolk QOL-DN and mNIS+7. No new safety concerns were identified.
Disclosure: This study was sponsored by Ionis Pharmaceuticals (Carlsbad, CA, USA).

Neurogenetics

O124

Estimated lifetime prevalences of autosomal mitochondrial disorders based on allele frequencies of pathogenic variants in exome databases

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Background and aims: Currently, only limited epidemiological data about mitochondrial diseases are reported, and a large proportion of them may be seriously underestimated. We expected to provide an accurate description approximating the actual prevalence of autosomal mitochondrial diseases.
Methods: We estimated the lifetime prevalence of autosomal mitochondrial diseases based on the allele frequency of pathogenic and likely pathogenic variants using the Hardy-Weinberg equilibrium. 22 autosomal recessive mitochondrial disorders were assessed (Table). Publicly available exome databases (gnomAD) and our in-house database as of August 2017 were queried to collect a list of variants of all candidate genes. Phenylketonuria (PKU) served as a proof of concept to verify the validity of our method.
Results: The estimated lifetime prevalence of PKU was 15.4 (12.1-19.3)/100,000, thus being very similar to the numbers known from the German newborn screening (18.7 (21.6-16.9)/100,000). The total estimated lifetime prevalence of the 22 investigated autosomal mitochondrial disorders was 14.0 (9.6-20.3)/100,000 in our in-house database, 16.8 (14.6-19.5)/100,000 in European (Non-Finnish) population and 10.0 (8.8-11.4)/100,000 in worldwide population according to the gnomAD dataset. The individual estimated lifetime prevalences of the 22 investigated disorders can be provided upon request.
Conclusion: In view of the marked difficulties in performing traditional epidemiological studies in rare disorders, the estimation of lifetime prevalences by using allele frequencies of pathogenic variants in exome databases seems to be a useful approach.
Disclosure: Nothing to disclose

O125

UFM1 founder mutation in the Roma population causes severe variant of Hypomyelination with Atrophy of the Basal ganglia and Cerebellum (H-ABC)

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Background and aims: Hypomyelination with Atrophy of the Basal ganglia and Cerebellum (H-ABC) is a rare leukodystrophy caused by dominant mutations in TUBB4A. A few cases are negative for TUBB4A mutations. We aimed at identifying a second gene defect in H-ABC.
Methods: We performed homozygosity mapping and Whole Exome Sequencing (WES) to detect the disease-causing variant. We used a Taqman assay for population screening. We developed a luciferase reporter construct to investigate the effect of the promoter mutation on expression.
Results: 16 patients fulfilling the MRI criteria for H-ABC presented distinctive caudate nucleus abnormalities (figure 1) and exhibited severe encephalopathy. The majority had a Roma ethnic background. Single nucleotide polymorphism array analysis in 5 patients identified one large overlapping homozygous region on chromosome 13. WES in 2 patients revealed a homozygous deletion in the promoter region of UFM1. Sanger sequencing confirmed homozygosity for this variant in all patients. All patients shared a common haplotype, indicative of a founder effect. Screening of 1000 controls from different European Roma panels demonstrated an overall carrier rate of the mutation of 4.5% (range 3% up to 25% in a small isolate). Transfection assays showed that the deletion reduced expression in specific central nervous system cell lines.

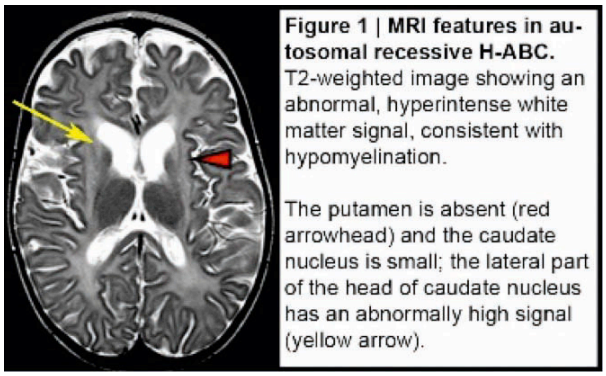

Figure 1 | MRI features in autosomal recessive H-ABC. T2-weighted image showing an abnormal, hyperintense white matter signal, consistent with hypomyelination.

The putamen is absent (red arrowhead) and the caudate nucleus is small; the lateral part of the head of caudate nucleus has an abnormally high signal (yellow arrow).

Conclusion: UFM1 encodes ubiquitin-fold modifier 1 (UFM1), a member of the ubiquitin-like family involved in posttranslational modification of proteins. Its exact biological role is unclear. This study is the first to associate a UFM1 gene defect with a disease phenotype and sheds new light on possible UFM1 functional networks.
Disclosure: Nothing to disclose

O126

Phenotypic and neuroimaging expression of NKX6-2 mutations lead to a new distinct disease with spastic ataxia and hypomyelination

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Background and aims: Despite advances in genetic testing a large number of hyopomyelinating disorders remain a genetic mystery. We identified a new distinct phenotype of spastic-ataxia with hyopomyelination negative for previously known hyopomyelinating genes.
Methods: We used a combination of homozygozity mapping, exome sequencing, immunobloting, clinical and neuroimaging for novel gene discovery. Using gene expression and network analysis with Weighed Genes Co-expression we placed the new gene within a regulatory pathway.
Results: We mapped this phenotype to deleterious bi-allellic mutations in NKX6-2 in 14 cases of different ethnic backgrounds providing evidence for a high NKX6-2 mutation burden in hypomyelinating leukodystrophy disease spectrum. We show that the phenotypic and neuroimaging expression in NKX6-2 is mutation-specific and that phenotypes with epilepsy in the absence of overt hypomyelination, as well as diffuse hypomyelination without seizures can occur. Our data suggests that the phenotypic consequences of NKX6-2 mutations is classified in three main subgroups: severe global psychomotor delay with widespread hypomyelination, spastic-ataxia with hypomyelination and spastic-ataxia with seizures.In-silico analysis of human brain expression and network data shows that NKX6-2 is involved in oligodendrocyte maturation and may act within the same pathways of genes already associated with central hypomyelination.
Conclusion: Combining genetic, phenotypic and functional data this study contributes with the discovery of novel NKX6-2 pathogenic mutations and provides new insights into NKX6-2 related disease. Therefore, our case series suggests that NKX6-2 mutations should be considered in patients with autosomal recessive, very early onset of nystagmus, cerebellar ataxia with spasticity particularly when associated with typical neuroimaging signs of hypomyelination.
Disclosure: Nothing to disclose

O127

The natural history of mitochondrial stroke-like episodes: observational cohort study from the UK

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Background and aims: Stroke-Like Episodes (SLE) are one of the most devastating neurological features identified in mitochondrial disease. However, the natural history of SLE due to different genotypes is not well characterised.

Methods: An observational, national cohort study over an 18-year period (2000-2017).

Results: 108 patients presenting with SLE were identified. The most common genetic defect was the m.3243A>G mutation (66%), followed by recessive POLG mutations (20%) and other mtDNA point mutations (14%). The mean age of occurrence of the first SLE was significantly higher in mtDNA group compared to POLG group (35 vs 19 years, $p<0.001$). Patients with POLG mutations were more likely to present with an explosive onset SLE without preceding clinical symptoms compared to mtDNA mutations (47% vs 9%, $p<0.001$). Common neurological features associated with SLE were headache, focal seizures (motor and/or occipital), visual field loss and dysphasia. MRI signal abnormalities involving the parietal and occipital lobes were common, irrespective of the genotype. Stroke-like lesions involving the prefrontal cortex and thalamic lesions were more common in POLG than mtDNA mutations (frontal: 32% vs. 13%; thalamic: 53% vs. 10%, $p<0.05$). Higher mortality was observed in POLG group compared to the mtDNA group (62% vs. 38%, $p=0.049$) during the follow-up; the mean age of death was significantly different between two groups (28 vs 46 years, $p=0.001$) (Figure 1).

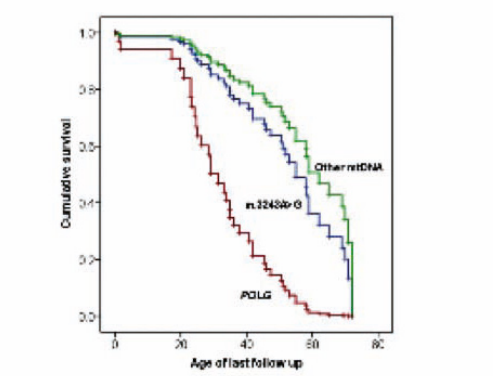

Figure 1. Comparison of survival in different genotypes. Log rank, $p<0.001$

Conclusion: These findings highlight that focal seizures are intrinsic to the development of SLE and the outcomes are dependent on the underlying genetic defect.

Disclosure: This work was supported by The Wellcome Trust (203105), Newcastle University Centre for Ageing and Vitality, UK NIHR Biomedical Research Centre for Ageing and Age-related disease award to the Newcastle upon Tyne Hospitals NHS Foundation Trust, NIHR and the UK NHS Specialist Commissioners which funds the "Rare Mitochondrial Disorders of Adults and Children" Diagnostic Service in Newcastle upon Tyne, London and Oxford. This work also received infrastructure support from the UK MRC Centre Mitochondrial Disease Patient Cohort (13/NE/0326). YSN holds an NIHR Clinical Lectureship in Neurology. RP and MH are supported by an MRC grant (G0601943).

O128

Next Generation Sequencing results in an Italian cohort of hereditary optic neuropathy patients

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Background and aims: Hereditary Optic Neuropathies (HON) have a common pathophysiologic mechanism involving in most cases mitochondrial dysfunction. In more than 50% of cases the causative genes are unknown. Next Generation Sequencing (NGS) allows screening simultaneously several candidate genes. We aimed at genetically screening consecutive HON patients negative for LHON and OPA1 mutations.

Methods: Using the Illumina sequencing platform, we designed a custom panel of 35 targeted nuclear genes already described or suspected to be causative for HON, syndromic or non-syndromic. So far, we investigated 129 unrelated HON probands.

Results: Mutations in HON related genes were identified in 47/129 cases (36%), even if in 24 cases these variants must be further validated (segregation analysis, in vitro studies). Among the 23 consolidated positive results, we found mutations in ACO2 (n=5), AFG3L2 (n=5), WFS1 (n=4), OPA1 (n=4), SPG7 (n=2), RTN4IP1 (n=1), SDHA (n=1) and TMEM126A (n=1) genes. The most frequent mutated genes in our cohort (including also the cases under validation) were WFS1, ACO2 and AFG3L2. Interestingly, AFG3L2 gene mutations, previously described only in two non-syndromic HON families, were found in additional five families. Also its paralogous gene, SPG7, has been found mutated in two additional recessive cases with isolated ON. Finally, ACO2 turns out as a frequent gene associated with not-syndromic HON.

Conclusion: In conclusion, NGS-based diagnostics improves the rate of successful identification of unsolved HON cases, enlarging their genetic landscape. Furthermore, this approach allowed expanding the clinical spectrum of genes involved in mitochondrial functions previously associated with multisystemic disorders.

Disclosure: Nothing to disclose

O129

A randomized trial of Deferiprone for Pantothenate Kinase-Associated Neurodegeneration (PKAN)

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Background and aims: Pantothenate Kinase-Associated Neurodegeneration (PKAN) is the most common form of Neurodegeneration with Brain Iron Accumulation (NBIA), a heterogeneous group of rare hereditary neurodegenerative disorders. Treatment with an appropriate iron chelator holds promise to decrease brain iron levels in NBIA, which may slow or stop disease progression.

Methods: Randomized, double-blind, placebo-controlled trial designed to evaluate efficacy and safety of deferiprone (DFP) in PKAN. Patients were randomly assigned in a 2:1 ratio to receive DFP or placebo for 18 months.

Results: Of 100 screened subjects, 89 were enrolled, with 59 randomized to DFP and 30 to placebo. After 18 months, there was a marked decrease of iron in the globus pallidus (as measured by quantitative MRI R2* mapping) in the DFP group (R2* change -36.1 Hz) but virtually no change in the placebo group (R2* change -0.5 Hz, $p<0.0001$). The primary endpoint was a change in the total Barry-Albright dystonia scale. Patients in both treatment groups worsened over time but the progression in the DFP group was slower (-2.48 points) than that in the placebo group (-3.99 points). The overall difference between the two groups approached statistical significance ($p=0.0761$) and was significant in favor of Deferiprone for patients with atypical PKAN. DFP was associated with an excellent safety profile.

Conclusion: DFP led to marked reduction of iron accumulation in the brain and showed a trend towards slowing of clinical progression in this devastating disease. Upcoming data from an open extension trial will provide additional data on 36 months of DFP treatment.

Disclosure: This study was funded by the European Commission 7th Framework Programme (FP7/2007-2013, HEALTH-F2-2011, grant agreement No. 277984, TIRCON). Study drug and Placebo as well as additional funding was provided by the drug manufacturer, ApoPharma Inc., Toronto, Canada.

Neuroimmunology

O130

Neurofilament Light chain (NfL) serum concentration reflects disease severity in patients with MOG-Ab associated disorders

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Background and aims: Neurofilament Light chain (NfL) is a marker of axonal injury, increased in Serum/Cerebrospinal Fluid (CSF) of patients with several neurological disorders, including inflammatory conditions associated with Myelin Oligodendrocyte Glycoprotein Antibodies (MOG-Ab). Analysis of NfL levels according to clinical status has never been reported in this condition.
Methods: We collected clinical, MRI, and laboratory data of consecutive patients positive for serum MOG-Ab, tested with a live-cell immunofluorescence assay at the Neuropathology Laboratory, University of Verona, between March 2014 and December 2017. Serum and, when available, CSF and follow-up samples were analysed for NfL concentration using a high sensitive technology (Simoa, Quanterix). A group of aquaporin-4 antibodies (AQP4-Ab) positive cases and Healthy Controls (HC) were also included.
Results: 48 patients were enrolled (25 MOG-Ab positive, 11 AQP4-Ab positive and 12 HC) with comparable age at first sampling. Serum NfL concentration was higher in MOG-Ab positive subjects (median 11.4 pg/ml, range 2.5-97) than in HC (median 6.62, range 3.76-11.54) and, to a lesser extent, AQP4-Ab positive cases (median 8.8, range 2-80.3). NfL levels were higher in MOG-Ab positive patients with a severe attack at sampling (severe motor impairment/severe encephalopathy/severe visual impairment with visual acuity <2; median 17.15, range 4-97) compared with cases with a mild-to-moderate event (median 10.9, range 2.5-21.4) and tended to decrease during the follow-up. Further analyses according to other clinical features and MRI status are ongoing.
Conclusion: Our data confirm the presence of axonal damage in MOG-ab associated disorders and support the role of NfL as possible biomarker in these diseases.
Disclosure: Nothing to disclose

O131

Mimics of Autoimmune Encephalitis

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Background and aims: The identification of multiple antibodies has evoked a growing interest in Autoimmune Encephalitis (AIE), especially as these are treatable. The recently published criteria for AIE include a novel diagnosis of "presumed seronegative AIE", a diagnosis by exclusion and based on strict criteria. The aim of our study was to evaluate these criteria, determine the occurrence for AIE mimics and how to differentiate these from AIE.
Methods: In this retrospective cohort study, we included children and adults referred for AIE to our academic center for neuro-inflammation, the Dutch national reference center (July 2016-December 2017). Ancillary testing included lumbar puncture, MRI, and cerebral biopsy when considered necessary. All patients underwent extensive antibody testing in serum or CSF. Patients were classified according to the 2016 Graus criteria.
Results: 93 patients were referred, 62% female. The median age was 50 years (range 1-79). Antibodies were identified in 45 patients, while 15 patients fulfilled criteria for specific neuroinflammatory disorders (like CLIPPERS). Seronegative AIE was diagnosed in 10 patients, while the other 23 had AIE mimics. Most frequently AIE mimics were CNS malignancies, primary psychiatric disorders and functional disorders (all n=4). Confounding factors were non-specific antibodies (like VGKC or TPO), false positive cell-based assays, and (temporary) steroid responsiveness.
Conclusion: AIE mimics are found within the group of seronegative AIE and AIE associated with non-specific antibodies. AIE is a diagnosis not to miss, but physicians should avoid making this diagnosis lightly, as treatment and prognosis differ.
Disclosure: This research project is partially funded by the Dutch epilepsy foundation (NEF, project 14-19) and the Netherlands Organisation for Scientific Research (NWO).

O132

Evaluation of treatment response in adults with relapsing MOG-Ab associated

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Background and aims: Myelin Oligodendrocyte Glycoprotein Antibodies (MOG-Ab) in adult patients are related to relapsing acquired demyelinating syndromes. However, the treatment response in this population is currently unknown. We aimed to describe the clinical characteristics at first attack, and response to different therapies strategies in adult patients with relapsing MOG-Ab-associated diseases

Methods: Retrospective study from France and Spain including 125 relapsing (≥2 episodes) patients aged ≥18. First, we performed survival analysis to investigate time to relapse between treated with immunosuppressants (Azathioprine, Mycophenolate Mophetil, [MMF], rituximab, cyclophosphamide or corticoids/immunoglobulins), Multiple Sclerosis (MS)-disease Modifying Drugs (DMD) and non-treated patients, adjusting by a Propensity Score method. Second, we Assessed Annualized Relapse Rates (ARR) and disability pretreatment and on-treatment, in those patients with at least 6 months of follow-up

Results: Median age at onset was 34.1 years (range 18.0-67.1), the female:male ratio 1.2:1 and 96% were caucasian. After a median follow-up of 53.7 months (range 2.0-564.5), 82 (65%) patients had received immunosuppresants, and 10 (8%) MS-DMD. Patients starting immunosuppressants were at lower risk to experience a further relapse in comparison to non-treated (HR 0.51, 95%CI, 0.29-0.95; $p<0.025$). No differences were observed between MS-DMD and non-treated patients. ARR mean (standard deviation) was reduced from 1.05 (1.20) to 0.42(0.79) with Azathioprine (n=11, p=0.040), from 1.19(1.11) to 0.23(0.60) with MMF (n=11, p=0.032), and from 1.08(0.98) to 0.42(0.88) with rituximab (n=26, p= 0.010). No differences were observed with MS-DMD.

Conclusion: In adults with relapsing MOG-Ab-associated diseases, immunosuppressant therapy (Azathioprine, MMF and Rituximab) but no MS-DMD is associated with reduced risk of further relapse.

Disclosure: Nothing to disclose

O133

Syndrome and outcome of antibody-negative limbic encephalitis

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Background and aims: To report the clinical characteristics of 12 patients with limbic encephalitis (LE) who were antibody-negative after a comprehensive immunological study.

Methods: Review of clinical records of 163 patients with LE. Immunohistochemistry on rat brain, cultured neurons, and cell-based assays were used to identify neuronal autoantibodies. Patients were included if 1) there was adequate clinical, CSF, and MRI information to classify the syndrome as LE, 2) MRI images were accesible for central review, and 3) serum and CSF were available and confirmed negative for neuronal antibodies.

Results: 12 (7%)/163 LE patients (median age: 62 years; range: 40-79; 9 [75%] male) without neuronal autoantibodies were identified. The most frequent initial complain's were deficits in short-term memory leading to hospital admission in a few weeks (median time: 2 weeks; range: 0.5-12). In four patients the short-term memory dysfunction remained as isolated symptom during the entire course of the disease. Seizures, drowsiness, and psychiatric problems were unusual. Four patients had solid tumors (1 lung, 1 esophagus, 2 metastatic cervical adenopathies of unknown primary tumor) and 1 chronic lymphocytic leukemia. CSF showed pleocytosis in 7 (58%) with a median of 13 white blood cells /mm3 (range: 9-25). Immunotherapy included corticosteroids, intravenous immunoglobulins, and combinations of both drugs or with rituximab. Clinical improvement occurred in 6 (58%) of 12 assessable patients.

Conclusion: Antibody-negative LE is more frequent in older males and usually develops with predominant or isolated short-term memory loss. Despite the absence of antibodies, patients may have an underlying cancer and respond to immunotherapy.

Disclosure: Nothing to disclose

O134

Aquaporin-4 autoantibodies from Neuromyelitis Optica Spectrum Disorder patients cause complement-independent spinal cord pathologies and motor deficits in mice

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Background and aims: Neuromyelitis Optica Spectrum Disorders (NMOSD) are CNS inflammatory disorders. Autoantibodies against aquaporin-4 (AQP4-IgG) are pathogenic in NMOSD. Neuroinflammation is initiated upon binding of AQP4-IgG to astrocytic AQP4. The role of complement-independent pathophysiologies is uncertain. We aim to study the complement-independent pathological effects of AQP4-IgG in mice.
Methods: Mice were pretreated with complete Freund's adjuvant and pertussis toxin to disrupt blood-brain barrier, then received daily intraperitoneal injection of IgG purified from AQP4-IgG-seropositive NMOSD patients (IgG(AQP4+)) or healthy individuals (IgG(Healthy)) for 8 days. Motor function was tested by walking across narrow beams. Cervical cord was collected for immunofluorescent analysis.
Results: Human IgG infiltrated into spinal cord parenchyma. There was no deposition of complement activation product (C5b9). Mice received IgG(AQPd+) showed astrocytic injuries/loss compared to mice received IgG(Healthy) indicated by significant loss of AQP4 and glial fibrillary acidic protein immunoreactivities. These mice displayed decrease in the glutamate transporter, excitatory amino acid transporter 2, on immunostaining. There were extensive microglial/macrophage activation on ionized calcium-binding adapter molecule 1 (Iba1) and cluster of CD68 immunostaining, respectively. Spinal cord of mice received IgG(AQP4+) had patchy demyelination and axonal injuries/loss on myelin basic protein and neurofilament immunostaining. Mice received IgG(AQP4+) required longer time with more paw slips to walk across narrow beams compared to mice received IgG(Healthy). Treatment with NMDA receptor antagonist, MK-801, significantly improved motor function of IgG(AQP4+) mice.
Conclusion: AQP4-IgG mediated complement-independent pathologies including AQP4 and astrocytic loss, neuroinflammation, demyelination and axonal injuries/loss may involve glutamate excitotoxicity and microglia/macrophage activation; these pathologies may be improved by NMDA receptor antagonist.
Disclosure: Nothing to disclose

O135

Thrombotic and non-thrombotic neurological manifestations in Primary Antiphospholipid Syndrome

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Background and aims: Central nervous system involvement in primary Antiphospholipid Syndrome (pAPS) can be thrombotic (t-pAPS - stroke, TIA, Sneddon syndrome, and cerebral venous thrombosis) or non-thrombotic (nt-pAPS - epilepsy, headaches, movement disorders, myelitis, neuropsychiatric deficits).
Methods: Retrospective review of clinical records in a series of 73 pAPS patients from Neurology and Immunology outpatient clinic of Centro Hospitalar do Porto – Portugal.
Results: 53 patients (72.6%) had history of neurological manifestations; 37 of them were women (69.8%) and had a mean age at pAPS diagnosis of 46years±14 and at neurological manifestation onset of 43years±14. The most frequent neurological manifestation was ischemic stroke (41.5%) and the least was chorea (3.8%). The neurological group was divided into t-pAPS (67.9%) and nt-APS (32.1%) subgroups. These subgroups were similar regarding sex, age at onset, titles of antiphospholipid antibodies, event recurrence and outcome after disease onset. Vascular risk factors (88.9% vs. 52.9%, p=0.011) and cognitive dysfunction (41.7% vs. 11.8%, p=0.029) were more prevalent in t-pAPS, while myelitis (8.3% vs. 41.2%, p=0.008) and ocular symptoms (5.6% vs. 47.1%, p=0.001) were more prevalent in nt-pAPS. Hypocoagulation rates were not significantly different between subgroups (69.4%vs.43.8%, p=0.079), but there is a tendency to start hypocoagulation more promptly in the t-pAPS.
Conclusion: In our cohort, patients with thrombotic vs. non-thrombotic p-APS with neurological manifestations had distinct features regarding frequency of vascular risk factors, cognitive dysfunction, myelitis, and ocular symptoms. The underlying pathophysiology of nt-pAPS events is yet to be fully elucidated. Even though no standard treatments are currently available for non-thrombotic manifestations, in clinical practice hypocoagulation is frequently used.
Disclosure: Nothing to disclose

Sunday, 17 June 2018

Cerebrovascular diseases 1

O201

Short and long-term risks of stroke after orthodox-definition transient ischaemic attack versus disqualified monosymptomatic events: Oxford vascular study

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Background and aims: Urgent medical treatment after Transient Ischaemic Attack (TIA) is highly effective in preventing early recurrent stroke. Diagnosis of TIA based on the National Institute of Neurological Disorders and Stroke (NINDS) criteria, disqualifies many monosymptomatic events with sudden-onset, non-progressive focal symptoms (e.g. diplopia, dysarthria). Patients with these NINDS-excluded events are often not investigated or treated, but reliable data on prognosis are lacking. We studied stroke risk after NINDS-TIAs, NINDS-excluded events and Minor Ischaemic Stroke (MIS).
Methods: Patients seeking medical attention after transient neurological symptoms or MIS were ascertained prospectively in a population of 92,728 in Oxfordshire, UK from 2002-14. Transient events were classified at baseline as NINDS-TIA, NINDS-excluded events, or other diagnosis. Patients with NINDS-TIA and MIS were treated strictly according to secondary prevention guidelines. NINDS-excluded events had treatment according to physician judgment. 90-day and 10-year risks of stroke were determined by face-to-face follow-up.
Results: Among 3116 patients (1002 MIS, 665 NINDS-TIA, 382 NINDS-excluded events and 1057 other diagnoses), NINDS-TIAs had a similar 90-day stroke risk to MIS (8.9%,6.7-11.1 vs 7.8%,6.0-9.6). Although the NINDS-excluded events had a lower 90-day risk (4.2%, 2.4-5.2) it was still 30 times higher than the expected background risk (p=0.0002), and the stroke risk from 90-days to 10-year follow-up was similar to that in NINDS-TIA (11.7%, 7.0-16.4 vs 10.9%, 7.4-14.4; p=0.84).
Conclusion: NINDS-excluded events account for over a third of all TIAs, have high short- and long-term risks of stroke, and require urgent medical treatment. Diagnostic criteria for TIA should be broadened to include these disqualified events.
Disclosure: The Oxford Vascular Study had support from the Wellcome Trust, National Institute for Health Research, Oxford Biomedical Research Centre, Medical Research Council, Dunhill Medical Trust and Stroke Association. Maria Tuna contribution to this research benefited from a scholarship awarded by the Calouste Gulbenkian Foundation.

