ePresentation Sessions

Saturday, June 16 2018

Ageing and dementia 1

EPR1001

Annual trends of prevalence and incidence of Alzheimer's dementia and vascular dementia in the entire Korean population: A national cohort study for 10 years

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Background and aims: We investigated annual trends regarding the prevalence and incidence of dementia based on the National Health Insurance System database covering the entire Korean population. In addition, we assessed a cut-off age for dementia diagnosis, and the risk factors for Alzheimer's dementia(AD) and vascular dementia(VD).
Methods: The prevalence and incidence of dementia of the entire Korean population aged ≧40 years was investigated using a database covering 2006 to 2015. The diagnosis was classified by the ICD-10 codes. The Youden index was estimated to determine optimal cut-off age for dementia diagnosis.
Results: The prevalence and incidence of AD showed increasing trends. The age-standardized prevalence of AD was 3.17, 11.28, and 15.75 per 1,000 persons, and the incidence of AD was 1.83, 4.49, and 5.21 per 1,000 persons in 2006, 2012, and 2015 respectively, while the prevalence of VD also showed increasing trends: 0.30, 1.98, and 2.27 per 1,000 persons in 2006, 2012, and 2015 respectively. However, the incidence of VD showed no increasing trends after 2011: 0.24, 0.80, and 0.78 per 1,000 persons in 2006, 2012, and 2015 respectively. The cut-off age for diagnosis of AD or VD are 69 and 65 years old. Vascular risk factors such as diabetes mellitus, hypertension and atrial fibrillation affected the risk of developing dementia.
Conclusion: Contrary to the findings for VD, the prevalence and incidence of AD is still increasing in Korea. The cut-off age for dementia diagnosis and modification of vascular risk factors may be of relevance for early diagnosis and intervention in dementia.
Disclosure: Nothing to disclose

EPR1002

Concordance of amyloid PET and CSF metabolic biomarkers in Alzheimer's disease and how to improve it: data from the Czech Brain Ageing Study

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Background and aims: Current guidelines for Alzheimer's disease (AD) shift the focus from clinical findings to biomarkers. Most widely used metabolic biomarkers are cerebrospinal fluid (CSF) levels of amyloid-β1-42 (Aβ1-42), total-tau (t-tau), and phosphorylated tau 181 (p-tau), as well as amyloid positron emission tomography (PET). However, the concordance between amyloid PET and CSF biomarkers is not well established and interpretation of biomarkers in clinical settings may also be challenged by analytical procedures and cut-off values. Our aim was to investigate the use CSF biomarkers in prediction of amyloid PET positivity, concordance of biomarkers, and propose cut off values in clinical settings.
Methods: 44 patients with mild cognitive impairment or mild dementia classified as possible AD (National Institute on Aging–Alzheimer's Association criteria) underwent MRI, neuropsychological assessment, flutemetamol PET and CSF sampling. PET was evaluated visually and dichotomized. AUCs of ROC curves for Aβ1-42, p-tau and p-tau/Aβ1-42 ratios were compared. Optimal cutoff points were based on the highest Youden's J indices.
Results: Concordance between PET and Aβ1-42 was highest (88%), followed by p-tau (75%). Concordance between both CSF biomarkers combined and PET was 74%. P-tau181/Aβ1-42 ratio (AUC=0.975, P<0.001), followed by Aβ1-42 (AUC=0.905, P=0.001) and p-tau181 (AUC=0.797, P=0.001) levels were found to discriminate PET positive and negative patients. A p-tau181/Aβ1-42 ratio of 0.098 provided 88,0% sensitivity and 100% specificity.
Conclusion: In our cohort 26% patients the results of Aβ1-42 and p-tau combined versus amyloid PET were disconcordant. Therefore we propose p-tau/Aβ1-42 ratio with reasonable sensitivity and specificity for identification of amyloid PET positive patients.
Disclosure: Nothing to disclose

EUROPEAN JOURNAL OF NEUROLOGY

EPR1003

Biomarkers in differential diagnosis of dementia using a data-driven approach

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Background and aims: Despite an increasing number of biomarkers, differential diagnosis in dementia remains challenging. In this study we aim to investigate the value of different biomarkers to diagnose different types of dementia using a data-driven approach.

Methods: We included 844 subjects (302 controls, 356 Alzheimer's disease (AD), 87 frontotemporal lobe dementia (FTLD), 61 dementia with Lewy Bodies (DLB), 38 vascular dementia (VaD)). We used a multivariate model based on the disease state index classifier, to assess the value of 6 cognitive tests, 3 cerebrospinal fluid biomarkers (Beta-amyloid 1-42, total tau, phosphorylated tau) and 14 automated MRI biomarkers (e.g volumes, voxel- and tensor based morphometry) for pair-wise differentiation between the dementia types. As performance metric we used balanced accuracy, defined as the average of sensitivity and specificity, which was computed using 10-fold cross-validation. The optimal sets of determinants were searched by adding one-by-one a determinant that maximized the accuracy.

Results: Analysis of different types and optimal combination of determinants revealed high performance of cognitive tests in separating controls from the dementia subtypes (Table 1). CSF biomarkers performed best for the separation of AD from controls and other types of dementia. Automated MRI features had the highest accuracies for separation of VaD, DLB and FTLD. Combining all tests and biomarkers optimally increased the majority of accuracies, with a balanced accuracy ranging from 82 to 95.

Table 1 Results for optimized sets of determinants, reporting balanced accuracy.

	Controls vs. AD	Controls vs. FTLD	Controls vs. VAD	Controls vs. DLB	AD vs. FTLD	AD vs. VaD	AD vs. DLB	FTLD vs. VAD	FTLD vs. DLB	VaD vs. DLB
Cognitive tests	93	87	95	93	68	63	70	63	65	59
CSF	86	62	58	63	88	76	76	58	61	53
MRI	88	85	94	78	79	86	70	85	81	87
Cognitive tests + CSF	93	87	95	93	88	76	79	64	68	59
Cognitive tests + MRI	95	92	94	94	78	86	74	85	84	87
CSF + MRI	90	85	94	78	88	86	79	85	81	87
Cognitive tests + CSF + MRI	95	92	94	94	88	86	82	85	84	87

NOTE: The table shows the balanced accuracy achieved when using the optimal combination of determinants for cognitive tests, CSF and MRI. Moreover, the balanced accuracy when combining these modalities is reported. Balanced accuracies 85-100 are highlighted in dark green.

Conclusion: The results show that pair-wise differentiation between subtypes of dementia is optimized by different biomarkers. Data-driven approaches like this could contribute to improved use of biomarkers in clinical practice.

Disclosure: Juha Koikkalainen and Jyrki Lötjönen are shareholders and founders of Combinostics Ltd. They are also inventors in the following patents relevant to the subject of the study, for which Combinostics Ltd owns the IPR: 1. J. Koikkalainen and J. Lotjonen. A method for inferring the state of a system, US7,840,510 B2, PCT/FI2007/050277. 2. J. Lotjonen, J. Koikkalainen and J. Mattila. State Inference in a heterogeneous system, PCT/FI2010/050545. FI20125177.

EPR1004

Automatic classification of patients with Alzheimer's disease (AD) and mild cognitive impairment (MCI) who will convert to AD using deep neural networks

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Background and aims: To build and validate a deep learning (DL) algorithm that predicts the individual diagnosis of Alzheimer's disease (AD) and the development of AD in mild cognitive impairment (MCI) patients based on a single cross-sectional brain structural MRI scan.

Methods: 3D T1-weighted images from ADNI (352 healthy controls [HC], 294 AD, 253 MCI converters, 510 MCI stable) and subjects recruited at our Institute (non-ADNI dataset: 55 HC, 124 AD, 27 MCI converters, 23 MCI stable) were used. Deep neural networks (DNNs), which are mathematical representations of the human neural architecture with multiple hidden layers of artificial neurons, were applied. The whole dataset was randomly divided into a training/validation set (90%) and a testing set (10%). DNN performance was improved by adding to the original dataset synthetic images created using data augmentation algorithms, as well as transfer learning to subsequent comparisons.

Results: DNNs with different architectures and parameters were optimized. The results demonstrated that high level of accuracy was achieved in all of the experiments, with the highest accuracy rate of 99.2% achieved in the AD vs HC classification test using ADNI dataset. In a second dataset including ADNI and non-ADNI images, DNNs discriminated AD and HC with an accuracy of 98.2%. The DNN was also able to discriminate c-MCI from nc-MCI with an accuracy up to 75.1% with no difference between ADNI and non-ADNI images.

Conclusion: DNNs provide a powerful tool for the automatic individual patient diagnosis along the AD continuum.

Disclosure: The study was supported by the Italian Ministry of Health (GR-2011-02351217). Data collection and sharing was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012).

EPR1005

Changes in functional and structural brain connectome along the Alzheimer's disease continuum

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Background and aims: To investigate structural and functional brain architecture in patients with Alzheimer's disease (AD) and amnestic mild cognitive impairment (aMCI), stratified in converters (c-aMCI) and non-converters (nc-aMCI) to AD, and the relationship between healthy brain network functional connectivity and the topography of brain atrophy in patients.

Methods: Ninety-four AD patients, 47 aMCI patients (25 c-aMCI within 36 months) and 53 healthy controls underwent 3D T1-weighted, diffusion tensor and resting state functional MRI. Graph analysis and connectomics assessed global and local, structural and functional topological network properties and regional connectivity. Healthy topological features of brain regions were assessed based on their connectivity with the point of maximal atrophy (epicenter) in AD and aMCI patients.

Results: Graph analysis properties were severely altered in AD patients. Structural brain network was altered in c-aMCI patients relative to healthy controls in particular in the temporal and parietal brain regions, while functional connectivity did not change. Structural connectivity alterations distinguished c-aMCI from nc-aMCI cases. In both AD and c-aMCI, the point of maximal atrophy was located in left hippocampus (disease-epicenter). Brain regions most strongly connected with the disease-epicenter in the healthy functional connectome were also the most atrophic in both AD and c-aMCI patients.

Conclusion: Progressive degeneration in the AD continuum is associated with an early breakdown of anatomical brain connections and follows the strongest connections with the disease-epicenter. These findings support the hypothesis that the topography of brain connectional architecture can modulate the spread of AD through the brain.

Disclosure: Partially supported by grants form the Italian Ministry of Health (GR-2010-2303035) and the Alzheimer's Drug Discovery Foundation (20131211).

EPR1006

White Matter Hyperintensities in Alzheimer Disease: a comparison with normal aging.

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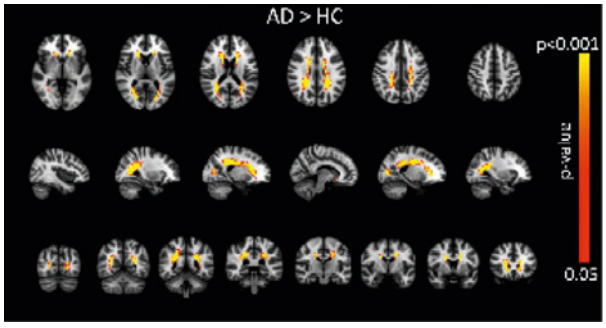
Background and aims: Higher white matter hyperintensities (WMH) load has been reported in Alzheimer's disease (AD) patients when compared to controls. Our study assessed possible differences in the spatial distribution of WMH between AD patients and age-matched elderly normals by means of lesion probability maps.

Methods: The present study included MRI scans of 130 probable AD patients (male/female=48/82) from the Prospective Dementia Registry Austria Study (PRODEM-Austria) and 130 age-matched (±0.5/5 years) healthy controls (HC) from the Austrian Stroke Prevention Family Study (male/female=50/80). There were no significant between group-differences in hypertension, hyper-cholesterolemia, diabetes, smoking and WMH volume normalized by intercranial volume. Manually segmented WMH masks were transformed in the MNI152 space using FSL-FNIRT, where voxelwise paired t-test was applied using the General Linear Model framework with FSL-randomise with 5000 permutations.

Results: The result of the voxelwise paired t-test comparison of lesion masks in AD patients versus age-matched HC, overlaid on the T1-MNI brain is shown in the below figure. AD patients showed a significantly higher likelihood of having WMH in a bilateral periventricular distribution than controls (p=0,05; threshold-free cluster enhancement corrected).



Axial, sagittal and coronal views illustrate the result of voxelwise paired t-test comparison of lesion masks in AD patients versus age-matched HC, overlaid on the T1-MNI brain. Yellow-red colors denote voxels in WMH were significantly more common in AD than in HC with p-values <0.05 (corrected). The color bar indicates the probability range.

Conclusion: The reason for the preferential location of WMH in periventricular brain areas in AD patients described in current study is unclear. Little is known about differential etiologies between periventricular and deep WMH. The MRC Cognitive Function and Ageing Neuropathology Study Group showed that periventricular lesions are related to immune activation resulting from disruption of the blood brain barrier, while the immune response seen in deep and subcortical WMH reflects an innate phagocytic phenotype.

Disclosure: Nothing to disclose

EPR1007

Double-blind argument for a synergistic therapeutic effect of a fixed low-dose combination of acamprosate and baclofen in Alzheimer's disease

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Background and aims: PXT-864, a fixed low-dose combination of acamprosate and baclofen, has shown multiple reversions of pathological alteration in cellular and animal models of AD (Chumakov 2014) in addition of good safety and preliminary evidence of efficacy in early clinical phases (CTAD 2016). If the synergistic profile of PXT-864 in preclinical studies has been clearly established, it remains a challenge in human due to the need of a rdesign including treatment arms under single drugs.
Methods: Patients with mild AD (n=45, progressive decline, no depressive disease) were evenly assigned to one of 3 doses of PXT864, for 36 weeks. The efficacy of PXT864 alone was assessed through cognitive-behavioural tests (per protocol dataset n=32) by dose and compared to historical placebo (Thomas 2016). The exposure to both drugs (Cmax) was measured at each visit evidencing various Cmax groups used to assess the synergy.
Results: On a composite score of 9 clinical endpoints, a synergistic profile using the various Cmax groups at 36 weeks was identified. An improvement on ADAS-Cog11 (1.16 point increase from baseline) in the higher Cmax group for both drugs was observed, whereas by dose, no improvement was observed. The mean change from baseline ADAS-Cog11 was significantly improved for D2 and D3 PXT864 alone vs historical placebo at W36 ($p<0.002$ and $p<0.014$, respectively) and for this higher Cmax group vs D3 ($p<0.052$).
Conclusion: The results provide a synergistic proof-of-action of PXT-864 in AD and our approach could become a key methodology for the development of drug combinations in neurodegenerative disorders.
Disclosure: Peter Schmidt, Viviane Bertrand, Rodolphe Hajj, Serguei Nabrotchkin, Mickaël Guedj, René Goedkoop, Daniel Cohen: Employees Pharnext

EPR1008

LTP-like cortical plasticity is associated with verbal memory impairment in Alzheimer's disease patients

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Background and aims: Experimental studies showed that synaptopathy induced by the neuropathological alterations of Alzheimer's disease (AD) impair synaptic plasticity and memory performance. In humans it is possible to investigate cortical plasticity by applying means of Transcranial Magnetic Stimulation. In AD patients such mechanisms have been widely investigated with TMS protocols such as Theta Burst Stimulation (TBS), showing a clear impairment of Long-Term Potentiation (LTP) cortical-like plasticity consistent with the AD murine models of altered hippocampal plasticity.
Methods: we assessed in 60 newly diagnosed AD patients means of cortical plasticity by applying TBS protocol in order to investigate its relationship with patients' neuropsychological performance.
Results: Long-Term Potentiation (LTP)-like cortical plasticity impairment is associated to a less efficient verbal memory ($r=0.45$; $p=0.002$), while neither visual-spatial long-term memory ($r=0.08$; $p=0.53$), general intelligence ($r=0.11$; $p=0.45$), executive functions (FVF: $r=-0.13$; $p=0.36$) or visual-spatial abilities ($r=-0.08$; $p=0.54$) showed any association. The relationship between LTP and verbal memory remained significant in a combined model adjusting for gender, disease duration, ApoE e4 status, A-beta, total tau and p-tau (beta=0.05, $p= 0.001$, 95% CI: 0.02 - 0.08)
Conclusion: These findings suggest that LTP-like cortical plasticity can be assessed non-invasively in vivo as a neurophysiological surrogate of memory in AD patients and reinforce the notion that LTP investigation may represent a valid and reliable tool to evaluate in vivo the weight of sinaptopathy responsible for cognitive dysfunction.
Disclosure: Nothing to disclose.

Cerebrovascular diseases 1

EPR1010

Reasons for Prehospital Delay in Acute Ischemic Stroke: Hints on Increasing the Rate of Recanalization Therapies – a Prospective Cohort Study

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Background and aims: Delays in the prehospital phase jeopardize the chances for stroke patients to be successfully treated with recanalization therapies (RT). Public education campaigns aiming to increase stroke preparedness and reduce prehospital delays showed contradictory results. Therefore, different approaches to optimize processes in the prehospital phase are required.
Methods: In this prospective cohort study, we included patients admitted to the University Hospital Basel Stroke Center, between 2015 and 2017 with an acute ischemic stroke confirmed on Magnetic Resonance Imaging. Trained study nurses interviewed all patients at bedside along a 28-item questionnaire.
Results: Overall, 337 patients were included. 147 (46%) patients arrived at the hospital within 4.5h, 190 (56%) more than 4.5h after symptom onset. 71 of 147 patients (48%) in the first group received RT compared to 11 of 190 (6%) in the delayed group. A general practitioner (GP) was called by one quarter (n=96, 28%) of patients, 16% in the early vs. 38% in the delayed group ($p<0.001$). In the subgroup who called the GP first, delays occurred due to prehospital face-to-face GP-visits and transportation delays. Calling the GP first was associated with a lower rate of RT (aOR 0.39, 95%-CI 0.19-0.80, p=0.01).
Conclusion: Even in a relatively small urban area, prehospital delay occurred in more than half of stroke patients, and was associated with a lower probability of receiving a RT. Calling the GP first, even within 3h of symptom onset, was associated with avoidable delays. Information campaigns targeted at the GP may increase RT rates.
Disclosure: Nothing to disclose

EPR1011

withdrawn

EPR1012

Quality of life in juvenile stroke

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Background and aims: The incidence of juvenile stroke is increasing. Considering younger age of patients and the potential long-lasting disability, the consequences of juvenile stroke may have a greater societal impact than those of stroke in elder population. We performed a systematic review of studies on quality of life (QoL) in juvenile stroke.
Methods: We have performed a systematic review of all studies on quality of life in juvenile stroke published in PUBMED before January 15, 2018. The search terms were "stroke", "juvenile", "young", "adult", "quality of life" and "resilience". After the abstract evaluation of 555 search results, only six studies we identified as appropriate for the review. The age criterion for juvenile stroke was set as 55 years and younger.
Results: The studies have shown a decline of quality of life in at least 46% of patients with juvenile stroke. On average, QoL was reduced by 37%. The following domains as measured on SF-36 were particularly impaired: physical role, physical functioning and emotional role. The factors influencing the QoL in juvenile stroke were ability to return to work, post-stroke depression, functional outcome, level of education and age of stroke onset.
Conclusion: This systematic review shows a significant decline of QoL in patients with juvenile stroke. Rehabilitation programs should consider the factors influencing QoL in these patients in order to improve outcome of juvenile stroke. Patients who are unable to return to work should receive necessary social support. In addition, our data underline the importance of screening procedures for post-stroke depression in this population.
Disclosure: Nothing to disclose

EPR1013

In-hospital stroke: characterisation in a tertiary hospital

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Background and aims: In-hospital Stroke (IHS) is a stroke that occurs in patients admitted for another diagnosis, and represents 2.2% to 17% of all strokes. Its characterisation is important to identify the circumstances in which occurs and the specific aetiologies.
Methods: Descriptive, retrospective study of IHS occurred between January 2014 and May 2017 at Hospital de Santa Maria. Neurological department and Critical Care Units IHS' were not included. Data was collected from inpatient neurology consultations request forms. Demographic characteristics, inpatient departments, causes of hospital admission, circumstances of stroke occurrence, type and aetiology were analysed.
Results: 64 IHS patients were included (mean age 68.7 years (SD=14.2); 40 (62.5%) males).
The main inpatient department cases distribution was: 16 (25%) in Cardiology; 7 (10.9%) Vascular Surgery; 6 (9.4%) Internal Medicine; 5 (7.8%) General Surgery; 5 (7.8%) Infectious Diseases; 5 (7.8%) Gastroenterology; 4 (6.3%) Cardiothoracic Surgery.
The most frequent causes of admission were elective procedures (18 cases: 8 Interventional Cardiology, 6 Vascular Surgery, 4 other surgeries), cardiac diseases (11), infections (11), gastrointestinal bleeding (5), vascular diseases (4) and kidney failure (4).
55 (85.9%) IHS were ischemic, 5 (7.8%) haemorrhagic and 4 (6.3%) cerebral venous thrombosis.
Besides TOAST aetiologies, multiple mechanisms related to admission (acute myocardial infarction, cardiac/vascular procedure) or associated with hospitalisation (e.g. hemodynamic changes) were identified as potential IHS triggers.
Conclusion: IHS represents a singular population with different risk factors and co-morbidities compared to community-onset strokes. Our findings allow us to organise a prevention-oriented care, to educate staff on stroke recognition and to improve management.
Disclosure: Nothing to disclose

EPR1014

Evaluation of the mechanisms of vascular regulation in middle cerebral artery stenosis using transcranial Doppler

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Background and aims: Stroke due to atherosclerotic intracranial arterial stenoses has high recurrence rate. It is important to identify greater risk patients. We aimed to study cerebral vascular reserve in Caucasian patients with unilateral MCA stenoses through cerebral autoregulation (AR), vasoreactivity (VR) and neurovascular coupling (NVC) tests.
Methods: Case-control study of a cohort of adult patients with unilateral MCA stenosis >50% (MRA), and healthy controls. Carotid stenoses >50% and large white matter lesions were excluded. Blood pressure (Finometer), MCA flow velocity (transcranial Doppler), electrocardiogram and tele-expiratory CO2 were evaluated. AR was evaluated by transfer function (coherence, gain and phase), VR to hypercapnia response, and NVC by cognitive N-Back test response.
Results: 30 patients and 23 age and gender adjusted controls. 16 had moderate (50-69%) and 14 severe (≥70%) stenosis; in both, efficacy of AR and VR to CO2 was significantly lower ipsilaterally to the stenosis ($p<0.05$). AR (phase), VR to CO2 and NVC were significantly different between controls and patients, only ipsilaterally to the stenosis ($p<0.05$), although for NVC only in the group of severe stenosis. AR (phase) was worse with higher stenosis degree ($p<0.05$), similar to that of VR to CO2 (although not statistically significant).
Conclusion: CO2 VR test and AR (phase) allow detecting cerebral vasomotor regulation disfunction even for moderate stenosis (50-70%), and also seem useful for measuring stenosis severity effect. NVC, on the other hand, is only altered in severe stenosis, suggesting preservation of functional hyperemia associated with cognitive activity until later stages of intracranial vascular disease.
Disclosure: Nothing to disclose

EPR1015

Association of obesity with other stroke risk factors in young adults of the Republic of Moldova

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Background and aims: Obesity is associated with an increased risk of stroke. Abdominal obesity is a stronger risk factor than body mass index (BMI) with a greater effect among younger persons. We studied the relationship between obesity and other stroke risk factors in the young adult population of the Republic of Moldova.
Methods: In November 2015, we initiated an epidemiological study in 2 villages located in the northern and central regions of the Republic of Moldova. Our study protocol included: questionnaire, clinical examination, electrocardiography, laboratory examinations and Doppler/Duplex ultrasound of the carotid arteries.
Results: In the study were included 412 subjects, 246 (60%) women and 166 (40%) men (mean age 36.6±9.2 years). The most common identified risk factors were abdominal obesity in 237 (57.5%) and obesity of different degrees in 125 (30.3%) subjects. Mean abdominal circumference (AC) in men was 94.02±14.16cm and 87.81±13.79cm in women. Increased total cholesterol, blood pressure (BP) ≥140/90 mmHg and carotid atherosclerotic plaques were more frequent in subjects with central obesity then in those with overweight and general obesity. AC significantly correlated with the systolic BP ($r=0.395$; $p<0.0001$), diastolic BP ($r=0.412$; $p<0.0001$), BMI ($r=0.872$; $p<0.0001$) and mean intima media thickness ($r=0.401$; $p<0.0001$).
Conclusion: Abdominal obesity was the most common risk factor for stroke in young adult population and was significantly associated with other stroke risk factors. Prevention of obesity and weight reduction need greater emphasis in stroke prevention programs.
Disclosure: Nothing to disclose

EPR1016

Cerebral venous thrombosis in Oslo 2008-2017

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Background and aims: Cerebral venous thrombosis (CVT) is an uncommon cause of stroke that mainly affects adults <45 years of age. Although headache, seizures and focal neurological deficits are the most common symptom, baseline symptoms can vary considerably resulting in challenging diagnostics. The purpose of this study was to assess risk factors and management in patients treated at Oslo University Hospital.
Methods: Patients admitted to Department of Neurology, Neurosurgery or Geriatrics from January 2008 to November 2017 with CVT was identified for patient administrative system by the ICD-codes I67.6 and I63.6. Information on symptoms, risk factors, etiology, diagnostics and management was collected retrospectively from the medical records.
Results: 130 patients with CVT were identified, 26 (20.0%) with traumatic (tCVT) and 104 (80.0%) with non-traumatic CVT (nCVT) Among the patients with nCVT headache was the most common symptom reported by 83.7%. Among female patients <50 years of age, 14% of reported cases occurred during pregnancy/puerperium and 50% on oral estrogen-containing contraceptives. Hereditary thrombophilia was identified as the main cause in 15%, a combination of different causes was identified in 1/3. However, in 1/3 of the cases no pro-thrombotic condition was identified. All patients were treated with anticoagulations. In addition, 10% of the patients with nCVT were treated with endovascular treatment and <5% was neurosurgical interventions.
Conclusion: Prognosis in CVT is generally good. In traumatic brain injury with skull fracture there is a considerable risk of CVT. Both nCVT and tCVT are treated with anticoagulation.
Disclosure: Nothing to disclose

EPR1017

The role of spinal imaging in the management of angioggram-negative spontaneouss subarachnoid haemorrhage: a single-centre experience

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Background: The non-aneurysmal SAH constitute 15% of all spontaneous subarachnoid haemorrhages (SAH), where no intracranial vascular pathology is found despite extensive neuroimaging investigations. Those non-aneurysmal haemorrhages are subdivided into perimesencephalic SAH (PMSAH) and non-perimesencephalic SAH (NPSAH). Searching for a spinal pathology might reveal a spinal arteriovenous malformation (AVM) as a cause of the haemorrhage in about 10% of the cases.
Objective: To evaluate the diagnostic yield of Magnetic Resonance Imaging (MRI) for the spinal column in searching for a spinal aetiology for angiographically-negative spontaneous subarachnoid haemorrhage (AN-SAH)
Methods: A retrospective analysis was conducted in the Walton Centre/Liverpool/UK, which is a tertiary stroke referral centre. The database of the patients who presented with spontaneous nonaneurysmal SAH, diagnosed by computed tomography (CT) or lumbar puncture, and negative CT angiography and digital subtraction angiography (DSA) was reviewed.
Results: There were 1457 patients admitted to The Walton Centre with non-traumatic, spontaneous SAH between January 2009 to December 2015. 300 patients (20.6%) were diagnosed with non-aneurysmal SAH. In 51 patients (17%), an entire spinal axis by standard T1- and T2-weighted MR-imaging was done. While cervical T1- and T2-weighted MR-imaging was conducted in 86 patients (28.7%). In all the 137 patients (45.7%), MR-imaging for the spinal axis did not identify any underlying spinal anomaly that contributing to the SAH formation
Conclusion: In spontaneous nonaneurysmal SAH patients, MR-imaging of the spinal axis has a very low diagnostic yield, and routine radiological investigation of the spinal axis in non-aneurysmal SAH patients' care pathway is therefore not recommended.
Disclosure: Nothing to disclose

Cerebrovascular diseases 2

EPR1018

Occurence and evolution of spasticity in stroke patients – prospective, longitudinal study

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Background and aims: The main aim of the study was to document occurrence and evolution of post stroke spasticity (PSS). Secondary goal was to identify predictors for the increase and the decrease in PSS during 12 months follow up.
Methods: In the longitudinal, multicentric, prospective cohort study assessments were done 7 days (V1), 6 (V2) and 12 (V3) months following the stroke onset. The demographic data, baseline characteristics, the Barthel Index, degree and pattern of paresis and muscle tone were evaluated and recorded. Spasticity was assessed using the Modified Ashworth Scale (MAS).
Results: A total of 402 consecutive patients with first-ever stroke of carotid origin and presence of motor deficit at the day 7 were included. Spasticity was present in 42.3% of patients at V1, 47.3% at V2 and 43.2% at V3. A significant number of patients experienced changes in spasticity between the visits: decrease/disappearance of spasticity was noted in 18.6% (V1 and V2) and 18.3% (V2 and V3) of patients, increase/new occurrence of spasticity in 30.7% (V1 and V2) and 13.6% (V2 and V3) of patients. Number of patients with severe spasticity increased throughout the year from 2.9% to 11.6% (V2) and 12.5% (V3).
Conclusion: Spasticity was noted in almost half of the included patients. The degree of spasticity often changed over time in both directions. The rate of severe spasticity increased steadily during the first year following stroke onset.
Disclosure: This study was supported by the Czech health research council of the Ministry of Health of the Czech Republic no. 15-31921Aand by a grant from the Internal Grant Agency of Palacky University LF-2018-017.