O202

Idarucizumab in cerebral ischemia or intracranial hemorrhage under Dabigatran therapy in Germany – a nationwide case collection

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Background and aims: Reversal of anticoagulation by NOACs is a rare but sometimes urgently needed therapeutic demand. Idarucizumab is a monoclonal antibody fragment with high affinity for Dabigatran reversing its anticoagulant effects within minutes. It is indicated for patients on Dabigatran with life-threatening or uncontrolled bleeding and those requiring emergency intervention. Case reports and smaller case collections suggest a benefit for Dabigatran-treated patients suffering ischemic stroke to regain eligibility for rt-PA thrombolysis.
Methods: To provide insights into the clinical use of Idarucizumab in patients under effective Dabigatran anticoagulation presenting with signs of ischemic stroke or intracranial hemorrhage in clinical routine, we asked all German neurological/neurosurgical departments to contribute their retrospective data collected from administration of Idarucizumab following product launch in January 2016 to December 2017.
Results: In 51 responding stroke centers 95 patients presenting with signs of stroke received Idarucizumab. 60 patients treated with Dabigatran presented with ischemic stroke. In patients receiving rt-PA thrombolysis following idarucizumab, 78% had a benefit from i.v. thrombolysis with a median NIHSS improvement of 6 points. No symptomatic bleeding complications were observed.
A total of 35 patients had intracranial bleeding as reason for admission. In 24 patients presenting with intracerebral hemorrhage, hematoma growth with clinical worsening was documented in four. Outcome was favorable with a median NIHSS improvement of 3.5 points and mRS 0-3 in 63%. Overall, mortality was low with 6%.
Conclusion: In conclusion, Idarucizumab is a beneficial therapeutic option for patients under Dabigatran treatment presenting with ischemic stroke or intracranial hemorrhage in daily German stroke center routine.
Disclosure: CC Eschenfelder is an employee of Boehringer Ingelheim.

O203

Cerebral thrombi are heterogeneous and their composition correlates with the density of the occluded vessel on CT scan

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Background and aims: Recently, mechanical thrombectomy has been shown to be able to recanalyse large occluded vessels with benefit in terms of disability and mortality. Thus, the introduction of endovascular procedures has allowed the availability of human thrombus material for histopathologic analysis, with a wide range of possible applications.

We aimed to perform a systematic histological analysis of cerebral thrombi retrieved in ischemic stroke to unravel their composition and to detect possible correlations with imaging biomarkers.

Methods: Histological analysis of 27 human thrombi retrieved by angiography in acute stroke patients has been performed. We investigated the clot composition, in terms of structural components (fibrin, platelets, red blood cells, von Willebrand Factor), by means of aspecific stainings (Hematoxilin and Eosin, Masson's Trichrome) and immunohistochemistry (fibrinogen, CD61 for platelets, vWF).

Results: We found that cerebral thrombi are macroscopically heterogeneous in terms of consistence, dimensions, color, gross appearance (Fig. 1). Even in their structural composition, all clots presented a heterogeneous pattern of red blood cells, platelets, fibrin and vWF. Fibrin was the most represented component within the retrieved thrombi (Fig. 2). Moreover, we found that the "Hyperdensity Artery Sign" of the occluded vessel on the CT scan strongly correlated with the eritrocyte composition of the thrombus (Fig. 3).

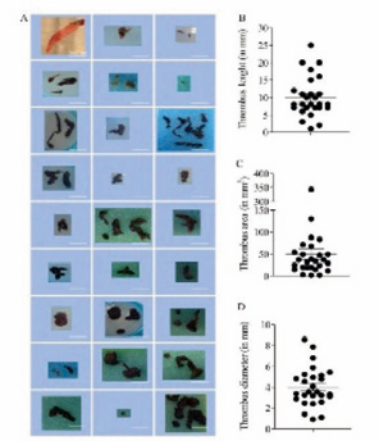

Fig. 1

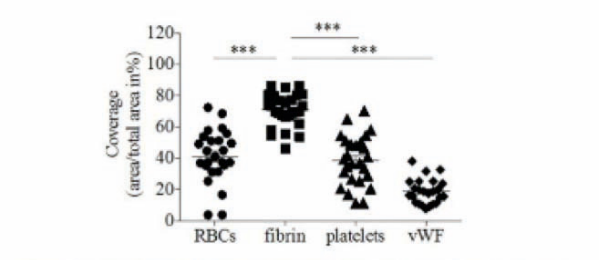

Fig. 2

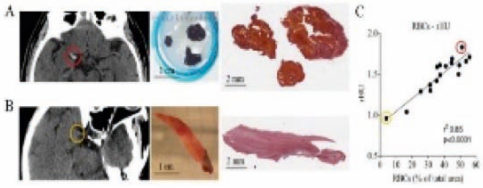

Fig. 3

Conclusion: Arterial cerebral thrombi are widely hetereogenoeus and their composition correlate with the density of the occluded vessel on CT scan. Our pilote study supports the importance of the analysis of thrombus composition as a possible future tool for understanding the mechanisms underlying stroke and improve stroke care.

Disclosure: Nothing to disclose

O204

Effect and safety of Tenecteplase in stroke patients with atrial fibrillation

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Background and aims: The purpose of this post hoc analysis of the NOR-TEST study was to assess the effect and safety of TNK versus tPA in patients with acute ischemic stroke a AF and to assess the outcome in stroke patients with AF compared to patients with Sinus Rhythm (SR).
Methods: The Norwegian Tenecteplase Stroke Trial (NOR-TEST) was a multi-centre, prospective, randomized, open-label, blinded endpoint, phase 3 study. Patients with suspected ischemic stroke were randomized to receive either TNK at a dose of 0.4mg/kg or tPA at a dose of 0.9mg/kg. In this post-hoc analysis we assessed the effect and safety of TNK versus tPA in patients with AF.
Results: 183 patients (16.6%) in the NOR-TEST population (n=1100) were diagnosed with AF. Compared to patients with SR, the patients with AF were older and had more serious strokes. There were no major differences in outcome between the TNK and tPA group in the subgroup of patients with AF. Male sex, lower age and NIHSS was associated with better outcome. Patients with AF were older, had more serious strokes, lower functional outcome and higher mortality.
Conclusion: This is the first randomized controlled study to report the effect and safety of Tenecteplase in acute ischemic stroke in relation to AF. There were no major differences in outcome between the TNK and tPA group although female patients with AF had more serious strokes and tendency of less effect of TNK.
Disclosure: Nothing to disclose

O205

Characterisation of TRPM4-blocking antibody in ischaemic stroke

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Background and aims: Current treatment of Acute Ischaemic Stroke (AIS) is limited to achieving early reperfusion via the use of intravenous recombinant tissue plasminogen activator, which is associated with increased risk of intracranial haemorrhage beyond its therapeutic time window of 4.5 hours. Transient receptor potential melastatin 4 (TRPM4) channel has been identified as a potential target for AIS treatment. TRPM4 expression is increased in ischaemic stroke and inhibition post-ischaemia preserves cerebral vascular integrity. This study aims to delineate the role of a novel TRPM4-blocking antibody, M4P, in amelioration of neuroinflammation in AIS, and to study the expression of TRPM4 and inflammatory markers in human stroke brain.
Methods: Transient middle cerebral artery occlusion (tMCAO) rat models were generated and treated with M4P and control treatments prior to early stroke reperfusion. Behavioural analysis was performed using the rotarod apparatus. Rats were sacrificed 1-day and 7-days post-surgery. Brains were stained with 2,3,5-triphenyltetrazolium chloride (TTC) and infarct area quantified using ImageJ software. Expression of TRPM4 and inflammatory markers in rat and human stroke brains were evaluated by immunohistochemistry.
Results: TRPM4 inhibition reduced infarct area in 1 day and 7 days rat tMCAO models, with improved motor function recovery. Immunohistochemistry demonstrated decreased expression of myeloperoxidase (MPO) and OX-42, with increased CD68 expression in M4P-treated rat brains. There was increased expression of TRPM4, glial fibrillary acidic protein and MPO in human stroke brains as compared to control brains.
Conclusion: This study provides preliminary evidence supporting the therapeutic effects of M4P in AIS through reduction of neuroinflammation.
Disclosure: Nothing to disclose

O206

Mechanical thrombectomy for acute ischaemic stroke in the very old

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Background and aims: Mechanical Thrombectomy (MT) for large vessel occlusion of anterior Acute Ischaemic Stroke (AIS) improves functional outcome at 3 months. The aim of this study is to determine the effectiveness of MT for anterior circulation AIS in the very old population.
Methods: We reviewed patients with a pre-stroke mRS≤2 and anterior circulation AIS who underwent MT between November 2014 and June 2017 with a full completed register. Patients were divided into those <80-years-old (n=134) and those≥80 (n=74). Baseline characteristics, procedure data, and endpoints were compared.
Results: Hypertension and previous TIA were more frequent in the very old (p=0.05, and 0.005 respectively). There were no differences between both groups regarding admission NIHSS (16.6 vs. 16.2, p=0.65), previous intravenous thrombolysis (63.5% vs. 65.7%, p=0.76), revascularization time (267 vs. 254min, p=0,52) and haemorrhagic transformation (36.5% vs 34.3%, p=0,76). Age≥80years was associated with poor (mRS>2) 3-month functional outcome compared to younger patients (67.6% vs. 46.3%, p<0.01). 24 patients (32,4%)≥80years were functionally independent at 3 months. No difference in death was observed between the groups (p=0.08). On logistic regression, age (p<0.01) and admission NIHSS (p<0.01) were associated with a poor 3-month outcome.
Conclusion: In our series, MT for AIS in patients ≥80years with pre-stroke mRS≤2 was associated with a higher risk of a poor 3-month outcome compared to younger patients. However, one-third of the very old were functionally independent at 3 months. Further research is needed to identify factors associated with favorable outcome in this age cohort.
Disclosure: Nothing to disclose

Epilepsy

O207

Will this child have epilepsy? Development and validation of a prediction model to assess the risk of epilepsy after (a) paroxysmal event(s)

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Background and aims: Early and accurate diagnosis of paroxysmal events in children may be difficult. We aimed to develop and externally validate a model to predict the likelihood of the diagnosis of epilepsy based on data available after first consultation.
Methods: Data were retrospectively collected from a consecutive cohort of children who visited the 'first-seizure clinic', a program designed to evaluate children with paroxysmal events of (yet) unknown origin. Children were excluded if follow-up was less than one year. Diagnosis of epilepsy was made after clinical follow-up and, if considered necessary, additional investigations. Input data for model development consisted of clinical characteristics and results from electroencephalography (EEG). Backward selection of strongest predictors was applied. The final model was externally validated by Receiver Operating Curve (ROC) analysis.
Results: A total of 451 children (model development) and 187 children (model validation) were included. Included predictors were the child's sex, age at first event, event description (presence of automatisms, lateralizing symptoms, weakness/loss of muscle tone, bilateral jerking and cramping), medical history (neurological, metabolic or genetic syndrome, psychiatric) and EEG results. Model performance, as tested in the validation cohort, was excellent with an area under the curve (AUC) of 0.86 [95% CI: 0.80-0.92], a PPV of 0.93 [0.83-0.97] and a NPV of 0.76 [0.70-0.80]. Model performance in a sub-population of children with uncertain diagnosis after initial consultation was good: AUC was 0.73 [0.58-0.87].
Conclusion: This model can reliably predict eventual diagnosis of epilepsy, also in children for whom diagnosis is uncertain after first consultation.
Disclosure: Nothing to disclose

O208

Late-onset epilepsy of unknown origin and progression to dementia: two faces of beta amyloid pathology

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Background and aims: Despite recent evidence suggests that amyloid pathology plays a role in epilepsy, little is known about the relationship between beta amyloid and late-onset epilepsy. This study aimed to define beta amyloid status and progression to Alzheimer's Disease (AD) among patients with Late-Onset Epilepsy of Unknown Origin (LOEU).
Methods: We evaluated CSF AD core biomarkers and cognitive performance in 40 non-demented seizure-free patients diagnosed with LOEU versus age/sex matched controls (n=43); 3-year follow-up was performed to assess cognitive decline.
Results: Mean age was 70.0±6.4 years; mean MMSE score at baseline was 26.8. Despite baseline cognitive performance were similar to healthy controls, LOEU patients had significant CSF abnormalities. Indeed, 15/40 patients were found to have pathological Aβ1-42 (<500 pg/ml; 37.5%), 3 of them (7.5%) with an AD-like CSF pattern according to NIA-AA criteria. Patients with pathological Aβ1-42 had a 3.4 hazard ratio for progression to AD dementia at follow-up (Table 1, Figure 1 for survival analysis). Nevertheless, about half (53.8%) of the patients with pathological Aβ1-42 had stable cognitive performances after a 3-year follow-up.

	Progression to AD dementia		Progression to any dementia	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Gender (male)	0.810 (0.181-3.629)	ns	1.273 (0.340-4.764)	ns
Age (years)	1.066 (0.953-13.192)	ns	1.080 (0.981-1.189)	ns
EEG	1.222 (0.272-5.489)	ns	1.222 (0.272-5.489)	ns
Levetiracetam	1.652 (0.368-7.418)	ns	0.805 (0.200-3.238)	ns
Poly-therapy	1.054 (0.126-8.788)	ns	0.903 (0.111-7.362)	ns
$Aβ_{1-42}$ (pg/mL)	0.996 (0.992-0.999)	0.019	0.998 (0.995-1.000)	0.040
t-tau (pg/mL)	1.005 (1.002-1.008)	0.002	1.004 (1.002-1.007)	0.002
p-tau (pg/mL)	1.005 (1.001-1.010)	0.003	1.005 (1.001-1.009)	0.025
$Aβ_{1-42}$/t-Tau ratio	0.049 (0.006-0.364)	0.003	0.049 (0.008-0.364)	0.003
$Aβ_{1-42}$/p-Tau ratio	0.735 (0.601-0.898)	0.003	0.843 (0.741-0.961)	0.010
$Aβ_{1-42}$+	3.433 (0.665-17.73)	0.140	2.264 (0.635-8.076)	0.210

Table 1. Role of clinical and biochemical characteristics on progression to AD dementia and dementia of any type according to Cox regression model.

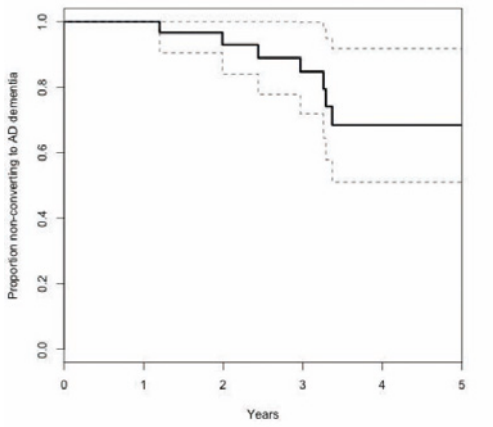

Figure 1. Survival curve for progression to AD dementia

Conclusion: The results of this study highlight a high prevalence of beta amyloid pathology among patients with LOEU, exposing them to higher risk of AD. Thus, LOEU patients should be screened for cognitive impairment to avoid late diagnosis. Moreover, the fact that half of LOEU patients with pathological Aβ1-42 experienced no cognitive decline suggests that beta amyloid might support epileptogenesis without impacting on cognition, pointing to an Aβ-mediated epilepsy.
Disclosure: Nothing to disclose

O209

Properties of epileptiform activity in the human hippocampus and temporal lobe intraoperatively recorded: preliminary results

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Background and aims: Pathophysiological mechanisms underlying generation of hippocampal spike is unknown. We analyzed interictal epileptiform activities intraoperatively recorded from the hippocampus and other temporal regions of adult patients with Temporal Lobe Epilepsy (TLE).
Methods: Five TLE adult patients with (N=2) or without (N=3) hippocampal sclerosis were included in this study. All of the patients underwent MR Imaging and video-EEG monitoring before the operation for localizing seizure onset and diagnosed as having unilateral mesial temporal lobe focus. After opening the anterior horn of lateral ventricle, recording was made under sevoflurane anesthesia using intrahippocampal multiple electrodes, hippocampal surface electrodes and temporobasal subdural electrodes.
Results: (1) Frequency of intrahippocampal spike was always higher than spikes from other areas.
(2) Intrahippocampal recording demonstrated that there was phase reversal in sclerotic hippocampi but there was not in nonsclerotic hippocampi.
(3) Even one transection perpendicular to the long axis desynchronized hippocampal spike.

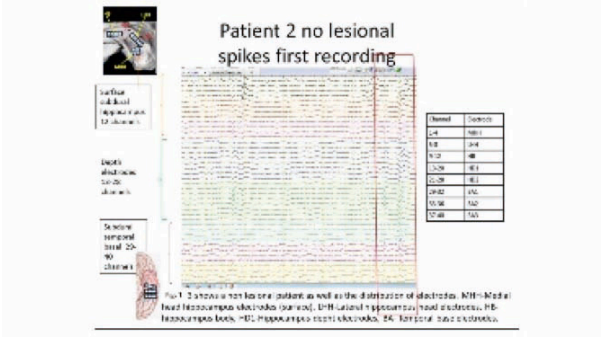

Fig.1 No lesional patient

Conclusion: - We speculate that the phase reversal occurred at the hippocampal sulcus and the subiculum was the spike generator in sclerotic hippocampus.
- Mechanisms underlying spike generation is likely to be different between sclerotic hippocampi and nonsclerotic hippocampi.
- Longitudinal synchronization may be essential for

generation of hippocampal spikes.

References: Emerson RG, Turner CA, Pedley TA, Walczak TS, Forgione M: Propagation patterns of temporal spikes. Electroencephalogr Clin Neurophysiol 94:338–348, 1995. Shimizu H, Kawai K, Sunaga S, Sugano H, Yamada T: Hippocampal transection for treatment of left temporal lobe epilepsy with preservation of verbal memory. J Clin Neurosci 13:322–328, 2006.

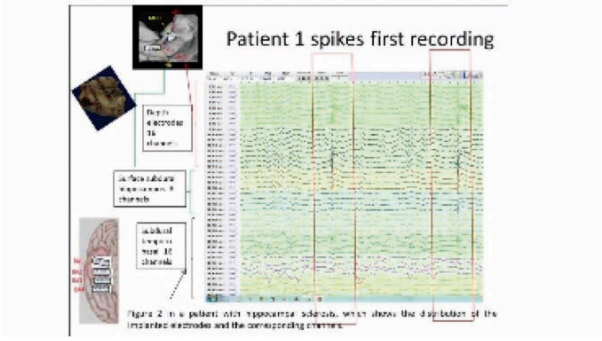

Fig. 2 Hipocampal sclerosis patient

Disclosure: Nothing to disclose

O210

MiR-134 serum expression in Mesial Temporal Lobe Epilepsy patients

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Background and aims: Several experimental and clinical studies have suggested that microRNAs (miRNAs) could be potential epilepsy biomarkers. Nowadays, research has been focused in miR-134, a brain-specific miRNA that plays important roles in dendritic spine development and neuronal structure regulation. An upregulation of miR-134 has been reported both in brain tissue of experimental models (Jimenez-Mateos 2012) and plasma from epileptic patients (Sun 2017). It has also been observed that some anti-seizure drugs down regulate mir-134 plasmatic levels (Sun 2017) highlighting the role of this miRNA in epileptogenesis. Our aim was to quantify miR-134 serum levels in a cohort of Mesial Temporal Lobe Epilepsy (MTLE) patients and correlate with clinical characteristics such as drug response.

Methods: MiR-134 expression levels were evaluated, by molecular biology techniques, in the serum of 46 MTLE-HS patients (26F, 43±12 years, age onset=13±11 years, 35 refractory to treatment) and 44 healthy individuals.

Results: We observed that miR-134 was higher in MTLE-HS ($p=0.00002$, Area Under the Curve=0.74), especially in those refractory to treatment, comparing to controls.

Conclusion: The results obtained in serum are in accordance with previous experimental and clinical studies, confirming that miR-134 may be a suitable epileptogenecis biomarker. These results also support the hypothesis that targeting miR-134 may be a novel therapy (Jimenez-Mateos 2015) that in conjunction with anti-seizure drugs could improve seizure control.

Disclosure: Partially, supported by a BICE Tecnifar Grant

O211

Laryngeal motor-evoked potentials as an indicator of vagus nerve activation

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Background and aims: In a preclinical study, we found that Vagus Nerve Stimulation(VNS)-induced Laryngeal Motor-Evoked Potentials (LMEPs) are reliable indicators of effective activation of cervical motor vagal fibers. In this study, we aimed to translate this technique to VNS-treated patients.

Methods: In five epilepsy patients (1M/4F), LMEPs were recorded at initiation of VNS therapy; in five (3M/2F) after one year of treatment; in 1/5 recordings at both time points were available. Six Ag/AgCl recording electrodes were cervically placed according to three perpendicular axes around the larynx. VNS parameters were programmed (pulse width: 130μs/250μs/500μs; frequency: 30Hz; duty cycle: 7s ON/18s OFF) and VNS output current was gradually ramped up (0.125mA/0.250mA steps) until individual tolerated thresholds.

Results: VNS-induced LMEPs could be recorded in all patients at both time points; axis 1A-1B was the best channel to reproducibly record LMEPs. VNS thresholds to evoke LMEPs ranged from 0.25-1.00mA. In the one patient tested twice, thresholds remained the same over time (0.25mA). Furthermore, VNS intensities to evoke LMEPs of half-maximum amplitude (x0) and slopes (b) were similar at start (x0=0.3134mA;b=0.0973μV/mA) and after one year (x0=0.3733mA;b=0.0855μV/mA).

Conclusion: VNS-induced LMEPs could be reproducibly, easily and non-invasively recorded in patients and LMEP characteristics seem to be similar at both time points. Furthermore, low output currents (0.25–1.00mA) are sufficient to activate vagal Aalpha-motor fibers. These LMEPs may help to more objectively optimize stimulation parameters using a correction factor in view of slightly higher thresholds for A- and B-fibers vs. low threshold Aalpha-motor fibers.

Disclosure: Charlotte Bouckaert is supported by an Aspirant grant from the “Fonds voor Wetenschappelijk Onderzoek (FWO) - Flanders”.

O212

National surveillance of mortality in children with epilepsy in the UK and Ireland

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Background and aims: Patients with epilepsy are significantly more likely to die prematurely than the general population, with causes ranging from associated co-morbidities to Sudden Unexpected Death in Epilepsy (SUDEP). However, the epidemiology of paediatric epilepsy mortality, especially relating to SUDEP, is poorly defined; existing studies are limited to local case series, and national incidence estimates are lacking.

Methods: This was a prospective, population-based active surveillance study using the established British Paediatric Surveillance Unit methodology. The population under study were children aged under 16 years in the UK and Ireland, who died between November 2016 and November 2017, with a simultaneous diagnosis of epilepsy.

Results: Over 13 months surveillance, 129 deaths in children with epilepsy were reported. 70% of cases were male and of white ethnic group. Age at death ranged from 5 months to 16 years and causes of death included pneumonia, sepsis, SUDEP and underlying genetic condition. 54% had global developmental delay. In 55% of cases, a general paediatrician or a paediatrician with neurology interest was the primary care provider whilst 35% had a paediatric neurologist. 90% of patients were on AEDs at the time of death. The two most prescribed AEDs are sodium valproate and Levetiracetam.

Conclusion: In this study, SUDEP contributed to less than 10% of deaths, consistent with previous reports in the literature. There is a clear need to better understand and reduce the number of epilepsy deaths in children in the UK, and national surveillance of SUDEP is warranted to better understand this entity in the paediatric population.

Disclosure: Nothing to disclose.

Neuro-oncology

O213

Increased efficacy of carboplatin after blood-brain barrier opening using low intensity pulsed ultrasound in preclinical models of glioblastoma

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Background and aims: The Blood-Brain Barrier (BBB) limits the penetration and efficacy of therapeutic agents used for treatment of most neurological diseases, including glioblastoma (GBM). Carboplatin, a chemotherapy used as a 2nd or 3rd-line treatment against GBM, is effective in vitro; however, the efficacy is limited in vivo because of the poor passage through the BBB. Temporarily increasing the permeability of the BBB using low intensity pulsed ultrasound (LIPU) combined with microbubbles injected systemically improves the penetration of carboplatin in the brain of non-human primates. The objective of this study was to evaluate the therapeutic efficacy of LIPU-mediated BBB opening followed by carboplatin infusion in human GBM orthotopic xenograft models.

Methods: Carboplatin concentrations with or without BBB disruption were measured in healthy mice to assess the level of drug penetration. Four cohorts of immunocompromised mice bearing either orthotopic xenograft of U87MG-Luc cell line or patients-derived cell line (PDCL) were treated with: (i) vehicle, (ii) LIPU alone, (iii) carboplatin alone, (iv) carboplatin after LIPU-mediated BBB opening.

Results: Carboplatin brain penetration was increased by a factor of 4.2 fold on the whole brain by LIPU-induced BBB opening. In mice with either PDCL or U87 gliomas, tumor growth was delayed ($p<0.05$) and survival was increased ($p<0.05$) when mice were treated by carboplatin + BBB disruption.

Conclusion: Carboplatin concentrations was significantly enhanced in the brain after BBB disruption by LIPU. By increasing carboplatin concentrations locally in the brain, carboplatin have significantly enhanced efficacy against GBM. This approach is currently being tested in patients with recurrent GBM (NCT02253212).

Disclosure: Antonin Dréan, Guillaume Bouchoux, Michael Canney, Frédéric Sottilini and Alexandre Carpentier are part of CarThera SAS.

O214

Clinico-radiological, molecular, therapeutic and prognostic features of medulloblastoma of the adult: results from an institutional series

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Background and aims: Medulloblastoma is a highly malignant, embryonal and cerebellar tumor of the childhood. In adults it is rare and shows distinct clinical, histopathological and treatment response features.

Methods: We retrospectively identified 44 adults (17-48 years), with medulloblastoma and collected the demographic, diagnostic and therapeutic data. We calculated PFS (Progression-Free-Survival) and OS (Overall Survival) with Kaplan-Meier method and used the log-rank test for univariate and multivariate analysis.

Results: We observed a male prevalence, and a median age of 31 years at diagnosis. Symptoms at onset were headache (75%), cerebellar dysfunctions (72%), myeloradicular and/or cranial nerve involvement in 12%. Tumor site was cerebellum in 30 patients (16 vermian and 14 hemispheric), infratentorial in 8, disseminated at diagnosis in 6. Histological examination showed a classic variant in 73%, a desmoplastic/nodular variant in 23% and anaplastic variant in one patient. Molecular characterization was available in 22 patients with 15 SHH and 7 non-WNT/non-SHH: mOS was significantly higher in SHH (58.5 months) versus non-SHH (38.5 months) patients. All cases underwent a gross-total or subtotal resection, 43 received adjuvant craniospinal irradiation, followed in 20 patients by systemic chemotherapy (CCNU, cisplatin, vincristine). Five-year OS and PFS were 80% and 66%, respectively. Age, gender, histological variant and extent of surgery were not significantly associated with OS and PFS in both univariate and multivariable analysis. High risk classification and metastatic disease at diagnosis were predictor of a worse prognosis.

Conclusion: Future trials need to consider a stratification for molecular subgroups, and for SHH groups new targeted agents are on the way.

Disclosure: Nothing to disclose

O215

Associations of anticoagulant use with outcome in newly diagnosed glioblastoma

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Background and aims: Our objective was to test the hypothesis that, despite bleeding risk, anticoagulants improve outcome in glioblastoma because of reduced incidence of venous thromboembolic events and modulation of angiogenesis, infiltration and invasion.

Methods: We assessed survival associations of anticoagulant use from baseline up to start of temozolomide chemoradiotherapy (TMZ/RT) (period I) and from there to the start of maintenance TMZ chemotherapy (period II) by pooling data of three randomized clinical trials in newly diagnosed glioblastoma including 1,273 patients. Progression-Free Survival (PFS) and Overall Survival (OS) were compared between patients with: anticoagulant use versus no use; therapeutic versus prophylactic versus no use; different durations of anticoagulant use versus no use; anticoagulant use versus use of anti-platelet agents, versus neither nor. Cox regression models were stratified by trial and adjusted for baseline prognostic factors.

Results: Anticoagulant use was documented in 75 patients (5.9%) in period I and in 104 patients (10.2%) in period II. Anticoagulant use during period II, but not period I, was associated with inferior OS compared to no use on multivariate analysis (p=0.001, HR=1.52, 95% CI: 1.18-1.95). No decrease in OS became apparent when only patients with prophylactic anticoagulant use were considered. No survival association was established for anti-platelet agent use.

Conclusion: Anticoagulant use was not associated with improved OS. Our analysis does not support the notion that anticoagulants exert relevant anti-tumor properties in glioblastoma.

Disclosure: Nothing to disclose

O216

Stroke and "stroke-like" events after brain radiotherapy: a large series with long-term follow-up

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Background and aims: Patients with history of brain irradiation may develop acute "stroke-like" deficits independent of tumor progression. Diagnosis of these conditions may be challenging, as both cerebrovascular disorders and late-delayed paroxysmal syndromes – such as SMART, PIPG and ALERT – may present with acute focal deficits. The aim of this report is to provide a comprehensive description of the phenotypes associated with these conditions, highlighting the key elements to reach an accurate diagnosis.

Methods: Cases were collected among six different neuro-oncology departments in Italy and France. Ten patients were followed prospectively, while 15 other patients were identified by retrospective review of institutional databases.

Results: 25 patients with history of brain irradiation admitted for acute "stroke-like" deficits were included in the study. Four clinical-radiological subgroups were identified: - Group 1: severe encephalopathy and "stroke-like" deficits with multifocal enhancing white matter lesions or normal MRI (ALERT syndrome, 3 patients); - Group 2: "stroke-like" deficits and unilateral cortical-subcortical abnormalities on MRI (SMART syndrome and PIPG, 12 patients); - Group 3: long-lasting focal deficits and lacunar ischemic lesions on MRI (lacunar strokes, 6 patients); - Group 4: rapidly-transient focal deficits and normal MRI (TIA-like episodes, 4 patients). Despite treatment with antiepileptic drugs, high-dose steroids, and/or antiplatelets, 16 out of the 25 patients had relapses (median follow-up: 4 years).

Conclusion: Accurate diagnosis of the conditions in this spectrum is of utmost importance to distinguish patients with acute cerebrovascular disorders or ALERT syndrome, who would benefit from specific work-up and treatment. Brain MRI with diffusion-weighted imaging is essential for this purpose.

Disclosure: Nothing to disclose

O217

Long-term follow-up of Optic Pathway Gliomas in children with neurofibromatosis type-1: an oncology hospital experience

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Background and aims: Optic Pathway Gliomas (OPGs) are the most prevalent intracranial tumours in children with Neurofibromatosis type 1 (NF1). Although commonly indolent, OPGs may have an aggressive clinical course and their approach is often challenging. The aim of this study was to evaluate the outcome of OPGs diagnosed in patients with NF1 during pediatric age, followed up to 22 years.
Methods: Retrospective review of demographics, neurological and ophtalmological evaluations, neuroimaging and treatments applied to all children with OPGs and NF1 presenting to an oncology hospital, 1991-2017.
Results: Of 62 children (31 males, 31 females, median age at diagnosis 4,0 years), 27 (44%) were treated (based on clinical or imagiological progression), in 4 of whitch the initial decision had been watchful surveillance. Of the treated patients, all were submitted to chemotherapy, 4 underwent surgery, 1 radiotherapy. Visual acuity improved in 9, stabilized in 12 and worsened in 3. Complete response was obtained in 1 patient, partial response in 19 and disease stability in 6. One patient died. One patient is currently under treatment, the remaning 25 have stable disease. Patients who didn't undergo treatment remain neuro-ophtalmological stable, 2 had spontaneous tumour regression. Mean follow up time is 7.9 years.
Conclusion: Despite the complex management of patients with NF1 and OPGs, inherent to their variable natural history and difficulties in clearly defining neuro-ophtalmological progression and response to treatment in the pediatric population, our results suggest that careful surveillance is acceptable in most patients and that a majority of patients who undergo treatment benefit from it.
Disclosure: Nothing to disclose

O218

Association between kynurenine metabolism in peripheral blood mononuclear cells and cognition in lung cancer patients undergoing chemotherapy

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Background and aims: Kynurenine (L-KYN) pathway plays important role in immunosuppression, inflammation and neurodegeneration. The aim of the study was to evaluate kynurenine metabolism, expression of translocator protein 18kDa (TSPO-reflects microglia-line activation), G Protein-coupled Receptor (GPR35-KYNA receptor) and kynurenine aminotransferase II (KAT) in Peripheral Blood Mononuclear cells (PBMCs) in relation to cognition in lung cancer patients.
Methods: The study included 221 lung cancer patients hospitalized in Clinic of Oncology in Poznan. The expression of TSPO, GPR35, KAT in PBMCs was evaluated by means of ELISA. At baseline and after 6 months neurological examination, MiniMental State Examination (MMSE), Trail Making Test (TMT) A and B evaluations were performed.
Results: Down-regulation of TSPO expression in PBMCs was associated with better MMSE score (29.00; 28.0-29.0) than in patients with up-regulated TPSO (28.0; 26.0-28.7; P=0.016). TMT-A performance was better in patients with lowered TPSO (8.41±3.68s) than in subjects with up-regulated TPSO (12.92±7.30s; P=0.002). TSPO expression in PBMCs negatively correlated with MMSE score (Kendall's tau=-0.182; P=0.0178) and positively with TMT-A (Kendall's tau=0.168; P=0.0309) at baseline. Up-regulation of KAT expression in PBMCs was associated with improved MMSE 6 months after baseline (28.4±0.7) comparing to subjects with inhibited KAT (27.1±1.8). KAT and MMSE scoring correlated positively 6 months after baseline (Kendall's tau=0.308; P=0.0234).
Conclusion: The effective metabolism of kynurenines in PBMCs may play a protective role against cognitive decline, while stimulation of microglia cell-line can be considered as an independent pathomechanism leading to cognitive impairment in lung cancer patients.
Disclosure: The study was funded by National Science Center Poland (UMO-012/07/B/NZ7/04354)

Miscellaneous 1

O219

Predicting long-term neurological outcome after cardiac arrest with serum Neurofilament Light chain

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Background and aims: Serum biomarkers may improve prediction of neurological outcome after cardiac arrest. Neurofilament Light Chain protein (NFL) has shown promise as a marker of neuronal injury in other neurological diseases. We therefore hypothesized that serum NFL could be used to identify patients with poor neurological outcome after cardiac arrest.

Methods: Using an ultrasensitive immunoassay, we analyzed prospectively collected serum samples from 695 patients from the Target Temperature Management Trial. The serum NFL levels at 24h, 48h and 72h were correlated with poor neurological outcome (Cerebral Performance Category Scale 3-5; severe cerebral disability, coma, or brain death) at 6-month follow-up.

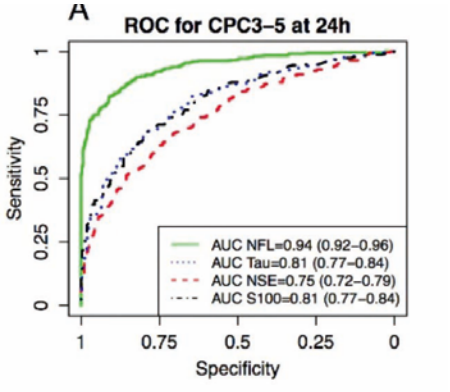

Fig 1 ROC-curve 24h biomarkers

Results: We found significantly increased levels of serum NFL in poor outcome patients ($p<0.0001$) at 24h-72h after cardiac arrest. NFL had significantly greater accuracy for poor outcome (AUC 0.94-0.95 at 24-72h) than the serum biomarkers tau, S-100 and neuron-specific enolase. Serum NFL had greater sensitivity and comparable specificity for predicting poor outcome compared to highly malignant patterns on EEG, generalized cerebral oedema on head computed tomography, bilaterally absent somatosensory evoked potentials and absent pupillary/corneal reflexes.

Conclusion: Serum NFL is a highly predictive marker of long-term poor neurological outcome from 24h after cardiac arrest and is a promising tool to complement neurological prognostication. Further studies are necessary to validate our results.

Disclosure: KB and HZ are co-founders of Brain Biomarker Solutions in Gothenburg AB, a GU Venture-based platform company at the University of Gothenburg. KB has served as a consultant or at advisory boards for Alzheon, BioArctic, Biogen, Eli Lilly, Fujirebio Europe, IBL International, Merck, Novartis, Pfizer, and Roche Diagnostics. All other authors declare no COI.

O220

Brain-computer interface technology for upper limb rehabilitation after stroke: a translational effort

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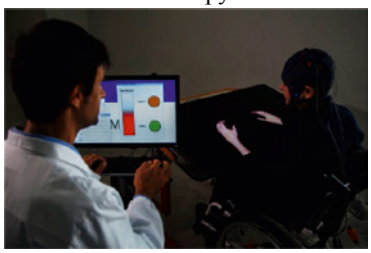
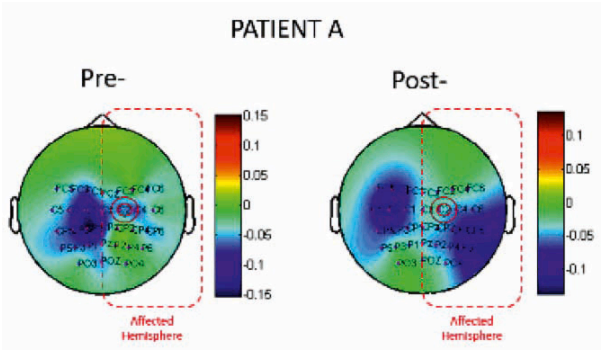
Background and aims: Evidence suggests that sensorimotor Brain-Computer Interface (BCI) systems can be beneficial for post-stroke motor recovery. Following a successful Randomized Controlled Trial (RCT) a translational effort was made at our instution with the implementation of the Promotœr, an EEG-based BCI training station (see Figure 1) which is currently employed to support upper limb Motor Imagery (MI) training in add-on to standard therapy.



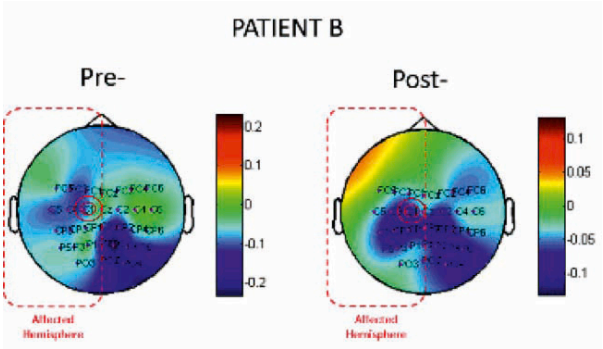
The patient is seated on a wheelchair with arms resting on a pillow. A visual representation of forearms and hands is given on a dedicated screen, resembling the patient's own hands. The patient is asked to perform MI of affected hand and the therapist is provided with continuous feedback of the patient's EEG activity. (Figure 1)

Methods: Training setting is shown in Figure 1. Desynchronization occurring electrodes placed above the affected sensorimotor area at sensorimotor relevant frequencies is fed back to therapist and patient and reinforced along the training (2-3 weekly sessions of 40 minutes duration, for a minimum of a 1 month training). Before and after training patients undergo an EEG assessment to evaluate the expected reinforcement of MI-induced brain activation in the affected hemisphere (pre – post training).

Results: 25 patients underwent training with the Promotœr; 21 suffered from ischemic or haemorrhagic unilateral stroke, 4 had other type of acquired brain injury resulting in motor impairment of the upper limb; 12 patients were in the subacute phase (< 6 months from the event) while 13 where chronic. In total approximately 300 BCI training sessions were carried out. Two illustrative cases are presented in which a reinforcement of sensorimotor related activity on the affected hemisphere was observed (Figures 2, 3).



Pre- and Post- EEG assessment in representative patient A (77 y/o woman with recent ischemic stroke in right MCA territory with severe left hemiparesis). Statistical maps of Rsquare values of Rest vs- left hand motor imagery at 13-14 Hz (frequency employed for BCI control; electrodes used for BCI training are circled in red). (Figure 2)



Pre- and Post- training EEG assessment in representative patients B (20 y/o man with traumatic haemorrhage in the left hemisphere and severe right hemiparesis, 1 y from event). Statistical maps of Rsquare values of Rest vs- right hand motor imagery at 9-10 Hz (frequency employed for BCI control; electrodes used for BCI training are circled in red). (Figure 3)

Conclusion: The Promotœr represents a successful story of translational research in BCI for stroke rehabilitation. Results retrace those of a published RCT and support the feasibility of BCI training in the context of a real rehabilitation program.

Disclosure: Nothing to disclose

O221

Clinical features and risk factors in Metronidazole-induced encephalopathy: a systematic review of 121 patients

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Background and aims: Metronidazole, a commonly used antibiotic drug, can cause encephalopathy leading to diagnostic challenges. The condition is rare, and a detailed description of the phenotype is lacking. In this systematic review we investigated the clinical features and possible risk factors in Metronidazole-induced encephalopathy.
Methods: We performed a systematic literature search using PubMed to identify cases concerning Metronidazole-induced encephalopathy. Additionally, references were handsearched. Inclusion criteria were: available human case series or reports. Exclusion criteria were other languages than English. The following data were extracted: age, gender, country, comorbidities, indication for treatment, dose and duration, presenting symptoms, MRI findings at diagnosis and follow-up, and outcome.
Results: We found 641 publications of which 97 papers comprising 121 patients were included. Typical presentation included dysarthria, gait instability and cerebellar symptoms. Liver disease was the most common preexisting condition. MRI showed a characteristic pattern of reversible symmetrical hyperintensities on T2/FLAIR of the dentate nuclei in 90% of patients. Most patients improved significantly after discontinuation of Metronidazole. Poor outcome was associated with severe comorbidity and self-medication.
Conclusion: Metronidazole-induced encephalopathy should be considered in patients with newly initiated or prolonged Metronidazole treatment presenting with neurological symptoms and characteristic MRI changes. Patients with liver disease may be at increased risk. Prognosis is good if recognized early.
Disclosure: Nothing to disclose

O222

Predicting factors for quality of life following Traumatic Brain Injury: CROCFLAME catamnesis

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Background and aims: Predicting factors for long-term outcome in chronic Traumatic Brain Injury (TBI) are still insufficiently known and psychiatric long-term sequels are often not diagnosed, thereby restricting patients´ quality of life. This catamnesis survey was carried out to elucidate influencing factors on quality of life.
Methods: 439 out of 1266 patients suffering from mild, moderate or severe TBI and admitted to neurorehabilitation between 2005 to 2015 were contacted. Health-Related Quality of Life (HRQoL) was assessed (QOLIBRI: 0-100). A score below 60 indicates either an affective or anxiety disorder, a score below 40 both disorders. HRQoL was quantified (%; mean±SD) and correlated to TBI severity, etiology, age at TBI, age at survey, sex, decompressive craniectomy (DC), tracheostomy, shunt device using multivariate regression and stepwise forward selection.
Results: 43% was the overall and 72% the net survey response rate. 30% underwent DC, 44% tracheostomy, 58% received a shunt device. 64% indicated sufficient HRQoL with a QOLIBRI total score equal or greater 60 (65.50±22.57). 36% suffered at least from one psychiatric disorder, of which 16% suffered from an affective and anxiety disorder. Less pronounced TBI severity and DC (adjusted R2=0.068) slightly correlated with better HRQoL.
Conclusion: Most patients had a good HRQoL up to 10 years after TBI. TBI severity is not a strong predictor for HRQoL. Decompressive craniectomy has a slight positive impact on better HRQoL. 36% indicated insufficient HRQoL, most likely due to anxiety and/or depressive disorders. Hence, psychiatric disorders need enhanced attention to predict and improve HRQoL in chronic TBI patients.
Disclosure: Nothing to disclose

Monday, 18 June 2018

Ageing and dementia

O302

ABBV-8E12, a humanized anti-Tau monoclonal antibody for the treatment of Early Alzheimer's Disease and PSP: multiple dose, randomized, double-blind, placebo-controlled phase-2 studies

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Background and aims: ABBV-8E12 is a humanized anti-tau monoclonal antibody being developed for treatment of Early Alzheimer's Disease (AD) and Progressive Supranuclear Palsy (PSP). Results of a phase 1 study in PSP patients (NCT02494024) showed that when administered as a single dose up to 50mg/kg, ABBV-8E12 exhibited an acceptable safety/tolerability profile to support repeat-dose testing in patients with tauopathies. Here we present the designs of ongoing phase 2 studies in Early AD and PSP patients.
Methods: One phase 2, double-blind, placebo-controlled study assesses the 96-week efficacy and safety of ABBV-8E12 in Early AD patients (NCT02880956). A total of 400 male and female subjects, aged 55 to 85 years, will be enrolled at approximately 65 global study sites. A second phase 2, double-blind, placebo-controlled study assesses the 52- week efficacy and safety of ABBV-8E12 in PSP subjects (NCT02985879).
Results: Primary efficacy outcome in the Early AD study is the change in CDR – Sum of Boxes (CDR-SB) from baseline to Week 96. Primary efficacy outcome in the PSP study is the change in the PSP Rating Scale total score from baseline to Week 52. Adverse events will be monitored.
Conclusion: A significant unmet medical need exists for the development of disease-modifying drugs for AD and PSP which directly impact the biology of the diseases and reduce the associated burdens. ABBV-8E12 has shown an acceptable safety and tolerability profile in patients with PSP during phase 1 testing. The current studies are designed to evaluate the efficacy and safety of ABBV-8E12 in patients with Early AD and PSP.
Disclosure: This work was funded by AbbVie Inc. AbbVie participated in the study design, research, data collection, analysis and interpretation of data, writing, reviewing, and approving the publication.