EPR1019

Arterial stenting in echolucent carotid plaques is more frequently asssociated with adverse outcomes: a systematic review and meta-analysis

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Background and aims: Several studies have confirmed that echolucent plaques are associated with higher rates of emboli signals and in-stent restenosis compared to echogenic plaques. There are controversial data according to carotid artery stenting (CAS) interventions on echolucent plaques and recurrent symptoms. In this meta-analysis we aimed to evaluate associations between carotid plaque echolucency and adverse outcomes following CAS.
Methods: Electronic databases (PubMed, EMBASE and Cochrane Center Register) were systematically seaeched up to September 2017. Studies with ultrasound-based characterization of carotid artery plaque echogenicity and its association with adverse outcome after CAS were eligible for this study.
Results: Out of 412 studies found after the first medical databases search, we identified five studies appropriate to be qualitatively and quantitatively analyzed, which evaluated different adverse outcomes in patients with echolucent plaques after CAS. Pooled analysis showed that CAS in echolucent carotid plaques is associated with higher risk of stroke (OR 2.33; 95% CI 1.73-4.65, p=0.015), microembolization (OR 2.77; 95% CI 1.40-5.45, p=0.003), and in stent restenosis (OR 3.8; 95% CI 1.93-7.44, p<0.001). In general, pooled OR of adverse outcomes for CAS performed in echolucent compared to echogenic plaques was 2.92 (95% CI 1.97-4.32), p<0.001.
Conclusion: Compared to echogenic plaques the echolucent ones are more frequently associated with recurrent stroke, distal embolization and in-stent restenosis.
Disclosure: Nothing to disclose

EPR1020

Scale of connective tissue dysplasia signs in patients with spontaneous cervical artery dissection

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Background and aims: Spontaneous cervical artery dissection (sCeAD) is the most frequent cause of ischemic stroke in young adults. Connective tissue dysplasia (CTD) can be considered as a risk factor for dissection, due to dysplastic change of arterial wall.
To assess clinical signs of CTD in patients with CeAD.
Methods: We examined 82 patients (mean age 38.3±13.5; 52 females, 63.4%) with CeAD, verified by MRI/MRA and 40 healthy volunteers (mean age 38.5±6.7; 25 females 62.5%). We evaluated 48 signs included in the Villefranche diagnostic criteria for the vascular type of Ehlers–Danlos syndrome, Ghent criteria for Marfan syndrome, Beighton criteria of joint hypermobility and others, as well as history of headache. Each sign was counted as present or absent.
Results: Signs suggesting CTD were detected more frequently in the group with sCeAD (mean score 7.9±3.6 vs 4.6±2.5; $p<0.0039$). Regression analysis was performed to determine diagnostic-prognostic value of CTD signs. This allowed us to identify main:history of headache ($p=0.022$), arterial hypotension ($p=0.012$), extensive bruising ($p=0.011$) and additional diagnostic criteria:translucent skin ($p=0.034$), hight palate ($p=0.034$), nasal bleeding ($p=0.043$), blue sclera ($p=0.05$), predisposition to constipation ($p=0.05$). In the presence of the 4 main and 2 additional criteria, the predictive value of dissection according to regression model is 77% (ROC analysis: AUC 0.90, 95% CI, 0.84–0.96).
Conclusion: We showed that clinically detectable connective tissue abnormalities are prevalent in patients with sCeAD. The presence of the 4 main and 2 additional diagnostic criteria of CTD has a high predictive value of CeAD and can be used as its diagnostic-prognostic criteria.
Disclosure: Nothing to disclose

EPR1021

Biochemical and Imaging Biomarkers of Atrial Fibrillation in Cryptogenic Stroke Patients

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Background and aims: Ischaemic stroke in atrial fibrillation (AF) patients is often territorial and affecting more arterial areas of blood supply. Elevated blood levels of D-dimer and NT-proBNP were described in AF stroke patients. The aim of the study was to compare the association of selected biochemical biomarkers and MRI imaging characteristics with occurrence of paroxysmal AF and frequent supraventricular extrasystoles (SVES) on 30-days Holter ECG monitoring in cryptogenic stroke patients.
Methods: Retrospective monocentric analysis of consecutive ischaemic stroke patients admitted to comprehensive stroke centre in 2.5 years' period with cryptogenic etiology of stroke at discharge who underwent 30-days Holter ECG monitoring. As potential biomarkers, we compared blood levels of D-dimer and NT-proBNP. MRI was performed within initial hospitalization. SVES were described as frequent if occurred in more than 1% of ECG record.
Results: 178 patients were monitored (average age 60 years, 54% men, 9% had AF, frequent SVES 13%, less frequent SVES 27%). Mean levels of D-dimer differed significantly among the groups (AF 255 ng/ml, frequent SVES 396 ng/l, less frequent SVES 274 ng/l, others 129 ng/ml). Mean levels of NT-proBNP did not differ significantly among the groups. In patients with AF or frequent SVES we found more old ischaemic lesions on MRI (82.9% vs. 61.5%, $p=0.003$). In occurrence of territorial, lacunar or infarction in more areas of blood supply the groups did not differ.
Conclusion: Cryptogenic stroke patients with detection of AF or frequent SVES on 30-day Holter ECG monitoring had higher levels of D-dimer and significantly more old ischaemic lesions on MRI.
Disclosure: Nothing to disclose

EPR1022

Glucose variability and post-stroke hyperglycemia: the key factors underlying poor outcomes in patients with Diabetes Mellitus

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Background and aims: Diabetes Mellitus (DM) has been identified as a prognosis factor of poor outcome after ischemic stroke (IS) but the mechanism underlying it has not been elucidated yet. We analysed the influence of DM, post-stroke hyperglycemia, glucose variability (GV) and HbA1c in the prognosis of IS.

Methods: Secondary analysis of the GLIAS II study. Acute stroke patients were classified into two study groups: DM group (patients with previous history of DM) and a non-DM group. Capillary finger-prick glucose levels were measured every 4 hours the first 48 hours after an IS. Glycaemia >155mg/dL was the cut-off point of post-stroke hyperglycemia. GV was measured by the standard deviation (SD) of the mean glucose values. HbA1c was tested in all patients. The outcomes were death or dependency and mortality at 90 days.

Results: 213 patients were included. 64 (30%) had a previous history of DM. No differences in death or dependency (mRS score >2: 31.7% DM vs. 26.4% non-DM; P=.500) at three months were found. The DM group showed a trend to higher mortality (12.7% vs. 5.7%, P=.096). The logistic regression analysis adjusted by the stroke severity showed that GV and post-stroke hyperglycemia were independently associated with mortality at three months. Post-stroke hyperglycemia was also associated with higher risk of death or dependency. DM and HbA1c were not related to the outcome.

	Crude OR			Adjusted OR		
	P	OR	95% CI	*P*	OR	95% CI
Mortality						
NIHSS admission	.009	1.1	1.02 – 1.18	ref	ref	ref
DM	.09	2.4	.8-6.7	.15	2.21	.75-6.59
Glycemia >155mg/dL	**.05**	**2.9**	**.9-8.7**	**.04**	**3.27**	**1.03-10.36**
GV	.06	1.02	.9-1.05	**.03**	**1.03**	**1-1.06**
HbA1c	.22	1.26	.86-1.83	.19	1.29	.87-1.89
Death or dependency						
NIHSS admission	<.001	1.14	1.08 – 1.2	ref	ref	ref
DM	.44	1.29	0.67-2.48	.45	1.32	.64 – 2.7
Glycemia>155mg/dL	.19	1.5	.81-2.78	**.04**	**2.04**	**1.0 - 4.03**
GV	.34	1	.99-1.02	.07	1.02	.99-1.04
HbA1c	.13	1.21	.94-1.55	.08	1.26	.97-1.64

Logistic regresion analysis for mortality and dependency or death adjusted by NIHSS score and each of the following: DM, Glycemix variability, HbA1c and Post stroke hyperglycemia.

Conclusion: The presence of post-stroke hyperglycemia and GV were associated with poor prognosis after IS independent of the diagnosis of DM and HbA1c values.

Disclosure: Nothing to disclose

EPR1023

Can we cut off mortality rates by one third? An analysis of in-hospital acute stroke mortality in a tertiary stroke centre in Romania.

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Background and aims: In-hospital mortality rates in acute stroke patients vary between 3%-20% mainly depending on acute management and quality of stroke-unit care. The aim of this study was to assess the rates and causes of deaths in patients hospitalized for acute stroke.
Methods: We performed a retrospective analysis of prospectively collected data for all patients admitted with acute stroke between January 1st and June 30th 2017. We assessed demographic, clinical characteristics, rates and causes of in-hospital mortality.
Results: During this period, 766 acute stroke patients were admitted in our Department, of which 689 (89.9%) had an ischemic stroke and 77 (10.1%) a haemorrhagic stroke. 99 (12.92%) of the admitted stroke patients died during hospitalization. The mean hospitalization length until the moment of death was 7.5 days. The mortality rate was 11.03% among patients with ischemic stroke and 29.87% among patients with haemorrhagic stroke. 51.5% of in-hospital mortality was attributed to stroke severity, whereas 34.3% of deaths were related to infectious complications (mainly pneumonia and urinary tract infections), 8.08% to cardiac pathology (acute coronary syndromes and cardiogenic shock), 3.03% to massive gastrointestinal bleeding, 2.02% to pulmonary embolism and 1.07% to other causes.
Conclusion: At least 35% of the in-hospital stroke related deaths in our centre are attributable to preventable factors. Improving the measures taken for the prevention of infectious and cardiac complications in these patients could lead to a significant decrease of in-hospital stroke mortality rates.
Disclosure: Nothing to disclose

EPR1026

Atrial fibrillation in patients with first-ever stroke: incidence trends and antithrombotic therapy before the event

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Background and aims: Atrial fibrillation (AF) is the most common cardiac arrhythmia among adults. In this study, we investigated the incidence of AF-related ischemic stroke over the past decade in South Korea and trends of preventive antithrombotic therapy use before stroke in a Nationwide cohort.
Methods: The data source for this study was a Nationwide sample cohort comprising 1,025,340 individuals (2% of the entire population of Korea) that was established by the countrywide health insurance system. A total of 10,215 patients with acute ischemic stroke (AIS) were selected from the cohort between 2004 and 2013.
Results: AF was identified in 1,662 (%) patients, and 979 patients had preexisting AF before AIS. The annual proportion of patients with AIS with AF gradually increased from 13.4% to 22.6% over the studied time period (p for trends <0.001). Only 14.4% of patients with AF with a high risk for stroke were receiving OAC therapy before the stroke. On the other hand, the proportion of patients treated with antiplatelet agents had increased from 17.8% in 2004 to 46.7% in 2013, while that of patients receiving no antithrombotic therapy decreased from 64.4% in 2004 to 42.2% in 2013.
Conclusion: The number of patients with AIS and AF has steeply increased over the last 10 years in Korea. However, a small portion of patients with AF were receiving OAC therapy before the stroke and about half of the patients did not receive any antithrombotic medication.
Disclosure: Nothing to disclose.

Cognitive neurology/neuropsychology 1

EPR1027

Validation of Montreal Cognitive Assessment-Basic Arabic Version in Low Educated Adults with Mild Cognitive Impairment

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Background and aims: Mild Cognitive Impairment (MCI) may be an early sign of dementia. Educational level can affect its accurate recognition by neurocognitive tools. We aimed to evaluate the Montreal Cognitive Assessment Basic (MoCA-B) Arabic version to detect MCI in adults with low education.
Methods: 116 illiterate or low educated (up to 9 years) adult Egyptians; (MCI=46) according to the National Institute on Aging-Alzheimer's Association clinical criteria, and 70 cognitively normal controls were assessed using the clinical dementia rating scale and the MoCA-B-Arabic Scores.
Results: MCI patients scored significantly lower than controls on all subscales and total MoCA-B-Arabic (P <.001). At the cutoff 24/25, the scale has 84.8% sensitivity and 82.9% specificity for MCI detection. Area under the receiver operating characteristic curve (AUC) was 0.886, P <.001. Internal consistency was 0.733 and test retest reliability was 0.972. The total score differed with literacy level. Correction for education yielded 76.1%, sensitivity and 82.9% specificity and AUC was 0.877, P <.001. The suggested total score correction was able to differentiate correctly between patients with MCI and normal controls with an accuracy of 80.1% at a cutoff 24/25.
Conclusion: MoCA-B-Arabic is reliable and valid in detecting MCI among illiterate and low educated Egyptian adults.
Disclosure: Nothing to disclose

EPR1028

Pure word deafness after lesion in the left superior temporal gyrus

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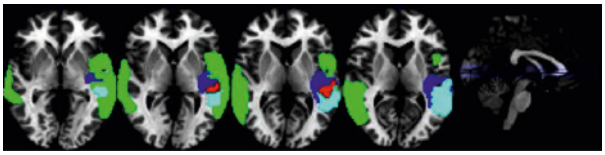
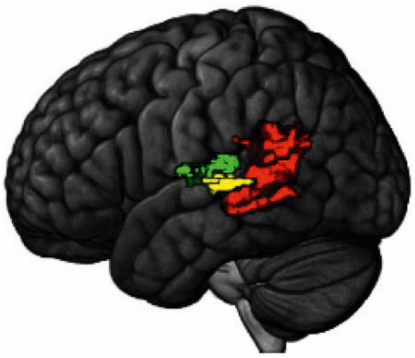
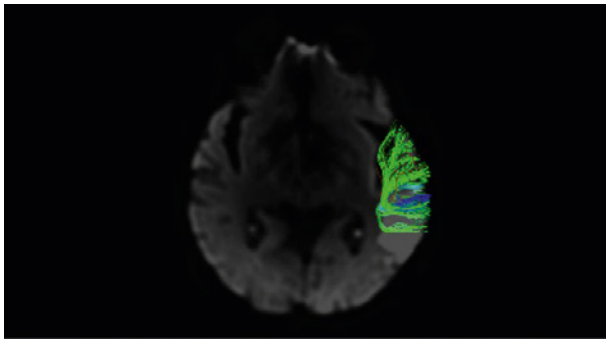
Background and aims: Pure word deafness is a rare neurologic disorder, characterized by selective deficits in auditory speech comprehension with preserved speech production and written language comprehension. Due to the scarcity of published cases, the critical lesion site in the temporal lobe responsible for PWD remains debated.
Methods: We report three detailed cases of pure word deafness that occurred after a stroke. We performed MRI normalization and lesion overlapping to identify common lesion sites in these patients. Furthermore, we mapped their lesions onto a tractography atlas to quantify the severity of white matter tracts disconnection and performed diffusion tension imaging-based (DTI) tractography in one of our patients to identify fiber tracts specifically lesioned in this patient.
Results: Lesion overlap showed a unique cortical region in the middle part of the left superior temporal gyrus (STG), anterior to the classical location of Wernicke's area and postero-lateral to Heschl's gyrus. Regarding white fibers' integrity, all three patients had disruption in the posterior long segment of the left arcuate fasciculus and in the left inferior fronto-occipital fasciculus. Finally, in one of the patients, tractography revealed two main fiber tracts affected, arising from middle STG, one projecting to the left Heschl's gyrus, and the other to the left inferior frontal gyrus.


lesion overlap



lesion overlap/ region of interest



DTI tractography

Conclusion: These cases provide clinical support for recent functional neuro-imaging studies suggesting a causal role for left mid to anterior temporal gyrus in auditory word-form recognition and suggest that lesions of its afferent and efferent projection fibers contribute to the pathology of PWD.

Disclosure: Nothing to disclose

EPR1029

The effect of prolonged-release fampridine on cognitive performance, fatigue, depression and quality of life of MS patients: results from the Ignite study

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Background: Fampridine improves impaired axonal conduction associated with central nervous system demyelination. Long-term effects of fampridine have not been fully explored.

Objectives: To assess cognitive function, quality of life, depression and fatigue in Multiple Sclerosis (MS) patients treated with fampridine after 6 and 12 months of treatment.

Methods: 60 patients (31 female, median EDSS 6.0 (4-6.5), mean age 50.9±9.5) were enrolled in the study. Patients were examined with T25FW and BICAMS battery and were asked to complete MSIS-29, MFIS, BDI-II and MUSIQOL questionnaires. Patients were sub-grouped in responders (n:40) and non-responders (n:20) according to T25FW performance after 2 weeks on treatment.

Results: After 6 months, statistically significant improvement was observed in MSIS29 ($p<0.001$), in T25FW ($p<0.001$) and SDMT($p<0.001$) for responders. After 1 year on treatment, statistically significant improvement was observed in MSIS29 ($p=0.004$), T25FW ($p <0.001$), SDMT (($p<0.001$) and MUSIQOL ($p=0.03$) for responders. Non-responders did not present any statistically significant improvement in all tests during the study duration

Conclusions: According to study results, fampridine may have a beneficial effect on information processing speed though not other domains of cognitive function in MS patients. Study data have provided some evidence that fampridine treatment may reduce the impact of MS in daily activities and improve quality of life but has no effect on subjective fatigue and mood.

Disclosure: Study is supported by a Biogen Idec research grant via the Aristotle University Research Committee.

EPR1031

Measuring sentence production in primary progressive aphasia

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Background and aims: To test the ability of the Sentence Anagram Test (SAT) in distinguishing non-fluent (nfv) and logopenic variants (lv) of primary progressive aphasia (PPA) which are the two most difficult PPA forms to be distinguished based on speech production.
Methods: We recruited 13 nfvPPA, 9 lvPPA and 4 semantic PPA (svPPA) patients. Participants underwent SAT, which included canonical and non-canonical sentences. Performance accuracy and time for completing total and sub-session items were recorded. Performances at syntax comprehension test were also investigated. Neuropsychological features were compared between nfvPPA and lvPPA groups. The four svPPA were not included in the statistical analysis and were only used for a qualitative example of grammar unaffected performance.
Results: PPA groups took similar time to complete all the SAT sub-sessions. Compared to lvPPA, nfvPPA patients showed worse accuracy for both canonical and non-canonical sentences. Likely due to initial comprehension deficits in lvPPA with longer disease duration, both groups of patients performed similarly in the syntax comprehension test. As expected, svPPA qualitatively performed better than the other groups in all investigated domains.
Conclusion: The SAT is a powerful tool for distinguishing nfvPPA and lvPPA. Although some lvPPA had longer disease duration, the SAT was still able to detect the differences in the two variants. Future studies in larger samples should test the performance of these measures for a correct classification at the single subject level.
Disclosure: The study was supported by the Italian Ministry of Health (grant number GR-2010-2303035).

EPR1032

Behavioral and physiological markers of feigned memory impairment

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Background and aims: The detection of malingering in cognitive performance is an important clinical challenge. The study goal is to explore behavioral and physiological responses in a performance validity test under normal vs. feigning conditions.
Methods: Twenty healthy women (mean age=32±6; mean education=17±1) recruited in the community performed a digital version of Test of Memory Malingering (TOMM) adapted for eye-tracking recording (iView X™ Hi-Speed 1250 System). Half performed TOMM under normal effort and half were instructed to feign memory impairment as if they were in the initial stages of dementia to receive retirement or disability benefits. Number of correct responses (CR), response time (RT), and fixation time (FT) in old vs. new stimuli were recorded. Mann-Whitney test were used for group comparisons and ROC curves were applied for diagnostic test evaluation.
Results: The feigning group produced fewer CR on both evaluation trials and retention trial ($p<0.001$), had longer RT on evaluation 1 ($p=0.007$) and 2 ($p=0.004$), and had shorter total FT (during the 3 seconds visualization period prior to RT) in old stimuli during evaluation 1 ($p=0.013$) and 2 ($p=0.019$). No significant other group differences ($p>0.05$) were identified regarding RT, first FT, and total FT. ROC curves revealed that behavioral measures (CR and RT) had AUC >0.9 on both evaluation trials and that the AUC for total FT was 0.8 on both evaluation trials.
Conclusion: Healthy individuals feigning memory impairment have a distinct behavioral and physiological response pattern, reflecting an increased effort to inhibit a natural response.
Disclosure: Study funded by Bial Foundation research grant 430/14

Epilepsy 1

EPR1033

Short-term risk of recurrence after a first unprovoked seizure

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Background and aims: Our objective are to evaluate the risk of recurrence after a first unprovoked seizure at one month and the associative risk factors of recurrence at 1 month as well as the recurrence risk at 3 months.

Methods: This is a prospective observational study based on a consecutive series of 140 adult patients admitted in Emergency Department (ED) for a first unprovoked seizure during one year. All the included patients were followed in a specialized consultation at 1 month maximum. The collected data was exhaustive including: demographic criteria, clinical examination, recurrence at 1 and 3 months, EEG, Imaging, precipitating factors, type of seizure and prescribed treatment.

	Recurrence at 1 month n=80		P Value
	Yes n=9 (11%)	No n=71 (89%)	
EEG N	5(55.5 %)	46(64.8%)	0.59
EEG Abnormal	4(45%)	19(27%)	0.271
EEG<48H Abnormal	4(45%)	17(23.9%)	0.232
EEG <48 N	3(66.6%)	32(45.1%)	0.724
EEG P	0	5(7%)	1.00
EEG <48 P	0	5(7%)	1.00
EEG FL	4(44.4%)	14(19.7%)	0.109
EEG <48 FL	4(44%)	11(15.5%)	0.058
Imaging anomalies	3(33.3%)	11(15.5%)	0.188
Precipitating factors	1(11.1%)	21(29.6%)	0.432
Age >60 years	4(44.4%)	28(39.4%)	1.00
SEX	M:3(33%) F:6(66.6%)	M:46(64%) F:25(35.2%)	0.082
BDZ	3(3.33%)	3(4%)	0.017
Generalized	2(22.2%)	7(10%)	0.266
Focal	6(66.6%)	19(27%)	0.015

Table 1: Different studied risk factors and their significance.
EEG N: EEG Normal; EEG<48H Abnormal: Abnormal EEG performed in less than 48 hours after the first epileptic seizure; EEG < 48 N: Normal EEG performed less than 48 hours after the first epileptic seizure; EEG P: Paroxysm discharges on EEG; EEG < 48 P: Paroxysm discharges observed on EEG performed less than 48 hours after the first epileptic seizure; EEG FL: Focal slowness on EEG, EEG < 48 FL: Focal slowness on EEG performed less than 48 hours after the first epileptic seizure; BDZ: Benzodiazepine. Generalized: clinical generalized seizure type; Focal: clinical focal seizure type.

Risk factors and their significance

Results: Among the 140 patients diagnosed as first unprovoked seizure by the ED, only 80 patients have their diagnosis confirmed at 1 month. Nine patients had recurrence before one month (11%). We were able to define specific valid risk factors of short term recurrence: focal seizure (p=0.015), abnormal EEG in the first 48 hours as focal slowness (p=0. 058) and imaging abnormalities (p=0.19). The risk of recurrence at 3 months was 16% in a total of 38 patients.

Conclusion: Most patients came in the ED did not have any recurrence seizure in the first month (89%). So, we do not suggest any pre-medication in ED waiting for their first consultation especially without our risks factors. The valid risk factors are: EEG in the first 48 hours, Type of seizure and Imaging. The delay of 1 month is absolutely safe.

Disclosure: Nothing to disclose

EPR1034

Language fMRI in epilepsy: Current standards in practice

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Background and aims: Functional MRI is validated for lateralizing language areas in pre-surgical planning, but teams often remain uncertain about fMRI's strengths and weaknesses. In this talk the key evidence supporting fMRI's use will be summarized through two extensive international surveys of clinicians and analysts completing language fMRI in epilepsy.

Methods: Respondents included 82 clinicians involved in selecting patients for epilepsy surgery, and 63 analysts completing language fMRI. Respondents were typically from academic centers (clinician survey 85%; analysts, 82%) and treated primarily adults (44%/42%), adults and children (40%/36%), or children alone (16%/22%).