O303

EEG microstates - association with cognitive impairment and Alzheimer's Disease CSF biomarkers

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Background and aims: Spontaneous mental activity is characterized by sub-second changes of quazi-stable brain states called functional microstates that are thought to represent crucial steps of information processing. Electroencephalography (EEG) reflects brain electrical activity at the level of synapses and has a high temporal resolution compatible to the resolution of human information processing. Since synaptic dysfunction is an early event and best correlate of cognitive decline in Alzheimer's Disease (AD), EEG microstates might serve as valuable early markers of AD. The present study investigated differences in EEG microstates parameters between a large number of healthy elderly and memory clinic patients and how they correlate to conventional Cerebrospinal Fluid (CSF) markers of AD in cognitively impaired individuals.
Methods: The EEG microstate analysis will be performed on resting state EEG data following well-established standard procedures in controls (n=308) and patients along AD continuum (subjective cognitive decline, n=210; mild cognitive impairment, n=230; AD, n=197) who underwent standard clinical investigation and CSF biomarker analysis (Aβ, t-tau and p-tau). The contribution, occurrence and duration of the four optimally fitted EEG microstate class topographies that presumably represent usage of different cognitive resources will be obtained since they are sufficient to explain most of the data and are comparable to the literature.
Results: The preliminary results of the ongoing large-scale EEG analysis showed significant, gradient-like correlation of EEG microstates parameters with cognitive status and conventional CSF biomarkers of AD.
Conclusion: Novel functional EEG markers of brain synchronous activity contribute to understanding and detecting early disruption of neurocognitive networks in AD.
Disclosure: Nothing to disclose

O304

Added value of multimodal structural MRI to the clinical diagnosis of primary progressive aphasia variants

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Background and aims: To determine the added value of multimodal Magnetic Resonance Imaging (MRI) to language assessment for the differential diagnosis of primary progressive aphasia (PPA) variants.
Methods: 59 patients [29 nonfluent (nfvPPA), 15 semantic (svPPA), 15 logopenic (lvPPA) variants] and 38 healthy controls underwent a comprehensive language assessment, 3DT1-weighted and diffusion tensor (DT)-MRI. Cortical thickness (CT) and DT-MR indices from the white matter tracts were obtained. A random forest analysis identified MRI features associated with each clinical syndrome. Finally, using ROC curve analysis, the individual patient classification was performed using the language features alone ('language model') and by adding to this model the contribution of multimodal MRI, i.e. the combination of CT and DT-MRI measures.
Results: The language model alone was able to differentiate svPPA from both nfvPPA and lvPPA patients with high accuracy (AUC 0.88-1.00 and 0.97-1.00, respectively). When CT of the left inferior parietal lobe, DT-MRI metrics of genu of the corpus callosum and of left frontal aslant tract were added to the language model, the discriminatory ability of nfvPPA relative to lvPPA significantly increased from AUC 0.77 ('language model' only) to 0.94 ('language+MRI model').
Conclusion: Language features alone are able to distinguish svPPA from the other two PPA variants with very high accuracy. On the contrary, multimodal MRI may improve the differential diagnosis of nfvPPA and lvPPA and can reflect their different underneath pathology.
Disclosure: Partially supported by grants from the Italian Ministry of Health (GR-2010-2303035 and GR-2011-02351217).

O305

Enrichment of clinical trials in prodromal AD using ventricular volume to identify individuals at increased risk of rapid disease progression

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Background and aims: Neurodegeneration detected on MRI has been applied for trial enrichment. The goal of this study is to investigate enrichment strategies based on MRI structural biomarkers to identify prodromal MCI patients with fast cognitive decline.
Methods: 81 Aβ42/P-tau positive amnestic MCI patients (Aβ42/P-tau ratio<7.8 for APOE4 non-carriers, <15.2 for carriers) were selected from the WP5 of PharmaCog (E-ADNI). Patients performed cognitive (ADAScog13) and MRI assessments every 6 months for 2 years. Linear Mixed Model was conducted with baseline structural biomarker, time and biomarkerXtime interaction as factors to predict longitudinal changes in ADAS-cog13. Biomarker cut-offs extraction was settled by applying the mixture model. Sample size was calculated to detect a reduction of 30% of the outcome slope in a 2-year clinical trial.
Results: The analysis of the proportion of variability in ADAScog13 over time reported a significant biomarkerXtime interaction for lateral ventricle volume (LVV, P-value=0.003, standardized β=0.287, $\eta 2$=0.29). LVV mixture model derived cut-off (14330 mm3) was applied to distinguish patients with large and small LVV. Without LVV enrichment, hippocampal and dentate gyrus

volumes were the biomarkers requiring the lowest sample size (52, 55 subjects vs 294 for ADAScog13). By selecting the subgroup with large LVV, the sample size in a clinical trial could be reduced of 30% for hippocampal volume, 25% for dentate gyrus volume and 40% for Adascog13.
Conclusion: These results demonstrate the utility in using the baseline lateral ventricle volume as enrichment strategy for prodromal AD trials.
Disclosure: Pharmacog is funded by the EU-FP7 for the Innovative Medicine Initiative (grant n°115009).

O306

Metabolic correlates of reserve and resilience in MCI due to Alzheimer's Disease (AD)

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Background and aims: We explored reserve and resilience in late-converter MCI-AD and in slowly-progressing amyloid-positive MCI patients (AMY+MCI) by assessing both topography and extent of neurodegeneration on FDG-PET, also stratifying as per educational level.
Methods: We analyzed 94 MCI-AD patients later converted to AD-dementia and 46 AMY+MCI. Using a data-driven approach based on conversion time, MCI-AD patients were divided into 'typical AD' and late-converter subgroups. Based on the MMSE annual rate reduction, AMY+MCI were divided into tertiles, thus obtaining smoldering (first tertile) and aggressive (third tertile) subgroups. Finally, the whole group of MCI-AD and AMY+MCI was divided into quartiles according to their education. FDG-PET of typical-AD, late converters, aggressive and smoldering AMY+MCI subgroups as well as education-based subgroups were compared to controls with SPM8. Late-converter and smoldering AMY+MCI subgroups were also compared with 'typical AD' and aggressive AMY+MCI subgroups, respectively.
Results: Late converters showed relatively preserved metabolism in right middle temporal gyrus and left orbitofrontal cortex with respect to typical-AD. Given expected higher reserve, when compared to CTR High-EDUC subgroup demonstrated a more extended bilateral hypometabolism in posterior parietal cortex, posterior cingulate/precuneus than Low-EDUC. Instead, Except-EDUC patients showed less extended cluster of hypometabolism and a post-hoc analysis demonstrated that metabolism in middle and inferior temporal gyri was relatively spared in this subgroup with respect to the other MCI patients.
Conclusion: Middle and inferior temporal gyri seem to be sites of resilience (when relatively preserved) rather than a hallmark of a more aggressive pattern (when hypometabolic). Education may affect brain metabolism through both reserve and resilience mechanisms.
Disclosure: Nothing to disclose

Peripheral nerve disorders 2

O307

Peripheral neuropathy in the context of systemic vasculitis and other autoimmune diseases: the importance of etiologic characterization

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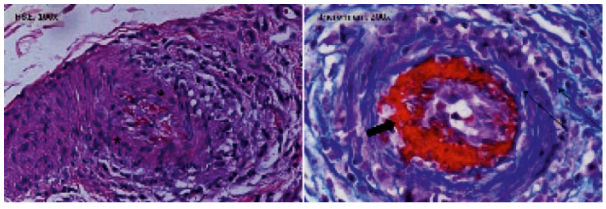
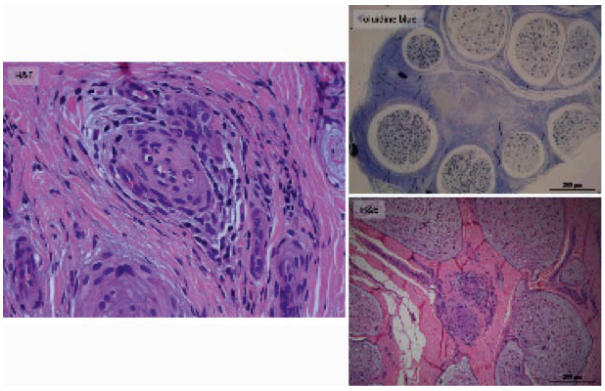
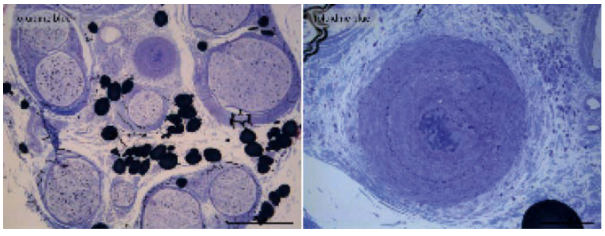
Background and aims: Peripheral neuropathies may present in the context of systemic vasculitis and other autoimmune diseases. Their treatment and prognosis depend on etiologic characterization.
Methods: Diagnostic evaluation and follow-up of four cases of CHEDV Neuromuscular Clinic.
Results: Case 1: A 57-year-old male was admitted with bilateral lower limb weakness and hypoesthesia in the left ulnar nerve territory. Blood panel: high ESR, proteinuria, ANA, anti-MPO and anti-SSA/B positive. EMG/NCS: sensitive axonal polyneuropathy. Skin biopsy: microscopic polyangiitis. Under azathioprine.
Case 2: A 53-year-old male was admitted with bilateral lower limb sensorimotor deficit and hypoesthesia in the right median nerve territory. Blood panel: elevated liver enzymes and positive serology for HBV. EMG/NCS: asymmetric sensorimotor axonal polyneuropathy. Nerve biopsy: possible vascular/vasculitic etiology. The diagnosis of polyarteritis nodosa was established. Under tenofovir.
Case 3: A 54-year-old female, previously diagnosed with Churgh-Strauss vasculitis, was admitted with bilateral lower limb sensorimotor deficit, dysesthesia and right hand paresis. Blood panel: eosinophilia, high IgE and positive anti-MPO. Chest CT scan: chronic eosinophilic pneumonia. EMG/NCS: sensorimotor axonal polyneuropathy with active denervation. Nerve biopsy: possible vasculitic process. Under cyclophosphamide.
Case 4: A 34-year-old female was admitted with sensory complaints of left sural and right median nerve territories. Blood panel: diminished complement levels. EMG/NCS: multifocal axonal impairment. Nerve biopsy: possible vascular/vasculitic process. The cause of vasculitis remains unknown. No medication.



Skin biopsy revealing an inflammatory infiltration in arteriole wall with disruption of internal elastic lamina and fibrinoid necrosis, allowing the diagnosis of leukocytoclastic vasculitis.



Nerve biopsy revealing a perivascular inflammatory cell infiltration, in a perineural blood vessel, and an asymmetric involvement of nerve fascicles, fulfilling criteria of probable vasculitic neuropathy.



Nerve biopsy showing an asymmetric involvement of nerve fascicles and a vessel with fragmentation of internal elastic lamina reflecting a cicatricial process and suggesting a vascular/vasculitic process.

Conclusion: This series reveal the etiologic and phenotypic diversity of peripheral neuropathies related with systemic vasculitis and other autoimmune diseases. The therapeutic approach and prognosis was distinct in each patient, emphasizing the importance of a prompt diagnosis.
Disclosure: Nothing to disclose

O308

Mutations in MME cause autosomal recessive late-onset CMT type-2 disease

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Background and aims: Mutations in the metalloendopeptidase gene (MME) gene were initially identified as causative for autosomal recessive CMT2. Subsequently, other authors published variants in MME linked to late-onset autosomal dominant polyneuropathies. Our goal is to deepen the phenotype of our patients with changes in MME and try to delineate the pattern of inheritance.
Methods: We screened 197 index case subjects with hereditary neuropathy Charcot-Marie-Tooth (CMT)/Distal hereditary motor neuropathy (DHMN) and 10 patients with familial Amyotrophic Lateral Sclerosis (fALS) by a custom panel of 119 genes. Beyond the index case subjects, we included additional affected and unaffected family members for segregation analysis. All patients were examined by experienced neurologists in their respective centers.
Results: We found 18 variants of MME in a total of 20 index cases; 9 families (13 cases) had bi-allelic MME mutations (3 homozygosis and 6 compound heterozygosis) and 11 showed a heterozygous variant. All patients with bi-allelic variants had similar phenotype consistent with late-onset axonal neuropathy. Segregation analysis in patients with heterozygous variants did not show positive results; the phenotype of these patients showed a wide spectrum including CMT1, CMT2, DHMN and familial ALS.
Conclusion: MME mutations segregating as an autosomal recessive pattern showed late-onset CMT2 phenotype. We couldn't demonstrate that variants in heterozygosis in MME were the cause of neuropathy in our cases. Our results highlight the need for deeply investigating the mode of inheritance not only for academic interest but also especially for genetic counseling.
Disclosure: Funding: grants IIS La Fe 2015/0085, ISCIII (PI12/00946; PI15/00187)

O309

Validity and reliability of the Transthyretin Amyloidosis Neuropathy Score (TTR-ANS): a new outcome measure designed specifically for Familial Amyloid Polyneuropathy (TTR-FAP)

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Background and aims: The systemic Transthyretin (TTR) amyloidoses are a group of clinically heterogeneous, devastating diseases for which a remarkable development of new therapies has occurred. An axonal length-dependent neuropathy with variable involvement of other organs is one of the phenotypes associated with these diseases, frequently referred to as Familial Amyloid Polyneuropathy (TTR-FAP). Herein we report the development, construct validity and reliability of a clinical scale specifically for TTR-FAP (TTR-ANS).
Methods: We used our experience as a reference center for hereditary TTR Amyloidosis to develop TTR-ANS. We performed a cross-sectional study using electronic clinical registries of 60 patients representing mild, moderate and severe disease stages. TTR-ANS was independently applied by two observers. Correlations with existing clinical scales – Neuropathy Impairment Score (NIS; including Total and Lower Limbs, NIS-LL), Norfolk, Karnofsky, Polyneuropathy Disability Score (PND), time from symptom onset, disease stages and neurophysiology measurements were analyzed.
Results: TTR-ANS includes three major sub-scores: small fiber sensory neuropathy (subjective sensory neuropathy and objective pain sensitivity assessment), autonomic neuropathy (gastrointestinal, genitourinary and cardiovascular manifestations) and large fiber neuropathy (reflexes, touch and vibration sensitivity and motor function). Smaller sub-scores evaluating kidney, heart, eye and central nervous system functions are also included. As expected, total TTR-ANS correlates highly with disease stages, time from disease onset and NIS/NIS-LL, with the two scales diverging predominantly in the autonomic neuropathy sub-score.
Conclusion: In a single center retrospective study, TTR-ANS has shown construct validity and reliability. Future validity prospective studies and studies of TTR-ANS responsiveness to therapy are ongoing.
Disclosure: Nothing to disclose

O310

Statins and cryptogenic axonal polyneuropathy: a literature review and case-control study

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Background and aims: Polyneuropathy is one of the most common neurological disorders (prevalence 2-4%). In approximately 25% no cause is found and the diagnosis Cryptogenic Axonal Polyneuropathy (CAP) is made. Nerve biopsies in these patients are suggestive of microvascular etiology. This is supported by studies showing an association between CAP and metabolic syndrome. However, this association might be confounded by statin use. Case reports have presented patients with suspected statin induced polyneuropathy, but outcomes from larger studies have been conflicting. With an increasing number of patients using statins, it is very important to know whether a real relationship between statin use and polyneuropathy exists. To answer this question we present our findings from our prospective case-control study and systematic review.
Methods: We conducted a prospective case control study comparing exposition to cholesterol lowering drugs between CAP patients and controls before index date (onset of symptoms or firs visit for controls). We calculated odds ratio's both for statins and cholesterol lowering drugs seperately and corrected for possible confounders such as lipid spectrum, cardiovascular diseases and risk factors.
Results: 340 CAP patients and 289 controls were included. We found a negative association between ever use of cholesterol lowering drugs and statins before index date and CAP. Results were similar for current use. There was no difference in dosage or exposition duration between groups. We found no evidence of a positive association between statins and CAP in current literature.
Conclusion: There is no evidence of sufficient quality supporting an association between statin use and CAP.
Disclosure: This study was funded by the Prinses Beatrix Spierfonds, the Netherlands.

Cerebrovascular diseases 2

O311

Predicting intracerebral haemorrhage expansion with non-contrast CT: the BAT Score

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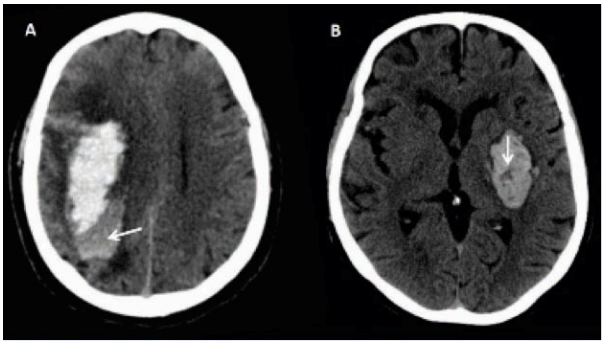
Background and aims: While the CT angiography spot sign performs well as a biomarker for Hematoma Expansion (HE), CT angiography is not routinely performed in the emergency setting. We developed and validated a score to predict HE based on non-contrast CT (NCCT) findings in acute intracerebral haemorrhage (ICH).
Methods: After developing the score in a single center cohort of ICH patients (n=344), we validated it in a large clinical trial population (n=954) and in a multicenter ICH cohort (n=241). The following NCCTmarkers of HE were analysed: hypodensities, blend sign, hematoma shape and density, and fluid level. HE was defined as hematoma growth>6 mL or >33%. The score was created using the estimates from multivariable logistic regression after final predictors were selected from bootstrap samples.
Results: Presence of blend sign (odds ratio (OR) 3.09,p=0.002), any intrahematoma hypodensity (OR 4.54, p<0.0001) and time from onset to NCCT<2.5 h (OR 3.73, p=0.0002) were predictors of HE. A 5–point score was created (BAT score:1 point for Blend sign, 2 points for Any hypodensity and 2 points for Timing of NCCT<2.5h). The c statistic was 0.77 in the development population,0.65 and 0.70 in the validation cohorts. A dichotomised score (BAT score>3) predicted HE with 0.50 sensitivity, 0.89 specificity and 0.82 accuracy.



Illustrative example of blend sign (A, arrow) and intrahematoma hypodensity (B, arrow) on admission non-contrast computed tomography.

Conclusion: An easy to use 5-point prediction score can identify subjects at high risk of HE. This tool requires just a baseline NCCT scan and may help select ICH patients for anti-expansion clinical trials.
Disclosure: The present study was supported by the following awards from the National Institute of Neurological Disorders and Stroke: 5R01NS073344, 1U01NS062091-01A2, K23NS086873. PREDICT was supported by Canadian Stroke Consortium and NovoNordisk Canada. The funding sources did not have any involvement in study design; data collection, analysis, and interpretation; writing of the manuscript; or decision to submit the study for publication.

O312

Direct oral anticoagulants versus Vitamin K antagonists after a recent ischaemic stroke: a pooled individual patient data analysis

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Background and aims: We compared the clinical benefit of Direct Oral Anticoagulants (DOAC) and Vitamin-K antagonists (VKA) in patients having Atrial Fibrillation (AF) with a recent ischemic stroke or TIA.
Methods: We conducted an individual patient data analysis of 7 prospective studies and analyzed the association between type of anticoagulation (DOAC vs. VKA) with a composite endpoint (recurrent ischemic stroke (AIS), intracerebral hemorrhage (ICH) or mortality) using mixed effects Cox proportional hazards regression models and calculating adjusted hazard ratios (HRadj) with 95% confidence intervals (95% CI).
Results: Of 4912 patients [median age 78years (IQR71-84); 2331 (47.5%) female; 4739 (96.5%) ischemic stroke as index event, median NIHSS-at-onset 5 (IQR2-12)], 2256 (45.9%) patients received VKA and 2656 (54.1%) received DOAC after the index stroke. The median time from index stroke to start of oral anticoagulation was 5days (IQR2-14) for VKA and 5days (IQR2-11) for DOAC (p=0.53). There were 262 AIS (4.4%/year), 71 ICH (1.2%/year) and 439 deaths (7.4%/year) during the total follow-up of 5970 patient years. DOAC treatment reduced the risk of the composite endpoint (HRadj 0.78, CI95% 0.64-0.94, p=0.01). In a secondary analysis, DOAC reduced the risk of ICH (HRadj 0.34, CI95% 0.16-0.71, p=0.01) and mortality (HRadj 0.71, CI95% 0.56-0.90, p<0.01) while the risk of recurrent AIS did not differ between DOAC and VKA treatment (HRadj 0.98, 95%CI 0.72-1.35, p=0.91).
Conclusion: In patients with AF, DOACs commenced in a median of 5 days after stroke seem to have a clinical benefit compared to treatment with VKA, mainly due to a lower risk for ICH and mortality.
Disclosure: The research presented in this abstract is investigator-driven.