Results: Primary findings from the clinical survey included the fact that fMRI is used both for lateralizing language and, frequently (44% of programs), guide surgical margins. Programs reported both cases of unpredicted decline (17%) and unexpected preservation of function (54%). The analytic survey identified the most-commonly used language tasks, which include noun-verb generation, verbal fluency, and object naming. A de-facto standard processing stream is evident, with analysis most often completed in the open-source software SPM. Clinical fMRI is already executed in a wide range of languages.

Conclusion: Language fMRI is well established for presurgical language mapping in epilepsy. These surveys reveal a great diversity in protocols, however, and highlight a need for highly standardized and validated forms of fMRI. They also underscore the importance of not using fMRI maps to guide surgical margins. An ongoing study to validated clinical language fMRI in multiple languages will be discussed, as will key points for successful use of fMRI in the clinic.

Disclosure: This work was supported by Yale CTSA [UL1TR000142] from the National Center for Advancing Translational Science (NCATS), National Institutes of Health USA; and the Swebilius Foundation.

EPR1035

IL-1 signals in epileptogenesis and epilepsy-induced sleep disruptions

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Background and aims: Epilepsy is often associated with sleep disturbance, but the interaction between sleep and epilepsy is not clear. Interleukin-1 regulates sleep and participates in epileptogenesis. NMDA receptor also play a key role in epileptogenesis. Therefore, we herein study the activation of NMDA receptors via the IL-1 signaling pathways, e.g., Src kinase and NF-kappaB, in epileptogenesis and epilepsy-induced sleep disruption.
Methods: Spontaneously generalized seizures were induced by intraperitoneal injection of pentylenetetrazol (PTZ), the sleep-wake activity was analyzed, and the seizure threshold was determined. NR1 and phosphorylated-NR2B were determined by the Western blotting. Activators and inhibitors of Src kinase and NF-kappaB were administered intracerebroventricularly.
Results: Occurrence of spontaneous seizure was higher in the wildtype treated with PTZ than that in the IL-1R1 kockout (KO) mice treated with PTZ. NREM sleep was decreased in wildtype mice treated with PTZ, but it was not altered in IL-1R1 KO mice. The expression of NR1 subunit protein and the phosphorylation of NR2B at Tyr1472 in the hippocampus and the hypothalamus were significantly lower in the IL-1R1 KO mice treated with PTZ when comparing to those in the wildtype mice treated with PTZ. Furthermore, administering inhibitors of Src kinase or NF-kappaB blocked PTZ-induced NMDA activation, and suppressed epileptogenesis and sleep disturbance in wildtype mice. In contrast, activators of Src kinase and NF-kappaB restored the IL-1 signaling in the IL-1R1 KO mice.
Conclusion: Our results indicate that the increase of NMDA receptor activity by the IL-1 signal contributes to the PTZ-induced epileptogenesis and the epilepsy-induced sleep disruption.
Disclosure: Nothing to disclose

EPR1036

TC-G 1008, GPR39 (zinc receptor) agonist decreases seizure threshold in maximal electroshock seizure threshold test and facilitates kindling development in pentylenetrazole kindling model in mice

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Background and aims: Previously described as an orphan, GPR39 receptor was shown to be activated by zinc ions. It was demonstrated that zinc-enriched mossy fiber stimulation-dependent up-regulation of potassium-chloride co-transporter 2 (KCC2), which is indispensable for GABAA receptor function, was not observed in slices from GPR39 knockout animals (Chorin et al. 2011), suggesting that GPR39-dependent up-regulation of KCC2 activity provides homeostatic adaptation to an excitotoxic stimulus by increasing inhibition. Thus, GPR39 has been proposed as a novel target for dampening seizures.
Methods: Using recently synthesized selective GPR39 agonist, TC-G 1008, we assessed the effects of GPR39 activation in vivo, in a seizure test and a model of epilepsy, i.e., maximal electroshock seizure threshold (MEST) test and pentylenetrazole (PTZ) kindling model, respectively.
Results: Liquid chromatography tandem mass spectrometry analysis revealed that TC-G 1008 is brain penetrant, reaching substantial brain concentrations 15–30 min following its administration at a dose of 20 mg/kg. In MEST test, TC-G 1008 (5, 10 and 20 mg/kg) and zinc (8 and 16 mg/kg, given as zinc chloride) decreased seizure threshold, while a common anticonvulsant drug, valproic acid (VPA) (150 mg/kg), exerted the opposite effect. In the PTZ model, TC-G 1008 (10 mg/kg) facilitated kindling development. 93% of mice that received TC-G 1008 and 77% of mice that received zinc (8 mg/kg) exhibited at least three consecutive stage 5 seizures vs. 62% of control mice and none of VPA treated mice.
Conclusion: Our in vivo data obtained using TC-G 1008 argue against GPR39 activation as a therapeutic strategy for alleviating seizures/epilepsy.
Disclosure: The study was supported by a grant from the National Science Centre 2016/20/S/NZ7/00424 (UD).

EPR1037

Coffin-lowry syndrome as a rare cause of X-linked drop attacks

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Background and aims: Coffin-Lowry syndrome (CLS) is a rare X-linked syndrome characterized by psychomotor, intellectual disability and facial dysmorphic features. Non-epileptic drop episodes occur in 3-7% and epileptic seizures in 5-30%. It is unusual for a female present the classic phenotype.
Methods: Case Report
Results: A 21-year-old female, child of non-consanguineous Caucasian parents, with a psychomotor development delay, attention deficit and hyperactivity. The pregnancy was complicated with pre-eclampsia and preterm delivery occurred at 36 weeks. No history of CNS infections or febrile seizures was reported.
When she was 3 years old, she presented multiple episodes of unprovoked sudden falls without loss of consciousness.
At the age of 7, she developed daily motor seizures with nocturnal predominance.
Objective examination showed craniofacial and osteoarticular dysmorphisms with tapering fingers and hyperlaxity.
Cranial MRI showed enlargement of the ventricular system due to subcortical atrophy.
Video-EEG recorded asymmetric tonic seizures in sleep and episodes of non-epileptic falls not external-stimulus induced.
She was treated with carbamazepine, levetiracetam, zonisamide, clonazepam, with partial benefit on epileptic seizures and without any improvement in drop episodes.
The karyotype (46,XX) was determined and exome sequencing analysis was performed and the variant c.1756dup (p.Ala586Glyfs*11) was detected in heterozygous state in the RPS6KA3 gene, confirming the diagnosis of CLS.
Conclusion: This report suggests that CLS should be considered in the differential diagnosis of drop attacks in the presence of the typical phenotype even among females.
Disclosure: Nothing to disclose

EPR1038

A service evaluation of patients attending A&E with seizures

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Background and aims: Epilepsy is the most common, chronic neurological condition with a prevalence of 0.5% and an incidence of 3 to 5%. Despite anticonvulsant use, there are approximately 60,000 A&E attendances and 40,000 hospital admissions in the UK per year. Over EU 15 billion is spent annually on treatment in Europe.
Aims: To clinically characterise patients with seizures attending A&E and audit their management and follow-up with respect to NICE guidance and local hospital guidelines.
Methods: Using A&E triage records a list of all patients attending St George's Hospital in London with a seizure within a six month period was derived. By referring to clinical records, management in A&E and beyond was audited.
Results: 382 adults with seizures were identified. 33% attended A&E in the previous 12 months with a seizure. Of those with epilepsy (n=187), 9% were on no drug. In all seizure cases, documentation was often incomplete and a collateral history was only obtained in 44% cases. 44% of patients were admitted, and of these, 15% were unnecessary according to criteria outlined by Iyer et al. Only 8% were asked if they were a driver, alcohol intake was not documented in 44% and illicit drug use was absent in 57%. Only 37% were referred to a neurologist or epilepsy specialist.
Conclusion: As a third of the patients attended A&E in the previous 12 months, it is clear that thorough history taking to determine factors provoking seizures and better management in the community is necessary to prevent recurrence of seizures.
Disclosure: Nothing to disclose

EPR1039

MMP-2 and disease activity in epilepsy patients

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Background and aims: Various blood-brain barrier (BBB) markers are elevated in epilepsy. In this study we examined levels of MMP-2 and TIMP-2, which are important proteins involved in BBB activation and restoration, in patients with epilepsy after generalized tonic-clonic seizures (TCS) and in the interictal period.
Methods: Serum levels of MMP-2 and TIMP-2 were examined in two groups: I - 50 patients during one hour after TCS; and II - 62 epilepsy patients, seizure-free for a minimum of 7 days, and measured by ELISA. Seizure count for group II was performed for one year before and one month after blood collection. Levels of MMP-2 and TIMP-2 were also examined in control group matched for sex and age, with no history of epilepsy.
Results: Serum levels of MMP-2 were higher in epilepsy patients both in the group after TCS and in the stable group (group I: 216.4 ng/ml±75.3 vs. 186.6±8.7 ng/ml; group II: 374.3 ng/ml±12.5 vs. 193.7±8.5 ng/ml). We also observed a tendency for higher levels of serum TIMP-2 in both groups of epilepsy patients in comparison to controls. Interestingly, in the examined groups of patients we found higher levels of BBB markers in patients in the interictal period.
Conclusion: We observed that epilepsy patients have increased markers of BBB activation both after seizures, suggesting abrupt changes in BBB, and in the interictal period, indicating persistence of neuroinflammation. Due to a noticeable dispersion of obtained data it is necessary to conduct further research.
Disclosure: National Science Centre grant 2012/07/N/NZ4/01969

EPR1040

Transcranial brain parenchyma sonography of basal ganglia in the evaluation of the clinical course of juvenile myoclonic epilepsy

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Background and aims: Abnormal neural networks in the thalamus, limbic areas, brainstem and cerebellum seem to be associated with juvenile myoclonic epilepsy (JME). Cognitive and behavioral difficulties in JME are suggested to relate with alterations in basal ganglia. These structures are implicated in the modulation of epileptic spike-wave discharges generalization in patients with idiopathic generalized epilepsy.
Aim: To evaluate the influence and potential clinical significance of abnormal findings in subcortical structures associated with JME.
Methods: This retrospective study included 40 JME patients who were followed-up from January 1985 to December 2016 at the Clinic of Neurology and Psychiatry for Children and Youth in Belgrade, and received transcranial parenchymal sonography (TPS). Relation of clinical parameters (seizure control, cognitive functioning, behavior) with TPS results was assessed.
Results: Duration of remission for at least one year was achieved in 71% of patients (mean duration of remission 8.9 years), while 10% had pseudo-resistant epilepsy. Dysexecutive syndrome and psychiatric comorbidities were noted in 30.4% and 25% of patients, respectively. Pathologically hyperechogenic substantia nigra (SN) and red nucleus (RN) on TPS were found in 35% and 32.5% of patients, respectively. There was no statistically significant influence of seizure control on TPS findings. However, compared to the control group, hyperechogenicity of the right-sided SN and both RN was significantly more common in JME patients.
Conclusion: To our knowledge, this is the first study to demonstrate structural changes of SN and RN in JME. Our results suggest additional non-lesional abnormalities of BG and midbrain structures in JME patients.
Disclosure: Nothing to disclose

Headache and pain 1

EPR1041

Salivary inflammatory markers in tension type headache and migraine sufferers

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Background and aims: No research has been performed for the role of salivary inflammatory markers in Tension type headache(TTH) and migraine. We studied whether headache attacks are associated with changes in CRP, IL-1β and IL-6 in saliva. We, also investigated whether these markers in TTH and migraine could be influenced by psychiatric comorbidities such as depression and anxiety.
Methods: This is a cross-sectional study of 19 migraine and 19 TTH patients that attended our outpatient headache clinic and 15 healthy controls between January-March 2016. We accessed theirs demographics, headache features, anxiety and depression as measured by the Hamilton Anxiety Rating Scale (HAM-A) and the Beck Depression Inventory (BDI). Salivary IL-6, IL-1β and CRP were collected in distinct time points as A- headache free period, B – during headache, C- one day after headache attack, and measured by ELISA kits
Results: IL-1β significantly decreased from point A to B, while increased from B to C in headache groups. They had greater IL-1β levels at time point B as compared with controls. No significant differences were found in time variation of CRP, IL-1β and IL-6 levels between migraine and TTH ($p>0.05$). CRP measured at point B was negatively correlated with HAM-A, and BDI scores. IL-6 was negatively correlated with BDI scores at point B ($r=0.52$, $P<0.001$)
Conclusion: For the first time, it seems to exist a similar variation of salivary inflammatory cytokines in headache groups. CRP and IL-6 were correlated with higher anxiety and depression scores during headache attack in headache groups.
Disclosure: Nothing to disclose

EPR1042

Retinal fiber layer and choroid thickness are reduced in cluster headache: results from an Optical Coherence Tomography study

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Background and aims: Cluster headache (CH) is the most frequent trigemino-autonomic headache with severe unilateral pain probably due to an increased venous load in the inflamed cavernous sinus.We aimed to evaluate structural abnormalities in the retina of episodic CH patients using Optical Coherence Tomography (OCT).
Methods: This observational and cross-sectional study screened CH patients according to the International Classification of Headache Disorders, referring to the Headache Centre of the University of Catania in the period between 1st September 2016 and 30th April 2017. We also recruited 23 healthy-controls. CH patients previously treated with O2 therapy were excluded. For right (RE) and left eye (LE) we studied the mean retinal nerve fiber layer (RNFL) thickness, single quadrants analysis and choroid thickness (CT).
Results: Out of 42 CH patients, a total of 19 patients diagnosed as CH were enrolled. We found that average RNFL and inferior sector were thinner in CH compared to controls (90.1±7.4 vs 99.3±4.5μm, $p<0.01$ RE, 90.7±6.8 vs 100.2±6.5μm, $p<0.01$ LE, 118.5±7.9 vs 127.2±15.1μm, $p<0.01$ RE, 117.3±8.6 vs 126.3±12.3μm, $p<0.01$ LE, respectively). Moreover, CH patients showed a significant reduction in CT compared to controls (270.3±5.9 vs 333.2±3.1 μm, $p<0.01$ RE, 265.8±7.1 vs 334.5±4.1 μm, $p<0.01$ LE). The eye of the headache side presented thinner inferior sector (114.5±6.8 vs 122.5±9.0μm, $p<0.01$) and CT (258.6±4.5 vs 282.0±3.9μm, $p<0.01$) compared to the non-affected side.
Conclusion: We confirmed that retinal profile is affected in CH; in particular, the involvement of CT, especially in the affected side, could be explained by vascular changes of retinal vessel during CH attacks.
Disclosure: Nothing to disclose

EPR1043

Phase-3 safety data from studies comparing galcanezumab and placebo in patients with episodic and chronic migraine

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Background and aims: To evaluate the safety and tolerability of galcanezumab compared with placebo each given monthly (subcutaneous injection) for up to six months for prevention of migraine.
Methods: Data were integrated from three double-blind clinical studies (EVOLVE-1=NCT02614183; EVOLVE-2=NCT02614196; REGAIN=NCT02614261); two galcanezumab dose-groups (120- and 240mg) were pooled. Adverse events (AEs) that were treatment-emergent (TEAEs), discontinuation due to AEs (DCAEs), and serious AEs (SAEs) were analysed. Laboratory results, vital signs, and ECG results were also assessed.
Results: A total of 1,435 patients were treated with galcanezumab and 1,451 with placebo. TEAEs occurring in 1.5% or more of galcanezumab-treated patients, more frequently than among placebo-treated patients, and significantly different between galcanezumab and placebo included nasopharyngitis, injection site reaction, injection site erythema, injection site pruritus, and constipation. The proportion of DCAEs among galcanezumab-treated patients was low, and the proportion of patients who discontinued due to an injection-site related AE was less than 0.5%. None of the TEAEs related to injection site were reported as an SAE, and the majority of patients reported the events as mild or moderate in severity. Fewer than 2.0% of galcanezumab-treated patients reported an SAE. There were no clinically meaningful differences between galcanezumab and placebo in laboratory analytes, vital signs, or ECGs.
Conclusion: Galcanezumab (120- and 240-mg monthly) demonstrated a favorable safety and tolerability profile for the prevention of episodic and chronic migraine.
Disclosure: Sponsored by Eli Lilly and Company.

EPR1044

Efficacy of galcanezumab in patients who failed to respond to preventives previously: results from EVOLVE-1, EVOLVE-2 and REGAIN studies

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Background and aims: Galcanezumab (GMB) is a humanized monoclonal antibody against calcitonin gene-related peptide under development for prevention of migraine. Objective of this subgroup analysis of three Phase 3 studies of galcanezumab was to assess if differential treatment effects exist in patients who failed ≥2 previous preventives versus who had not.
Methods: EVOLVE-1 (NCT02614183), EVOLVE-2 (NCT02614196), and REGAIN (NCT02614261) were randomized, double-blind, placebo-controlled studies in patients with episodic (EVOLVE-1/2) or chronic (REGAIN) migraine. Patients were randomized 2:1:1 to receive placebo/GMB_120mg/GMB_240mg during double-blind treatment period lasting 6 (EVOLVE-1/2) or 3 (REGAIN) months. Subgroup analysis was conducted for change from baseline in number of monthly migraine headache days (MHD) and ≥50% response (reduction in number of MHD) for patients who failed ≥2 prior preventives (yes/no). Subgroup-by-treatment interactions were calculated using linear or generalised linear mixed models.
Results: In EVOLVE studies and REGAIN study, GMB_120mg/240mg statistically significantly improved ($p<0.001$) overall mean reduction of monthly MHD versus placebo in both subgroups (Table 1). Significant treatment-by-subgroup interactions were seen for GMB_240mg (EVOLVE studies) and GMB_120mg (REGAIN) suggesting better efficacy versus placebo for these doses in patients who failed prior preventives. Mean percentage of galcanezumab-treated patients with ≥50% response were significantly higher versus placebo for both subgroups.

Table 1. Overall change from baseline in number of monthly migraine headache days in patients with migraine who failed ≥2 previous preventives and who did not. Results are least square mean change from baseline [standard error] from integrated analysis of EVOLVE-1 and EVOLVE-2 studies, and from REGAIN study.

		Placebo	GMB_120mg	GMB_240mg
EVOLVE Studies (integrated set)	Failed ≥2 previous preventives	N=85 -0.81 (0.61)	N=43 -3.45 (0.78)	N=44 -3.85 (0.77)
	Did not fail ≥2 previous preventives	N=790 -2.68 (0.17)	N=393 -4.61 (0.20)	N=384 -4.36 (0.21)
REGAIN study	Failed ≥2 previous preventives	N=161 -1.44 (0.62)	N=66 -5.91 (0.79)	N=96 -5.50 (0.71)
	Did not fail ≥2 previous preventives	N=377 -3.69 (0.43)	N=207 -4.82 (0.48)	N=178 -5.77 (0.53)

Table 1

Conclusion: GMB_120mg/240mg is efficacious compared with placebo in reducing monthly MHDs in both patients who failed and did not fail ≥2 prior preventives. Treatment-by-subgroup interactions may be driven by lower placebo response in patients who failed preventives previously as magnitude of change for GMB-treated patients were similar in both subgroups.
Disclosure: Supported by Eli Lilly and Company.

EPR1045

Migraine with visual aura associated with thicker visual cortex

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Background and aims: Until recent years it was believed that migraine with aura (MA) was a disorder with no impact on brain structure. However, recent MRI studies have reported increased thickness of visual and somatosensory cortex in patients with MA, suggesting that such structural alterations were either due to increased neuronal density or result of multiple episodes of cortical spreading depression as part of aura attacks. Subsequent studies have yielded conflicting results, possibly due to methodological reasons, e.g., small number of subjects.
Methods: We recruited women aged 30-60 years from the nationwide Danish Twin Registry. Brain MRI of women with MA (N=166), their co-twins (N=30), and unrelated migraine-free twins (N=137) were performed at a single centre and assessed for cortical thickness in predefined cortical areas (V1, V2, V3A, MT, somatosensory cortex (SSC)), blinded to headache diagnoses. The difference in cortical thickness between patients and controls adjusted for age, and other potential confounders was assessed. Comparisons of twin pairs discordant for MA were also performed.
Results: Compared with controls, patients had thicker cortex in areas V2 (0.032 mm), V3A (0.037 mm), while differences in the remaining areas examined were not statistically significant. We found no association between the regions of interest and active migraine, or number of lifetime aura attacks. MA discordant twin pairs (n=30) only differed in mean thickness of V2 (0.039 mm).
Conclusion: Women with MA have a thicker cortex corresponding to visual areas. Our results indicate this may be an inherent trait rather than a result of repeated aura attacks.
Disclosure: Nothing to disclose

EPR1046

Genetic variants in KCNK18 gene in migraine patients with positive family history of this disease

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Background and aims: Migraine is common neurological disorder divided into two main clinical subtypes: migraine with aura (MA) and migraine without aura (MO). Migraine is multifactorial disease with genetic component. One of candidate gene in families with migraine is KCNK18 encoding TRESK channel. Mutation in KCNK18, leading to the loss of TRESK function, was found in a multigenerational family with MA. Genetic changes in KCNK18 may result in hyperexcitability of trigeminal nerve neurons and an increase in the susceptibility of migraine headache.
The aim of the study was to screen KCNK18 gene for polymorphisms and mutations in migraine patients with positive family history of this disease.
Methods: The study included 90 migraine patients (MA:39, MO:51) and 90 controls. Mean age of participants was 36±13 years. The HRMA and sequencing were used for genotyping.
Results: We identified two rare polymorphisms: c.28A>G, c.691T>C and mutation c.328T>C of KCNK18. The c.28A>G polymorphism was as common in migraine group as in controls and occurs both in MA and MO. c.691T>C was found in one family suffering from MO. The c.328T>C mutation, leading to loss of TRESK function, was found in one family with MO. Interestingly, migraine was not present in all individuals carrying the mutation, thus it suggest that other factors, such as female sex hormones may influence the migraine manifestation.
Conclusion: It seems that both polymorphisms and mutations in KCNK18 gene may be associated with MO. The overexpression of TRESK channels may be a potential target for the development of new migraine therapy.
Disclosure: Nothing to disclose

EPR1047

Idiopathic intracranial hypertension without papilledema (IIHWOP) in chronic refractory headache

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Background and aims: To determine the prevalence of Idiopathic intracranial hypertension without papilledema (IIHWOP) testing revised diagnostic criteria by Friedman in refractory chronic headache (CH) patients.
Methods: This is a prospective observational study. Each patient underwent ophthalmologic evaluation and Optical Coherence Tomography; brain magnetic resonance venography (MRV) and a lumbar puncture (LP) with opening pressure (OP) measurement. CSF withdrawal was performed in patients with CSF OP>200 mmH20. IIHWOP was defined according Friedman's diagnostic criteria. Effect of CSF withdrawal was evaluated clinically in a 6 month follow-up and with a MRV study at 1 month.
Results: Forty-five consecutive patients were enrolled. Five were excluded due to protocol violations. Analyses were conducted in 40 patients (32 F, 8 M; mean age 49.4±10.8). None had papilledema. Nine patients (22.5%) had OP greater than 200mmH2O, two of them above 250 mmH2O. Two (5%) had neuroimaging findings suggestive of elevated intracranial pressure. One of them (2.5%) met the newly proposed diagnostic criteria by Friedman for IIHWOP. After CSF withdrawal seven (77.8%) of the nine patients improved. No changes in neuroimaging findings were found.
Conclusion: We found a low prevalence (2.5%) of IIHWOP in refractory CH patients according actual diagnostic criteria. In agreement to Friedman's criteria, our result confirm that diagnosis of IIHWOP should be based on CSF OP and the combination of neuroradiological findings. However, where to set the CSF OP upper limit in IIHWOP needs further field testing. Although IIHWOP is a rare clinical condition, it should be considered and treated in refractory CH patients.
Disclosure: Nothing to disclose

EPR1048

Abnormal pattern of intracortical facilitation in migraine without aura. Preliminary results of a paired-pulse TMS study.

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Background and aims: Paired-pulse TMS paradigms can be used to test connectivity within the primary motor cortex in migraine sufferers. Aim of the present study was to provide additional information on short intracortical inhibition (SICI), long intracortical inhibition (LICI) and intracortical facilitation (ICF) using different intensities of the test stimulus (TS) in patients suffering from migraine without aura (MwoA).
Methods: We enrolled 16 patients suffering with episodic MwoA and 16 healthy subjects. Both patients and controls were randomly assigned to two groups: the first group underwent assessment of SICI and LICI, whilst in the second group we evaluated ICF. In each subject we assessed SICI, LICI and ICF by using three different suprathreshold intensities of the TS (intensities eliciting motor evoked potentials of 0.2, 1 and 4 mV). Interstimulus intervals (ISI) of 2 ms and 100 ms were used for testing SICI and LICI respectively, whilst ICF was carried out by using 10 ms ISI.
Results: When testing ICF, maximum increase in conditioned MEP amplitude was observed in migraineurs at the lower stimulation intensity of the TS. This intensity was indeed unable to induce significant facilitation in the healthy subjects, where maximum facilitation was observed at the higher stimulation intensities. No significant differences were observed between patients and healthy subjects as regards SICI and LICI.
Conclusion: Our results strengthen the notion of altered tuning of cortical excitability in migraine. In particular, we provide evidence of hyperresponsivity of the glutamatergic intracortical circuits that could be revealed only by using a low stimulation intensity.
Disclosure: Nothing to disclose

EPR1049

Abnormal peripheral and central visual processing in migraine

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Background and aims: Sound induced flash illusion (SIFI) is an illusory cross modal (audio-visual) phenomenon critically dependent upon excitability of visual cortex. A recent study with SIFI confirmed hyperexcitability of visual cortex in migraine; patients with migraine show abnormality of chromatic perception. Here we explored the relationship between peripheral chromatic and central visual dysfunction in patients with migraine

Methods: 15 migraine patients with aura (MWA) and 15 without aura (MWoA) were studied interictally and compared with 12 healthy controls

all subjects underwent the following examinations:

1. SIFI with flashes and beeps in different combinations to generate illusions of 'fission' (one flash with 2 beeps perceived as 2 flashes) or 'fusion' (2 flashes with one beep perceived as 1 flash); 2. colorimetric test to explore dysfunction in color perception. 3. Multifocal electroretinogram (mfERG) to evaluate the functional contribution of retinal receptor.

Results: MWA and MWoA patients showed significantly reduced SIFI of fission than controls ($p<.01$). 8 MWA and 9 MWoA patients presented dysfunction of color perception. They showed significantly more reduced SIFI with than those with no abnormality in chromatic perception ($p<.05$). No significant changes emerged in mfERG when comparing patients vs control; MWA vs MWoA, patients with and without chromatic perception dysfunctions.

Conclusion: results confirmed hyperexcitability of visual cortex in MWA and MWoA. Moreover, greater excitability levels are found in patients with chromatic perception abnormalities suggesting a potential pathophysiological relationship between peripheral and central visual dysfunction. However, results of nornal mfERG response seem to exclude direct dysfunctional involvement of visual receptors, making likely abnormalities at different retinal levels of the neural pathway (bipolar cells?).