O313

Cerebrovascular lesions during normal aging: a neuropathological study with 7.0-tesla magnetic resonance imaging

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Background and aims: Successful aging is associated with regional brain shrinkage and an increased cerebrovascular risk. The present post-mortem study investigates whether the increase of small cerebrovascular lesions is more frequent in normal elderly persons compared to adult ones.
Methods: 34 persons with normal cognition and without a stroke history underwent an autopsy. The incidence and the severity of cerebrovascular lesions in post-mortem brains of 20 adult (average age: 43±12 years) and 14 elderly (average age: 75±8 years) brains were examined. The neuropathological examination included a T2 and T2* 7.0-tesla MRI on three coronal sections.
Results: The neuropathological examination revealed more severe White Matter Changes (WMCs) and an increase of Cortical Micro-Bleeds (CoMBs) in the elderly compared to the adult brains. No differences were observed concerning Cortical Micro-Infarcts (CoMIs). Similar findings were observed on MRI examination: increased severity of WMCs and incidence of CoMBs were found to the same extend in the frontal, the central and the occipital section of the elderly brains. CoMIs were on the other hand more or less similarly low and distributed in the three sections of the adult and elderly brains.
Conclusion: During the aging process only increased severity of WMCs and of the incidence of CoMBs are observed. CoMIs, which are the most specific cerebrovascular lesions, are not amplified by getting older. The brain changes during normal aging are not due to the increased impact of cerebrovascular disease but rather the consequence of the age-related neuronal degeneration.
Disclosure: Nothing to disclose.

O314

Correlates of pontine small vessel disease: a post-mortem study

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Background and aims: The pons has not been included in most Small Vessel Disease (SVD) pathology scores. We aim to investigate the relationship of pontine SVD and SVD in other brain areas, and extracranial and intracranial artery atheromatous disease.
Methods: A semi-quantitative score was applied to assess the extent of atheroma in aorta, coronary, cervical and intracranial arteries in a human post-mortem control cohort. SVD scores (1 point for each: arteriolosclerosis, perivascular space enlargement, microbleeds/large and lacunar infarcts, fibrinoid necrosis) were obtained from pons, frontal WM (FWM), occipital WM(OWM) and basal ganglia(BG). A multivariate model was used to explain the pons SVD score taking into account age, gender, aorta+coronary, cervical and intracranial artery atheroma, and heart weight.
Results: A total of 36 cases were studied (mean age 58.7±13.15 years, 58.3% females). SVD changes were found in 52.8% (N=19) of the cases, only >2 in 2 cases. Pons SVD score (0.75±0.87) was slightly lower (p=0.01) than SVD scores in FWM (1.42±1.2), OWM (1.4±1.4) and BG (1.6±1.2). Pons SVD was weakly correlated with FWM SVD (r=0.37, p=0.026) and OWM (r=0.349, p=0.04) and did not correlate with BG SVD. In multivariate analysis only intracranial artery atheroma associated with pons SVD (b=0.44, p=0.014).
Conclusion: Pons SVD was relatively independent from SVD in other brain regions. However, Pons SVD was closely related to intracranial artery atheroma which is consistent with limited imaging data.
Disclosure: Nothing to disclose

O315

Atrial fibrillation in cryptogenic stroke: the Nordic Atrial Fibrillation and Stroke Study (NOR-FIB)

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Background and aims: The optimal duration and timing of cardiac rhythm monitoring after cryptogenic stroke is unknown. Identification of reliable biomarkers indicating AF will be valuable in the selection of patients for prolonged cardiac rhythm monitoring. The purpose of the study is to assess the incidence of AF detection using implantable cardiac monitors (Reveal LINQ®) in patients with cryptogenic stroke or TIA and to identify biomarkers that can be used as predictors of incident AF.
Methods: Our study is a multi-center prospective observational study of the occurrence of AF in cryptogenic stroke/TIA patients with implantable cardiac monitors for 12 months. Blood samples measuring biomarkers are taken in the acute phase and at 12 months´ follow-up. Estimated number of patients to be included in the study is 500.
Results: By January 2018, the total number of patients included in 7 out of 18 participating centres, is 45. Out of 45 included patients, AF has been detected in 7 patients, resulting in detection rate of 15,5%. Treatment with anticoagulants has been initiated in all patients with AF. The pilot study has identified biomarkers that seem to be useful for the detection of AF in cryptogenic stroke/TIA.
Conclusion: Updated interim analysis of included patients will be presented as well as new results from extended analyses of biomarkers.
Disclosure: Nothing to disclose

O316

Integrity of the Circle of Willis as an important predictor of early catastrophic outcome after endovascular thrombectomy in middle cerebral artery occlusion stroke

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Background and aims: To evaluate whether proximal collaterome influences early catastrophic outcome (defined as hospital death) in patients treated with Endovascular thrombectomy (ET) due to middle cerebral artery occlusion stroke.
Methods: We consecutively included stroke patients with acute occlusion of the M1 portion of Middle Cerebral Artery (MCA) who underwent ET either as a standalone treatment or with intravenous thrombolysis. We recorded demographics, National Institutes of Health Stroke Scale (NIHSS) scores, baseline clinical and radiographic characteristics, and in-hospital death. Incomplete Circle of Willis (iCW) was defined as absence of crossflow through anterior communicating artery and absence of posterior communicating artery ipsilateral to the affected side on the CT angiography.
Results: In total, 152 patients were studied [median age 73 (interquartile range [IQR] 59-80), median admission NIHSS score 17 (IQR 12-21)]. In-hospital death rate following the intervention was 14.5% (n=22). The survivors were younger [median age 73(58-79) vs 81(69-86)], had lower NIHSS [17(12-20) vs 20(17-26)], and lower rates of anticoagulant medication intake [12.3% vs 36.4%], all $p<0.01$. In a logistic regression analysis adjusted for age, NIHSS, anticoagulation, infarct volume, symptomatic hemorrhage, in-hospital death was strongly associated iCW [OR 8.3(CI 1.2-56.8)].
Conclusion: iCW is associated with early catastrophic outcome after ET in patients with MCA occlusion. Development of strategies to augment proximal collaterome in this critical group of patients is urgently needed.
Disclosure: Nothing to disclose

Motor neurone diseases

O317

AVXS-101 phase-1 gene replacement therapy clinical trial in SMA type-1: continued event free survival and achievement of developmental milestones

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Background and aims: Spinal Muscular Atrophy is a devastating, monogenic neurodegenerative disease. Children with SMA1 will never sit unassisted or maintain head control or achieve CHOP-INTEND score of >40. Moreover, a natural history study reported that 75% die or require permanent ventilation by 13.6 months. This trial explores safety and efficacy of a gene replacement therapy. AVXS-101 delivers the SMN gene in a one-time intravenous dose.

Methods: In this Phase 1 trial, 15 patients with SMA1 confirmed by genetic testing (with 2xSMN2 copies) were enrolled. Patients received low-dose AVXS-101 (Cohort 1, n=3) or proposed therapeutic dose (Cohort 2, n=12). The primary objective was safety and secondary objectives included survival (avoidance of death/permanent ventilation) and ability to sit unassisted (video confirmed by external independent reviewer). CHOP-INTEND scores and other motor milestones were additional objectives.

Results: AVXS-101 appeared to have a favorable safety profile and to improve survival at data cut-off (20January2017). All patients reached 13.6 months free of permanent ventilation and none have died (3 live >30 months). Cohort 2 patients demonstrated improvement in motor function: 11/12 achieved head control and sat with support, and 9/12 sat unassisted. Two patients stood and walked independently.

Conclusion: In contrast with the natural history, a one-time intravenous administration of AVXS-101 appeared to demonstrate a positive impact on the survival of both cohorts and a dramatic, sustained impact on motor function of Cohort 2: 11/12 patients achieved CHOP-INTEND scores and motor milestones rarely/never seen in this population. A clinical update will be given at the time of presentation.

Disclosure: This clinical trial is sponsored by AveXis, Inc.

O318

Integrated miRNAs analysis of ALS iPSCs and iPSCs-derived motor neurons towards the development of a molecular therapy for ALS

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Background and aims: Amyotrophic Lateral Sclerosis (ALS) is characterized by progressive degeneration of Motor Neurons (MNs). The mechanisms underlying the disease are almost unknown, even if dysregulation in RNA metabolism, including microRNAs (miRNAs) processing, has been increasingly recognized. Since miRNAs are highly expressed in central nervous system and are required for MNs survival, they may play important roles in the aetiology or progression of neurodegenerative diseases such as ALS.

We aim to analyze miRNAs profiling in human induced Pluripotent Stem Cells (iPSCs) and iPSC-derived spinal MNs from ALS subjects compared to healthy controls.

Methods: We reprogrammed patient and control fibroblasts in iPSCs and subsequently we differentiated them into spinal MNs. Then, we isolated miRNAs contained in extracellular vesicles from iPSCs and MNs culture media. Finally, we performed Next Generation Sequencing (NGS) analysis on our lines.

Results: We obtained a transcriptome analysis of human iPSCs, MNs, and exosomes in ALS. Among miRNAs deregulated in ALS MNs, we found miRNAs involved in MNs survival and p53 pathways and, interestingly, relevant targets of these miRNAs, including apoptotic factors, were aberrantly increased in ALS MNs. Moreover, two other altered miRNAs were implicated in synapsis and neurogenesis. Finally, we silenced selected miRNAs targets with morpholino antisense oligonucleotides in the SOD1G93A murine model evaluating survival, neuromuscular function and neuropathology.

Conclusion: The identification of specific miRNAs relevant to ALS pathology can lead to the discovery of new disease biomarkers and potential therapeutic targets. This approach can increase the chances of modifying complex diseases by modulating entire gene networks through a specific miRNAs subset.

Disclosure: Nothing to disclose

O319

RNA-Sequencing and motif analysis of Human Motor Neurons implicates selective role of SMN/SYNCRIP complex and Motif 7 in Spinal Muscular Atrophy

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Background and aims: Spinal Muscular Atrophy (SMA) is a neuromuscular disorder that represents the leading cause of genetic death during childhood. SMA is caused by mutations in Survival Motor Neuron (SMN) gene resulting in a loss of function of the SMN protein, which plays a crucial role in pre-mRNA processing. The exact pathogenetic mechanisms and the reasons of selective motor neurons (MNs) vulnerability are still not completely understood.

Methods: To address this question, we generated MNs from control and SMA patient-derived induced pluripotent stem cells (iPSCs) and performed deep RNA sequencing and bioinformatic analyses.

Results: We detected SMA-specific molecular changes in MNs, including alterations in axonal and synaptic genes that involved Synaptotagmin 13, a key component of the synaptic machinery, and neurexin2 (NRXN2), a protein essential for MN survival and function. The overexpression of NRXN2 could extend human SMA-MN survival and increase axon length. Motif enrichment analysis of differentially expressed/spliced genes revealed a common Motif-7, which is a target for SYNCRIP. SYNCRIP is an RNA binding protein and a splicing modulator of SMN that promotes the inclusion of exon 7 in SMN2. Interestingly, it interacts only with full-length SMN and not with the Δ7 truncated form. SYNCRIP overexpression rescued SMA-MNs phenotype, thanks to the consequent increase of SMN and of their down-stream target NRXN2, through a positive loop mechanism.

Conclusion: The study of complementary pathways disrupted in human SMA is important to identify alternative therapeutic targets besides direct SMN increase. This finding represents a crucial step towards the discovery of efficacious therapies for all SMA subtypes.

Disclosure: The study was supported by a Cariplo grant awarded to Stefania Corti.

O320

Structural connectivity alterations in Amyotrophic Lateral Sclerosis are modulated by the topology of the anatomical brain connectome

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Background and aims: To test whether the spatial patterning of structural brain alterations in Amyotrophic Lateral Sclerosis (ALS) is modulated by the topology of the anatomical brain network using connectomics.

Methods: 58 ALS patients and 34 controls underwent T1-weighted and Diffusion Tensor MRI. Graph analysis and connectomics were used to define the "healthy" connectome in controls and assessed global and local topological network properties in ALS patients. Regions of subsequent stages of ALS pathology were defined according to the Braak pathological propagation pattern.

Results: ALS patients showed reduced local efficiency and nodal strength of the sensorimotor network relative to controls. At the regional network level, ALS patients compared to controls showed alterations involving sensorimotor network and connections linking motor to basal ganglia and frontal regions. In the healthy subject connectome, brain regions of subsequent stages of ALS pathology are shown to be more closely interconnected with the primary motor cortex (ALS-epicenter) than regions of more distant stages. The topological distance between the epicenter and brain nodes of subsequent stages of pathology in controls correlated with the structural connectivity between the same regions in ALS patients, such that more closely connected regions in controls exhibited more severe alterations of structural connectivity in ALS patients.

Conclusion: In ALS, graph analysis and connectomics represent a powerful approach to detect upper motor neuron degeneration, extra-motor brain changes and network disorganization associated with the disease. Altered structural connectivity was greater between closely connected regions. Axonal connections may influence the spatial spreading of pathology in ALS.

Disclosure: Study supported by: Italian Ministry of Health (#RF-2011-02351193).

O321

Amyotrophic Lateral Sclerosis (ALS) spatial epidemiology in the Mount Etna region, Italy: further evidences for a pathogenetic role of volcanogenic metals

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Background and aims: Spatial epidemiology could give important clues on environmental causes of a disease. Previously, we described a higher incidence of Amyotrophic Lateral Sclerosis (ALS) in the eastern flank of the Mount Etna when compared to the western one and volcanogenic metals have been proposed as a possible explanation.
We aimed to perform a cluster analysis of ALS cases in the Mount Etna region.

Methods: ALS cases residents in the province of Catania and who had experienced the onset of symptoms during the 2005-2015 period were included. Address at the moment of onset was considered for each case. Cluster analysis was performed using both Kulldorff's spatial scan statistic and Moran's Index.

Results: A total of 193 ALS cases have been identified. The mean annual crude incidence rate was 1.63/100 000 person-years (95% CI 1.40-1.86). Kulldorff's statistics identified a spatiotemporal cluster including 13 communities in the eastern flank of the mount Etna. Here, 12.73 cases were expected and 33 were observed (SIR 2.59; 95% CI 1.78-3.64, p-value 0.003) (Fig. 1). Moran's Index confirmed a positive spatial autocorrelation in the same area (Fig. 2).

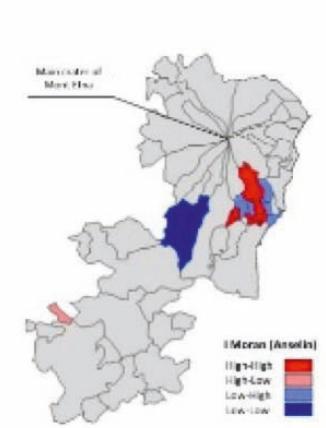

Fig. 2. Moran's Index in the Mount Etna region. Moran's Index studies spatial correlation by quantifying the similarity in incidence between neighbor areas.

Fig. 1. Spatiotemporal cluster identified by Kulldorff's spatial scan statistics in the Mount Etna region.

Conclusion: Our study showed a higher ALS incidence cluster in the eastern flank of Mount Etna. Despite the retrospective nature of the study, the adoption of two proper spatial analyses independents from an a priori hypothesis strengthen the validity of our results. These findings further suggest the possible role of volcanogenic metals in ALS pathogenesis.

Disclosure: Nothing to disclose

Cognitive neurology/neuropsychology

O322

Locus coeruleus atrophy assessed with 3T MRI in typical and atypical Alzheimer's Disease and correlations to neuropsychological data

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Background and aims: The Locus Coeruleus (LC), a noradrenergic nucleus, shows early alteration in Alzheimer's Disease (AD). This involvement has been poorly studied in vivo while it could constitute a therapeutic target. The objectives were to investigate the LC signal in typical and atypical AD using 3T MRI and to evaluate the impact of LC involvement on neuropsychological data.

Methods: Three groups of subjects matched for age were studied: controls, patients with typical AD, and patients with atypical AD (logopenic primary progressive aphasia) defined by clinical-biological criteria, with CSF biomarkers. All subjects had a standardized neuropsychological assessment and a 3 Tesla MRI including a sequence designed to quantify the LC neuromelanin signal. Treatments were comparable in both AD groups.

Results: 8 controls, 17 typical and 9 atypical AD patients were included. The LC signal was significantly lower in the typical and atypical AD groups compared to controls (p=0.002 and p=0.013, respectively). In patients with typical AD, the episodic memory scores (free and total recall) were positively correlated with the LC signal (Figure 2: p=0.023, p=0.028, respectively).

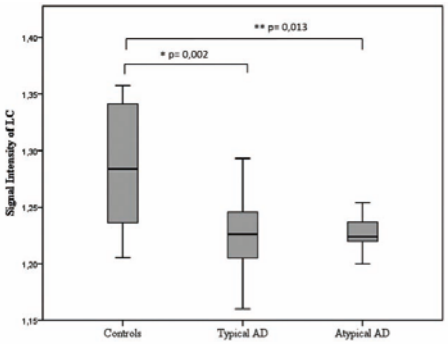

Figure 1: Box plot of the LC signal intensity in controls and patients with typical and atypical Alzheimer's disease. Plots indicate median, the boxes indicate the upper and lower quartiles. Whiskers are defined as the lowest/highest values still within the 1.5 interquartile range from the box. AD=patients with Alzheimer's disease.

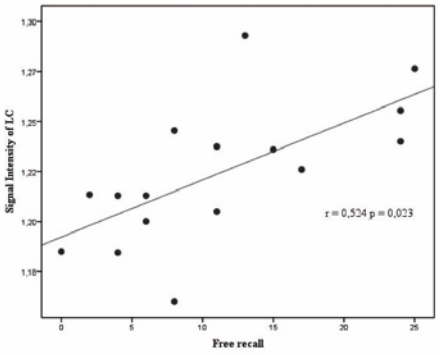

Figure 2: Correlation between LC signal intensity and verbal episodic memory test (free recall) in typical Alzheimer's disease patients. AD=patients with Alzheimer's disease.

Conclusion: We found a clear decrease of LC signal assessed by 3T MRI in typical and atypical AD, independently of the clinical presentation. The positive correlations with the episodic memory scores suggest that the LC plays a crucial role in maintaining cognitive function, probably via the norepinephrine system. AD patients may thus benefit from innovative therapeutic approaches targeting the noradrenergic system.

Disclosure: Public fundings

O323

Reduced dynamism of functional connectivity is associated with cognitive impairment in Multiple Sclerosis patients: a dynamic functional connectivity study in a multi-center setting

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Background and aims: To investigate the relationship between Multiple Sclerosis (MS)-related Cognitive Impairment (CI) and time-varying Functional Connectivity (FC) using a dynamic Resting State (RS) FC approach.
Methods: RS fMRI scans from 62 MS patients and 65 healthy controls (HC) were obtained at seven European sites. MS patients underwent clinical/cognitive evaluation. Independent component analysis was used to identify 43 relevant intrinsic FC components. Between-group differences of network FC were evaluated using a dynamic approach and then grouping FC correlation matrices into recurrent states of transient FC. Summary dynamism measures were computed for each group.
Results: 23 MS patients (37%) were cognitively impaired (CI) (> two abnormal neuropsychological tests). Dynamic FC analysis revealed, in HC and MS, 3 recurrent FC states: two states characterized by strong inter-network connectivity and one characterized by weak inter-network connectivity. CI-MS patients had lower dwell time in the high-connectivity State2 compared to cognitively preserved (CP)-MS (p=0.05). Compared to CP-MS, CI-MS patients exhibited lower dynamic fluidity (less switches between states) (p=0.01) and operated over a restricted dynamic range (p=0.01). Between-group comparison of connectivity strengths revealed lower FC in MS vs HC between cortical-subcortical networks. In connectivity State3, CI vs CP-MS patients showed reduced FC between cortical-subcortical networks.
Conclusion: In both HC and MS patients, dynamic RS FC analysis was able to detect recurrent patterns of strong and weak inter-network RS FC. Time-varying RS FC patterns were less dynamic in CI than in CP-MS patients and HC, suggesting that slow inter-network connectivity is associated with worse cognition in MS.
Disclosure: Nothing to disclose

O324

Association between neuropsychiatric symptoms, cognitive functioning and structural brain changes in Clinically Isolated Syndrome

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Background and aims: Neuropsychiatric symptoms and impairment of cognitive functioning are present in patients with multiple sclerosis and are associated with structural brain changes, but have been less studied in Clinically Isolated Syndrome (CIS).
Objective: To characterize neuropsychiatric symptoms (depressive symptoms, anxiety, apathy and fatigue), cognitive functioning and disability and their associations with structural brain changes in CIS.
Methods: Patients with CIS (n=67) and demographically matched healthy controls (n=46) underwent neurological (using Expanded Disability Status Scale - EDSS) and neuropsychological examination including questionnaires of neuropsychiatric symptoms and subjective cognitive functioning using Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ). Next, both groups underwent MRI (magnetic resonance imaging) of brain with measurement of global, regional and lesion load volume.
Results: The CIS group had more depressive and anxiety symptoms ($p \leq 0.026$). The groups did not differ in apathy, fatigue and MSNQ score. There was no correlation of the EDSS score with neuropsychiatric symptoms. Cognitive functioning unlike clinical disability was associated with depressive symptoms and anxiety ($p \leq 0.001$). Higher depressive symptoms correlated with higher lesion load in the right temporal lobe (p=0.013). Higher apathy was associated with higher lesion load in the right and left insulas and right occipital lobe ($p \leq 0.026$). Higher anxiety correlated with lower white matter volume (p=0.045).
Conclusion: We demonstrated that increased depressive symptoms and anxiety are present in patients witch CIS unlike impaired cognitive functioning. Next, neuropsychiatric symptoms are associated to cognitive

functioning an are the result of structural brain changes in specific brain regions unlike disability.
Disclosure: Nothing to disclose

O325

Transcranial Direct Current Stimulation (tDCS) over lateral parietal cortex facilitates object-location and face-word associative memory

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Background and aims: Management of memory impairments presents one of the most challenging issues in cognitive neurology and neurorehabilitation. Anodal tDCS was shown to increase activation in the targeted cortical area and related subcortical structures. The current study explores whether physiological modulation of the putative hippocampus - lateral parietal cortex neural loop can bring enhancement in associative memory performance.
Methods: Two double-blind, cross-over sham-controlled experiments were conducted. In both experiments, in two separate sessions, either anodal tDCS or sham were delivered over lateral parietal cortex (Figure 1). In Experiment 1 left-sided stimulation and face-word associative memory task were used, while in Experiment 2 right-sided stimulation and object-location task were used (Figure 2). Two distinct groups of 20 healthy subjects participated in each of the experiments.

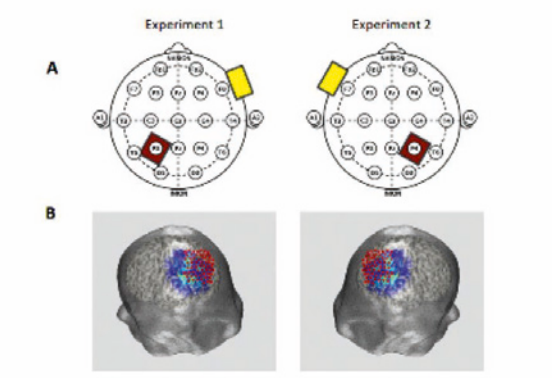

Figure 1. A. Position of the electrodes in two experiments - anode (red) was over lateral parietal cortex while cathode (yellow) was over contralateral cheek. B. Simulation of the induced electric fields under anode (Comets Toolbox, Lee at al. Journal of Neuroscience Methods, 2017, 277: 56–62).

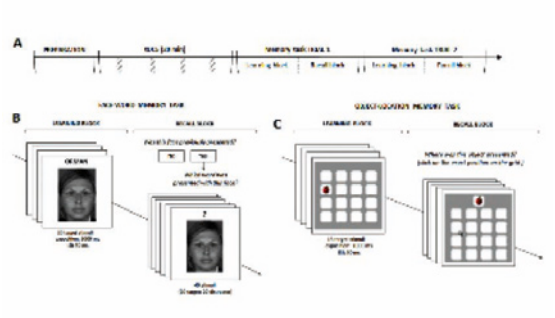

Figure 2. A. Study design. B. Face-word memory task (Experiment 1). C. Object-location memory task (Experiment 2).

Results: The 2x2 repeated measures ANOVA for face-word task showed main effects of stimulation condition [F(1,19)=7.908, p=.011] and of between-trials learning [F(1,19)=6.357, p=.021], but no interaction effect [F(1,19)=0.223, p=.642]. Similar results were for object-location task, i.e. main effects of stimulation condition [F(1,19)=5.400, p=.031] and learning [F(1,19)=23.840, p<.001], but no interaction effect [F(1,19)=0.444, p=.531].

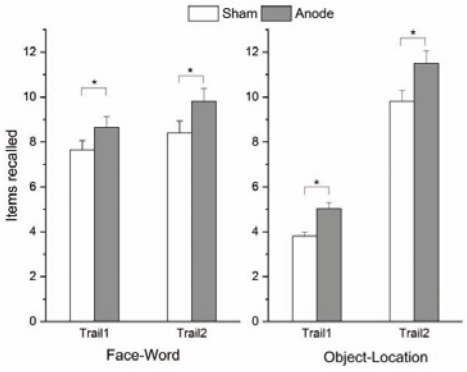

Figure 3. Results (group mean and standard error) from both experiments. Significant difference between conditions (i.e. active vs. sham) is indicated with asterix.

Conclusion: Results suggest that anodal tDCS over lateral parietal cortex is able to facilitate performance in associative memory tasks regardless of the modality of the associations. The tDCS-induced improvement does not interfere with, but acts as add-on to the repetition-induced improvement. Noninvasive neuromodulation seems as a promising new tool for memory enhancement.
Disclosure: The study was supported by project grant (#175012) from the Ministry for Education, Science and Technological Development of Republic of Serbia. Authors have nothing else to disclose.

O326

Assessment of auditory localisation in patients with disorders of consciousness

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Background and aims: Visual pursuit and pain localisation are both considered as signs of consciousness but auditory localisation is not. The objectives of this study are to assess the frequency of auditory localisation in patients with disorders of consciousness and to compare brain metabolism of unresponsive patients with and without auditory localisation in order to determine if this behaviour could be considered as a sign of consciousness.
Methods: We considered retrospectively 228 patients with severe brain injury. We looked at how many of these patients presented auditory localisation. We then measured cerebral metabolism using Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) in a subset of patients in an unresponsive wakefulness syndrome who showed auditory localisation and compared it to unresponsive patients who did not show such behaviour.
Results: Auditory localisation was observed in 10% of unresponsive patients, in 43% of minimally conscious state minus, in 62% of MCS plus (i.e., language processing preserved) and in 76% of patients who emerged from the MCS. FDG-PET results showed brain metabolism differences between unresponsive patients with and without localisation in auditory and consciousness related brain regions.
Conclusion: Our results indicate a relationship between the presence of auditory localisation and the level of consciousness in patients with disorders of consciousness. UWS patients with auditory localisation also showed more preserved brain metabolism than UWS without localisation. These findings suggest that auditory localisation could be considered as a sign of consciousness.
Disclosure: Nothing to disclose

O327

Persistent allocentric navigation deficits indicate hippocampal damage in Transient Global Amnesia

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Background and aims: Although TGA is defined as a temporary loss of working memory, recent studies indicate more persistent deficits in episodic/spatial memory. In the present study, real-space orientation was investigated longitudinally in TGA as a surrogate marker of hippocampal function.
Methods: 18 TGA patients and 14 age-matched controls had to find target items in a realistic spatial environment. Throughout the experiment subjects wore a gaze-controlled, head-fixed camera that recorded their visual exploration behaviour. In 8 patients [18F]-fluorodeoxyglucose was injected during the acute stage at the beginning of the task, to detect navigation-induced brain activations. DWI lesions were recorded by MRI and mapped to the hippocampus in TGA patients.
Results: After 3d of symptom onset, patients with TGA navigated significantly worse and had a higher error rate than controls in allocentric ($p=0.002$) but not egocentric route planning ($p=0.16$), despite recovery of non-spatial working memory. Spatial disorientation increased with age, TGA duration, and hippocampal DWI lesion size. Navigation-induced brain activation was increased in the right anterior hippocampus, retrosplenial/parietal/mesiofrontal cortex and dentate nucleus bilaterally compared to controls. Allocentic navigation deficits improved slightly within 3m after TGA onset, but were still significant compared to controls ($p=0.05$). Patients above age 65 had a worse course of recovery. The navigation strategy of TGA patients was severely altered in the acute stage and during follow-up: they used fewer shortcuts and stayed longer at crossings.
Conclusion: TGA patients show persistent deficits in allocentric real-space navigation indicating enduring microstructural hippocampal damage. PET imaging indicates a recruitment of extrahippocampal hubs of the cerebral navigation network.
Disclosure: The study was performed as a project of the German Center for Vertigo and Balance Disorders (DSGZ) (grant number 01 EO 0901) with support of the German Federal Ministry of Education and Health (BMBF).

MS and related disorders 2

O328

Efficacy of Ozanimod versus Interferon beta-1a by DMT treatment experience and EDSS categorisation from a multicenter, randomised, double-blind, phase-3 study of relapsing Multiple Sclerosis

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Background and aims: Ozanimod is an oral, once-daily immunomodulator selectively targeting sphingosine 1-phosphate receptors 1 and 5. Annualised Relapse Rate (ARR) was evaluated by pre-specified baseline subgroups that included prior Disease-Modifying Treatment (DMT) status, Expanded Disability Status Scale (EDSS; ≤3.5 or >3.5), sex, age (≤40 or >40 years), and presence of GdE lesions.

Methods: Patients with Relapsing Multiple Sclerosis (RMS) in the RADIANCE Part B (NCT02047734) study received ozanimod HCl 1 or 0.5 mg vs Interferon (IFN) beta-1a 30 μg for 24 months.

Results: In 1313 patients, ARR over 24 months was significantly reduced for Ozanimod 1mg (0.172, P<0.0001) and 0.5mg (0.218, P=0.0167) compared with IFN beta-1a (0.276). ARR was lower with Ozanimod 1mg (0.157) and 0.5mg (0.228) vs IFN beta-1a (0.246) among DMT-naïve patients (71% of population) as well as lower for Ozanimod 1mg (0.205) and 0.5mg (0.191) vs IFN beta-1a (0.357) among DMT-experienced patients (see Table). ARR was lower with Ozanimod 1mg (0.146) and 0.5mg (0.183) than with IFN beta-1a (0.237) in patients with baseline EDSS ≤3.5 (85% of population), with similar effects for EDSS >3.5.

Conclusion: Ozanimod had significantly lower ARR than IFN for both doses; in addition, Ozanimod showed reduced ARR across a broad range of subgroups, with 1mg generally having better rate ratios than 0.5mg, supporting the potential of Ozanimod as an effective oral treatment in a broad spectrum of patients with RMS.

Disclosure: Nothing to disclose

O329

Multiple Sclerosis Impact Scale and brain volume are independent predictors of cognitive impairment in Secondary Progressive Multiple Sclerosis

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Background and aims: Cognitive deficits in Multiple Sclerosis (MS) affect up to 70% of patients with progressive MS. We investigate the associations between the disease specific Multiple Sclerosis Impact Scale psychological subscale (MSIS-29v2-PSYCH), Magnetic Resonance Image (MRI) normalised brain volume and cognitive impairment in people with Secondary Progressive MS

(SPMS).
Methods: A group of SPMS patients were recruited at baseline from a randomised phase 2 clinical trial(MS-SMART). Patients were assessed using a cognitive test battery to define cognitive status based on conservative criteria (standard deviation of z-score of -1.96 on ≥2 tests), and completed the MSIS-29v2 questionnaire. Normalised brain volume(NBV) was measured using the geodesic information flow and SIENAX algorithms. We analysed associations of cognitive impairment with MSIS-29v2-PSYCH subscale and brain volume using binary logistic regression.
Results: 60 subjects were analysed with baseline characteristics. We find NBV and MSIS-29v2-PSYCH to be independent predictors of cognitive impairment after adjusting for age, gender and years of education. There is a significant negative association between NBV and cognitive impairment (OR: 0.45; 95% CI: 0.21-0.84; p=0.0191) and a significant positive association between MSIS-29v2-PSYCH and cognitive impairment (OR: 1.89; 95% CI: 1.03-3.72; p=0.0491).
Conclusion: MSIS-29v2-PSYCH is therefore useful predictor of cognitive impairment in a SPMS patients, but in our logistic regression methodology may be confounded by NBV. Longitudinal data will confirm MSIS-29v2-PSYCH as a marker of MS future cognitive status.
Disclosure: The MS-SMART (NCT01910259) trial is a project funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. It is also supported by the UK and National Multiple Sclerosis Society; the National Institute for Health Research University College London Hospitals Biomedical Research Centre and University College London; NIHR Leeds CRF (DenTCRU). CJW and RP were supported in this work by NHS Lothian via the ECTU. The remaining authors declare no conflict of interests with respect to this work.

O330

Siponimod affects disability progression in SPMS patients independent of relapse activity: results from the phase III EXPAND study

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Background and aims: In the EXPAND study, Siponimod reduced the risk of Confirmed Disability Progression (CDP) in patients with Secondary Progressive Multiple Sclerosis (SPMS). We assessed the impact of Siponimod on CDP in patients with/without relapses to uncouple the treatment effect on CDP from the effect of relapses.
Methods: We analysed the impact of Siponimod on CDP by: (a) subgroup analysis using the Cox model on time to 3 month- (m)/6m-CDP in patients with/without relapses in 1- and 2-years before study; (b) principal stratum analysis to estimate the effect in patients who would not have relapsed on-study by m12, m18 and m24, regardless of treatment; (c) Cox model on time to 3m/6m-CDP in the overall population, censoring at time of first relapse.
Results: For non-relapsing patients in 1- and 2-years before study, risk reductions were 18% (HR, 0.82 [CI:0.66;1.02]) and 13% (0.87 [0.68;1.11]) for 3m-CDP and 25% (0.75 [0.59;0.96]) and 18% (0.82 [0.62;1.08]) for 6m-CDP, respectively. For relapsing patients in 1- and 2-years before study, risk reductions were 33%/33% (3m-CDP) and 30%/37% (6m-CDP), respectively. In the principal stratum estimate, siponimod reduced 3m-CDP by 14–20% and 6m-CDP by 29–33% in non-relapsing patients across the 3 intervals, suggesting that these patients can achieve a large portion of the effect on overall population. Cox model censoring at relapses confirmed beneficial effect reaching nominal statistical significance (6m-CDP: HR 0.77 [0.62;0.96]).
Conclusion: Siponimod reduces the risk of CDP in SPMS patients with/without relapses; our analyses indicate that its effect on disability is largely independent from its effect on relapses.

Disclosure: This study was funded by Novartis Pharma AG, Basel, Switzerland. Detailed disclosures of each author will be included in the poster.

O331

Phase-2 multicenter study results of Ublituximab, a novel glycoengineered antiCD20 monoclonal Antibody (mAb), in patients with Relapsing Multiple Sclerosis (RMS)

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Background and aims: Ublituximab, a novel chimeric mAb targeting a unique epitope on the CD20 antigen, is glycoengineered to enhance affinity for all variants of FcγRIIIa receptors, demonstrating greater Antibody-Dependent Cellular Cytotoxicity Activity (ADCC) than Rituximab. This enhanced ADCC potency may offer benefits over currently available anti-CD20s in terms of lower doses and shorter infusion times. This Phase-2 study examines Ublituximab's effect on B-cell depletion and key clinical measures in RMS patients.
Methods: TG1101-RMS201 is a 52-week, Phase-2, placebo-controlled, multicenter study designed to assess the optimal dose and infusion time of Ublituximab in RMS subjects. All subjects, including placebo subjects (post-placebo phase), receive 3 Ublituximab infusions on Days 1, 15, and Week 24.
Results: All subjects (24/24) exceeded the target level of 95% B-cell depletion within 4 weeks of Ublituximab treatment. To date, 11 of 24 subjects have completed all assessments in the 52-week trial, where 87% remain relapse-free and 81% are confirmed free of disability progression. There was 100% reduction of T1 Gd-enhancing lesions at 52 weeks. Common adverse event (AE) was IRRs (all grade 1 or 2, in 17% of subjects). No severe AEs were associated with Ublituximab treatment. Faster infusion time (as low as 1 hour) did not correlate with an increased IRR frequency.
Conclusion: The Phase-2 results suggests Ublituximab, with infusion times as low as one hour, is safe and well tolerated, with favorable clinical and MRI outcomes at Week 52. We will be reporting the immunological and clinical data set for all subjects at the date of presentation.
Disclosure: This Phase-2 study was supported by TG Therapeutics, Inc.

O332

Measuring disease activity in Multiple Sclerosis: do we need spinal cord MRI?

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Background and aims: Magnetic Resonance Imaging (MRI) of the Spinal Cord (SC) is recommended during diagnostic process in suspected Multiple Sclerosis (MS), while its role in monitoring disease evolution or as a surrogate marker in clinical trials, is still controversial. We hypothesise that using brain MRI only might fail in detecting inflammation in a proportion of patients. Thus we aimed to study the frequency of SC acute inflammatory activity and whether it occurs independently from brain activity.
Methods: From MS registry, we selected patients fulfilling the following criteria: 1) diagnosis of MS; 2) having received at least two different MRI (brain and SC) scan at two time point (at least 30 days apart); 3) MRI reports available. Inflammatory activity was defined as the presence of at least one Gd enhancing lesion according to its location (brain/SC-both).
Results: Demographical and clinical data are listed in Table 1. A total of 5717 scans were reviewed, 4537 (79,3%) did not present Gd enhancement. Of the 1180 scans left, 651 (55,2%) showed brain Gd enhancing lesions only, 232 (19,7%) a concomitant presence of brain and SC Gd enhancing lesions, while 297 (25,2%) showed SC Gd enhancing lesions exclusively

Table 1. Demographical and clinical characteristics of patients included in the study

Number of Patients in the original MS registry	1332
Number of patients selected	828
Proportion Female/Male	572/256
*Medium age (SD)	34.7 (9.7)
*Median Expanded Disability Status Scale (EDSS) [range]	2.0 [0-8]
*Medium Disease Duration (SD)	5.8 (6.3)
Medium scans for patient (SD)	7 (2)

* Calculated according to the first scan date

Demographical and clinical characteristics of patients included in the study

Conclusion: Our study demonstrates that inflammatory activity can be detected frequently in SC and occurs in approximately 25% alone. Limiting MRI monitoring to brain, underestimates inflammatory activity thus requiring a larger sample in clinical trials. MRI monitoring of SC in clinical practice will allow neurologists to switch treatment to more powerful drugs in a larger number of patients
Disclosure: Nothing to disclose

O333

A neurometabolic profile of SPMS: the relationship between brain metabolites and clinical disability

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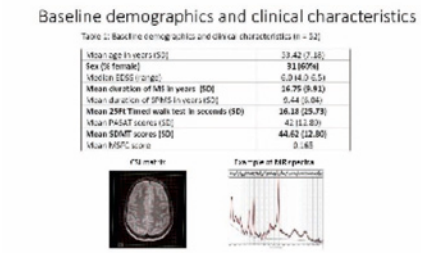
Background and aims: Neurometabolite concentrations measured using magnetic resonance spectroscopy imaging (1H-MRSI) could be potential biomarkers of progression in Secondary Progressive Multiple Sclerosis (SPMS). Here we explore the neurometabolic characteristics of a SPMS cohort and investigate their associations with clinical disability.

Methods: A baseline cross sectional analysis of 52 patients was performed from a trial of neuroprotection in SPMS (MS-SMART NCT01910259). Subjects underwent a standardised 1H-MRSI protocol (2D-PRESS TE=35ms) to measure neurometabolites. Spectra were then analysed using LCmodel to obtain absolute values for neurometabolites including total N-acetyl aspartate (tNAA) and myo-Inositol (mIns). Subjects underwent the Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT) and Expanded Disability Status Scale (EDSS) as part of a clinical assessment.

Kendall's tau-b correlation coefficients followed by multivariable linear regression analysis adjusted for age, gender, disease duration, EDSS and T2 lesion volume, were used to investigate the association between clinical outcome measures and neurometabolites.

Results: Table 1 reports the demographics and clinical characteristics of the cohort. Significant correlations were seen between tNAA, and PASAT (t=0.315,p=0.001) and SDMT scores (t=0.315, p=0.001). tNAA/tmIns showed significant correlation with PASAT (t=0.336,p=.001) and SDMT (t=0.306,p=0.002). Regression analysis showed that tNAA and tNaa/tmIns statistically significantly predicted SDMT and PASAT scores.



Conclusion: We have shown tNAA and tNAA/mIns, markers for neurodegeneration and gliosis, correlate with measures of cognition and can predict the presence of cognitive deficits in SPMS, making them strong candidates for biomarkers of cognitive impairment in MS.

Disclosure: The MS-SMART (NCT01910259) trial is a project funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. It is also supported by the UK and National Multiple Sclerosis Society; the National Institute for Health Research University College London Hospitals Biomedical Research Centre and University College London; NIHR Leeds CRF (DenTCRU). CJW and RP were supported in this work by NHS Lothian via the ECTU. The remaining authors declare no conflict of interests with respect to this work

Sleep disorders

O334

Sleep microstructure in Parkinson's Disease: Cycling Alternating Pattern (CAP) as a sensitive marker of early NREM sleep instability.

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Background and aims: Sleep disorders are frequent in Parkinson's Disease (PD). Apart from the occurrence of REM behavior disorders, in the early phase of disease standard sleep macrostructure evaluation was inconclusive. We analyzed NREM sleep microstructure (CAP) in a group of PD patients, in order to provide an objective measure of sleep disruption.
Methods: We recruited 31 PD patients (mean age 59.5±12.4 years; mean Hoehn-Yahr (H-Y) stage: 3.4±1.8) and 34 age-matched non-parkinsonian subjects (mean age 61.5±15.2 years) as control group. All patients underwent a full-night laboratory polysomnography (PSG). Conventional sleep macro/microstructure analysis were performed. Patients were then divided into two groups: group 1 (H-Y stage≤2) and group 2 (H-Y stage≥3).
Results: In group 2 of PD patients alterations of both sleep macrostructure and microstructure were found, compared to controls. More interestingly, PD subgroup with milder disease (group 1) presented sleep macrostructure, movements and respiratory parameters not significantly different from controls, while CAP rate was significantly higher and proportion of A1 phase of CAP was reduced. Multivariate logistic regression showed that disease duration, disease severity and arousal index emerged as independent predictive factors for CAP rate ³ 55% (Table 1) and A1 phase of CAP £ 40% (Table 2).

	Exp (B)	C.I.	p
Age	1.02	0.3 - 1.3	NS
H&Y: 3-4	10.7	1.4-14.2	0.002*
Disease duration	7.8	1.2-11.5	0.01*
% REM	0.4	0.1-3.9	NS
Sleep efficiency	0.8	0.2-2.4	NS
RBD	0.3	0.1-4.8	NS
PLM index	1.3	0.5-2.8	NS
Arousal index	2,1	0.9-5.1	0.05*

Table 1. Independent predictive factors for CAP rate>55%

	Exp (B)	C.I.	p
Age	1.12	0.2 - 1.5	NS
H&Y: 3-4	5.1	1.8-16.2	0.04*
Disease duration	8.7	2.3-11.5	0.001*
% REM	0.7	0.1-5.2	NS
Sleep efficiency	0.5	0.2-2.1	NS
RBD	0.6	0.2-3.5	NS
PLM index	1.7	0.3-3.2	NS
Arousal index	3.1	0.7-7.2	NS

Table 2. Independent predictive factors for A1 proportion<40%

Conclusion: The main result of our study consists in the disclosure of altered NREM sleep microstructure in PD, even at an earlier stage of the disease, so suggesting early alteration of the central pathways involved in the NREM sleep building-up and stability.
Disclosure: Nothing to disclose

O335

Reliability of a standardized test to document cataplexy to identify hypocretin deficiency

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Background and aims: Type 1 narcolepsy (NT1) diagnosis requires the evidence of cerebrospinal hypocretin deficiency (biological disease fingerprint) or the presence of neurophysiological criteria coupled with definite history of cataplexy. We recently standardized a laboratory test to video document cataplexy under emotional stimulation, and the current study aimed at testing its predictive value towards hypocretin deficiency in consecutive drug-free patients.
Methods: We analyzed in a population of 151 consecutive patients (101 with NT1, 28 with other hypersomnias of central origin, and 22 with subjective sleepiness complaint) the diagnostic potential of our standardized test for cataplexy documentation against the evidence of hypocretin deficiency with ROC curve analysis. Video recordings were analyzed by a technician blind to clinical suspicion, and occurrence of possible hypotonic phenomena were subjectively confirmed by patients (positive test).
Results: Positive test results had an area under the ROC curve of 0.805±0.043 ($p<0.0001$) against the biological disease marker of NT1. The most useful parameters at semi-quantitative blind assessment were ptosis (area=0.732±0.048, $p<0.0001$), head drop (area=0.682±0.051, $p=0.001$), and mouth opening (area=0.674±0.051, $p=0.002$) under emotional stimulation, while trunk dyscontrol and assessments in baseline conditions did not provide any significant result.
Conclusion: Video documentation of suspected cataplexy may help to identify NT1. Further studies should evaluate the potential diagnostic value of automatic hypotonia detection from video recordings of facial expression during emotionally triggered laughter.
Disclosure: Nothing to disclose

O336

Effects of acute exposure to high altitude on RLS symptoms and PLMS: a bilateral study

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Background and aims: Peripheral tissue hypoxia has been associated with restless legs syndrome (RLS) symptoms and is correlated with RLS severity. A higher RLS prevalence was reported at high altitude compared to coastal regions. Aim of this study was to investigate the influence of acute exposure to high altitude on Periodic Leg Movements during Sleep (PLMS) in patients with RLS and matched controls.
Methods: 20 patients with RLS and 13 healthy sex- and age-matched controls were investigated in a altitude chamber in randomised order: one night in a simulated altitude environment with normobaric hypoxia corresponding to 3000m above sea level, and a control night at Innsbruck local altitude (574m). Before each night, a Suggested Immobilisation Test (SIT) was performed in the same environment. Polysomnography and PLMS scoring were performed according to AASM criteria.
Results: Median age of participants was 49 (range 40-52) years. Median IRLS in the patient group was 16 (range 13-28). Motor symptoms during SIT and during the whole night were more severe at 3000m as compared to Innsbruck local altitude in the patient group. In subgroup analysis, this was confirmed for untreated patients and for patients under dopaminergic therapy. PLMS index showed no difference between the two nights ($p>0.05$)
Conclusion: We found a trend towards more severe RLS symptoms at high altitude. RLS therapy may modulate the effects of hypoxia on RLS symptoms and PLM. In RLS pathogenesis, peripheral hypoxia may represent a downstream secondary alteration, due e.g. to iron dysregulation or dopaminergic dysfunction. Further studies with larger sample sizes are needed.
Disclosure: We are thankful to Sten Sevborn and the Swedish RLS Foundation for supporting the participation of patients from Sweden in this study.