Disclosure: Nothing to disclose

Motor neurone diseases 1

EPR1050

Imaging denervation in amyotrophic lateral sclerosis for future clinical trials: 12-month follow-up from a longitudinal cohort study

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Background and aims: A key area-of-need in motor neuron disease/amyotrophic lateral sclerosis (MND/ALS) research is a tool to objectively track disease progression over short timescales, to reduce duration and cost of clinical trials, and facilitate translation of promising novel therapeutics from laboratory to clinic. Previous studies have focused on the central nervous system. The aim of this study was to assess the utility of whole-body MRI to depict muscle denervation changes over 12 months in patients with ALS, and compare radiology to clinical and neurophysiological measures.
Methods: A prospective longitudinal observational cohort study was performed. Twenty-nine ALS patients and 22 age and sex-matched healthy controls were assessed with clinical measures, electrophysiological motor unit number index (MUNIX) and T2-weighted whole-body muscle magnetic resonance imaging (MRI), at first presentation to our clinic, and at 4 months. Patients were reassessed at 12 months. Between-group differences, associations and longitudinal changes were assessed using multivariable linear regression models, adjusted for age and gender.
Results: ALS patients had higher relative T2 signal and lower MUNIX than controls at baseline. Higher relative T2 signal was associated with greater weakness and lower MUNIX. Relative T2 signal in bilateral tibialis anterior increased over 4 months in ALS patients. Further changes in relative T2 signal in leg muscles, clinical scores and neurophysiology were evident at 12 months.
Conclusion: Whole-body muscle MRI offers a new approach to the objective assessment of denervation in ALS and detects progressive changes. Muscles inaccessible to conventional clinical and neurophysiological assessment may be investigated.
Disclosure: This research was supported by charitable funding from grant awards from the British Medical Association (Vera Down Grant) and Neurocare/Ryder-Briggs Trust, and supported by the NIHR Sheffield Biomedical Research Centre for Translational Neuroscience. The funding bodies had no role in the conduct of the study.

EPR1051

Development of ALS therapy using AMPA receptor RNA aptamers

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Background and aims: Failure of RNA editing at the GluA2 Q/R site resulting from downregulation of RNA editing enzyme adenosine deaminase acting on RNA 2 (ADAR2) occurs in motor neurons of sporadic Amyotrophic lateral sclerosis (ALS) patients. Expression of Q/R site-unedited GluA2 triggers a slow death of motor neurons via Ca2+-permeable AMPA receptor-mediated mechanism in conditional ADAR2 knockout mice (AR2 mice), a mechanistic model of ALS. Therefore, amelioration of exaggerated Ca2+ influx by antagonists of AMPA receptors is a potential therapeutic strategy for ALS. Here we report our test of a class of RNA aptamers acting as AMPA receptor RNA inhibitors for their safety and efficacy in AR2 mice.
Methods: After confirming the in vivo stability and local CNS delivery, we have tested the efficacy and safety of the aptamer by continuous cerebroventricular infusion for 2 weeks in AR2 mice. As a short-term measure, changes in the behavior and TDP-43 subcellular localization were examined.
Results: An RNA aptamer FN1040 has effectively normalized the TDP-43 mislocalization in the ADAR2-lacking motor neurons without causing sedative or other adverse effects in the AR2 mice. Because exaggerated Ca2+ influx exacerbates TDP-43 mislocalization, the normalization of subcellular localization of TDP-43 indicates the amelioration of Ca2+ influx through the abnormally Ca2+-permeable AMPA receptors that contain Q/R site-unedited GluA2 in the ADAR2-lacking motor neurons in the AR2 mice.
Conclusion: The efficacy and the lack of sedative effects of an RNA aptamer targeting AMPA receptors indicate a high potential of developing AMPA receptor aptamers into an ALS drug.
Disclosure: Nothing to disclose

EPR1052

Sensory disturbance and sphincter dysfunction in a slowly progressive motor neuron disease caused by a novel SOD1 mutation

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Background and aims: Superoxide dismutase 1 (SOD1) has been the first gene discovered as causative of amyotrophic lateral sclerosis (ALS), accounting for 20-25% of familial cases. The presence of misfolded SOD1 protein suggests a gain of function pathogenic mechanism. Patients carrying SOD1 mutation usually present lower limb onset and predominant lower motor neurons (LMN) involvement; sensory disturbance and bladder dysfunction were reported.
Methods: We describe the case of a 57-year-old patient who developed a slowly progressive gait disorder, preceded by sphincter incontinence with thermal and pain hyposensitivity. Spinal cord magnetic resonance imaging, lumbar puncture and spinal angiography were performed to rule out a spinal cord pathology.
Results: Neurophysiological exams showed neurogenic alterations in lower limbs and pathological central motor conduction, consistent with ALS. Genetic screening for ALS identified a novel point mutation in SOD1 gene at codon 122 (c.365A>G, pE122Q). Mutation Taster and Poly-Phen 2 algorithms predicted the mutation to be likely causative. The patient's brother recently reported left hand weakness and muscle atrophy and was found to carry the same SOD1 variant, increasing the suspicion of a new pathogenic mutation. Induced pluripotent stem cells (iPSCs) were generated from patient peripheral blood and differentiated towards motor neurons; the phenotypic characterization is ongoing. Furthermore, we are planning to study a model of Drosophila melanogaster harboring E122Q mutation in SOD1.
Conclusion: Bladder dysfunction, sensory impairment, slow progression and prevalent LMN involvement were previously reported in association with ALS with SOD1 gene mutations. E122Q mutation seems to represent a new missense mutation of SOD1 gene in ALS patients.
Disclosure: Nothing to disclose

EPR1053

Contribution of rare homozygous variants in ALS in a homogenous population

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Background and aims: Amyotrophic lateral sclerosis (ALS) has multiple etiologies, among them genetic. Disease-causing genes were discovered for over 60% of familial and over 10% of apparently sporadic cases.
The present study aims to detect rare homozygous variants in ALS in a relatively homogenous population.
Methods: We performed whole-exome-sequencing (WES) of 43 patients of North Africa Jewish origin. Filtering identified very rare recessive damaging variants in the gnomAD browser, in genes previously associated with ALS. Two variants were genotyped in an additional cohort of 70 unrelated patients and 400 controls of the same ethnic background.
Results: We identified 32 rare homozygous variants in genes associated with autophagy, mitochondria, RNA-binding and cytoskeleton. These include genes previously reported as upregulated (LZTS3) or downregulated (ARMC4, CFAP54, and MTHFSD) in ALS patients, and genes previously associated with other neurodegenerative or neuromuscular diseases: HTT, ATM, ZFYVE26 and MFN2. The homozygous variants in MFN2 and NEK1 were further evaluated. Their allele frequencies were 11.2 and 1.9 times higher in patients than in controls (p=0.031 and NS), with no homozygotes in controls. Seven ALS patients (16.3%) were homozygotes for more than one variant.
Conclusion: WES homozygosity analysis in our unique homogenous population identified rare homozygous variants, suggesting involvement of new genes and contribution of recessive alleles in ALS. We report for the first time that the MFN2 p.Arg663Cys mutation is associated with ALS, and suggest that the stress granules genes, MTHFSD and EIF4G3, are involved in ALS. Our data also support oligogenic inheritance in ALS.
Disclosure: Nothing to disclose

EPR1054

The HFE H63D (p.His63Asp) polymorphism is a modifier of ALS outcome in Italian and French patients with SOD1 mutations

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Background and aims: In a previous study we found that the HFE H63D polymorphism did not influence ALS phenotype and survival, with the possible exception of SOD1-positive patients. Since the small number of SOD1 patients in that series, we evaluated whether such polymorphism is a modifier of phenotype and survival in a larger series of SOD1-mutated patients.

Methods: 185 Italian and French SOD1-positive patients were included. Mutations were classified as severe or mild according to the median survival of the sample (7.1 years). The adherence to the Hardy-Weinberg equilibrium was tested for the HFE alleles. We used the Student's t-test or ANOVA for comparisons between means, the $\chi 2$ test for the comparison between categorical variables, the Levene's test to confirm the equality of variances. Survival was calculated using the Kaplan-Meier modeling (differences were measured by the log-rank test). Multivariable analysis was performed with the Cox proportional hazards model (stepwise backward).

Results: The following allelic frequencies were found: CC 127 cases (68.6%), GC 53 cases (28.6%), and GG 5 cases (2.7%). They respected the Hardy-Weinberg equilibrium. The H63D polymorphism did not influenced age and site of onset. In univariate analysis, patients carrying the H63D polymorphism had a longer median tracheostomy-free survival (p=0.031). The presence of the H63D polymorphism remained significant in Cox multivariable analysis using as covariates age at onset, site of onset, positive family history, nation, and severity of mutations (hazard ratio, 0.52, 95% CI 0.32-0.85, p=0.01).

Conclusion: In SOD1 patients the HFE H63D polymorphism resulted significantly associated with a longer survival.

Disclosure: Nothing to disclose

EPR1055

Multiparametric unconventional MRI study in early stage of ALS disease

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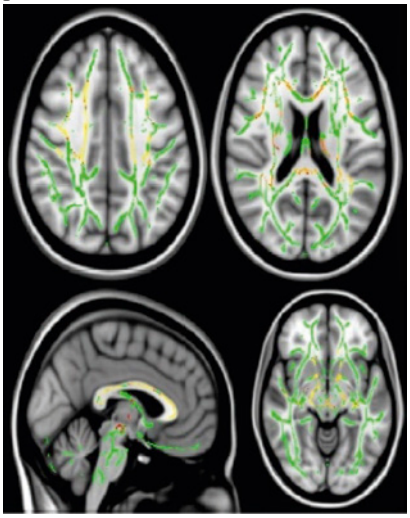
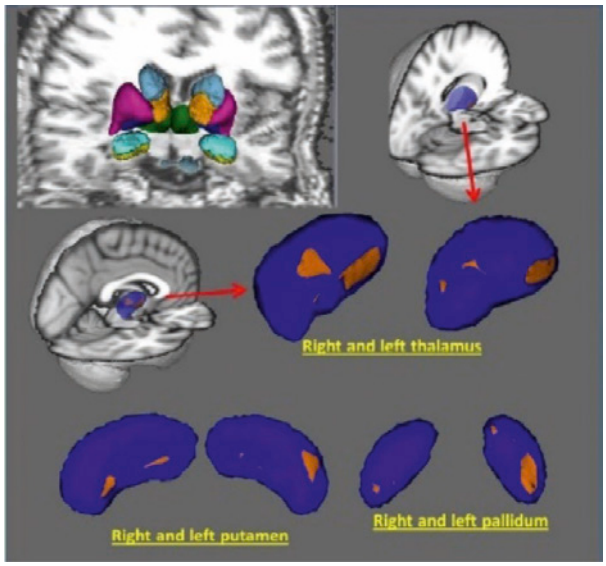
Background and aims: Great efforts are made to define a typical structural pattern in Amyotrophic Lateral Sclerosis (ALS) by unconventional magnetic resonance imaging (MRI). Although there are various studies, no univocal pattern has been identified. The aim of this study was to evaluate the microstructural changes in a cohort of patients at the time of the diagnosis.

Methods: We enrolled 38 incidental ALS patients who underwent brain MRI at the time of the diagnosis (duration from onset: 13.31±10.08 months) and 19 healthy controls (HC) matched for sex and age. We evaluated Cortical thickness (CTh) in motor and extra motor areas using Freesurfer, Fractional Anisotropy (FA) of the cortico-spinal tracts using FSL, probabilistic tractography of whole brain using TBSS, volumes and shape of subcortical gray matter (SGM) using FIRST.

Results: CTh analysis shows reduction in both precentral gyri (dx p=0.025; sx p=0.026). FA of the cortico-spinal tracts was significantly increased than HC (dx p=0.007, sx p=0.020). Tractography identified white matter changes also in fornix and mid-body corpus callosum. No differences were found in SGM volumes, although shape analysis demonstrated alterations in both thalami, globi pallidi and putamina.



Probabilistic Tractography in ALS patients compared to Healty controls. Yellow, orange and red show white matter (FA) alterations (p<0.005)



Three-dimensional vertexwise patterns of changes in basal ganglia. Orange colour indicates morphological modification beetween ALS patients and healty controls.

Conclusion: An involvement of the motor system has been confirmed in the early phases of ALS. As suggested by recent studies, we postulate that the dorsal and mid-body of the corpus callosum have a central role in the spread of the disease. SGM are affected by microstructural damage in the early stages.

Disclosure: Nothing to disclose

EPR1056

The relationship between motor phenotypes and cognitive impairment in ALS: a population-based study

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Background and aims: Amyotrophic Lateral Sclerosis (ALS) may present with different motor phenotypes. It is associated with cognitive impairment in half of cases, ranging from frank Frontotemporal Dementia (FTD) to mild deficits. We aimed at evaluating if motor phenotypes differ according to the frequency and severity of cognitive deficits.

Methods: 1,173 incident ALS cases from the Piemonte and Valle d'Aosta Register for ALS were eligible from 2009 to 2016. 63% of patients (N=751) underwent neuropsychological assessment and were enrolled. According to Strong et al (2009), patients were classified as ALS-FTD (19.5%), ALS with cognitive impairment (23.7%), ALS with behavioural impairment (4.5%), ALS with normal cognition (52.3%). Motor phenotype was classified as lower motor neuron prevalent (22.2%), upper motor neuron prevalent (14.7%), classic (33.4%), bulbar (29.7%). The association between cognitive impairment and motor phenotype was assessed by using stepwise backward logistic regression analysis, adjusted for sex, age at onset, education, hypertension, diabetes mellitus, marital status, and C9orf72 expansion.

Results: 54.6% of patients were male, with an average age at diagnosis of 67.0 (SD 10.3). Sixty-one patients carried the C9orf72 expansion (8.8%). Significant associations were detected only for bulbar patients, for whom the likelihood of developing any grade of cognitive impairment was 88% higher than that of non-bulbar patients (OR=1.88; 95% CI=1.30-2.70), while the risk of developing FTD was two-fold than that of non-bulbar patients (OR=2.17; 95% CI=1.40-3.37).

Conclusion: Bulbar patients showed a higher risk of developing cognitive impairment, especially FTD, compared to non-bulbar patients, that seemed relatively less vulnerable to cognitive decline.

Disclosure: Nothing to disclose

Movement disorders 1

EPR1058

Parkinsonism in higher level gait disorders: the role of amyloidopathy

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Background and aims: Parkinsonism is frequently described in older adults with higher level gait disorders (HLGD). However, the neuropathological substrate of parkinsonism and the clinical impact of this parkinsonism have been never studied in these patients. This cross-sectional study aims to compare the CSF total tau, Aβ1-42, and phosphorylated tau levels in older adults with HLGD with and without parkinsonism and to study the clinical impact of parkinsonism on gait parameters and cognitive performances.
Methods: CSF biomarkers (i.e., total tau, Aβ1-42, and phosphorylated tau) were measured by ELISA in 49 non-Parkinson's disease patients with HLGD (77.7±6.6 years; 32.7% women). Gait parameters were quantified with an optoelectronic system and cognitive performances with a comprehensive neuropsychological assessment. Parkinsonism was defined by presence of bradykinesia and at least one of the following signs among muscular rigidity, rest tremor or postural instability.
Results: Fourteen HLGD patients (28.6%) presented a parkinsonism. CSF Aβ1-42 level was decreased in HLGD patients with parkinsonism (β:-189.4; 95%CI [-352.3;-26.6]; p=0.024) even after adjusting for age, gender, comorbidities and total white matter burden; while CSF total tau and phosphorylated tau levels were similar between HLGD patients with and without parkinsonism. HLGD patients with parkinsonism presented decreased cognitive performances in attentional and executive domains but similar gait parameters than those without parkinsonism.
Conclusion: Parkinsonism in HLGD patients represents a clinical marker of amyloidopathy. This phenotype is clinically associated with impaired cognition, but similar quantitative gait parameters in comparison to HLGD patients without parkinsonism.
Disclosure: This study was funded by the Geneva University Hospitals (PRD 11-I-3 and PRD 12-2013-I) and the Swiss National Science Foundation (320030_173153).

EPR1059

Variability of vestibular evoked myogenic potentials parameters in different periods of motor fluctuations in Parkinson's disease

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Background and aims: Research of vestibular evoked myogenic potentials (VEMP) can assess the condition of the sacculocervical reflex and objectify the abnormalities in vestibulospinal paths, the disturbances of which contribute greatly to the development of postural instability in PD. Change in severity of postural disorders can be observed in PD patients with motor fluctuation.
Aim: To investigate the VEMP parameters in correlation with the severity of postural instability and to estimate their variability within «on-off»-periods.
Methods: 47 PD patients with motor fluctuation and 30 healthy individuals aged 38 to 65 years were investigated. We evaluated the latent period (LP) P1 (p13) and N1 (n23) of VEMP (module EP25; company Interacoustics (Denmark)). The severity of postural instability was evaluated from 0 point (normal) to 4 (patient cannot stand without help).
Results: We discovered a significant increase in the LP P1 and N1 components in a group of patients with PD in comparison with the control group, it indicated a slowdown of the vestibular-spinal conducting. The correlation analysis revealed a strong correlation between the severity of postural disorders and LP P1, N1 components (RSpearman =0.70; p =0.0005). Statistically significant increase in the LP P1 and N1 components were observed within the «off»-period in comparison with «on»-period (p=0.01) However, variability VEMP parameters within «on-off»-periods was noted only in 20 patients.
Conclusion: Our data show that the study can evaluate the pathophysiological processes underlying postural disorders. Account the variability VEMP parameters with their normalization within «on»-period can help in deciding the feasibility of neurosurgical treatment.
Disclosure: Nothing to disclose

EPR1060

Exposure to environmental factors and clinical presentation of Parkinson's Disease patients in Greece: data analysis of the Hellenic Biobank of Parkinson's Disease

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Background and aims: PD is a multi-factorial disorder with unknown etiology. Epidemiological data about PD in Greece are scant. The aims of this study are to investigate the association between environmental exposure and PD development and to describe clinical features of PD patients in Greece.
Methods: Our data derived from the Hellenic Biobank of Parkinson's Disease, consisting of blood samples, medical and lifestyle information about PD patients and controls during 2006-2017. Cases with A53T mutation in SNCA or mutations in GBA1 gene were excluded. OR and 95% CI were calculated for each factor.
Results: 575 PD patients and 340 controls were included. The mean onset age of PD was 62.87 (±12.311), onset age of dopaminergic treatment 63.71 (±11.990), disease duration 6.13 (±6.125) and dopaminergic treatment duration 5.30 (±5.920) years. The first symptom was tremor (54.4%), bradykinesia (25.6%), gait disturbances (7%), rigidity (4.9%), dystonia (1.7%) and postural impairment (0.9%). The side of onset was right (41.4%), left (32.9%) and bilateral (18.3%). Coffee consumption and pesticide exposure were not associated with PD development. Cigarette smoking was associated with lower risk of PD development in men (OR=0.526, 95% CI=0.324-0.853) and women (OR=0.462, 95% CI=0.296-0.724). Cigarette smoking was associated with lower risk of "normal"-onset PD (>50 years) (OR=0.693, 95% CI=0.512-0.939), but not with early-onset PD (≤50 years).
Conclusion: Cigarette smoking is associated with lower risk of "normal", but not early-onset PD in this Greek population, confirming most studies, but also suggesting that this environmental factor may affect PD development only in specific subgroups.
Disclosure: Nothing to disclose

EPR1061

Differences between familial and sporadic Parkinson's Disease in Greece: data analysis of the Hellenic Biobank of Parkinson's Disease

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Background and aims: The aim of this study is to compare sporadic and familial PD regarding their associations with clinical characteristics and environmental exposures.
Methods: Our data derived from the Hellenic Biobank of Parkinson's Disease, consisting of blood samples, clinical and lifestyle information of PD cases and controls during 2006-2017. Cases with A53T mutation in SNCA or mutations in GBA1 gene were excluded. OR and 95% CI were calculated for each factor.
Results: 160 patients with familial and 407 patients with sporadic PD were included. Early-onset of PD (≤50 years) was associated with family history of PD (OR=1.613 95% CI=1.019-2.555). Coffee consumption was associated with lower risk of PD only in the case of familial PD (OR=0.535, 95% CI=0.303-0.944). Psychotic manifestations and dyskinesias were more common in familial PD (OR=1.685, 95% CI=1.002-2.834 and OR=3.312, 95% CI=1.193-9.199 respectively). Gender, cigarette smoking, pesticide exposure, tremor, bradykinesia, rigidity, gait disturbances, autonomic dysfunction, dystonia, dementia, depression and motor fluctuations were not found to be associated with family history of PD.
Conclusion: Familial PD in this Greek cohort was associated with early-onset of PD, psychotic manifestations and dyskinesias. Coffee consumption was associated with lower risk of PD development only in the case of family history of PD, indicating that the interaction between coffee and specific genetic factors may be needed for the protective influence of coffee consumption on PD development.
Disclosure: Nothing to disclose

EPR1062

Validation of Ambroxol and UDCA treatments in cellular models of autosomal dominant Parkinson's disease

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Background and aims: The genetic findings in Parkinson's disease (PD) shed a light on the pathogenesis and possible therapeutic targets for the disease. In this view, we investigated the function of mitochondrial respiratory chain complexes and the glucocerebrosidase (GCase) activity in LRRK2 (Leucine-Rich Repeat Kinase 2) and GBA (Acid Beta-Glucocerebrosidase) mutated fibroblasts from PD patients. Thereafter, we assessed the efficacy of drugs to rescue the enzymatic activities.
Methods: We used a spectrophotometric assay to measure the activity of mitochondrial respiratory chain complexes in control fibroblasts and in LRRK2 or GBA mutated cells; we compared the results before and after treatment with UDCA (Ursodeoxycholic Acid). GCase activity was assessed before and after the treatment with Ambroxol. p62, LC3 and LAMP1 protein levels were assessed by Western Blot at baseline and after Ambroxol treatment.
Results: Complex III activity was slight reduced in LRRK2-mutated fibroblasts. UDCA did not induce a significant improvement in the mitochondrial function. The GCase activity was reduced in GBA mutated cells and in most lines with LRRK2 mutations. Ambroxol was effective in improving the levels of enzyme activity and determined an increase of all markers of autophagy (p62, LC3, LAMP1), whose pre-treatment levels were pathologically low.
Conclusion: Mitochondrial and GCase function play a relevant role in PD. Therefore, the search for drugs capable of acting on these targets is of primary importance. The in vitro administration of Ambroxol produced promising results and opens the possibility of its use in other cellular models and in clinical trials on GBA-PD and idiopathic-PD.
Disclosure: Nothing to disclose

EPR1063

Progression of Parkinson's disease: 2-year longitudinal study of clinical and MRI changes in patients at different stages of the disease

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Background and aims: To investigate motor and cognitive/behavioural changes, cortical thickness and white matter (WM) alterations over time in patients at different stages of Parkinson's disease (PD).
Methods: 83 early (Hoehn and Yahr [HY] 1-1.5) and 60 mild-to-severe (HY 2-4) PD patients underwent clinical motor and neuropsychological evaluations and MRI at study entry and every year for 2 years. 66 healthy subjects performed baseline assessments. Cortical thickness measures and diffusion tensor (DT) MRI metrics of WM tracts were evaluated.
Results: At baseline, motor disability was greater in mild-to-severe PD relative to early cases, while cognitive/behavioural functions were similar. Over 2 years, both groups showed a deterioration of motor skills, significantly in early PD, and a decline in depression, anxiety and apathy; mild-to-severe PD experienced greater cognitive decline. At baseline, mild-to-severe PD patients showed a more severe and widespread cortical thinning relative to controls and early PD patients; on the contrary, early PD patients showed a significant cortical thinning over time relative to mild-to-severe PD. DT MRI at baseline showed focal WM abnormalities in early PD patients relative to controls; mild-to-severe PD cases showed a more widespread damage than early PD involving also extramotor WM pathways. WM damage progressed over time in both groups of patients in both motor and extramotor circuits.
Conclusion: MRI may be a useful tool to monitor the progression of PD. Cortical thickness investigation is promising to evaluate the early phase of the disease, while the analysis of microstructural WM involvement may represent a potential biomarker for monitoring also advanced PD stages.
Disclosure: Supported by: Ministry of Education and Science Republic of Serbia (Grant #175090).

EPR1064

Subthalamic nucleus high frequency and Levodopa treatment effects on effort-based decision-making in Parkinson's disease

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Background and aims: Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder entailing several behavioural dysfunctions. It is now well admitted that Levodopa and, in more advanced PD, high frequency subthalamic deep brain stimulation (STN-DBS), influence motivated behaviours. The aim of the present work was to determine the influence of STN-DBS, Levodopa and the association of both treatments on effort- and reward-based decision-making.
Methods: We recruited 13 PD patients and 13 matched healthy controls (HC). Our experimental task involved taking a decision based on variable rewards (3 levels) and effort (12 levels). If the participants judged that the reward was worth realising the effort, they had to squeeze a dynamometer with the necessary force. All PD patients completed the task in 4 conditions: without treatment, with Levodopa or STN-DBS alone, with both Levodopa and STN-DBS. Using mixed model, we analysed the acceptance rate, decision time and applied force on the dynamometer.
Results: Our results showed a decrease of acceptance rate and applied force for PD patients without treatment in comparison to HC. Taken alone, Levodopa induced no changes in comparison to the condition without treatment. In contrast, STN-DBS, either with and without Levodopa, improved all measures, leading to an undistinguishable profile from HC.
Conclusion: From our results, we can conclude that Levodopa remains insufficient for cost-benefit computation. In contrast, STN-DBS modifies decision-making processes by normalizing all our measures. We can hypothesise that STN-DBS, but not Dopamine, helps to restore the integration of information from cortical territories.
Disclosure: This study was sponsored by Assistance Publique – Hôpitaux de Marseille, and funded by the Agence Nationale de la Recherche (France, ANR-09-MNPS-028-01).

EPR1065

The effect of exenatide on specific non-motor symptoms in Parkinson's disease – a post-hoc analysis

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Background and aims: Exenatide is a GLP-1 receptor agonist that was recently studied for potential disease-modifying effects in an RCT in patients with Parkinson's disease, showing positive effects on motor severity which were sustained 12 weeks beyond the period of exenatide exposure.
Methods: This post-hoc analysis was conducted to explore the possible effects of exenatide compared to placebo on individual non-motor symptoms. Patients were assessed using the non-motor symptoms-scale (NMS), MDS-UPDRS Part 1, Montgomery–Asberg depression rating scale (MADRS), Mattis Dementia rating scale and the Parkinson's disease questionnaire (PDQ-39).
Results: Compared to placebo, patients treated with exenatide had greater numerical improvements in individual domains assessing mood/depression across all observer-rated outcome measures after 48 weeks including the "mood/apathy" domain of the NMSS, -3.3points (9% CI -6.2, -0.4), p=0.026; the "mood" score (Q1.3+Q1.4 of the MDS-UPDRS Part 1), -0.3points (95%CI -0.6, -0.1), p=0.034; and MADRS total score, -1.7points (95%CI -3.6, 0.2), p=0.071, in addition to improvement in the "emotional well-being" domain of the PDQ-39 of 5.7 points ((95%CI -11.3, -0.1), p=0.047).
Conclusion: There were consistent changes in mood that were of a magnitude that would be subjectively meaningful to patients and were not associated with changes in motor severity or other factors, suggesting exenatide may exert independent effects on mood dysfunction. These exploratory findings will contribute to the design of future trials that will confirm the extent of motor and non-motor symptom effects of exenatide in a larger cohort of patients.
Disclosure: The research was funded in part by the Michael J. Fox Foundation for Research and the Cure Parkinson's Trust

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EPR1066

Dyspnea: an underestimated non-motor symptom in Parkinson's disease?

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Background and aims: Among the non-motor symptoms (NMS) associated with Parkinson's disease (PD), dyspnea remains one of the less explored. The aim of our study was to determine the prevalence of dyspnea in a monocentric cohort of 153 non-demented PD patients (mean age: 63.9±7.4 years old; mean disease duration: 9.2±6.1 years), with no history of lung or heart diseases. Then, the clinical features of the dyspneic and non-dyspneic PD patients were assessed.
Methods: The following questions were asked to all the participants: "In the last month, did you suffer from breathlessness?" and "Did you experience difficulty to breath normally?" If the answer was positive for at least one among the two questions, dyspnea was confirmed. Patients with an abnormal cardiovascular and pulmonary clinical examination were excluded.
Results: In our cohort, the prevalence of dyspnea was 39.2% (31.5-47). Adjusted for disease duration, PD patients with dyspnea had a significant higher MDS-UPDRS I ($p<0.001$), II ($p<0.001$), III ($p<0.001$) and IV ($p<0.001$) scores, a significant lower MoCA ($p<0.001$) and a higher PDQ8 ($p<0.001$). Other NMS had a strong associations with dyspnea: cognitive impairment (OR, 7.5; 95% CI [3.9-14.6]), fatigue (OR 6.16; 95% CI [3.30;11.51]) and constipation problems (OR, 4.2; 95% CI [2.4-7.3]).
Conclusion: Dyspnea seems to be a frequent NMS in PD with an impact on autonomy and quality of life. It could also be an early axial manifestation of the disease. Further studies are needed to assess the potential correlation with objective alteration in lung volumes, respiratory muscles strength or response to hypoxia.
Disclosure: Nothing to disclose

EPR1067

Autosomal recessive Hereditary Spastic Paraparesis due to SPG 7 mutation – a case series

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Background and aims: Autosomal recessive hereditary spastic paraparesis is rare. SPG7 mutation accounts for 1.5-7% of all the HSP but it is the cause of undiagnosed ataxia in 18.6% in a recent case series. We present a case series of slowly progressive ataxia due to SPG 7 mutation.
Methods: We collected the details of 4 confirmed cases of HSP due to SPG7 mutations. We analysed their clinical presentation, family history, outcome of the radiological and genetic investigations.
Results: All patients had gradual onset slowly progressive spastic ataxia but family history of undiagnosed ataxia was present in one. External ophthalmoplegia, optic atrophy and peripheral neuropathy were also common. One had peripheral neuropathy.
80% of the patients showed some degree of cerebellar atrophy in Magnetic resonance imaging.
One had homozygous mutation in exon 11 of the SPG7 gene (c1529C>T pAla510Val). One of the heterozygous mutatnts showed a novel c1617delC ,p(Val540fs) frameshift mutation in exon 12 of the SPG 7 gene. . Since this mutation led to frameshift it is likely to be pathogenic though we could not study the full family to ascertain pathogenicity beyond doubt. One had compound heterozygous mutation (exon 12,14) of c1529C>T pAla510Val and c1672A>T p(Lys558). The last person had heterozygous c1529c>T,p(Ala510Val) mutation in exon 11 and the c1672A>T ,p(Lys 558) mutation in exon 13 of the SPG 7 gene
Conclusion: SPG7 mutation should be remembered as an important cause of undiagnosed ataxia especially where next generation sequencing is not widely avaialbale or affordable.
Disclosure: Nothing to disclose

EPR1068

Neurostructural alterations associated with Rapid Eye Movement Sleep Behavior Disorder in Parkinson's disease

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Background and aims: Rapid Eye Movement (REM) Sleep Behavior disorder (RBD) is a parasomnia observed in up to 60% of Parkinson's disease (PD) patients and associated with a more severe phenotype of this disease. The pathophysiology is partially elucidated. It is known that brainstem play a central role, but more and more evidence appear for a limbic involvement.
The aim of current study was to evaluate the volumetry of subcortical structures in PD patients and to compare results between PD patients with and without RBD.
Methods: Sixty-six participants were included: 22 PD withRBD (PD-RBD), 22 PD without RBD (PD-noRBD), 22 healthy control. RBD was diagnosed by videopolysomnographic recording according to the ICSD-3 criteria. Subjects with impulse control disorders, depression or apathy were excluded. Normalized brain structure volumes were measured on T1-weighted-MRI with volBrain software. The subcortical structures considered were the brainstem, the caudate, the putamen, the thalamus, the globus pallidus, the amygdala, the nucleus accumbens and the hippocampus.
Results: PD patients with RBD showed smaller volume than PD without RBD in the left nucleus accumbens (0.209 mm3 versus 0.233 mm3, p=0.036) and a tendency to be smaller in the left globus pallidus in PD patients with RBD compared to healthy control (0.823 mm3 versus 0.766 mm3, p=0.05).
Conclusion: There is a specific atrophy of the left nucleus accumbens in PD-RBD compared to PD-noRBD. This observation underlines the hypothesis of a more severe PD-RBD phenotype and supports the hypothesis of potential mesocorticolimbic involvement in the pathophysiology of RBD.
Disclosure: Neurodis Fondation

EPR1069

Perinatal insults and neurodevelopmental disorders may impact age of diagnosis of Huntington's disease

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Background and aims: The objectives of this study were to determine whether early-life factors, like perinatal insults or neurodevelopmental disorders, are associated with the age of diagnosis of Huntington's disease (HD).
Methods: We used data from 13,863 participants from REGISTRY and Enroll-HD, two large international multi-center observational studies. Disease-free survival analyses of mutation carriers with an HTT CAG repeat expansion size above 36 were computed through Kaplan-Meier estimates of median survival time until a diagnosis of HD. Between groups, comparisons were computed using a Cox proportional hazard survival model adjusted for the CAG-repeat expansion length. All tests were two-sided with a significance level of 0.05.
Results: Our results showed that insults in the perinatal period were associated with an earlier median age of diagnosis of 45.00 years (95%CI: 42.07-47.92) compared to 51.00 years (95%CI: 50.68-51.31) in the reference group, with a CAG-adjusted hazard ratio of 1.61 (95%CI: 1.26-2.06). Neurodevelopmental disorders were also associated with an earlier median age of diagnosis of 47.00 years (95%CI: 43.63-50.36) with a CAG-adjusted hazard ratio of 1.41 (95%CI: 1.15-1.73).
Conclusion: These results, derived from large observational datasets and using robust survival analysis methods, show that perinatal insults and neurodevelopmental disorders are associated with earlier ages of diagnosis of magnitudes similar to the effects of known genetic modifiers of HD. Given their clear temporal separation, these early events may be causative of earlier HD onset. Even with a survival analysis, this association does prove causation. Further research is needed on the basis of this interaction.
Disclosure: Nothing to disclose

EPR1070

Stay in motion with Parkinson's Disease – a 12-week rehabilitation program for People with Parkinson's Disease

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Background and aims: Many clinical studies have proven the benefits of physiotherapy on both motor and non-motor symptoms of Parkinson's patients. Different rehabilitation programs are being used, ranging from conventional physiotherapy with or without dual tasking, over training in a virtual reality setting to even dancing, tai chi and boxing.
Methods: We - a team of two physiotherapists, two occupational therapists, a rehabilitation specialist and a neurologist - started a 12-week, twice weekly training program designed for PD patients. During these 12 weeks, four sessions of occupational therapy and four educational moments were organized. Before and after the training course we evaluated motor (MDS-UPDRS-III, mini BESTest, 6 minute walk test, 10 meter walk test) and non-motor (PDQ-39, NMSS and BDI) symptoms.
Results: In this pilot study we included 9 patients with idiopathic Parkinson's disease of whom six were male. The median age was 67 years and a median disease duration was 4 years. A Hoehn and Yahr scale of 1 was the median for this group with a levodopa equivalent daily dose was 450 mg. We observed a positive trend in both motor and non-motor symptoms but due to the small sample size the differences did not reach statistical significance.
Conclusion: Many different rehabilitation techniques are being used to treat Parkinson's Disease. We present a pilot study with a multidisciplinary approach, which shows positive trend for both motor and non-motor symptoms. More studies with a larger sample size should be done to establish which rehabilitation regime is most desirable.
Disclosure: Nothing to disclose

EPR1071

Breakdown of Affective-Cognitive Network in Functional Dystonia

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Background and aims: To explore the role of affective-cognitive network (ACN) in two clinical phenotypes of functional dystonia (FD): fixed (FixFD) and mobile dystonia (MobFD).
Methods: Resting state (RS) fMRI was obtained from 40 FD patients (12 FixFD; 28 MobFD) and 43 healthy controls (14 young FixFD-age-matched [yHC] and 29 old MobFD-age-matched [oHC]). Functional connectivity (FC) was assessed using a seed-based approach with ventromedial prefrontal cortex (vmPFC), right temporoparietal junction (rTPJ), dorsal anterior cingulate cortex (dACC), bilateral medial dorsal nucleus (MDN) of thalamus and cognitive part of cerebellum (Cog-cerebellum) as seeds.
Results: Compared to HC, both FD groups showed enhanced FC between the right Cog-Cerebellum and the bilateral associative parietal cortex, with greater enhancement in FixFD compared with MobFD. Compared to oHC, MobFD showed reduced FC between vmPFC, left MDN and the bilateral anterior PFC; and enhanced FC between bilateral MDN and the bilateral associative parietal and visual cortices. Compared to yHC, FixFD showed reduced FC between vmPFC, right MDN, rTPJ, dACC and bilateral PFC and premotor cortex; and between dACC and right primary motor cortex and insula. Compared to MobFD, FixFD patients showed enhanced FC between dACC and primary and premotor cortices.
Conclusion: The two FD phenotypes showed similar ACN altered connectivity in PFC reflecting patient difficulties in cognitive control and motor inhibition. Sensorimotor connectivity was more disrupted in the FixFD group, with unique involvement of dACC and rTPJ, crucial for emotion regulation, awareness and sense of agency. These findings suggest that brain functional architecture could modulate the phenotypic expression of FD.
Disclosure: Study supported by the Ministry of Education and Science Republic of Serbia (Grant #175090).

EPR1072

The Faroese PD cohort: Clinical and epidemiological data from the longitudinal study

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Background and aims: The Faroe Islands, a geographic population isolate in the North Atlantic with ~50,000 inhabitants, is well suited for complex trait mapping given its isolation and reduced heterogeneity (genetic and environmental), excellent genealogic records dating back >400 years and large pedigrees. An elevated risk of PD and high exposure to environmental risk factors has previously been established. Data from three previous cross-sectional studies (1995, 2005 and 2011) have highlighted clusters of multi-incident pedigrees. Complex segregation analysis of PD on the islands, based on clinical diagnoses and genealogic data, is suggestive of a strong genetic contribution. However, so far known pathogenic mutations and rare coding variability in loci linked to PD have largely been excluded. The aim of the longitudinal study, commenced in 2015, is to 1) prospectively describe clinical phenotypes and quantify trait components associated with prodromal and manifest disease; 2) to assess the contribution of known (and perhaps novel) genes and environmental factors influencing susceptibility and/or progression of PD or trait components.
Methods: Recruitment to cohort via national hospital registries ongoing. Standardized neurologic evaluation (UK Brain Bank Criteria), UPDRS, Hoehn& Yahr staging, assessment of non-motor features, including standardized testing for autonomic failure, depression, hyposmia, and sleep disturbance.
Comparative exome analyses are currently ongoing.
Results: As of January 2018, the Faroese PD cohort for the longitudinal study consists of approx. 300 PD patients, 253 controls, and 156 unaffected relatives. The first clinical and epidemiological data from the study will be presented.
Conclusion: Conclusion will be presented at the congress.
Disclosure: The study is supported by grants from the Faroese Research Foundation and the Danish Parkinsons Disease Foundation.

EPR1073

Evaluation of non-motor fluctuations in Parkinson's disease by a visual analogue scale in Surgical Candidates

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Background and aims: In Parkinson disease (PD) despite the high impact of non-motor symptoms, evaluation of non-motor fluctuations (NMF) is not part of the presurgical evaluation for deep brain stimulation (DBS). Our aim was to evaluate the severity of non-motor symptoms in OFF and ON state compared to motor scores obtained in the same conditions.
Methods: Data from PD surgical candidates were collected in three centers. NMF were assessed using a visual analogue scale. The scale was made up of the 11 most frequent fluctuations that we have detected in previous studies (Witjas et al, 2002), each item being rated from 0 to 10. The scale was obtained in OFF and ON state during the presurgical evaluation as the UPDRS III, the QUIP and the PDQ 39.
Results: 77 patients (58 men; 19 women) were included. The mean score of the NMF in OFF state was 36.8 and improved by 49% after levodopa intake (19). The UPDRS III improved by 68% (from 31 to 10). No correlation was found between the non-motor and the motor scores in OFF state neither between the OFF non-motor score and the PDQ 39 or the QUIP. The degree of dopa sensitivity of the motor and the non-motor scores were not correlated.
Conclusion: NMF were present in all the patients in OFF state and improved dramatically after levodopa intake but less than the motor score. The study will be continued on a larger population of patients, and we will evaluate the effect of STN-DBS on the NMS.
Disclosure: Nothing to disclose

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EPR1074

DYT5a – phenotypic variability and anticipation in a Portuguese family

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Background and aims: Dopamine responsive dystonia (DYT5) is characterized by childhood onset dystonia and a sustained response to low doses of levodopa. The DYT5a variant results from a mutation in the GCH1 gene, with autosomal dominant transmission and greater penetrance in females. It is typically manifested by foot dystonia with diurnal fluctuation and later development of parkinsonism. We aim to characterise a three generations family with diagnosis of DYT5a.
Methods: Clinical analysis of 20 individuals from a Portuguese family with DYT5a.
Results: We present a family of three generations (n=20) where thirteen individuals present deletion in GCH1 gene, with greater penetrance in females (83.3% vs 28.6%). Seven are symptomatic. The matriarch (90 years old) started with classic parkinsonian syndrome in her 50's. Two women (B1,B2) in the second generation manifested disease also in 50's: painful feet and hand dystonia (B1), restless legs syndrome, parkinsonian signs and foot dystonia (B2). The men of second generation are asymptomatic carriers. Four elements in the third generation are symptomatic: a 19-year-old girl with severe foot dystonia and pyramidal signs since the age of 8; a 13-year-old girl with painful episodes of foot and hallux dystonia since the age of 4; a 40-year-old man with mild foot dystonia started at age 39; a 25-year-old man with paroxysmal hand dystonia started at age 24. All showed improvement with levodopa even after decades of treatment.
Conclusion: In this family with DYT5a is evident a variable phenotype among three-generations, a predominance of female involvement and a phenomenon of anticipation. To our knowledge this is the biggest family reported.
Disclosure: Nothing to disclose

EPR1075

WTX101 – A novel copper-protein-binding agent for Wilson Disease demonstrates long-term neurological improvement in an ongoing extension of a Phase-2 study (WTX101-201)

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Background and aims: WTX101 (bis-choline tetrathiomolybdate) is a first-in-class copper-protein-binding agent that reduces plasma non-ceruloplasmin bound copper (NCC) by forming tripartite complexes with albumin and increases biliary copper excretion. Here, we present preliminary 72-week data from the ongoing extension of a Phase-2 study in patients with Wilson Disease (WD).
Methods: All 22 patients who completed the 24-week open-label, single-arm study opted to continue once-daily WTX101 treatment in the extension. Assessments up to 72 weeks included disability and neurological status using the Unified Wilson Disease Rating Scale (UWDRS), copper control, hepatic status and safety.
Results: At study entry, 86% of patients had various degrees of WD-related neurological symptoms. From baseline to week 72, mean (SD) UWDRS disability score improved from 6.6 (10.0) to 1.2 (2.1) and neurological score from 22.8 (21.0) to 9.9 (10.7). UWDRS neurological score improved by ≥4 points in 12 patients, stabilised (±3 points) in 5 patients and worsened by ≥4 points in 2 patients . Mean (SD) NCC level corrected for copper in tripartite complexes was 3.6 (2.1) μM at baseline and decreased to 0.5 (0.7) μM at week 72. Liver function tests and Model for End-Stage Liver Disease (MELD) score improved or remained unchanged at week 72. Two discontinuations were considered unrelated to WTX101 treatment.
Conclusion: Once-daily WTX101 treatment improved neurological status and disability, and controlled free copper in patients with WD over 72 weeks. WTX101 was generally well tolerated and, together with its simplified dosing, WTX101 has the potential to address unmet needs in WD.
Disclosure: This study was funded by Wilson Therapeutics AB

EPR1076

Rationale and design of an open-label, randomised, 26-week study comparing levodopa-carbidopa intestinal gel to optimized medical treatment on non-motor symptoms in patients with advanced Parkinson's disease – INSIGHTS study

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Background and aims: To examine levodopa-carbidopa intestinal gel, LCIG (also known as carbidopa-levodopa enteral suspension in the US), on non-motor symptoms (NMS) compared with individually-optimised, conventional PD therapies, ie optimised medical treatment (OMT) in advanced Parkinson's disease (APD).

With conventional therapies, many APD patients experience inadequate motor control and complications. Despite decreased "off" time and increased "on" time without troublesome dyskinesia and reports of NMS improvement, no studies compare the effect of LCIG vs OMT on NMS, including sleep [ref1,2].

Methods: INSIGHTS is a phase-3b, randomised, open-label, multicenter, 26-week study comparing the effect of LCIG vs OMT on NMS in APD (NCT02549092). The study population includes levodopa-responsive APD patients with motor fluctuations no longer controlled by oral PD medications and who experience sleep disturbances as confirmed by a score >18 on the modified Parkinson's Disease Sleep Scale (PDSS-2). Approximately 88 patients will be enrolled and randomised in a 1:1 ratio to either LCIG or OMT. Primary endpoints include changes from baseline in the Non-Motor Symptoms Scale (NMSS) and the PDSS-2 total scores. Key secondary endpoints measure activities of daily living, quality of life, and safety assessments.

Results: At the current cut-off date, 37 patients have been randomised in the study. Nearly all patients are white and ≥60 years of age.

Conclusion: This is the first study comparing the effects of LCIG and OMT on NMS and sleep, and it will provide important information for physicians, patients, and caregivers when assessing the benefits of APD treatment.

1.Fernandez. Mov-Disord. 2015. 2.Antonini. Parkinsonism-Relat-Disord. 2015.

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.

EPR1077

A long-term study on effectiveness of levodopa-carbidopa intestinal gel treatment in advanced Parkinson's disease patients

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Background and aims: To present the design and baseline characteristics from an ongoing global study assessing long-term effectiveness of levodopa-carbidopa intestinal gel, LCIG (also known as carbidopa-levodopa enteral suspension in the US), treatment in Advanced Parkinson's disease (APD) patients under routine clinical care.

LCIG, delivered via percutaneous gastrojejunostomy, has been shown to improve "Off" time, dyskinesia, non-motor symptoms (NMS), and quality of life (QoL) in APD patients. However, prospective, long-term data on LCIG effectiveness in routine clinical practice are limited.

Methods: This global, multi-center, single-arm, open-label observational 3-year study, examines APD patients treated with LCIG under routine clinical care (DUOGLOBE), and is the first observational study of LCIG conducted in the USA. Approximately 200 patients from over 50 global centers are being enrolled according to local product label. Primary efficacy outcome is the mean change in "Off" time. Secondary endpoints include dyskinesia duration/severity (UPDRS IV and the Unified Dyskinesia Rating Scale), Activities of Daily Living (UPDRS-II), motor function (UPDRS-III) and fluctuations (UPDRS item 39), QoL (8-item PD Questionnaire), and NMS, including sleep/daytime sleepiness assessed with the NMS Scale, PD Sleep Scale (PDSS-2) and the Epworth Sleepiness Scale. Caregiver burden will be measured and adverse events monitored.

Results: As of September 14, 2017, baseline demographics and disease characteristics were available for 121 patients (Table 1).

Table 1. Baseline patient demographics and disease characteristics

Demographics and Disease Characteristics	N = 121
Age, years, mean (SD)	70.6 (8.0)
Gender, female, n (%)	43 (35.5)
Race, white, n (%)	117 (96.7)
PD duration, years, mean (SD)[a]	11.2 (4.6)
Dyskinesia duration, hours, mean (SD)[a,b]	4.1 (3.51)
"Off" time, hours, mean (SD)[a,b]	5.8 (3.46)

[a] N=106; [b] Normalized to a 16-hour waking day

PD = Parkinson's disease

Conclusion: Long-term effectiveness data on LCIG in the treatment of APD patients under routine clinical care is limited. The current study is designed to provide a better understanding of the long-term effectiveness profile of LCIG for the treatment of APD.
Disclosure: AbbVie **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.

EPR1079

Radioactive copper incorporation in the diagnosis of Wilson's disease

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Background and aims: Wilson's disease (WD) is an inherited disorder of copper metabolism that leads to accumulation of copper in the liver and other tissues. Early diagnosis of WD enables the initiation of effective treatment, which is crucial for prognosis. However, routine diagnostic methods do not always provide a final diagnosis. The aim of the study was to evaluate radioactive copper incorporation in the diagnosis of WD.
Methods: We retrospectively analyzed data of patients diagnosed with WD based on radiocopper testing; later, the diagnosis was confirmed by DNA analysis. Incorporation of 64Cu was measured at 2, 24 and 48 h following intravenous injection. Diagnostic accuracy (area under the receiver operating characteristic curve [AUC]), sensitivity, specificity and predictive value were assessed for 24 h/2 h and 48 h/2 h 64Cu ratios and compared with serum measurements of ceruloplasmin, copper, non-ceruloplasmin-bound copper and urinary copper excretion.
Results: Patients having two pathogenic ATP7B mutations (n=74) had significantly lower 24 h/2 h and 48 h/2 h 64Cu ratios than heterozygote (having only one mutation) controls (n=21) (mean 0.14 and 0.12 vs 0.49 and 0.63, respectively; both P<.001). Of note, 24 h/2 h and 48 h/2 h 64Cu ratios had excellent diagnostic accuracy, with AUCs approaching 1, and only urinary copper excretion displayed similar positive features. Other copper metabolism tests had lower accuracy, specificity and sensitivity.
Conclusion: The radioactive copper test had excellent diagnostic accuracy to distinguish homozygote/compound heterozygote and heterozygote WD carriers and may be useful to monitor the efficacy of new therapies for WD.
Disclosure: Nothing to disclose

EPR1080

Motor and cognitive progression in GBA-related PD patients submitted to Deep Brain Stimulation

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Background and aims: Parkinson's disease (PD) patients carrying a glucocerebrosidase gene mutation (GBA-related PD) have been associated to worse cognitive decline after Deep Brain Stimulation (DBS), although the overall response to DBS is still poorly understood. We aimed to evaluate the motor and cognitive outcome after DBS in GBA-related PD.
Methods: Comparison of motor and cognitive outcomes between GBA-related PD and idiopathic PD (iPD) patients after subthalamic nucleus (STN)-DBS. Pre- and post-DBS MDS-UPDRS and MMSE were assessed. Post-DBS evaluations were performed in 4 conditions concerning ON/OFF medication and/or stimulation.
Results: 8 GBA-related PD and 10 iPD patients, with no significant differences in gender, age at disease onset (AO), time to DBS, pre-DBS levodopa response, follow-up post-DBS and pre- and post-DBS levodopa equivalent daily dose. Post-DBS MDS-UPDRS-III MedON/StimON was significantly different between groups (40.1±9.1 GBA-PD; 28.8±11.2 iPD; P=0.05). In GBA-related PD, post-DBS MDS-UPDRS-III MedON/StimON was worse than pre-DBS MDS-UPDRS-III MedON (40.1±9.1 vs 24.5±8; P=0.017). MMSE did not differ significantly between groups. 6/8 GBA-related PD patients were evaluated in the 4 post-DBS conditions. Stimulation significantly improved MDS-UPDRS-III (MedOFF/StimOFF 57.7±14.8 vs MedOFF/StimON 36.7±14.3; P=0.026), but the benefit with stimulation (post-DBS MDS-UPDRS-III MedOFF/StimOFF vs MedOFF/StimON) was worse compared to benefit from levodopa pre-DBS (pre-DBS MedOFF vs MedON)
Conclusion: GBA-related PD patients benefit from acute STN-DBS stimulation, although less than iPD patients. Motor symptoms of GBA-related PD seem to worsen 4.5 years after STN-DBS, whereas we found no cognitive decline. More data is warranted but available evidence do not support excluding GBA-related PD patients from DBS.
Disclosure: Nothing to disclose

EPR1081

Study protocol: Care of Late-Stage Parkinsonism (CLASP): A longitudinal cohort study

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Background and aims: Parkinson's disease (PD) is a chronic progressive disorder leading to increasing disability. While the symptoms and needs of patients in the early stages of their disease are well characterized, little information is available on patients in the late stage of the disease.

Methods: The Care of Late-Stage Parkinsonism (CLaSP) study is a longitudinal, multicenter, prospective cohort study to assess the needs and provision of care for patients with late stage Parkinsonism and their carers in six European countries (France, Germany, Netherlands, Portugal, Sweden, UK). In addition, it will compare the effectiveness of different health and social care systems. Patients with Parkinsonism with Hoehn and Yahr stage ≥IV in the "On"-state or Schwab and England stage 50% or less in the "On"-state are evaluated at baseline and three follow-up time-points. Standardised questionnaires and tests are applied for detailed clinical, neuropsychological, behavioural and health-economic assessments. A qualitative study explores the health care needs and experiences of patients and carers, and an interventional sub-study evaluates the impact of specialist recommendations on outcome using the UPDRS-ADL part.

Results: For the baseline evaluation of the cohort study, at least 70 patients will be recruited per country.