O337

Actigraphy ultradiam and circadian rhythmicity in disorders of consciousnes

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Background and aims: The Unresponsive Wakefulness Syndrome and Minimally Conscious State (UWS; MCS) are characterized by the absence or the presence but severe disordered signs of consciousness in spite of the presence of preserved sleep-wake cycles. Spectral entropy has used to find periodicity on EEG signals of DOC (disorders of consciousness) patients. Circadian and ultradian are fisiological rhythmits found in all living organisms.
Methods: We used data from 126 patients (controls, EMCS, LIS, MCS, MCS+, MCS-, MCS*, and UWS). We recorded the movements on the wrist for 7 consecutive days, then we use average 5 complete days in 24 hours to compute the circadian rhythmicity and in 120 min to compute the ultradian rhythmicity. Spectral entropy is used to compute to find the signficant diffference inthe amplitude of the movements and its periodicity (spectral amplitude) is used to find the rhythmicity.
Results: We have found a circadian rhythmicity in DOC patients within 18 hours in average and and ultradiam rhythmicity between 40 to 80 min.
Conclusion: The actigraphy can give useful information about the circadian and ultradian rhytmicity in DOC patients.
Disclosure: Nothing to disclose

O338

Autoreactive T-cells in narcolepsy patients target multiple antigens of hypocretin-producing neurons

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Background and aims: Narcolepsy is an orphan chronic neurological disorder caused by the selective loss of neuronal cells of the lateral hypothalamus that produce the neuropeptide hypocretin (HCRT). There is increasing evidence that narcolepsy is an immune-mediated, T cell-mediated disorder that manifests in genetically (HLA-DQB1*06:02) predisposed individuals upon exposure to environmental factors, such as infection. However, unambiguous identification of HCRT-specific T cells in narcolepsy patients is still lacking.
Methods: Assessment of narcolepsy patients and controls included clinical, sleep laboratory and laboratory (CSF, blood) data. In order to characterize memory T cells, we combined antigenic stimulation, T cell cloning, and TCR deep sequencing.
Results: We isolated autoreactive CD4+ and (occasionally) CD8+ T cell clones specific for HCRT and other self-antigens expressed by HCRT-producing neurons (e.g. TRIB2) from 80% of patients (n=18), including those lacking the HLA-DQB1*06:02 allele, but were found in only 20% of healthy HLA-DQB1*06:02 donors. The CD4+ T cell response was polyclonal, and directed against multiple epitopes. Autoreactive T cell clones recognized exogenous peptides but failed to respond to whole proteins, suggesting that the epitopes recognized are generated by extracellular processing. TCR sequencing of CSF T cells identified clonotypes present in blood of the same and also in some cases of different patients.
Conclusion: Our data demonstrate the existence of autoreactive CD4+ and CD8+ T cells that target different neuronal antigens in narcolepsy patients. These data have potential implications for the (early) diagnosis and (causal) treatment of narcolepsy and its borderland.
Disclosure: Nothing to disclose

O339

Differential diagnosis in excessive daytime sleepiness based on sleep- and vigilance tests: a preliminary analysis of the Bern sleep database

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Background and aims: After excluding the most frequent causes of excessive daytime sleepiness, e.g. sleep apnoea, a few ambiguous diagnoses remain, and their differential diagnosis is still challenging. Sleep and vigilance tests are used as additional and supportive tools in the process of diagnosing. This study aimed to determine the extent to which these tests can help to differentiate between Narcolepsy with Cataplexy (NC), without Cataplexy (N), Idiopathic Hypersomnia (IH), Non-Organic (psychiatric) Hypersomnia (NOH), and psychiatric Fatigue Syndromes (FS).

Methods: The Bern sleep database contains >17,000 sleep and vigilance tests. We retrospectively analysed those 102 NC, 63 N, 86 IH, 155 NOH, and 167 FS patients who underwent ≥1 MSLT and ≥1 additional sleep or vigilance test. The patient groups were compared with each other (=10 pairs) for each test (ANOVA, post-hoc Bonferroni; significance level $p<0.05$).

Results: Mean values differed significantly in 8/10 diagnoses-pairs in both the maintenance of wakefulness test (MWT) and the multiple sleep latency test (MSLT), and in the other tests: Epworth sleepiness scale (7/10), Steer Clear test (6/10), pupillary unrest index (5/10), psychomotor vigilance test (4/10), actigraphy inactivity index and sleep efficacy in polysomnography (2/10).

Conclusion: The MWT and the MSLT are the most valuable diagnostic tests to differentiate between N-NC-IH-NOH-FS. This is relevant if tests must be limited to a low number. However, single sleep and vigilance tests have a rather poor differentiating power and combining a higher number of tests to accurately diagnose patients suffering from excessive daytime sleepiness may be favourable.

Disclosure: Nothing to disclose

Tuesday, 19 June 2018

Headache and pain

O401

Cluster Headache is more than the extreme pain attack: a prospective diary study of 500 Cluster Headache attacks

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Background and aims: In contrast to the premonitory and resolution phases of migraine, only little is known about the pre-ictal and post-ictal phase of a Cluster Headache (CH) attack. We aimed to describe the nature, prevalence and duration of symptoms in the pre-ictal, ictal and post-ictal phases of CH attacks.
Methods: 57 patients with episodic CH (eCH) or chronic CH (cCH) participated in this prospective observational study. Patients reported presence and duration of 34 CH and migraine related symptoms in the pre-ictal, ictal and post-ictal phases of up to 10 CH attacks/patient. Symptoms were grouped in 3 categories: Local and painful; Local and painless (including autonomic symptoms) and general symptoms. Duration of symptoms presented as medians.
Results: In total 500 CH attack descriptions were obtained. Pre-ictally local and painful symptoms, occurring 10 minutes before the attack, were reported in 54.4% of attack; Local and painless symptoms occurring 10 minutes before, occurred in 35.0% of attacks; and general symptoms, occurring 20 minutes before 46.0% of attacks. Post-ictally local and painful symptoms, lasting 30 minutes were reported after 43.6% of attacks; local and painless symptoms lasting 20 minutes, after 40.8% of attacks; and general symptoms, lasting 37.5 minutes after 66.4% of attacks.
Conclusion: Pre-ictal and post-ictal symptoms are very frequent in CH indicating that a CH attack is not restricted to the pain-phase alone. Since the origin of CH attacks is unresolved, studies of pre- and post-ictal symptoms could contribute to the understanding of CH-pathophysiology and potentially early abortive treatment strategies.
Disclosure: Nothing to disclose

O402

Increased preictal beta-ERD-response of primary sensorimotor cortex during brief hand movements with sensory stimulation in migraine

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Background and aims: Different neurophysiological modalities have shown cyclic alterations in the migraine brain. In the present blinded longitudinal study we aimed to evaluate if neurophysiological properties of sensorimotor cortex changed before the migraine attack. We applied low-beta (12 – 19 Hz) Event Related Desynchronization (ERD) because it is thought to represent cortical activity of afferent inputs during movement tasks.
Methods: Thirty-three migraine patients and thirty-one healthy controls underwent three consecutive EEG-examinations. Participants executed repeated movement tasks with and without sensory discrimination, and we analyzed ERD from sensorimotor cortex 1 – 3 seconds after movement onset. We chose a cutoff of 36 hours before each headache attack to define the preictal phase, and twelve migraine patients were available for the interictal – preictal paired analysis.
Results: A significant ERD-response was seen during the combined sensorimotor task. There were no differences between migraine patients in the interictal phase and healthy controls. However, in the preictal period the migraine patients had a significant increase in lower beta-ERD compared to the interictal phase in the contralateral sensorimotor cortex for both tests (Paired student's t-test, sensorimotor p=0.038; motor p=0.049).
Conclusion: Neurophysiological function of the sensorimotor cortex measured as lower beta-ERD changed from normal interictal values to increased ERD-responses preictally in migraine patients. We interpret the findings as alterations in cortical processing of sensory input before the migraine attack. Increased ERD suggests that a cortical or thalamo-cortical hyperactivity is present even before the onset of headache.
Disclosure: Nothing to disclose

O403

Identifying natural subgroups of migraine based on profiles of Comorbidities and Concomitant Conditions: results of the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study

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Background and aims: Migraine is a complex disease. Identifying natural subgroups (endophenotypes) may facilitate biological and genetic characterization and individualization of treatment. We sought to identify natural subgroups of migraine based on profiles of Comorbidities and Concomitant Conditions (CCCs).
Methods: The CaMEO Study is a prospective web-based survey study designed to characterize the course of migraine and related comorbidities in a systematic US sample of people meeting modified ICHD-2 criteria. Respondents were asked if they ever had a specific condition/symptom and, if present, if the symptom/condition was confirmed/diagnosed by a "doctor"; 62 CCCs were available for analysis. Latent Class Analysis (LCA) modeled the optimal number of classes and a parsimonious set of CCCs
Results: Of the 12,810 respondents, 11,837 reported ≥1 CCC and were included in this analysis. An 8-class model was empirically selected containing 22 comorbidities/variables. Each class had a distinct CCC pattern, characterized as follows: Class 1, many CCCs; Class 2, respiratory/psychiatric; Class 3, respiratory/pain; Class 4, respiratory; Class 5, psychiatric; Class 6, cardiovascular; Class 7, pain; Class 8, few CCCs. The distribution of individuals across models was variable with one-third of respondents in Class 8 (few CCCs) and <10% in Class 1 (many CCCs). Demographic and clinical characteristics varied across classes.
Conclusion: LCA modelling identified 8 underlying patterns of comorbid health problems among people with migraine. These classes show differences in headache features and treatment patterns not used to form the classes. Subsequent research will assess prognostic differences among the classes.
Disclosure: The funding source for this study is Allergan plc (Dublin, Ireland)

O404

The long-term efficacy and safety of OnabotulinumtoxinA for the prevention of chronic migraine in patients with medication overuse: results of the COMPEL study

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Background and aims: This sub-analysis of COMPEL Study data evaluates long-term efficacy and safety of OnabotulinumtoxinA in those with acute pain Medication Overuse (MO).
Methods: The 108-week, multicentre, open-label COMPEL Study enrolled adults with CM receiving OnabotulinumtoxinA 155U for 9 treatments. Patients completed a daily diary recording headache days; Migraine Disability Assessment (MIDAS) was collected via patient-completed questionnaires. Adverse events were monitored. MO was defined as those using acute pain medication at baseline on ≥5 diary days/week and then ≥2 days/week with the additional requirements for simple analgesics ≥15 days/month or for ergotamines, triptans, opioids or combination analgesics, ≥10 days/month. Observed data are reported.
Results: Of the 716 enrolled patients, 639 patients (89.2%) used acute pain medication; with 456 patients (63.7%) classified as having MO. Compared to patients without MO, those with MO were slightly older (44.1 [10.9] vs 41.1 [11.7] years), and more likely to be Caucasian (84.9% vs 74.9%). Mean (SD) headache day frequency at week 108 significantly decreased from baseline in the analysis population: 22 (4.8) to 11.3 (7.4) days (P<0.0001). In the subgroup analysis, the effect of onabotulinumtoxinA was similar in patients with and without MO on reduction in headache days (–11.4 [7.2] vs –12.5 [7.5] days), and MIDAS scores (–41.8 [48.0] vs –48.7 [59.6], P<0.0001. OnabotulinumtoxinA was well tolerated in the MO population, with no new safety concerns.
Conclusion: Results suggest that OnabotulinumtoxinA reduces headache day frequency and improves disability and is well tolerated in the MO population.
Disclosure: The funding source for this study is Allergan plc (Dublin, Ireland)

O405

Phase-3 study (SPARTAN) of Lasmiditan compared to placebo for acute treatment of migraine

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Background and aims: Investigated Lasmiditan in a double-blind, phase-3 study (SPARTAN; NCT02605174) on headache pain and the patient-centric measure of most bothersome symptom (MBS; nausea, phonophobia, or photophobia) at 2 hours post-dose.

Methods: Patients with a Migraine Disability Assessment Score >11 were randomised 1:1:1:1 to Lasmiditan (200mg, 100mg, or 50mg) or placebo. Patients took first dose within 4 hours of a migraine attack and, if needed, took a randomly assigned second dose. Primary and key secondary analyses compared patients in the lasmiditan 200-mg group with placebo who were headache pain-free and MBS-free at 2 hours post-first dose, respectively.

Results: Proportion of patients headache pain-free and MBS-free at 2 hours post-first dose was significantly greater with Lasmiditan 200mg (38.8%, 48.7%; p<.001 both), 100mg (31.4%, 44.2%; p<.001 both), and 50mg (28.6%, 40.8%; p<.01 both) than placebo (21.3%, 33.5%). In lasmiditan 200mg, 100mg, 50mg or placebo groups, 29.1%, 34.5%, 40.3%, and 48.1% took a second dose, respectively. Proportion of patients who experienced a TEAE after the first dose of lasmiditan 200mg, 100mg, 50 mg or placebo were 39.0%, 36.1%, 25.4%, and 11.6%, respectively and most frequently reported dizziness, paresthesia, and somnolence.

Conclusion: SPARTAN met the primary and key secondary endpoint of pain-free and MBS-free at 2 hours for Lasmiditan 200mg. Lasmiditan 100mg and 50mg were also significant on the same endpoints compared to placebo. Safety was consistent with a previous Lasmiditan trial, with dizziness reported as the most frequent TEAE.

Disclosure: Sponsored by Eli Lilly and Company and/or one of its subsidiaries.

O406

Field testing the diagnostic criteria for headache attributed to Transient Ischemic Attacks

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Background and aims: The International Classification of Headache Disorders diagnostic criteria for Headache Attributed to Transient Ischemic Attacks and many other secondary headaches are based primarily on the opinion of experts. Here we formally analyze, for the first time, the diagnostic criteria for headache attributed to Transient Ischemic Attacks.

Methods: Consecutive patients with Transient Ischemic Attacks were extensively interviewed soon after admission. Eligible patients had focal brain or retinal ischemia with resolution of symptoms within 24 hours without presence of new infarction on magnetic resonance imaging with diffusion weighted imaging (n=112) or computed tomography (n=8). Data were collected on previous headaches, headaches around the time of Transient Ischemic Attacks and characteristics of Transient Ischemic Attacks using validated neurologist conducted semi-structured interview forms.

Results: 120 patients with Transient Ischemic Attacks were included. A new type of headache occurred within 24 hours of Transient Ischemic Attacks in 13%, a preexisting type of headache with altered characteristics in 7.5% and without altered characteristics in 6.6%. The risk of headache was much greater with posterior circulation Transient Ischemic Attacks than with anterior. Only 24% of the headaches fulfilled the criteria of the International Classification of Headache Disorders. We propose new criteria fulfilled by 94% of the headaches and argue that specificity remains good.

Conclusion: Existing diagnostic criteria for headache attributed to Transient Ischemic Attacks are too insensitive. We suggest new diagnostic criteria with high sensitivity and argue why they are still valid.

Disclosure: Nothing to disclose

Miscellaneous 2

O407

Reduced pupillary modulation in patients with relapsing-remitting Multiple Sclerosis is associated with longer disease duration and higher disease severity

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Background and aims: Pupillary dysfunction is common in patients with Relapsing-Remitting Multiple Sclerosis (RRMS) and may be due to central MS lesions. So far, it is unclear whether the degree of pupillary autonomic dysfunction is associated with disease-duration and severity. Therefore, we aimed at evaluating correlations between pupillary autonomic modulation and disease-duration and severity in RRMS-patients.
Methods: In 85 RRMS-patients (mean age 37.4±10.4 years, 58 women, disease-duration 91.1±81.0 months), we performed light reflex pupillography using a CIP 9.08TM pupillometer (45-min dark-adaptation, 1.25-ft candles background illumination; 200ms light stimulation at 104 cd brightness). We determined pupil-diameter, early and late re-dilatation velocities as sympathetic parameters, light-reflex-latency, reflex-amplitude, and constriction-velocity as parasympathetic pupillary indices. MS-severity was assessed by the Expanded-Disability-Status-Scale (EDSS) and the Multiple-Sclerosis-Functional-Composite (MSFC). The Spearman signed rank test was used to determine correlations between pupillary parameters and disease-duration, EDSS- and MSFC-scores. Significance was set at $p<0.05$.
Results: EDSS-scores were 2.5 [1.5-3.5] (median; interquartile range), MSFC-scores were -0.11±0.80. Pupil-diameter correlated negatively with age, disease-duration and EDSS-scores. Early re-dilatation velocity correlated negatively with age, disease-duration and EDSS-scores and positively with MSFC-scores. Reflex-latency correlated positively with age, disease-duration and EDSS-scores, and negatively with MSFC-scores. Reflex-amplitude correlated negatively with age, disease-duration, and positively with MSFC-scores. Constriction-velocity correlated negatively with age, EDSS-scores and positively with MSFC-scores.
Conclusion: In our RRMS-patients, the decrease in sympathetic and parasympathetic pupillary autonomic modulation was associated with longer disease-duration and higher disease-severity. These additional markers of MS severity and progression may be easily assessed by the non-invasive light reflex pupillography.
Disclosure: Nothing to disclose

O408

Early hemodynamic profile in tilt-induced vasovagal syncope

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Background and aims: Little is known about whether asystole during syncope is reflected in the hemodynamic pattern of Vasovagal Syncope (VVS) during Tilt Table Testing (TTT) in the 10 minutes before syncope.
Methods: TTT data were gathered from the database of our tertiary Syncope Unit. Inclusion criteria were probable VVS, based on a clinical history and syncope during TTT, established using continuous Blood Pressure (BP), Heart Rate (HR), EEG and video data. Exclusion criteria were additional diagnoses or incomplete data. We sampled BP, HR, Cardiac Output (CO), Stroke Volume (SV) and Total Peripheral Resistance (TPR) every second of 10 minutes before syncope and compared their course over time using vectors from singular value decomposition. We first analysed these variables for all cases and then compared groups with and without asystole.
Results: Over all 154 patients, BP started to decline ~6 minutes before syncope after which the decrease accelerated. The mechanism behind low BP is likely the consistent decrease in SV, not sufficiently countered by an increase in HR or TPR, so CO fell. In patients with asystole BP decreased later but much more steeply then in those without asystole ($p=<0.01$).
Conclusion: We confirm that the main factor explaining low BP in tilt-induced VVS is a decrease in SV, probably due to an inability to prevent venous pooling. Asystole during syncope is reflected in a specific hemodynamic pattern well before syncope.
Disclosure: Nothing to disclose

O409

‘JUMP’, an innovative trans-pathology transitional care program for young adults with chronic neurological disease

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Background and aims: The “JUMP program” is a trans-pathology multi-disciplinary transitional program developed at the Pitie-Salpêtrière Hospital, Paris which optimises the transition of young adults with chronic neurologic conditions into adult services while addressing adolescent-health related challenges. The JUMP team comprises of two coordination nurse specialists, 13 neurology sub-specialists and a dedicated team of medical specialists and allied health-care professionals.
Methods: Demographic and clinical details of patients in the JUMP program were collected. Two satisfaction outcome measures were sent to patients and their parents; an 18-item On Your Own Feet Transfer Experience Scale (OYOF-TES) rated on a five-item Likert scale (total score=90) and a 10-point visual analogue scale.
Results: A total of 133 patients were referred to the JUMP program. The median age at inclusion to the JUMP program was 19.7 years (range: 14.6 – 36.1 years), 73 patients (54.9%) were female. All patients met the coordination nurse specialists who tailored the transition process to address the current life concerns of each patient. In addition to their neurologist of referral, 67% saw an allied-health professional. The mean transfer experience, as assessed by the visual analogue scale, was 9.19 (range, 6 - 10, SD 1.13). The mean score of the OYOF-TES for patients was 75.2 (SD=7.5; range, 62 - 89) and 63 (SD=9.5; range, 58 – 90) for parents.
Conclusion: The JUMP program, which is rooted in a multi-disciplinary and coordinated approach to transitional neurology care, demonstrated high levels of satisfaction on satisfaction outcome measures completed by patients and their parents.
Disclosure: Nothing to disclose

O410

Characterization of a Listeria monocytogenes meningitis mouse model

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Background and aims: L.monocytogenes is the third most common cause of bacterial meningitis in adults. Further understanding of the pathophysiology of listeria meningitis is needed to improve the prognosis. We describe the development of the listeria meningitis mouse model.
Methods: C57BL/6 mice were inoculated in the cisterna magna (1µl) with increasing doses (105-109CFU/ml) of L.monocytogenes strain ST1 in a non-treatment survival study. In a time-point study mice were inoculated with 108 CFU/ml and euthanized after 6 and 24 hours. Cerebrospinal fluid, blood, brain, liver, lung and spleen were collected to analyse bacterial counting and inflammatory markers. In a treatment-survival study mice were inoculated with 109 CFU/ml and treated with 50-200mg/kg/24hours Amoxicillin intraperitoneally. Effect of increasing frequency of treatment per 12 hours or adding Gentamicine (20mg/kg/24hours) were analysed. In the treatment-survival time-point study mice were euthanized after 16 ad 24 hours.
Results: A 20% survival rate was reached in the non-treatment-model in 48 hours (105 CFU/µl). In the treatment-model a 50% survival rate was reached after 72 hours(100mg/kg/24h amoxicillin). Increasing the dosage, frequency or adding Gentamicin did not improve clinical outcome. Time-point experiments showed increase of bacterial outgrowth in blood, CSF and all organs between 6 and 24 hour. In the treatment model, the bacterial outgrowth decreased after i.p. treatment with Amoxicillin (16 vs. 24hours).
Conclusion: We developed a Listeria meningitis mouse model, which can be used for future studies to analyse the pathophysiology, the host’s immune response, new (adjunctive) treatment options and bacterial genetic factors to improve outcome.
Disclosure: Nothing to disclose

O411

Cerebral lesion localization in patients with acute pure vestibular and ocular motor strokes: results from the prospective EMVERT trial

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Background and aims: To prospectively investigate cerebral lesion localization in patients with acute isolated rotational vertigo, dizziness or double vision due to acute unilateral stroke.
Methods: 342 adult patients submitted to the ER with acute vertigo, dizziness or double vision of unclear etiology were enrolled prospectively in the EMVERT trial and underwent a standardized protocol of clinical, video-oculographic and posturographic measurements as well as a MRI within 7d after symptom onset. The MRI protocol included DWI-/FLAIR-/T2-/T2*-/3D-T1-weighted sequences and a TOF-angiography. MRIs with acute DWI lesions were further processed using SPM-based algorithms for lesion mapping.
Results: In 47 of the patients the MRI indicated acute stroke (13.6%). The most frequent chief complaint in these patients was dizziness (44.7%), followed by vertigo (38.3%) and double vision (17.0%). In patients with the chief complaint dizziness the lesions were found mostly in the lateral PICA and SCA territories (involving the flocculus/superior vermis), and the pontomesencephalic brainstem tegmentum (involving the ocular motor centers for the pitch and role plane). Patients with vertigo frequently had lesions in the medial PICA territory (including the vermis/nodulus/uvula), the pontomedullary brainstem (involving the vestibular nuclei) and the insular cortex (parieto-insular vestibular cortex). Patients with double vision had pontomesencephalic and meso-diencephalic lesions.
Conclusion: Prospective evaluation of lesion localization in acute vertigo and dizziness showed that mostly the cerebellum was affected by strokes, with some preference towards the medial cerebellar structures accociated with vertigo and lateral hemispherical structures accociated with dizziness. In the brainstem pontomedullary lesions induced vertigo, pontomesencephalic rather dizziness.
Disclosure: The study was performed as a project of the German Center for Vertigo and Balance Disorders (DSGZ) (grant number 01 EO 0901) with support of the German Federal Ministry of Education and Health (BMBF).