Conclusion: Through the combined assessment of a range of quantitative measures and qualitative assessments of patients with late stage parkinsonism, this study will provide for the first time in-depth and reliable information on the clinical presentation, needs and the health care provision in this population in Europe, and lay the foundation for improved outcomes in this population

Disclosure: This project was supported by a grant from JPND

MS and related disorders 1

EPR1083

Disease activity as assessed by the MAGNIMS score predicts long-term clinical disease activity (CDA)-free status and disability progression in patients treated with subcutaneous interferon beta-1a

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Background and aims: Post-hoc analysis of the MRI in MS (MAGNIMS) score at Year (Y)1 with long-term CDA-free status and disability progression in scIFNbeta-1a-treated patients using data from PRISMS.

Methods: In PRISMS-2, relapsing-remitting MS patients were randomised to scIFNbeta-1a 22 or 44mcg, or placebo, tiw for 2 years. Placebo patients were randomised to scIFNbeta-1a 22/44mcg at Y3. Patients were followed to Y15 post-randomisation (22mcg n=95; 44mcg n=95; placebo n=100). We classified scIFNbeta-1a patients by Y1 MAGNIMS score: 0, 1 or 2. CDA-free was defined as no relapses or disability progression (increase of 1 point from baseline in Expanded Disability Status Scale [EDSS] score, or 1.5 points in patients with EDSS 0). Median times (95% confidence interval [CI]) to first CDA event and EDSS progression from Y1, and retrospective hazard ratios (HR[95% CIs]) versus MAGNIMS score of 0, are presented.

Results: At Y1, 129, 108 and 130 scIFNbeta-1a-treated patients had a MAGNIMS score of 0, 1 and 2, respectively. Median time to CDA event was longer in patients with Y1 MAGNIMS score of 0 vs 1 and 2 (Figure 1). Median time to EDSS progression was longer in patients with Y1 MAGNIMS score of 0 (7.5 years) vs 1 (4.0 years) and 2 (2.5 years). Using MAGNIMS score of 0 as a reference, risk of EDSS progression was higher in patients with Y1 MAGNIMS scores of 1 and 2 (Table 1).

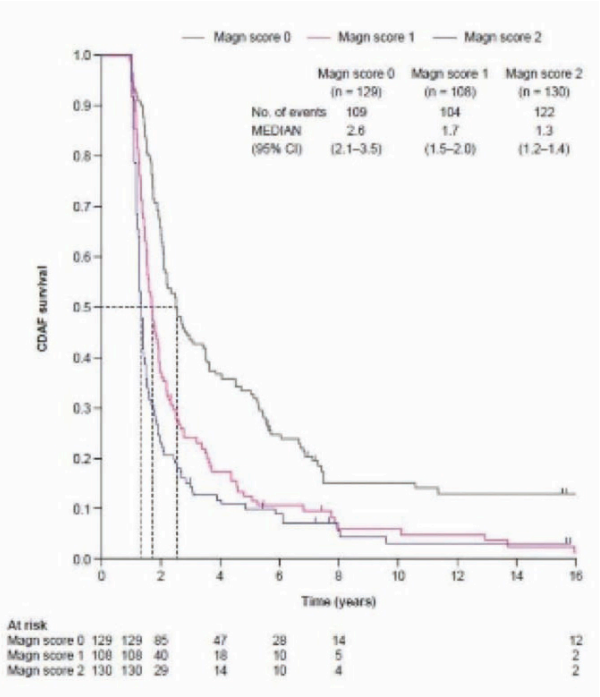

Figure 1: Median time to CDA event after Y1 by MAGNIMS score

	Hazard Ratio	Lower confidence limit	Upper confidence limit	P value
CDA				
MAGNIMS 1 vs 0	1.73	1.32	2.27	<0.0001
MAGNIMS 2 vs 0	2.48	1.87	3.17	<0.0001
EDSS progression				
MAGNIMS 1 vs 0	1.54	1.12	2.11	<0.0001
MAGNIMS 2 vs 0	2.14	1.58	2.89	<0.0001

Table 1: Hazard ratios for CDA and EDSS progression after Y1 by MAGNIMS score

Conclusion: In PRISMS, Y1 MAGNIMS score predicted risk of CDA event or disability progression in scIFNbeta-1a-treated patients.

Disclosure: Funded by Merck KGaA, Darmstadt, Germany

EPR1084

Infections seem to be more frequent before onset of pediatric multiple sclerosis: A Danish nationwide nested case-control study

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Background and aims: Infections are suspected environmental triggers for multiple sclerosis (MS). The relationship between the timing and cumulative number of childhood infections regarding pediatric MS risk is uninvestigated. The aim was to investigate whether childhood infections contribute to pediatric MS.

Methods: A nationwide nested case-control study with detailed MS case ascertainment including chart review was undertaken. For each MS case, we selected five control children using density sampling from the entire Danish population, matching controls to children with MS by sex and birthdate. We analyzed data with the cumulative number of childhood infections as exposure and MS as outcome. Hazard ratios (HR) including 95% confidence intervals (CI) were estimated using Cox regression.

Results: We identified 212 children with MS and 1,060 controls. Median age at MS onset was 15.3 years (range: 7.6–17.8 years); 72% were girls. Each infection during the preceding three years increased the hazard for MS by 11% (95% CI=1.01–1.22, p=0.04); having 5+ infections compared with 0-4 infections the preceding three years doubled the hazard for MS (HR 2.18; 95% CI=1.12–4.30, p=0.02).

Conclusion: Children with MS had more infections in the three years preceding MS clinical onset than age- and sex-matched control children; accordingly, immune response to infections may influence MS pathogenesis.

Disclosure: The study was supported by grants from the Danish MS Society, TEVA, Novartis and Genzyme.

EPR1085

Brain and spinal cord imaging features in neuromyelitis optica spectrum disorders

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Background and aims: Brain and cord MRI features of neuromyelitis optica spectrum disorder (NMOSD) are variable, with typical white matter (WM) lesions and atypical findings (short transverse myelitis, [STM]).

We evaluated the prevalence of typical/atypical hyperintense lesions of brain and spinal cord in a multicentric cohort of NMOSD patients and assessed differences of lesions distribution between NMOSD vs relapsing remitting multiple sclerosis (RRMS) patients.

Methods: Brain and spinal cord MRI scans were obtained from 116 NMOSD and 60 RRMS patients from 3 European centers. A qualitative (typical/atypical findings, cortical/temporal pole lesions and 2010 McDonald criteria fulfillment) and a quantitative (T2-lesion probability maps) analysis were performed.

Results: Cortical lesions did not occur and temporal pole involvement was infrequent (1%) in NMOSD vs RRMS patients ($p<0.0001$). 22% of NMOSD patients had typical encephalic lesions (18% brainstem periventricular/periacqueductal; 7% large hemispheric; 4% diencephalic; 7% cortico-spinal tract), 55% had long transverse myelitis (vs only one RRMS patient) and 28% had STM (vs 67.5% of RRMS, $p<0.0001$). 40% of NMOSD and all MS patients satisfied 2010 McDonald criteria for dissemination in space. In NMOSD, lesions were mostly located in periventricular, subcortical insular and periacqueductal regions. Compared to NMOSD, RRMS patients had higher occurrence of lesions in corpus callosum, periventricular zone and inferior longitudinal fasciculus, bilaterally.

Conclusion: Typical brain and cord lesions occur in a minority of NMOSD patients. A relatively high percentage of NMOSD patients satisfies 2010 McDonald criteria, prompting the development of better algorithms for the differential diagnosis of WM conditions.

Disclosure: Nothing to disclose

EPR1086

Correlations between amyloid-beta and white matter damage in multiple sclerosis: a 18F-florbetapir positron emission tomography study

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Background and aims: Positron emission tomography (PET) with amyloid-beta (Aβ) tracers is a promising tool to evaluate white matter (WM) damage in multiple sclerosis (MS). Recent findings showed a link between Aβ and myelination and suggested CSF Aβ levels as prognostic biomarker in MS. Aim of this study was to investigate 18F-florbetapir uptake in normal appearing (NA-) and damaged WM and to evaluate possible correlations with CSF Aβ levels.

Methods: Twelve patients with relapsing-remitting or progressive MS were divided according to clinical/radiological evidence of disease activity (n=8 active; n=4 not active). All patients underwent CSF analysis, brain MRI and 18F-florbetapir-PET. MRI and PET images were co-registered and WM-mean-standardised uptake values (WM-SUV) were calculated for each patient. We obtained brain volumes and calculated WM-lesion load (WM-LL) using SPM12.

Results: WM-SUV resulted lower in patients with active MS compared with not active MS (p=0.0081). Considering only active patients, CSF Aβ levels predicted WM-SUV (p=0.005) and were lower in patients with WM-SUV<1.0 compared to those with WM-SUV>1.0 (p=0.029). Notably, both WM-SUV and CSF Aβ levels correlated with NAWM volume (NAWMV; p=0.0047), but not with WM-LL.

Conclusion: We found a reduced 18F-florbetapir uptake in MS patients with active inflammation compared with not active patients. We discovered that NAWMV was a better predictor of WM-SUV compared to WM-LL. Interestingly, CSF Aβ levels correlated to NAWMV and were also found to be a predictor of WM-SUV. These findings suggest that the prognostic role of Aβ in MS may be directly linked to myelin microscopic damage.

Disclosure: Nothing to disclose

EPR1087

Risk of Becoming Wheelchair-Confined in Patients with Primary Progressive Multiple Sclerosis: Data from the ORATORIO Trial and a Long-Term Real-World Cohort from MSBase Registry

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Background and aims: Ocrelizumab is an approved treatment for relapsing or primary progressive multiple sclerosis (PPMS). We aimed to: (1) assess ocrelizumab's effect on time to wheelchair-confinement including the extended controlled period of ORATORIO (ORATORIO+ECP; NCT01194570); (2) understand long-term benefits by extrapolating results; (3) contextualise results using an MSBase registry cohort.

Methods: In ORATORIO+ECP, we: (1) analysed time to onset of 24-week-confirmed progression (24w-CP) to Expanded Disability Status Scale (EDSS)≥7.0; (2) conducted a Weibull extrapolation until patients reached median time to EDSS≥7.0. In MSBase, we analysed time to initial unconfirmed progression to EDSS≥7.0 and time to onset of 24w-CP to EDSS≥7.0, in PPMS patients with baseline EDSS 3.0–6.5, similarly to ORATORIO.

Results: In ORATORIO+ECP, ocrelizumab significantly reduced the risk of onset of 24w-CP to EDSS≥7.0: 30 (6.2%) of 488 ocrelizumab and 24 (9.8%) of 244 placebo patients reached the milestone (HR=0.54, 95% CI=0.31–0.92, p=0.022). Extrapolated median time to 24w-CP to EDSS≥7.0 was 12.1 years for placebo and 19.2 years for ocrelizumab (expected 7.1-year delay). In MSBase, 238 (30.7%) of 775 PPMS patients progressed to EDSS≥7.0 (median 12.4 years). Of these, 37 had no further visits, 35

regressed and 166 (69.7%) had 24w-CP to EDSS≥7.0 (median 12.0 years).
Conclusion: Ocrelizumab significantly delayed time to wheelchair-confinement in ORATORIO+ECP. The extrapolated median time to reach this disability milestone was similar to that in MSBase, suggesting ORATORIO patients, if left untreated, would progress similarly to a real-world population. The observed benefit with ocrelizumab potentially translates to a meaningful long-term benefit for PPMS patients.
Disclosure: Sponsored by F. Hoffmann-La Roche Ltd.

EPR1088

CADASIL and multiple sclerosis: an unexpected association

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Background and aims: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) represents a major differential diagnosis with multiple sclerosis (MS), as they share demographic, clinical and, especially, MRI findings. We present the exceptional case of a patient with both disorders.
Methods: To describe a case report.
Results: A 40-year-old healthy female developed over three years two acute partial myleitis and an optic neuritis. No migraine history was reported. Based on a cervical and brain MRI (showing myelitis and an extensive leukopathy affecting the anterior temporal poles and juxtacortical and corpus callosum typical lesions of MS) (images 1,2 and 3) and the finding of oligoclonal bands (OCB) in CSF, the patient was diagnosed with remittent-recurrent MS and treatment with interferon beta 1-b was initiated. Due to a later discover of an Arg332Cys mutation of the NOTCH3 gene in his father and cousin and a subsequent positive genetic analysis in our patient, a MS diagnosis was doubted in favor of a CADASIL. However, the acute-onset of typical clinical syndromes and the findings of OCB and MRI lesions reinforced both diagnoses. During its course, new acute worsening episodes with partial response to corticosteroids overlapped, so the treatment was changed to glatiramer acetate and, later, teriflunomide, remaining relapse-free during 3 years but with a significant disability (EDSS 6.5 after 12 years of disease) and a progressive cognitive decline.

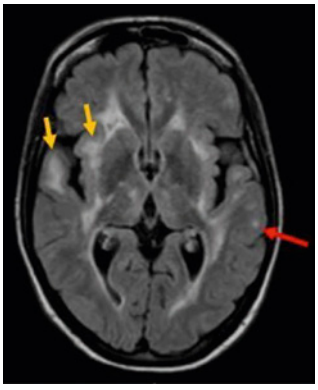

Image 1. Axial Cranial MRI. FLAIR. Anterior temporal lobe and diffuse extensive leukopathy suggestive of CADASIL (yellow arrow). Juxtacortical lesions (red arrow) typical in MS.

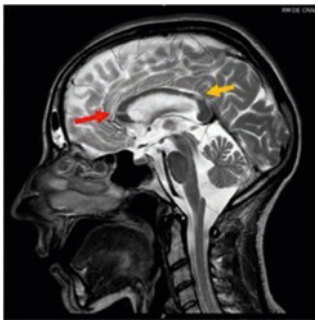

Image 2. Sagittal Cranial MRI. T2. Red arrow: lesion affecting the entire perpendicular axis of the corpus callosum, typical of CADASIL. Yellow arrow: lesion of the ependymal caudal part of the corpus callosum, typical of MS.

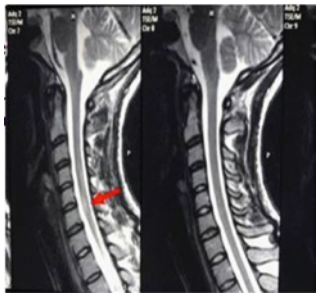

Image 3 Sagittal cervcial MRI. T2. Red arrow : typical MS myelitis.

Conclusion: To distinguish CADASIL and MS is a major differential diagnostic challenge. In an exceptional case with both diagnoses, an extreme difficulty is also observed in taking therapeutic decisions.

Disclosure: Nothing to disclose

EPR1089

Effect of Ocrelizumab on Relapse Rate, and Disability Progression and Improvement in Relapsing Multiple Sclerosis Patients in the Open-Label Extension of the Pooled OPERA Trials

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Background and aims: Efficacy and safety of ocrelizumab (OCR) in relapsing multiple sclerosis (RMS) were demonstrated in the 96-week double-blind control period of OPERA I/II (NCT01247324/NCT01412333). The efficacy of OCR therapy on clinical measures of disease activity, progression and improvement in the open-label extension (OLE) period was assessed.

Methods: At the start of the OLE, patients continued (OCR-OCR) or were switched from interferon-beta-1a (IFN-beta-1a) to OCR (IFN-OCR). Adjusted annualised relapse rate (ARR), time to onset of 24-week-confirmed disability progression (CDP) and time to onset of 24-week-confirmed disability improvement (CDI) were analysed.

Results: More than 89% of patients who entered the OLE period completed OLE Year 2. Among IFN-OCR patients, ARR decreased from 0.20 in the year pre-switch to 0.10 and 0.08 at Years 1 and 2 post-switch ($p<0.001$ Year 1 versus pre-switch; $p=0.31$ Year 1 versus Year 2). OCR-OCR continuers maintained the low ARR through the year pre-switch and the 2 years of the OLE (0.13, 0.11 and 0.08). OCR-OCR continuers versus IFN-OCR switchers had lower proportions of patients with CDP and higher proportions with CDI in the year pre-switch and Years 1 and 2 of the OLE (CDP: 7.7%/12.0%, 10.1%/15.6% and 13.8%/18.1%; $p<0.05$, all within visit comparisons. CDI: 16.8%/13.3%, 20.6%/16.6% and 23.7%/18.9%; $p<0.1$, all within visit comparisons).

Conclusion: Switching from IFN-beta-1a to ocrelizumab was associated with a consistent and robust reduction in ARR which was maintained through the OLE. The benefits of ocrelizumab on ARR, CDP and CDI as seen in the 2-year double-blind phase were maintained after 2 years in the OLE.

Disclosure: Sponsored by F. Hoffmann-La Roche Ltd.

EPR1090

Reduced expression of the IL7Ra signaling pathway contributes to T-cell pathogenesis in NMO.

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Background and aims: Identification of NMO-associated genes and their involvement in pathogenic pathways could provide a more comprehensive understanding of NMO etiology and the rationale for developing new drugs.
Objective: To characterize the abnormal immunological pathways involved in NMO pathogenesis.
Methods: An immunological gene expression array was performed on blood samples of NMO patients and HCs, followed by validation assays. The patient cohort included 65 NMO patients, 32 MS patients and 37 HCs.
Results: Two major clusters of genes were found associated with NMO: T-cell-associated genes and the TNF/NF-kB-signaling pathway. Analysis confirmed significantly reduced expression of IL7Ra in the peripheral blood of NMO patients (NMO376.4 vs HCs691.7, p=0.00005). IL7Ra expression was significantly lower in the NMO patients vs those in HCs and MS at both the mRNA and protein levels (1RQ;1.5RQ;2.09RQ p=0.01, 9ng/ml; 12.5ng/ml;12.2ng/ml NMO, HCs and MS). IL7Ra upstream transcription factors Foxo1 (0.67RQ vs 1.13RQ, p=0.003) and Ets1 (625.5 vs 851.25 counts, p=0.02), were also markedly reduced. In line with the essential role of IL7Ra in T cell survival, a significantly lower number of naïve T-cells (NMO19.4%; HCs32.9% p=0.05), and reduced T-cell survival signaling mediated by increased apoptosis was observed.
Conclusion: Two gene clusters were identified which distinguished NMO patients from HCs and revealed a major role for the IL7Ra pathway in the pathogenesis of NMO. This could provide a tool for better understanding of the disease and boost the development of new therapeutic approaches.
Disclosure: Nothing to disclose

MS and related disorders 2

EPR1091

Disease modifying treatment in paediatric-onset multiple sclerosis: A Danish nationwide population-based observational study

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Background and aims: Patients with paediatric-onset multiple sclerosis (MS) have a higher relapse rate and carries a worse prognosis than adult-onset MS. Early initiation of disease modifying treatment (DMT) may be beneficial for these children. The treatment pattern of DMT in paediatric-onset MS has never been described in Denmark. The aim of the study is to characterize the treatment of paediatric-onset MS since 1996, when DMT became available.
Methods: Data on DMT for paediatric-onset MS during 1996–2017 were sourced from the Danish Multiple Sclerosis Registry. All persons in the registry have a medical record validated MS diagnosis.
Results: We identified 195 children diagnosed with paediatric-onset (<18 years) MS during 1996–2017. Among these children, 123 (63%) received DMT before 18 years of age. The median age at treatment start was 16 years (range: 4–17 years), and the mean number of DMTs per child was 1.4 (initiated before 18 years of age). Interferons were the most common first-line treatment. Six children (11%) received natalizumab as first treatment. During follow-up, 107 (87%) children switched DMT or discontinued treatment. Fingolimod was prescribed more frequently than natalizumab as escalation therapy.
Conclusion: Taken together, 63% of children with MS were treated with DMT before the age of 18. Of this group, 87% switched DMT or discontinued treatment before 18 years of age. Future studies should focus on reasons for delay in initiating DMT, as well as causes of discontinuation and effectiveness of DMT in paediatric-onset MS.
Disclosure: Nothing to disclose

EPR1092

The role of metabolomics in the clinical parameters of Multiple Sclerosis: serotonin, tyrosine and metabolites

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Background and aims: Studying specific metabolomic pathways in Multiple Sclerosis (MS) patients can provide valuable clinical information to monitor the disease progression and form therapeutic protocols.
Methods: The authors attempted to quantify low molecular weight potential biomarkers for MS progress monitoring, by developing and validating a novel fast and sensitive analytical method in patients' serum.
Pre-treatment sera were obtained from 30 Relapse Remit MS patients (RRMS) during a clinical relapse, 20 patients with Clinical Isolated syndrome (CIS) and 20 healthy individuals age and gender matched. Disease duration, relapse rate (rr), number of Gadolinium enhanced lesions (GdE+), EDSS score and MSFC clinical subscales (Paced Auditory Serial Addition Test-PASAT, 9 Hole Peg Test-9HPT and 25 Feet test-25F) were recorded for each MS patient. High performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS) was applied for the simultaneous detection and quantification of the following suspected biomarkers: serotonin, tyrosine and its metabolite epinephrine
Results: Serotonin was significantly elevated in the RRMS group ($F(2,67)=4.963$, $p=0.010$) when compared with the control group. In addition, there was a moderate positive partial correlation between PASAT score and serotonin where the lower the serotonin serum concentrations the lower the PASAT score. Moreover, serum tyrosine and epinephrine concentrations act as confounding variables and seem to strengthen the serotonin-PASAT positive correlation. (Par= (9)0.660, $p=0.027$)
Conclusion: Our results strengthen the already established knowledge on serotonin effects in Th2 diseases, provide useful data on the possible role of serotonin on the pathophysiology of MS and some indications on the synergistic effect of the tyrosine and its metabolites.
Disclosure: Nothing to disclose

EPR1093

CSF β-amyloid predicts prognosis in patients with multiple sclerosis

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Background and aims: The importance of neurodegeneration in multiple sclerosis (MS) has being increasingly recognised. Hence, there is a need to identify reliable biomarkers of the process. This study aimed to investigate the potential prognostic role of cerebrospinal fluid (CSF) amyloid beta 1-42 (Aβ) levels; to evaluate their possible association with white matter (WM) and grey matter (GM) damage; to determine a cut-off of the CSF Aβ levels, in order to classify patients into low and fast disability accumulation groups.
Methods: Seventy patients with a new diagnosis of RRMS were recruited and followed-up. All patients underwent clinical assessment, brain MRI and lumbar puncture. We used T2-weighted scans to quantify WM lesion loads and voxel based morphometry to investigate relative cortical atrophy. Aβ levels were determined in CSF samples from all patients. Between-group comparisons and multiple regression analyses have been performed.
Results: We found lower CSF Aβ levels in patients reporting a worse follow-up EDSS score ($p<0.001$). Multiple regression analysis confirmed CSF Aβ concentration as a predictor of patients' EDSS increase at follow-up ($p<0.001$). Patients with a relative reduction of GM at 1-year follow-up had lower CSF Aβ levels than those with a stable GM volume ($p<0.05$). We identified the cut-off of 813 pg/ml for CSF Aβ levels to identify the patients with worse prognosis.
Conclusion: This study suggests that CSF Aβ levels may be represent a crucial feature in MS, as it may be a predictive biomarker of progression. To this aim, we proposed a new cut-off.
Disclosure: Nothing to disclose

EPR1094

Plasmapheresis as rescue therapy of relapses in multiple sclerosis. A retrospective clinical practice survey.

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Background and aims: Multiple sclerosis (MS) relapse treatment is usually based on intravenous high-dose steroid therapy as first choice. However, in case of poor response or worsening of symptoms, plasmapheresis, a procedure able to remove inflammatory molecules from the blood circulation, should be considered as alternative to a second chance with steroids. The aim of the present study was to investigate the impact of plasmapheresis as relapse rescue therapy in a cohort of MS patients.
Methods: We retrospectively investigated all MS patients with at least one relapse treated at the apheresis centre of Parma in the past ten years (2007-2017), collecting clinical data and considering as primary outcome EDSS score one- and six-month post-apheresis respect to pre-apheresis score.
Results: We analysed a total of 43 relapses from 37 patients (67.6% female, mean age 42.1±11.9 years, mean EDSS on relapse 4.9±1.6, 75.7% with relapsing-remitting course, 95.3% previously treated with steroids). We found an improvement with complete or partial regression of EDSS worsening in 83.8% of patients. At multivariate analysis, improvement after plasmapheresis was associated with female gender (96% vs 58% in males, $p=0.004$) and with a shorter interval between relapse and apheresis (36.7 vs 70.8 days, $p=0.02$). Regarding safety, we recorded only six, mainly mild or moderate. adverse events during treatment (14%).
Conclusion: We confirmed that plasmapheresis is an effective and safe rescue therapy of MS relapses not adequately responding to high-dose steroids.
Disclosure: Nothing to disclose

EPR1095

Is an intrathecal kappa-chain oriented immune response typical of Multiple Sclerosis (MS)?

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Background and aims: Intrathecal immune responses in MS prompted to develop assays in cerebro-spinal fluid (CSF) including detection of oligoclonal bands and Link (for IgG) or K indexes (for free light chain kappa). This study explores the occurrence of kappa-chain oriented response as typical of MS.
Methods: 137 patients were enrolled: 45 MS, 57 non-inflammatory neurological disease (NID), 29 neurological inflammatory disease other than MS(ID). Free light chain kappa (KFLC), lambda (LFLC) and IgG were measured in serum and CSF by nephelometry
Results: Serum KFLC/LFLC ratio in MS was 0.98±0.51, comparable to NID (0.81±0.29) and ID (1.23±0.66) whereas in CSF was 12.7±21.7 in MS significantly ($p<0.001$) higher than NID (0.84±0.58) and ID (1.65±1.84). Serum IgG/KFLC ratio was 809±270 in MS, comparable to NID (687±237) and ID (778±369). The CSF IgG/KFLC ratio was 23±25 in MS, significantly lower ($p<0.001$) than NID (151±92) and ID (128±98). Serum IgG/LFLC ratio was 737±366 in MS, comparable to NID (618±235) and ID (708±536). The CSF IgG/LFLC ratio was 96±108 in CSF, comparable to NID (101±54) and ID (148±123). The K index (Ki, ratio between KFLC and albumin quotient) was markedly ($p<0.0001$) higher in MS (80±96) than in NID (4.6±9.0) and ID (13.1±25), the L index was only slightly higher ($p=0.017$) in MS (16.4±17.7) than in NID (3.7±4.04) but not different from ID.
Conclusion: The high KFLC/LFLC ratio and low IgG/KFLC ratio in CSF suggest that a KFLC- oriented immune response occurs intrathecally in MS thus confirming the powerful diagnostic value of Ki.
Disclosure: Nothing to disclose

EPR1096

Effect of long-term Teriflunomide Treatment on Lymphocyte Counts and Infection Rates in Pooled Data From TEMSO, TOWER, TOPIC, and TENERE Core and Extension Studies

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Background and aims: In TEMSO (NCT00134563) and TOWER (NCT00751881), teriflunomide treatment was associated with early lymphocyte count reductions, whereas mean counts remained within normal range. In long-term extensions (TEMSO, NCT00803049), lymphopenia was uncommon, no higher than Grade 2, and not associated with increased infections. We pooled data from 4 teriflunomide phase 3 core studies (TEMSO, TOWER, TOPIC [NCT00622700], TENERE [NCT00883337]) plus extensions to evaluate lymphocyte counts and infection rates during long-term treatment.
Methods: Patients with relapsing forms of MS or a first clinical event suggestive of MS were treated for up to 11 years. Analysis included all patients exposed to teriflunomide 14 mg. Lymphocyte counts were obtained over the course of each study. Lymphopenia (2 consecutive lymphocyte counts <LLN) was graded by CTCAE, v4.0.
Results: Cumulative duration of exposure to teriflunomide 14 mg was 6055 patient-years. In pooled core and extension studies (n=1895), few patients experienced Grade 1 (4.9%; n=92/1895) or 2 (2.2%; n=42/1895) lymphopenia. Infections were reported in 62.0% (57/92) and 54.8% (23/42) of patients with Grade 1 or 2 lymphopenia, respectively, vs 56.9% (1002/1761) without lymphopenia. Serious infections occurred in 3.3% (3/92) and 7.1% (3/42) of patients with Grade 1 or 2 lymphopenia, respectively, vs 3.7% (66/1761) without lymphopenia.
Conclusion: In this pooled analysis of phase 3 studies, long-term treatment with teriflunomide 14 mg was not associated with high-grade lymphopenia, and low-grade lymphopenia was uncommon. Infection rates were similar in patients with or without lymphopenia, consistent with an immunomodulatory mechanism of action of teriflunomide with limited impact on protective immunity.
Disclosure: Study supported by Sanofi.

EPR1097

Serum neurofilament light chain levels are increased at the onset of PML in natalizumab-treated MS patients

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Background and aims: The monoclonal antibody natalizumab is a highly effective treatment for patients with multiple sclerosis (MS). However, the drug is associated with increased risk of progressive multifocal leukoencephalopathy (PML), a severe infection of the CNS caused by the reactivation of JC virus. Huge efforts have been made to improve risk stratification algorithms and to facilitate early disease recognition, but no serum biomarker is currently available for the condition.
The aim of the study was to assess whether serum neurofilaments light chains (Nfl) are a reliable biomarker for the early recognition of PML during natalizumab treatment.
Methods: Patients were recruited from 2 European cohorts of 304 patients with MS. The cohort comprised 25 patients developing PML under natalizumab treatment, 128 natalizumab treated and 151 untreated MS patients. Serum NfL concentration was assessed using an ECL immunoassay.
Results: Natalizumab-treated patients had similar NFLs 16.1 pg/ml (IQR 13.4-22.2) to other MS patients. At the onset of PML, serum Nfl were 10-fold higher than in the pre PML condition and in other natalizumab treated patients (266.2 pg/ml (IQR 63.5-354.2), and they continued to grow till the onset of immune reconstitution inflammatory syndrome (1000 pg/ml (IQR 303.5 - 1218), $p<0.0001$).
Conclusion: If replicated in future studies, serum NfL may represent a reliable and easily accessible biomarker of early PML detection in natalizumab treated MS patients.
Disclosure: Nothing to disclose

EPR1098

Ongoing neurodegeneration in the cervical cord of patients with early primary progressive MS

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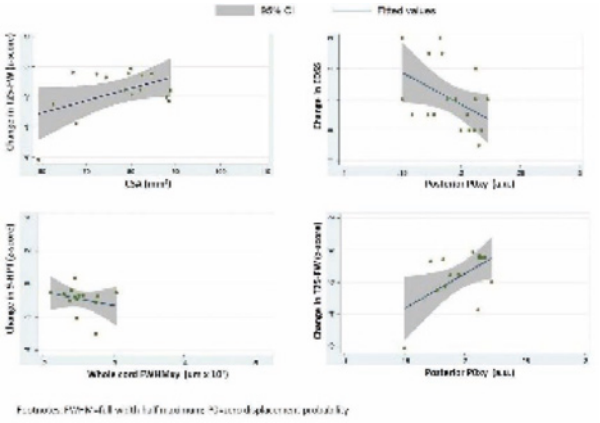
Background and aims: We reported abnormal Q-space imaging (QSI)-derived indices in the cervical cord of early primary-progressive (PP) MS patients at baseline, suggesting reduced structural integrity of neurons and demyelination (i.e., neurodegeneration).
To investigate if changes in QSI measures occur over 3 years and correlate with clinical changes; to explore the predictive value of baseline MRI measures.
Methods: 23 PPMS patients and 23 healthy controls (HCs) underwent spinal cord MRI at 3T, and after 1 and 3 years. Cord cross-sectional area (CSA) and QSI metrics of the whole cord and four columns were obtained. Patients were scored on several clinical scales, including the Expanded-Disability-Status-Scale (EDSS), 9-hole-peg (9-HPT) and timed 25-foot walk (T25-FW). Mixed-effect linear regression models assessed differences in MRI measures between groups and their association with clinical changes over 3-years, corrected for age and gender.
Results: Patients deteriorated clinically over 3-years (Table.1). They showed a faster rate of decline in CSA than HCs (RC=-0.96, [95%CI=-1.51,–0.14], $p=0.001$). In patients, there was an increase in the indices of perpendicular diffusivity in the lateral columns, which was associated with a deterioration in 9-HPT, and a decrease in parallel diffusivity in the anterior columns (all p values<0.05). A smaller CSA and higher perpendicular diffusivity of the whole spine and posterior columns at baseline predicted higher disability at 3 years (all p values<0.05) (Fig.2).

	Baseline		1-Year		3-Year	
	PPMS	HC	PPMS	HC	PPMS	HC
Number	23	23	20	18	22*	14
Age, mean (SD) (years)	51 (9.1)	44 (12.6)	52 (9.3)	46 (11.9)	53 (8.8)	46.3 (12.3)
Sex (M:F)	11:12	5:18	10:10	5:13	10:12	6:8
Disease duration, mean (SD) (years)	5.4 (1.7)	-	4.5 (1.8)	-	6.4 (1.7)	-
EDSS, median (range)	5.5 (2.5-6.5)	-	6 (4.5-7)	-	6.5 ^ (5.5-8)	-
9-hole peg test (9-HPT), mean (SD) (z-score)	-0.61 (1.10)	-	-0.99 (1.16)	-	-1.26 ^ (1.20)	-
Timed 25-foot walk test (T25-FW), mean (SD) (z-score)	0.26 (0.24)	-	0.18 (0.33)	-	-1.36 ^ (1.54)	-
Grip strength, mean (SD) (lbs force)	46.17 (23.90)	-	40.22 (24.81)	-	14.76 ^ (9.65)	-
CSA mean (SD) (mm^2)	76.99 (9.58)	81.65 (8.62)	75.41 (9.40)	81.42 (8.59)	73.23 * (8.31)	81.59 (9.11)

*=16/22 completed MRI and clinical assessment, 2/22 completed clinical assessment only, 4/22 telephone EDSS
^= Significant deterioration over 3 years, $p<0.05$
*=Faster reduction in CSA in PPMS patients than HCs

Cohort description



Scatter plots of baseline CSA and QSI-derived perpendicular diffusivity indices, predictor of changes in clinical scores over 3 years.

Conclusion: Progressive spinal cord neurodegeneration, as detected by changes in QSI metrics and development of cord atrophy on MRI, underlies disability worsening in PPMS.

Disclosure: RC, TS, NC, KAA, SO: no disclosures. FP: funded by NIHR BRC UCLH/UCL High Impact Initiative, Bioclinica Inc. MM: funded from ECTRIMS-MAGMNIMS. CT: funded form ECTRIMS, Teva Pharmaceuticals Europe, Ismar Healthcare. CGKW: funded from Spinal Research, Craig Neilsen Foundation, EPSRC, Wings-for-Life, UK-MS-Society, Horizon2020, NIHR/MRC. AJT: funded from Eisai, EXCEMED, International Progressive MS Alliance, National MS Society (USA) SAGE Publishers. FB: funded from Biogen-Idec, Janssen-Alzheimer Immunotherapy, Bayer-Schering, Merck-Serono, Roche, Novartis, Genzyme, Sanofi-aventis, EU-H2020, NWO, SMSR, EU-FP7, TEVA, Novartis, Toshiba. OC: funded from UK-MS Society, Rosetrees trust, NIHR UCLH BRC, Biogen, Novartis, Roche, Genzyme, Teva, GE healthcare.

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EPR1099

Pooled analysis of the efficacy of cladribine tablets 3.5 mg/kg in patients with EDSS ≥3.5 or

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Background and aims: In the CLARITY and ONWARD studies, cladribine tablets (CT) demonstrated efficacy across a spectrum of patients with relapsing multiple sclerosis (RMS). Patients with Expanded Disability Status Scale (EDSS) scores ≥3.5 are at higher risk of conversion from relapsing-remitting multiple sclerosis (RRMS) to secondary progressive multiple sclerosis (SPMS) with relapses. Combining data from the double-blind study periods enables the effects of 2 years' treatment with CT (3.5mg/kg cumulative dose) to be assessed in patients with higher EDSS at study entry.
Methods: Data from the 2-year, double-blind periods of CLARITY and ONWARD (n=1,067) were used to analyse the effect of CT 3.5mg/kg on annualised relapse rate (ARR) by comparing patients who entered the study with a baseline EDSS ≥3.5 (n=414) and the complementary subgroup with baseline EDSS ≤3.0 (n=653). ONWARD compared cladribine+interferon-beta and placebo+interferon-beta.
Results: Compared to placebo, CT reduced relapse rate by 60% and 53% for EDSS subgroups ≤3.0 and ≥3.5 respectively (Figures 1, 2). The treatment effect of CT 3.5 mg/kg versus placebo was similar between EDSS subgroups (subgroup by treatment interaction, your own>0.5). The treatment effect in both subgroups was nominally significant (p<0.0001).

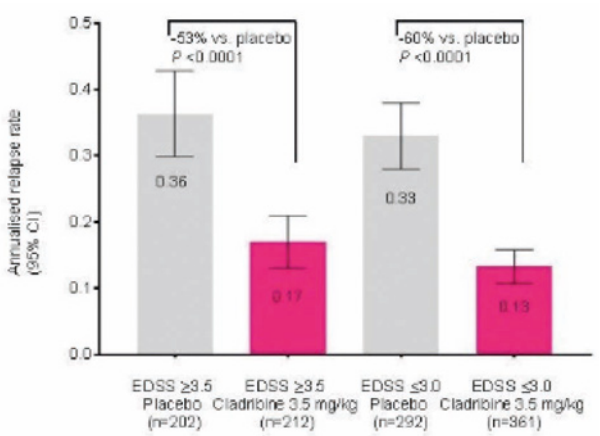

Figure 1: Mean Annualised Relapse Rates at 96 Weeks

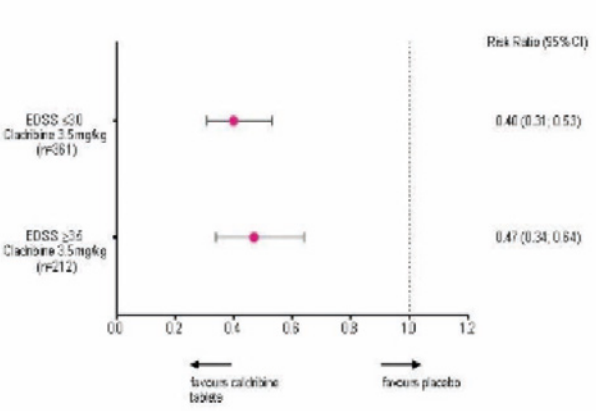

Figure 2: Forest Plot of Annualised Qualifying Relapse Risk Ratio

Conclusion: There was no meaningful difference in the observed ARR between EDSS subgroups supporting the concept that cladribine tablets 3.5 mg/kg is effective for patients with RMS, including those with higher EDSS and increased risk of conversion to SPMS with relapses.
Disclosure: This study was sponsored by EMD Serono Inc, a business of Merck KGaA, Darmstadt, Germany (in the USA), and Merck Serono SA, Geneva, an affiliate of Merck KGaA Darmstadt, Germany (ROW).

EPR1100

Pregnancy outcomes during the clinical development of cladribine in multiple sclerosis: an integrated analysis of safety for all exposed patients

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Background and aims: During clinical trials of cladribine in patients with multiple sclerosis (MS), contraception was specified for men and women of child-bearing potential. Despite these precautions, pregnancies occurred during the clinical trial programme. Here, we report pregnancy outcomes from an integrated safety analysis of patients exposed to cladribine during the clinical development programme in MS.
Methods: Pregnancy outcomes were recorded from an integrated analysis of safety of all exposed patients (cladribine n=1976, placebo n=802). Data on pregnancies recorded as adverse events were included from studies that involved treatment with parenteral cladribine or cladribine tablets.
Results: Overall, 64 pregnancies occurred among 57 women (44 pregnancies were in 38 women with exposure to cladribine; 20 in 19 women who received placebo). Proportions of live births, induced abortions (patient's decision), spontaneous abortions, and medically indicated abortions are presented in Table 1. Spontaneous abortion rates were consistent with epidemiological data on pregnancy outcomes. Three medically indicated abortions were carried out in 2 women who had received cladribine treatment; 2 were for ectopic pregnancies (occurring twice in the same patient), and 1 was for choriocarcinoma. Female partners of 9 cladribine-treated males experienced 10 pregnancies; 9 resulted in live births (1 unknown outcome). Female partners of 2 placebo-treated males experienced 2 pregnancies (unknown outcomes).

Number of pregnancies	Placebo (n=20)	Cladribine (n=44)
Live birth, n (%)	9 (45)	18 (41)
Induced abortion *, n (%)	4 (20)	14 (32)
Spontaneous abortion, n (%)	5 (25)	9 (20)
Medically indicated abortion, n (%)	1 (5)	3 (7)
Unknown, n (%)	1 (5)	0

*Patient's decision

Table 1: Pregnancy outcomes in the all exposed cohort

Conclusion: In this limited population of pregnancies with potential exposure to cladribine, no congenital malformations were identified. Because of the potential for teratogenicity, further study is warranted to better understand any risks that might be associated with cladribine in pregnancy.
Disclosure: This study was sponsored by EMD Serono Inc, a business of Merck KGaA, Darmstadt, Germany (in the USA), and Merck Serono SA, Geneva, an affiliate of Merck KGaA Darmstadt, Germany (ROW).

EPR1101

Efficacy of cladribine tablets 3.5 mg/kg in patients ≤50 and >50 years of age with relapsing-remitting multiple sclerosis (RRMS): a post hoc analysis from CLARITY

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Background and aims: In the CLARITY study, treatment with cladribine tablets (CT) significantly improved clinical outcomes vs. placebo in RRMS patients. Compared to older MS patients, younger patients with MS generally have a shorter disease duration and tend to have more inflammation and active disease. This post hoc analysis of CLARITY investigated whether the beneficial effects of CT are consistent in older and younger patients.

Methods: CLARITY patients randomised to CT 3.5 mg/kg or placebo were retrospectively stratified and analysed according to age; ≤50 years (n=761) and >50 years (n=109). Data for ARR and MRI outcomes (mean number of new T1 Gd+ and active T2 lesions) were compared between age subgroups.

Results: At baseline, the subgroup of patients aged >50 years had longer disease duration, higher EDSS score, larger T2 lesion volume, and lower incidence of ≥3 relapses in the previous year. In both the ≤50 and >50 years of age subgroups, CT reduced relapse risk compared to placebo by 59% and 52%, respectively (Figures 1 and 2). For placebo-treated patients, there were higher mean numbers of new T1 Gd+ and active T2 lesions for those aged ≤50 years compared to patients aged >50 (Figure 3). Despite the differences between the placebo-treated age groups, CT treatment demonstrated significant effects on MRI measures in both age groups (P<0.0001).

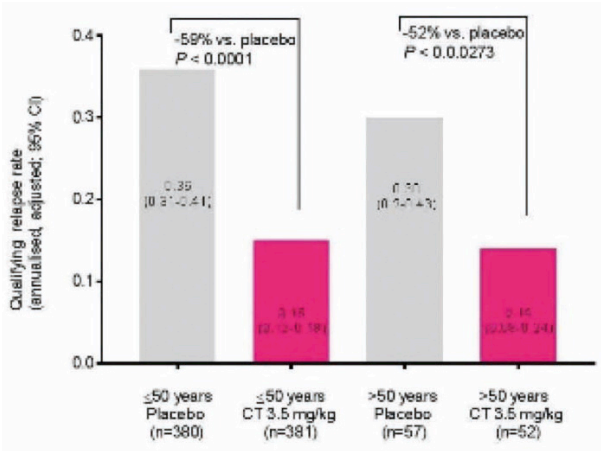

Figure 1: Estimated annualised relapse rates in patients with RRMS aged ≤50 or >50 years treated with cladribine tablets 3.5 mg/kg or placebo for 96 weeks in CLARITY

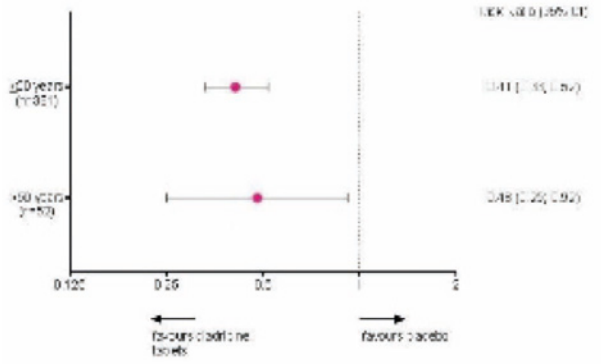

Figure 2: Annualised qualifying relapse risk ratio in patients with RRMS aged ≤50 or >50 years treated with cladribine tablets 3.5 mg/kg or placebo for 96 weeks in CLARITY

Conclusion: The results of this post hoc subgroup analysis suggest beneficial clinical and MRI effects of CT in RRMS patients aged ≤50 and >50 years, with improvements observed in ARR and MRI outcomes vs. placebo.

Disclosure: This study was sponsored by EMD Serono Inc, a business of Merck KGaA, Darmstadt, Germany (in the USA), and Merck Serono SA, Geneva, an affiliate of Merck KGaA Darmstadt, Germany (ROW).

EPR1102

Efficacy of cladribine tablets 3.5 mg/kg in patients with highly active relapsing multiple sclerosis (RMS): Pooled analysis of the double-blind cohort from CLARITY and ONWARD

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Background and aims: In the CLARITY (cladribine tablets [CT] vs. placebo) and ONWARD (CT added to interferon-beta vs. placebo added to interferon-beta) studies, CT demonstrated efficacy across a spectrum of patients with relapsing multiple sclerosis. Patients with high disease activity (HDA) are at higher risk of disability progression. Combining data from the double-blind (DB) periods of each study allowed the effects of 2 years' treatment with CT 3.5 mg/kg (CT3.5) to be assessed in these patients.
Methods: CLARITY and ONWARD patients randomised to CT3.5 or placebo were retrospectively analysed using two different HDA definitions based on relapse history, prior treatment, and MRI characteristics: high relapse activity (HRA) and HRA plus disease activity on treatment (HRA+DAT) (Figure 1).

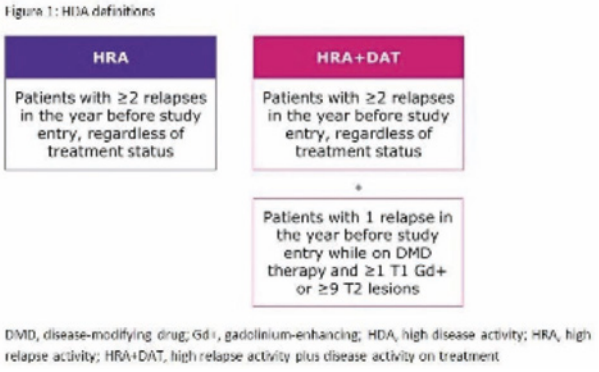

Figure 1: HDA Definitions

Results: In the overall combined DB cohort, CT3.5 reduced the risk of relapse and 3- and 6-month confirmed EDSS progression vs. placebo, an effect observed in both HDA subgroups. In the overall cohort and both HDA subgroups, patients receiving CT3.5 had a reduction in annualised relapse rate and in the number of new T1 Gd+ lesions, compared to patients receiving placebo. Compared to placebo, CT treatment increased the odds of achieving no evidence of disease activity (NEDA) in the overall population (OR, Cl: 3.95; 2.90-5.37), as well as in HRA and HRA+DAT subgroups (OR, CI: 6.94, 3.67-13.12 and 4.28, 2.62-6.99 respectively)
Conclusion: Both HDA and non-HDA patients receiving CT3.5 experienced significantly better relapse, MRI and NEDA outcomes, compared to placebo. HDA patients generally experienced better outcomes compared to non-HDA patients.
Disclosure: This study was sponsored by EMD Serono Inc, a business of Merck KGaA, Darmstadt, Germany (in the USA), and Merck Serono SA, Geneva, an affiliate of Merck KGaA Darmstadt, Germany (ROW).

EPR1103

Fingolimod may prevent RNFL thinning in multiple sclerosis when compared to first-line injectable treatments independently from disease activity

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Background and aims: Optical coherence tomography-OCT is used in multiple sclerosis-MS to measure retinal nerve fiber layer-RNFL and ganglion cell-inner plexiform layer (GCL-IPL) thickness as a marker of axonal-neuronal loss. A recent study suggested a protective role for Natalizumab on neuroretinal damage; we explored the role of Fingolimod-FTY in this field.
Methods: 90 patients with MS, 45 receiving FTY (mean treatment duration 2.59±1.2years) and 45 (mean treatment duration 4.19±3.6years) Interferon-IFN (n.24) or Glatiramer acetate-GA (n.21), underwent OCT with RNFL and GCL-IPL thickness measurement, with 1 year follow-up.
Results: No significant differences were found comparing IFN vs GA subgroups, so they were combined (IFN-GA). Over one year, patients under FTY had significantly lower RNFL thinning vs IFN-GA group (0.00±0.16µm vs -0.83±0.23µm; p=0.003), despite significantly lower baseline values (81.6±15.2µm vs 88.6±13.9µm; p=0.025). GCL-IPL thickness did not significantly differ between the two groups, both at baseline (IFN-GA 64.2±8.6µm vs FTY 61.1±9.7µm; p=0.097) and over time (-0.44±1.1µm for IFN-GA vs -0.09±1.3µm for FTY; p=0.303). Similar rates of disease activity (new relapses or new T2/Gd enhancing lesion at brain MRI) were found both in the year before baseline (24.3% for IFN-GA vs 28.8% for FTY; p=0.642) and during follow-up (15.3% for IFN-GA vs 13.3% for FTY; p=0.790).
Conclusion: These results suggest a neuroprotective role for FTY at the retinal level, independently from clinical and neuroradiological evidence of disease activity. Although a longer follow-up is warranted to confirm these observations, our findings appear consistent with experiences reporting reduced brain volume loss in patients receiving FTY.
Disclosure: part of this work was supported by NOVARTIS AG - Basel - Switzerland

EPR1104

Disability Outcomes in Young Adult Patients Treated with Fingolimod for up to 96 Months from Pooled FREEDOMS/ FREEDOMS II Extension Phases

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Background and aims: In the short-term, fingolimod demonstrated greater treatment benefits on disease activity in patients with relapsing remitting multiple sclerosis (RRMS) vs. placebo. Here we assessed disability outcomes in young adult patients (≤30 years) treated with fingolimod for up to 8 years.
Methods: Young adult patients from the pooled FREEDOMS core/extensions who were followed up for 8 years and received fingolimod 0.5mg (continuous group; N=163) or switched to fingolimod 0.5mg from placebo at Month (M) 24 (switch group; N=147), were included. The time-to-event outcomes: confirmed disability improvement (CDI; decrease in 6-month confirmed Expanded Disability Status Scale [EDSS] by ≤1.0/≤0.5 from baseline scores ≤5.5/≥6.0, respectively), CDI+ (CDI or 6-month confirmed 20% improvement in 9-hole peg test or the timed 25-foot walking test), 6-month confirmed disability progression (6m-CDP), EDSS score ≥4 and ≥6, and progression to secondary progressive MS (SPMS), were analysed using Kaplan-Meier estimates and Cox regression analyses.
Results: At baseline, young adults (vs. patients aged >30 years) had a shorter disease duration (4.5 vs. 10.5 years), lower EDSS (1.9 vs. 2.6), and larger brain volume (Table 1). At M96, a significantly higher proportion of patients in the continuous group (vs. switch group) achieved CDI (58.2% vs. 30.5%) and CDI+ (70.6% vs. 42.3%); a significantly lower proportion had 6m-CDP (20.1% vs. 34.7%) and reached EDSS ≥4 (24.1% vs. 34.1%), with no difference in EDSS ≥6 (10.2% vs. 10.3%). A very small number of patients reached SPMS in both groups (Table 2).

Table 1. Baseline characteristics of young adult patients aged <=30 years and patients aged >30 years in pooled FREEDOMS/FREEDOMS II

Characteristic	Young adult patients aged <=30 years (N=475)	Patients aged >30 years (N=1880)
Age, years	25.8±3.34	41.9±6.57
Duration of MS since first symptom, years	4.5±3.49	10.5±7.62
Number of relapses in previous 2 years	2.3±1.37	2.2±1.44
EDSS	1.9±1.19	2.6±1.31
9-HPT	21.1±5.95	22.7±9.84
T25FWT	5.5±4.64	6.1±4.30
Number of Gd+ T1 lesions	2.7±6.74	1.1±2.94
Volume of T2 lesions, mm³	5904.2±7373.41	5873.4±7840.79
Normalized brain volume, cm³	1571.2±75.38	1504.7±80.44

Data presented are mean±SD
9-HPT, 9-hole Peg Test; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; MS, multiple sclerosis; SD, standard deviation; T25FWT, Timed 25-Foot Walk Test

Table 1. Baseline characteristics of young adult patients aged ≤30 years and patients aged >30 years in pooled FREEDOMS/FREEDOMS II

Table 2. Kaplan-Meier estimates for time-to-event outcomes at Month 96

Disability outcome (M96 KM estimates, %)	Continuous group (Fingolimod 0.5mg)	Switch group (Placebo/Fingolimod)
n/N	36/82	17/78
CDI*	58.2	30.5
HR (95% CI), p-value	2.00 (1.11, 3.61), 0.0206	
n/N	42/82	22/78
CDI**	70.6	42.3
HR (95% CI), p-value	1.82 (1.14, 3.23), 0.0140	
n/N	22/183	33/147
6m-CDP†	20.1	34.7
HR (95% CI), p-value	0.46 (0.27, 0.80), 0.0038	
n/N	26/148	38/141
EDSS>=4	24.1	31.1
HR (95% CI), p-value	0.48 (0.29, 0.80), 0.0044	
n/N	10/153	12/147
EDSS>=6	10.2	10.8
HR (95% CI), p-value	0.49 (0.21, 1.14), 0.0971	
n/N	6/153	1/147
SPMS‡	4.9	1.8
HR (95% CI), p-value	4.25 (0.48, 38.55), 0.1933	

9-HPT, 9-Hole Peg Test; CDI, confirmed disability improvement; CDP, confirmed disability progression; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; KM, Kaplan-Meier; M96, month 96; n, number of subjects in the analysis; N, number of subjects in the event; SPMS, secondary progressive multiple sclerosis; T25FWT, Timed 25-Foot Walk Test

*CDI is defined as Sustained confirmed EDSS improvement (CEI) from baseline EDSS >=5.5 or by >=1.0 from baseline T25FWT >=6.0

**CDI is defined as CDI or Sustained confirmed 20% improvement in 9-HPT or T25FWT

†6m-CDP is defined as Sustained confirmed EDSS worsening (>=1.0 if baseline EDSS>=5.5, >=0.5 if baseline EDSS between 1.0 and 5.5, >=1.5 if baseline EDSS=0)

‡Diagnosis of SPMS implies an initial EDSS >=4.0 followed by a relapse free EDSS progression: >=1.0 if the initial EDSS was between 4.0 and 5.0, >=0.5 if the EDSS was >=5.5 that was confirmed after 6 months

Table 2. Kaplan-Meier estimates for time-to-event outcomes at Month 96

Conclusion: Early initiation of fingolimod in young adults with RRMS improved long-term disability outcomes.