Muscle and neuromuscular junction disease

O412

Molecular mechanisms of mitochondrial DNA disease: pathological and genetic studies in patients with Mendelian disorders of mtDNA maintenance

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Background and aims: The underlying genetic defect in patients with cPEO is either a primary mutation of the mtDNA or recessively and dominantly-inherited mutations in nuclear genes leading multiple mtDNA deletions in muscle.
Methods: Muscle biopsies of 16 patients with genetically- and clinically-characterized mitochondrial disease of nuclear origin (9 POLG, 4 TWNK, 2 RRM2B, 1 SLC25A4) and 4 controls were analysed using quadruple OXPHOS immunohistochemistry, quantifying the biochemical phenotype in individual muscle fibres. Further studies on 6/17 patients included the correlation of biochemical deficiency with the mtDNA abnormality in individual cells, following laser microcapture and determination of size and level of clonally-expanded mtDNA deletion within fibres by real-time PCR, long-range PCR and sequencing of breakpoints.
Results: The data from quadruple immunocytochemical studies show a distinct biochemical phenotype in patients with multiple mtDNA deletions, however, there was no difference between genotypes. Real-time PCR showed, that the level of deletion is increasing with the biochemical defect. In all patients, the levels of deletion of ND4/D Loop and ND4/ND1 are significantly increasing with the MRC profile. However, in all groups of fibres there seem to be very low levels of ND1 deletions.
Conclusion: It has already been shown, that patients harbouring multiple deletions have a distinct muscle respiratory chain profile. Three different groups of fibres were found in these patients: cells without deficiency, cells with isolated complex I deficiency and cells with combined complex I and complex IV deficiency. The correlation of biochemical deficiency with level of deletion is arguing against any point mutations as cause of the deficiency.
Disclosure: Nothing to disclose

O413

A phase 1/2 Golodirsen trial developed by the SKIP-NMD consortium to identify potential treatments for Duchenne Muscular Dystrophy: study design and patient characteristics

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Background and aims: Duchenne Muscular Dystrophy (DMD) is a rare, X-linked, recessive disorder causing progressive muscle loss and early death. The SKIP-Neuromuscular Disease (SKIP-NMD) consortium of academic, commercial, and advocacy partners formed and secured an EUFP7 grant to develop and evaluate Golodirsen, a phosphorodiamidate morpholino oligomer designed to skip exon 53 of the dystrophin gene.
Methods: Part 1 of this first-in-human phase 1/2 study of once-weekly intravenous Golodirsen was a double-blind dose titration study that enrolled males aged 6-15 years with DMD and genetic mutations amenable to exon 53 skipping, baseline 6-minute walk test (6MWT) distance >=250 m, and North Star Ambulatory Assessment (NSAA) total score >17/34 or rise (Gowers') time <7 seconds. Part 2 was open label and included assessments of change in motor function and strength, using traditional tools (6MWT, NSAA), newer outcomes (Performance of Upper Limb test, ActiMyo), dystrophin expression and disease-related biomarkers, pulmonary function, and lower limb pathology using magnetic resonance imaging and spectroscopy.
Results: Part 1 randomised patients to Golodirsen (n=8) or placebo (n=4). In part 2, all 12 patients from part 1 and 13 newly enrolled patients received Golodirsen. Baseline characteristics of all treated patients are summarised in the Table. Analysis of Week 48 muscle biopsies demonstrated dystrophin restoration in treated patients; full study results, including clinical outcomes, are expected in late 2019.

Table. Patient Demographic and Baseline Characteristics

Variable	All Golodirsen-Treated Patients (N = 25)
Age, years	
Mean (SD)	8.2 (2.16)
Range	6–13
Baseline weight, kg	
Mean (SD)	28.20 (9.14)
Range	17.1–49.0
Baseline 6MWT distance, m	
Mean (SD)	403.74 (56.66)
Range	290.0–512.0

6MWT, 6-minute walk test; SD, standard deviation.

Conclusion: The SKIP-NMD collaboration produced the successful design and initiation of a Golodirsen trial with unique, clinically relevant inclusion criteria and outcome measures, providing valuable advancement of DMD research on the effects of potential exon-skipping therapies.
Disclosure: This study was sponsored by Sarepta Therapeutics. Francesco Muntoni: Consultant to Sarepta Therapeutics. Volker Straub: Scientific advisory board member for Sarepta Therapeutics. Diane Frank: Employee of Sarepta Therapeutics, Inc. Andreea Seferian: Nothing to disclose. George Dickson: Inventor on related patent. Michela Guglieri: Nothing to disclose. Joana Domingos: Nothing to disclose. Laurent Servais: Nothing to disclose. Eugenio Mercuri: Nothing to disclose.

O414

Quantifying muscle amyloid content in inclusion body myositis using [18f] florbetapir positron emission tomography

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Background and aims: Inclusion Body Myositis (IBM) shares some histopathological features with Polymyositis (PM) but does not respond to conventional immunosuppressive treatments. Current investigations have low sensitivity for identification of amyloid deposits that are characteristic of IBM, contributing to frequent misdiagnosis.
We performed a prospective case control study comparing muscle amyloid content, quantified using a novel Positron Emission Tomography (PET) technique, in IBM and PM.
Methods: Ten cases with IBM and six controls with PM underwent clinical review, [18F]florbetapir PET/computed tomography, and magnetic resonance imaging (MRI) of whole-body skeletal musculature.
[18F]florbetapir standardised uptake value ratios (SUVRs, reference=lumbar fat pad) in skeletal muscle were compared between cases and controls. The relationship in IBM of [18F]florbetapir SUVRs to clinical and MRI-derived measures of disease severity were also investigated.
Results: [18F]florbetapir SUVRs were significantly higher in those with IBM for all muscle regions assessed (total SUVR 1.45 [IQR 1.28-2.05] versus 1.01 [IQR 0.80-1.22], p=0.005) (Figure 1).
Strong negative correlation between MRI-derived muscle inflammation levels and [18F]florbetapir SUVRs were observed only in calf muscles bilaterally (right -0.73, p=0.02; left -0.68, p=0.03). No significant relationship between [18F]florbetapir SUVRs and clinical measures of disease severity were identified.

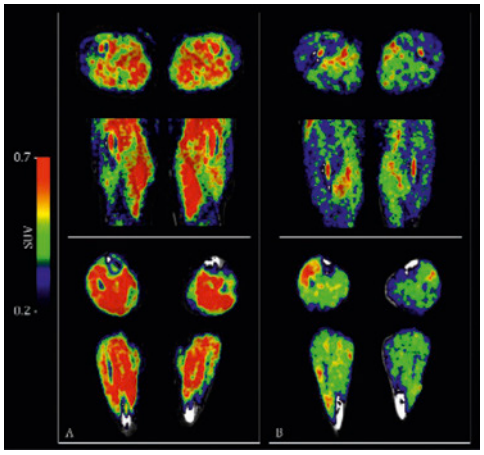

Figure 1: Differences in [18F]florbetapir positron emission tomography (PET) derived standardised uptake values (before reference tissue normalisation) between a case with inclusion body myositis (A) and a control with polymyositis (B)

Conclusion: Muscle amyloid imaging using [18F] florbetapir PET may be useful in the diagnostic workup of IBM, particularly when differentiating from PM. The observed correlation between inflammation and muscle amyloid content may provide clues to pathways of amyloidogenesis in IBM.

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O415

Cardiorespiratory function in Duchenne Muscular Dystrophy in a UK large tertiary care centre: longitudinal progression and the role of steroid treatment

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Background and aims: Duchenne Muscular Dystrophy (DMD) is the most common muscular dystrophy of childhood. The implementation of current standards of care has had a dramatic impact on motor performance and life expectancy. We aimed to characterise the current progression of cardiorespiratory function in face of these changes.

Methods: A retrospective longitudinal study including all patients with DMD followed up at the Dubowitz Neuromuscular Centre between 2000 and 2017. Clinical data was collected, including respiratory (forced vital capacity, FVC, and percentage predicted FVC) and cardiac function (fractional shortening, FS). We fitted average longitudinal models for each outcome. We performed time-to-event analysis for relevant thresholds.

Results: 312 patients were included with a mean age at baseline of 6 +/- 2.3 years old. We observed an increase in FVC up to age 13 years followed by relative stability.% FVC declined on average 6% per year after the age of 9 years old. At the age of 16 years, 5 out of 51 patients on steroids were on NIV versus 3 out of 5 steroid naïve patients. Overall%FS decreased by 0.6% per year. The median age at cardiomyopathy diagnosis was 15.4 years. However, stratifying by steroid treatment showed: for steroid naïve patients median age was 13.9 years and for those on steroids it was above 15 years of age.

Conclusion: We present the longitudinal progression for cardiorespiratory function in DMD. Our data indicate a benefit of steroid treatment in delaying the time to reach important not only respiratory but also cardiac milestones.

Disclosure: Nothing to disclose

O416

Vacuolated PAS-positive lymphocytes as screening tool and a possible therapeutic biomarker in late-onset Pompe disease (LOPD)

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Background and aims: To investigate the diagnostic value of PAS-positive vacuolated lymphocytes on blood smear (BSE) and their role as possible biomarker in LOPD patients
Methods: We examined blood smear of 26 LOPD patients, 10 treated and 16 untreated . Among the latter group, 7 patients initiated ERT and were tested again 6 months after ERT start. Blood smear was also evaluated from 82 controls and 19 patients with other Muscle Glycogenoses (MGSDs). PAS staining was used to t presence of lymphocytes with glycogen-filled vacuoles, 2) quantification of vacuolated lymphocytes
Results: PAS-positive lymphocytes were significantly higher in LOPD patients than in controls or other MGSDs ($p<0.05$ and $p<0.001$, respectively). ROC curve for discriminating between untreated LOPD patients and controls yielded an AUC of 1.00 (95%CI 1.00-1.00; $P<0.0001$). A PAS-positive lymphocyte cutoff level of >10 yielded a sensitivity of 100% (95%CI 78%-100%), a specificity of 100% (95%CI 96%-100%), and a positive predictive value of 100%. Patients studied before and after ERT showed a dramatic decrease of the number of PAS-positive lymphocytes ($P<0.0001$). In other MGSDs, PAS-positive lymphocytes were significantly lower that untreated LOPD patients, but higher than controls
Conclusion: Our data suggest that the BSE for PAS-positive lymphocytes quantification in peripheral blood films could be used as a simple and quick screening test to shorten diagnosis time in suspected Pompe patients. The quantification of vacuolated lymphocytes appears to be also a valuable tool for detecting and monitoring the therapeutic effects of drugs.
Disclosure: Nothing to disclose

O417

Statin-induced myopathies: beyond immuno-mediated necrotizing myopathies

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Background and aims: Statins are involved in the genesis of myopathies that persist after its withdrawal. Mostly immuno-mediated mechanisms but also degenerative mechanisms have been implicated in its pathogenesis.
To study patients with permanent myopathy following statin exposure that persist after discontinuing statins.
Methods: Prospective study of patients with statin-induced myopathy in a Neuromuscular Unit between 2008 and 2017. Demographic, clinical, laboratory, electromyographic, muscle MRI and biopsy data were collected.
Results: 46 patients, 56.5% woman and 43.5% men, mean age: 64 years. The course of the myopathy was mainly subacute (66%), but also chronic (27%) and acute (7%). Muscle weakness was predominantly proximal (96%) and involved axial muscles in 35%. Other symptoms: myalgias (52%), fatigue (25%), dysphagia (21%), exercise intolerance (18%), dysphonia (11%), dyspnea (7%) and cramps (4%).
65% of the patients were on atorvastatin (mean exposure time: 42 months). HyperCKemia was detected in 90% (425-5108 IU/L). Anti-HMGCR antibodies determined in 30 patients were positive in 11 (37%). EMG was myopathic in 88% and spontaneous activity was present in half of them.
Muscle MRI detected muscle involvement in 94%of patients and STIR sequences hyperintensity suggestive of edema in 19. Muscle biopsy was performed in all patients: inflammatory myopathy (73%) (immune-mediated necrotizing in 37%) and other myopathies in 27% (mitochondrial, necrotizing, other primary myopathies).
Conclusion: Statin-induced myopathies constitute a heterogeneous group of disorders in which autoimmune necrotizing forms predominate, although other types of inflammatory myopathy and other non-inflammatory myopathies are frequent. Detection of anti-HMGCR antibodies can be useful although its pathogenic implication is unknown.
Disclosure: Nothing to disclose

Movement disorders 2

O418

Non-invasive intervention for motor signs of Parkinson's Disease: the effect of vibratory stimuli

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Background and aims: It has been proposed that in healthy individuals the down weighting of sensory afferents prior to and during active movement is an essential step in initiating movement. This is realised by increasing the uncertainty on the estimate of the somatosensory signal. Here we tested the hypothesis that motor signs (bradykinesia and tremor) in Parkinson's disease can be ameliorated by non-invasive interventions (peripheral tactile vibration) that increase somatosensory uncertainty.
Methods: We assessed motor performance in a group of 16 right-handed Parkinson's Disease patients (ON medication; 10 out of 16 were also tested OFF medication) using three tasks: the nine-hole peg test and three drawing tasks. We recorded tremor with two accelerometers.
Each task was repeated three times and under three conditions: with no external stimulus; and when a vibratory stimulus was applied to the dominant wrist at a frequency of 200Hz with either a 20bpm or 60bpm modulating frequency.
Results: Parkinson's Disease patients showed a significant improvement in motor performance when a 200Hz vibratory stimulus with 60bpm trials was applied compared to 20bpm trials ($p<0.05$) and in absence of vibration. There was no significant difference in motor performance following no vibration and 20bpm trials ($p>0.5$).
Conclusion: These preliminary data are consistent with a novel the idea that vibrotactile stimulation results in less slowing and decrement in amplitude of a repetitive hand movement and less tremor compared to baseline measures in PD patients. Further work is required now to establish this finding and investigate further.
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The Nocebo effect in Parkinson's Disease

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Background and aims: The placebo effect is well recognized in Parkinson's Disease (PD) and is thought to be at least partially mediated by an increase in dopaminergic neurotransmission. Its counterpart, the nocebo effect, remains ill-characterized. This study aims to estimate and characterize the nocebo response in PD.
Methods: Databases were searched up to February 2017. Randomized, parallel-designed, placebo-controlled trials of patients with PD were included. Nocebo response was defined as the proportion of participants experiencing adverse events in the placebo arm. It was further characterized as the proportion of withdrawals, withdrawals due to AE and deaths in the placebo arm. Random-effects meta-analysis was used to pool data, with statistical heterogeneity being assessed with the I2 statistic. The same analyses were repeated with data from the intervention arm to provide a term of comparison.
Results: 239 randomized controlled trials (47,797 participants) were included. Pooled nocebo response was 55,8% (95% CI 51,5%–60,1%, 149 trials; I2=97.5%). 13,9% (95% CI 12,4%–15,4%, 229 trials; I2=90,54%) patients withdrew from trials, 5,7% (95% CI 5,0%–6,4%, 222 trials; I2=72,44%) did it because of AE and 0,6% (95% CI 0,5%–0,7%, 231 trials; I2=0%) died during follow up. Similar proportions were identified in patients in intervention arms.
Conclusion: The magnitude of the nocebo response in parallel-designed randomized clinical trials in PD is substantial. This information should be integrated in the evaluation, planning and designing of future clinical trials.
Disclosure: Nothing to disclose

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Generation and characterisation of iPSC-derived oligodendrocytes of patients with Multiple System Atrophy

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Background and aims: Multiple System Atrophy (MSA) is a fatal disease characterized by alpha-synuclein inclusions in oligodendrocytes and neuronal loss in the striatonigral pathway, cerebellum and autonomic system. However, the origin of aggregates and the molecular connection between oligondendrocytic alpha-synuclein accumulation and neurodegeneration are still unclear. In this project, we exploit the potential of induced Pluripotent Stem Cells (iPSCs) to address these challenges. The aim of this study is to generate and characterise iPSC-derived oligodendrocytes of MSA patients.
Methods: Fibroblasts obtained from skin biopsies of patients with MSA, alpha-synuclein gene (SNCA) duplication, and controls were reprogrammed to iPSCs using CytoTune-iPS 2.0-Sendai Reprogramming Kit (Life Technologies) based on viral transduction of factors Oct4, Sox2, Klf4 and c-Myc. Method by Douvaras and Fossati (2015) was applied to derive myelinating oligodendrocytes.
Results: iPSCs of two patients with MSA, one patient with SNCA duplication and two controls were differentiated into Olig2+, Nkx2.1+ oligodendrocyte precursors cells, then specified into myelinating oligodendrocytes expressing lineage-specific markers (O4, MBP). Morphological evaluation at different stages of maturation demonstrated typical oligodendrocytic changes, confirmed by immunocytochemistry and RT-PCR. Analysis of alpha-synuclein expression in patient and control lines showed that mRNA and protein are produced by progenitors, but decrease markedly in mature oligodendrocytes, with perinuclear localization suggesting the degradation of the protein. Conversely, myelinating oligodendrocytes with SNCA duplication displayed increased alpha-synuclein content.
Conclusion: IPSC-derived oligodendrocytes represent an effective tool to investigate MSA pathogenesis. Our results support the hypothesis that alpha-synuclein in MSA glial inclusions is not primarily produced in oligodendrocytes and accumulation does not result from endogenous overexpression.
Disclosure: Nothing to disclose

O421

Spastic-ataxia in a Portuguese cohort of hereditary ataxias

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Background and aims: Hereditary Spastic-Ataxias (HSA) are a heterogeneous group of disorders combining overt spasticity and ataxia. SACS, SPG7 and FXN are the genes most frequently associated. Our aim was to describe the clinical features and genes of HSA patients in our cohort of Hereditary Ataxias (HA).
Methods: Patients were identified from a clinical-epidemiological database. Information collected according to specific protocol.
Results: In 77 HA patients, 16 had HSA: six ARSACS, two SPG46, one SPG7, one SPG78, one SPG15, one L-2-hydroxyglutarate dehydrogenase (L2HGDH); four had no mutation identified. Onset was in early-childhood (<2y) in five (three ARSACS, one SPG15, one L2HGDH); late-childhood/adolescence (6-15y) in five (two ARSACS, two SPG46, one unknown mutation); during adulthood (20-52y) in six (one ARSACS, one SPG7, one SPG78, three unknown mutation). Presenting symptom was spastic gait (nine), disequilibrium (four), dysarthria, upper limbs dysmetria or cognitive delay (one each). After variable disease progression, all presented dysmetria, predominantly in upper limbs, and spasticity in lower limbs. Non-cerebellar/pyramidal symptoms included: neuropathy in six ARSACS, two SPG46, two SPG7, one SPG15, one unknown mutation; dystonia in ARSACS, SPG46 and L2HGDH (one each); seizures in ARSACS and unknown mutation (one each); Parkinsonism in SPG7 and SPG78 (one each). Five ARSACS, one SPG15, one unknown mutation were wheelchair-bound by their 30s-40s.
Conclusion: In our cohort, HSA represented a genetically diverse group of patients. As expected, many were ARSACS, but variants in SPG7, GBA2 (SPG46), ATP13A2 (SPG78), ZFYVE26 (SPG15), L2HGDH were also

identified. Phenotypical overlap among pathogenic variants in various genes poses a great challenge for genetic diagnosis.
Disclosure: Nothing to disclose

O422

Evaluation of gait and posture in essential tremor before and after unilateral Gamma Knife Thalamotomy

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Background and aims: Despite its high frequency, Essential Tremor (ET) pathophysiology remains poorly understood and few data about the existence of gait disorders in this affection are available. Our aim is to describe specific features of gait disorders and postural instability in patients with ET, and to evaluate the effect on motor skills of a unilateral Gamma Knife Thalamotomy (GKT).
Methods: 72 patients with severe ET underwent GKT (mean age :73 years). Targeting of the ventral intermediate nucleus (Vim) was achieved with Leksell Gamma Knife with a single shot through a 4-mm collimator helmet. The prescription dose was 130 Gy.
Severity of ET (Fahn-Tolosa-Marin Tremor Rating Scale), cognitive function, activities of daily living (Bain's functional scale for activities of daily living), gait and postural control were assessed before and 1 year after radiosurgery.
Results: The comparison between ET patients before surgery and control subjects showed poorer gait performances in the patients group.
All tremor components (rest, postural, and intention) of the rating scale and activities of daily living were improved after GKT. Cognitive functions like gait and postural control remained unchanged after GKT.
Conclusion: This study showed postural instability and gait impairment in ET, which may be related to a dysfunction of cerebello-thalamo-cortical pathway. Moreover, our work showed no deleterious effect of unilateral GKT on posture and gait skills. The unilateral and progressive nature of GKT could explain the absence of degradation of gait and posture. Unilateral GKT is a safe and efficient procedure for severe medically refractory tremor.
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Functional brain connectome architecture in a large cohort of Parkinson's Disease patients

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Background and aims: To investigate the functional network organization in patients with Parkinson's Disease (PD).
Methods: 134 PD patients (82 early PD [Hoehn and Yahr {HY} 1-1.5] and 52 mild-to-severe PD [HY 2-4]) and 99 controls performed clinical evaluation and resting state functional MRI. Graph analysis and connectomics assessed global and local topological network properties and regional functional connectivity (FC).
Results: Compared with controls, PD patients showed altered functional topological features (lower mean nodal strength and longer mean path length) of the sensorimotor and parietal areas relative to controls, with mild-to-severe cases showing the greatest alterations. Mild-to-severe PD patients had a reduced mean nodal strength in the temporal lobe relative to early PD patients. At the regional network level, compared to controls, PD groups showed decreased FC within basal ganglia/sensorimotor network, parietal regions such as posterior cingulate and precuneus bilaterally, and bilateral superior frontal and middle temporal areas. Compared to early PD cases, mild-to-severe PD patients were characterized by a greater involvement of basal ganglia/sensorimotor connections linking putamen, caudate and postcentral gyri bilaterally, parietal network involving posterior cingulate, precuneus and supramarginal bilaterally, and pathways to the bilateral hippocampus.
Conclusion: This study showed widespread motor and extra-motor functional network degeneration in PD patients at different disease stage. Network-based advanced MRI analyses might represent a powerful approach to understand the pathophysiological process across different stages of the disease and hold the promise to provide an objective in vivo marker of disease-related pathological changes.
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