Disclosure: Chitnis: personal compensation from Advisory board/consulting for Biogen-Idec, Novartis Pharmaceuticals and financial support for research activities from Merck-Serono and Novartis Pharmaceuticals Ghezzi: honoraria for speaking from Bayer-Schering, Biogen-Idec, Merck-Serono, Novartis, and Sanofi-Aventis; and for consultancy from Merck-Serono, Biogen-Idec, Teva and Novartis. Pohl: personal compensation for activities with Bayer Schering, Merck Serono and Teva. Silva and Häring: of Novartis Pharma AG, Basel, Switzerland. Meinert: nothing to disclose

EPR1105

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

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Background and aims: Ongoing safety reporting on disease-modifying therapies for multiple sclerosis (MS) is crucial to understanding the long-term benefit–risk profile. Data are reported from patients receiving ocrelizumab (OCR) in the Phase II study in relapsing-remitting MS (RRMS; NCT00676715) and in Phase III trials in relapsing MS (RMS; OPERA I/II [NCT01247324]/[NCT01412333]) and primary progressive MS (PPMS; ORATORIO [NCT01194570]). The purpose of the analyses was to report ongoing safety evaluations from OCR clinical trials and open-label extensions (OLEs).

Methods: Patients received intravenous OCR 600mg/24 weeks for 96 weeks in OPERA I/II and ≥120 weeks in ORATORIO. In the Phase II study, patients received 600mg or 2,000mg infusions through Week 24; treatment through Week 96 was OCR 600mg (patients receiving OCR 600mg, placebo or interferon-beta-1a) or 1,000mg (patients receiving OCR 2,000mg). Comparators were placebo (ORATORIO and Phase II) and interferon-beta-1a (subcutaneous/three times weekly [OPERA] or intramuscular/weekly [Phase II]). Patients completing controlled-treatment periods could enrol in the OLE with OCR 600mg/24 weeks. Data presented are from OCR recipients including those switching from comparators.

Results: As of February 2017, 2,301 patients with MS received OCR, resulting in 7,748 patient-years of exposure. Reported rates per 100 patient-years (95% confidence interval) were: adverse events (AEs), 226 (222-229); serious AEs, 7.18 (6.59-7.80); infections, 71.3 (69.5-73.2); serious infections, 1.86 (1.57-2.19); and malignancy 0.454 (0.316-0.632). Updated cross-trial information using a September 2017 data-cut will be presented.

Conclusion: The updated safety profile in the ocrelizumab MS all-exposure population is generally consistent with the controlled-treatment period for the RMS and PPMS populations.

Disclosure: Sponsored by F. Hoffmann-La Roche Ltd; writing and editorial assistance was provided by Articulate Science, UK.

EPR1106

Participant perspectives of a home-based palliative approach for people with severe multiple sclerosis: a qualitative study nested in a randomized controlled trial

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Background and aims: We undertook a multicenter randomized controlled trial to assess the effectiveness of a home-based palliative approach for adults with severe multiple sclerosis (MS) and their caregivers. Concurrently, we performed a qualitative study to investigate the experiences of the patients, their caregivers, patient referring physicians, and the teams who delivered the intervention. Our aim was to explore the strengths/challenges of the intervention, and circumstances that may have influenced its efficacy.

Methods: We performed semi-structured interviews with 12 patients and 15 informal caregivers (maximum variation strategy), two focus groups with patient referring physicians (four participants each), and one with the teams (nine participants).

Results: From data analysis (framework method) 38 sub-categories emerged, grouped into 12 categories and 3 themes: 'expectations,' 'met and unmet needs', and 'barriers'. Intervention benefits were improved control of symptoms and reduced sense of isolation of the patient-caregiver dyads. Limitations were: factors related to the experimental design; to the intervention; team issues; and external factors. The referring physician focus groups provided little experiential data.

Conclusion: The intervention reduced patient symptoms and sense of isolation of the dyads. The indirect role of the teams, and insufficient length of the intervention were key limitations. The experimental design imposed additional burdens on the dyads. Key barriers were the paucity of available services, demanding administrative procedures, and lack of networking facilities. These findings suggest two major requirements for home palliative care to be effective in this patient population: teams well-connected with MS rehabilitation services, and care delivered over the long-term, with variable intensity.

Disclosure: The Italian Multiple Sclerosis Foundation (Fondazione Italiana Sclerosi Multipla, FISM) funded the PeNSAMI trial (Grant No. 2014/S/1 to AS) and nested qualitative study.

Muscle and neuromuscular junction disease 1

EPR1107

Complement C5 Inhibitor RA101495 for the Treatment of Myasthenia Gravis

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[1]Neurology, University of North Carolina, Chapel Hill, NC, [2]Neurology, George Washington University, Washington, DC, [3]Neurology, Yale School of Medicine, New Haven, CT, [4]Neurology, University at Buffalo, Buffalo, NY, [5]Neurology, University of Miami, Miami, FL, [6]Ra Pharmaceuticals, Cambridge, MA, USA

Background and aims: Antibodies against acetylcholine receptor (AChR) activate the classical complement cascade in patients with myasthenia gravis (MG), and induce both, membrane attack complex (MAC) formation and tissue damage at the neuromuscular junction. Inhibition of C5 is a therapeutic target with a strong biological rationale for AChR-antibody positive MG. RA101495 is a subcutaneously-administered macrocyclic peptide that binds to C5 and inhibits its cleavage into C5a and C5b, thus preventing production of MAC. Phase 1 data supported initiation of a Phase 2 study with RA101495 in MG patients.

Methods: Healthy volunteers were randomized to receive single doses (n=14) or 7 daily doses (n=4) of RA101495 or placebo (n=10). Complement inhibition was evaluated using a validated antibody-sensitized sheep red blood cell lysis assay. Based on these data, a multi-center, randomized, double-blind, placebo-controlled Phase 2 study in AChR-antibody positive MG patients was initiated.

Results: In Phase 1, drug levels were consistent with predictions from in-silico modeling, i.e. steady increase over 7 days with daily dosing. The terminal half-life was approximately 7 days [Figure 1]. Near-complete inhibition of complement activity (≥95%) was achieved within 3 hours after the first dose and maintained for >24h [Figure 2]. No safety concerns were identified. Three RA101495-treated healthy subjects experienced mild, transient and self-limiting injection site erythema. The Phase 2 study design will also be discussed [Figure 3].

Conclusion: Subcutaneous self-administration of RA101495, if shown effective, may carry less treatment-related burden than currently available C5 inhibitor therapy and enable a broader population of MG patients to potentially benefit from this treatment modality.

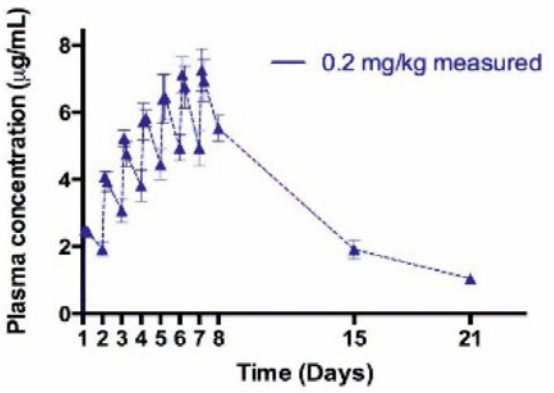

Figure 1, Pharmacokinetic Analysis: Plasma concentration of RA101495 in healthy volunteers dosed with 0.2mg/kg RA101495 daily

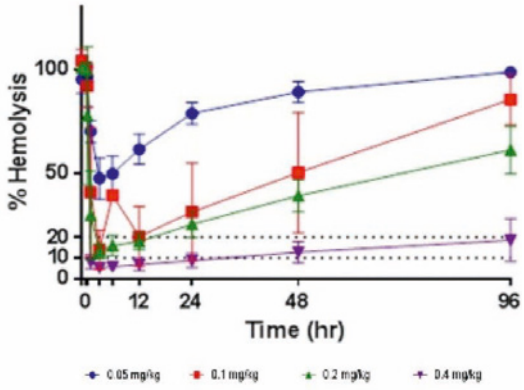

Figure 2, Pharmacodynamic Analysis: Hemolysis as assessed in sheep red blood cell lysis assay after single doses of RA101495 in healthy volunteers (placebo group had complete hemolysis throughout, not shown)

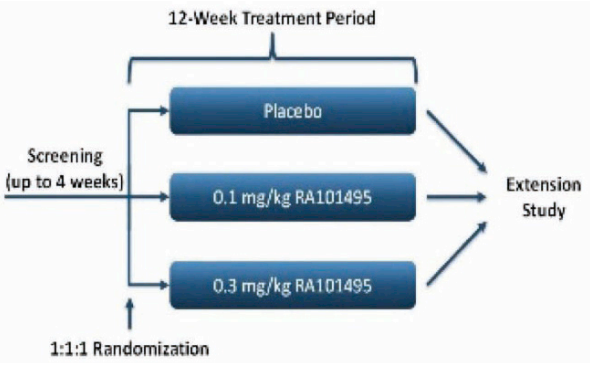

Figure 3, Study Design: RA101495 Phase 2 clinical trial in patients with myasthenia gravis

Disclosure: RA101495 clinical trials are sponsored by RA Pharmaceuticals, Inc.

EPR1108

Glycogenosis type V (McArdle's disease): Successful therapy with vitamin B6

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Background and aims: Mc Ardle's disease is characterized by exercise intolerance, muscle weakness and cramps. To date, no causal treatment is available and patients have to confine themselves to symptomatic therapy. Positive effects of vitamin-B6, an essential cofactor of myophosphorylase, on muscular endurance have been described in individual cases.

A patient with a previously undescribed homozygous mutation in the PYGM gene was treated with vitamin B6. The aim of this study was to verify clinically and biochemically an improvement reported by the patient.

Methods: We performed serial clinical examinations of muscle strength and endurance as well as forearm ischaemic exercise testing, with determination of lactate and ammonia in the presence and absence of vitamin B6 supplementation.

Results: Besides cessation of his muscle cramps, the patient's maximum walking distance doubled and plasma creatine kinase levels dropped significantly on vitamin B6. In the forearm exercise test, a normal increase of plasma lactate and ammonia was seen with vitamin B6, whilst only an insufficient response was recorded in the absence of vitamin B6. Molecular modelling of the myophosphorylase protein indicated that the mutation was located in the vicinity of the pyridoxine-binding site of the enzyme with a putative negative effect on pyridoxine binding.

Conclusion: The patient's mutation in the PYGM gene is located in the vicinity of the pyridoxine-binding site of the myophosphorylase protein and thus explains the favourable clinical and biochemical response to vitamin B6. A trial of vitamin B6 therefore seems justified in McArdle's disease, particularly if the mutation is located near the pyridoxine-binding site of myophosphorylase.

Disclosure: Nothing to disclose

EPR1109

Evaluating the usefulness of new line immunoassays for myositis antibodies in clinical practice: a retrospective study

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Background and aims: Myositis-associated(MAA) and myositis-specific antibodies(MSA) are detected in patients with inflammatory myopathies(IM) and are considered useful diagnostic biomarkers. Aim of our study was to assess the accuracy of MSA/MAA in diagnosing IM in our neuromuscular patients.

Methods: We have retrospectively analysed patients tested for myositis antibodies in our centre (2014-2017). The kit "Euroline:myositis 16Ag" has been used to assess the presence of: Mi-2alpha, Mi-2beta, TIF1gamma, MDA5, NXP2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1,SRP, PL-7, PL-12, EJ, OJ, Ro-52. Data on symptom at onset, CK, muscle biopsy and diagnosis were collected.

Results: 1232 patients were identified. Muscle biopsy was performed in 583 patients (47%). 148 patients had a confirmed IM, other diagnoses included: myopathy (n=356), other neuromuscular diseases (n=141), no neuromuscular diseases (n=587). The specificity was for MSA 95% and for MAA 89%, whereas the sensitivity was 21% and 22%. The positive predictive value was higher for MSA (54%) compared to MAA (37%) whereas the negative predictive value was the same for both MSA/MAA (80%). A positive test increases the post-test probability of having myositis of 30% (LR+=4) for MSA and 15% (LR+=2) for MAA, whereas a negative test does not significantly decrease the probability of having myositis (LR-=0.8 for both). In 154 patients the test was repeated at least twice and a high agreement between repeated measurements was found (82%).

Conclusion: Commercial immunoassays for myositis antibodies show low sensitivity and high specificity, they should therefore be used for confirmatory rather than screening purposes and repeating the test doesn't seem necessary. Combining antibody findings with clinical features will help developing specific diagnostic algorithms for IM.

Disclosure: Nothing to disclose

EPR1110

Neonatal cases of congenital myopathy due to RYR1 mutations: early findings at muscle biopsy and muscle MRI

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Background and aims: Mutations in RYR1 gene, encoding ryanodine receptor, are responsible for congenital myopathies (CM). These forms may be widely heterogeneous regarding inheritance, histopathological features, age of onset, clinical severity and evolution.

Methods: We selected a cohort of 9 patients affected by CM with pathogenic RYR1-mutations detected through Sanger sequencing or Next Generation Sequencing techniques. Phenotype spanned from paucisymptomatic hyperCKemia to severe neonatal presentation. Among them we focused on 4 severe congenital cases. All subjects underwent neurological evaluation, muscle biopsy and muscle Magnetic Resonance Imaging (MRI).

Results: Patients presented at birth with severe hypotonia and weakness, some of them even requiring long-term artificial ventilation (2) and percutaneous endoscopic gastrostomy (3). We identified 3 different and novel RYR1 mutations. Muscle biopsies showed an heterogeneous pattern, occasionally with unusual features (mitochondrial oxidative activity deficiency, neurogenic signs). Interestingly two biopsies were performed at a very young age, respectively at 5 and 37 days of life, and revealed abnormalities at ultrastructural analysis, leading to the diagnosis of congenital myopathy. Muscle MRI evidenced predominant involvement of gluteus maximus, adductor magnus, vastus and soleus muscles, with relative sparing of rectus femoris. One patient underwent intrauterine brain MRI.

Conclusion: Since now only few cases of neonatal RYR1-related myopathies with early muscle biopsy and MRI have been described. We report four neonatal cases with precocious evaluations. Muscle biopsy was not always specific, but typical features can be detected at electron microscopy examination. Instead, muscle MRI generally showed a typical pattern. These findings further enlarge our knowledge on this heterogeneous disorder.

Disclosure: Nothing to disclose

EPR1111

Myofibrillar myopathies: state of the art and new phenotypical features in a Parisian cohort

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Background and aims: Myofibrillar myopathies (MFM) are chronic neuromuscular disorders sharing common histological features, including myofibrillar disorganization beginning at z-disk, abnormal accumulation of protein aggregates and filamentous myofibrillar degradation products, and the presence of vacuoles. To date, DES, MYOT, CRYAB, ZASP, FLNC, BAG3, FHL1 and DNAJB6 are considered as the main genes responsible for MFM.

Methods: We retrospectively reviewed the clinical history, imaging, EMG, biological and histopathological characteristic of 75 patients with a diagnosis of MFM referred to the Institute of Myology in Paris.

Results: We characterized 29 patients with desminopathies, 10 patients with alpha-β-crystallinopathies, 11 patients with ZASP mutation, 5 patients with myotilinopathies, 13 patients with filaminopathies, 1 patient with a BAG3 mutation and 6 patients with DNAJB6 mutations. Beside the confirmation of previously described phenotypes, we report several unusual presentations: a bag3pathy, with an onset at childhood presented a rigid spine syndrome, a severe axonal sensorimotor neuropathy and no cardiac involvement; DNAJB6 mutation patients displayed predominantly a proximal phenotype (LGMD1D) in one family and a distal myopathy in the other.

Conclusion: MFM represent a clinically heterogeneous group of muscular disorders. This spectrum is expanding, leading to consider the diagnosis in conditions such as rigid spine syndrome or predominantly axial myopathies. MRI confirms its interest as a useful diagnostic tool especially in desminopathies.

Disclosure: Nothing to disclose

EPR1112

Serum anti-Mullerian hormone as a marker of fertility in women with myotonic dystrophy type 1 and 2

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Background and aims: Myotonic dystrophy (DM) represents the most common type of muscular dystrophy in adult age. Clinical signs and symptoms in type 1 (DM1) and type 2 (DM2) overlap. DM is a multisystem disorder that, among others, affects endocrine system and thus may have a negative impact on fertility. Recent studies suggest an impairment of fertility in female patients with DM1, while few data are available on female fertility in DM2.

One of the most important factors for fertility impairment is supposed to be decreased ovarian reserve. Anti-Mullerian hormone (AMH) is a peptide hormone that represents a simple and widely available measure of ovarian reserve unrelated to the menstrual cycle. The aim of our study was to compare ovarian reserve expressed as AMH values in women with DM1, DM2 and healthy volunteers.

Patients: A total of 15 reproductive-age females (mean age 36.0±8.6) with DM2, 11 age-matched females with DM1 (mean age 35.1±6.0) and 16 healthy controls (mean age 33.2±7.3) were included in this case control study.

Methods: An enzymatically amplified two-site immuno-assay was used to measure serum AMH level.

Results: Mean AMH levels were similar in females with DM2 (2.8±2.0 ng/ml) and healthy controls (2.9±1.7 ng/ml) (p=0.84), but were significantly lower in patients with DM1 (1.27±0.4) (p=0.02).

Conclusion: Our study confirms that decreased ovarian reserve represents one of the factors that may negatively influence fertility in women with DM1, but not in DM2.

Disclosure: Nothing to disclose

EPR1113

Clinical characteristics, management, and outcomes of Danon disease: A nationwide survey in Japan.

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Background and aims: Danon disease, an X-linked dominant vacuolar cardiomyopathy and skeletal myopathy, is caused by primary deficiency of lysosome-associated membrane protein-2 (LAMP-2). However, the clinical characteristics, management, and outcomes of Danon disease have not been well established.

Methods: Here, we sent questionnaires on Danon disease to 2,617 hospitals in Japan that have departments of neurology, cardiology, or pediatrics. We reviewed clinical histories, muscle specimens, and genetic analyses of the LAMP-2 gene.

Results: As a result, we identified 39 Danon disease patients (17 men and 22 women) from 20 families. Cardiomyopathy and ECG abnormalities were evident in all patients with Danon disease. Among the 20 patients who had died, 19 (95%) died of cardiac failure or sudden cardiac arrest. Hypertrophic cardiomyopathy (HCM) was documented in most patients. Wolf-Parkinson-White syndrome was noted at a relatively high incidence (25%). Heart transplantation, the most effective therapy, was performed in only one woman and is just now required by four patients. Some were supported by left ventricular assist devices, permanent pacemakers, and/or implantable cardioverter defibrillators. Pathologically, all patients showed autophagic vacuoles with sarcolemmal features in muscles. All patients had LAMP-2 gene mutations. Half of the probands showed de novo mutations.

Conclusion: In conclusion, Danon disease is a very rare muscular disorder and may be primarily caused by lysosomal dysfunctions. Cardiomyopathy is the most important prognostic factor and the main cause of death among Danon disease patients. Danon disease may be overlooked in patients with HCM, since other clinical features including myopathy can be mild, particularly in women.

Disclosure: Nothing to disclose

EPR1114

Reducing emergency hospital admissions in England: the importance of the co-ordination of care at specialised neuromuscular services

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Background and aims: A 2 part project conducted over a 6-year period aimed to identify the reasons for preventable unplanned admissions in order to improve care and reduce emergency admissions in patients with neuromuscular diseases (NMDs) in the South-East England.
Methods: Two NHS audits (retrospective case note studies) on unplanned admissions in patients with NMDs in the South-East of England were performed 5-years apart. Inclusion criteria were emergency admission codes and NMD diagnosis ICD-10 codes. Exclusion criteria were incomplete medical notes, elective admissions, absence of a NMD and obstetric admissions.
Intervention: In between both audits, recommendations and a partnership approach project were developed to co-ordinated care and to prevent known NMDs complications in the analysed regions.
Results: Audit 1 showed a substantial proportion of preventable admission in this patient population. Positive impacts of implemented changes included more referrals to specialised centres and more admissions under Neurosciences care (77% in 2014-2016, as compared to 14.9% in 2009-2011). Improvements also included a reduction in preventable admissions directly related to previously known NMDs (from 63% to 32.8%) and reduction in re-admissions (from 25.1% to 12.4%). Mortality rate dropped from 4.5% to 0.3%. Patients known to NMD specialised services had shorter hospital stay and fewer ITU admissions than patients who were not known to such services.
Conclusion: Audit 1 suggested issues related to patients' care contributed to the high frequency of unplanned admission in this patient population. Improvement in the provision of NMD services reduced emergency admissions and improved outcomes, which were successfully documented in Audit 2.
Disclosure: Nothing to disclose

Neurogenetics 1

EPR1115

Micro RNA in Muscular Dystrophies and Metabolic myopathies are useful biomarkers

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Background and aims: To investigate microRNAs (miRNAs) that are small non-coding RNAs that modulate a wide range of biological functions in various metabolic and myopathologic conditions we studied thhe circulating microRNAs in Becker and FSHD muscular dystrophy as well in lipid storage myopathies MiRNAs can be actively released by muscle, carried by exosomes, microparticles and apoptotic bodies or released after sarcolemmal damage.
Methods: We have particulary studied "Canonical myomiRs" (miR-1; miR-206; miR-133a and miR-133b), they are considered as markers of muscle regeneration, myogenesis, fiber type differentiation, degeneration, injury and might represent indicators of residual muscle mass consequent during chronic atrophy of muscle or its metabolic dysfunction in lipid storage myopathies.
Results: Circulating miRNA have been studied in several muscular dystrophy cases and myopathies such as FSHD and Becker muscular dystrophy, LGMD, Lipid Storage Myopathies. We investigated their level observed in various LGMD (transportinopathies, sarcoglycanopathies),BMD and FSHD as well a series of metabolic myopathies (i.e. NLSD-M, ETF dehydrogenase deficiency).Different level of micro RNAs were found while an upregulation of MiR 206 was seen in the course of FSHD and LGMD, MiR 133a and Mir133b were elevated in BMD and ETF dehydrogenase deficiency. In NLSDM an upregulation of all myo-MiRNA correlated with muscle imaging.
Conclusion: In neuromuscular disorders MiRNAs act as negative regulators, we have found a significantly higher expression of miR-206 in serum of several and metabolic and primitive genetic dtstrophies we observed differential serum expression of myomiRNA in a number ofl muscular dystrophies and metabolic myopathies.
Disclosure: Supported by Telethon GGP14066

EPR1116

Quality of life and modifiable lifestyle factors in Leber's Hereditary Optic Neuropathy mutation carriers

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Background and aims: Leber's Hereditary Optic Neuropathy (LHON) is the most frequent mitochondrial disease, leading to bilateral central vision loss and disability. LHON is caused by mitochondrial DNA point mutations, with incomplete penetrance. Risk of disease for carriers differs significantly between genders, with genetic and environmental factors modifying this risk.
Methods: 71 participants of the Munich prospective study on LHON mutation carriers, recruited between 2014 and June 2015, 16 years and older, were included. Systematic neurological and ophthalmological examinations were performed yearly. At each visit, questionnaires on smoking, alcohol, depression and quality of life (QoL) were completed. Nominal data were compared by chi-square tests and continuous data by t-tests, stratified by gender.
Results: 34 (48%) patients (28 male, 82%), and 37 asymptomatic LHON mutation carriers (7 male, 19%) were included. Median age at onset was 26.9 years (range 9.4-71.8), median disease duration was 2.5 years (range 0.4-36.6). The proportion of smokers before onset was significantly higher among patients than for the general population. 60% of LHON patients, who smoked before onset, reduced or stopped smoking after onset. In spite of scoring higher on physical health QoL subscales, asymptomatic female LHON mutation carriers showed worse results in mental health QoL subscore, compared to female LHON patients and female general population ($p<0.001$).
Conclusion: This study provides insights on LHON mutation carriers, with female asymptomatic carriers showing increased frequency of depressive symptoms and decreased mental health-related QoL, while highlighting modification of lifestyle factors in this population as potentially significant prophylactic measures.
Disclosure: Nothing to disclose

EPR1117

A case of adult-onset leukoencephalopathy with axonal spheroids and pigmented glia, presenting with young dementia and allodynia revealing a novel mutation.

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Background and aims: Adult onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), mainly caused by mutations in the colony stimulating factor-1 receptor (CSF1R) gene, is an underestimated progressive degenerative white matter disease with a wide spectrum of phenotypes that encompasses hereditary diffuse encephalopathy with spheroids (HDLS) and pigmentary orthochromatic leukodystrophy (POLD)[1]. We report a novel mutation of CSF1R in a 45-year-old woman presenting with a spastic hemiparesis, left-sided allodynia, gait ataxia, dysarthria and cognitive deterioration.
Methods: Case report and review of the literature.
Results: A 45-year-old woman without familial history developed allodynia, a left hemiparesis, cognitive impairment and depression. Examination showed a spastic hemiparesis, gait ataxia and dysarthria. Neuropsychological testing revealed frontal dysfunction. Brain MRI showed confluent periventricular white matter lesions, corpus callosum atrophy and diffusion-restricted lesions (figure 1), characteristic for ALSP. Brain CT showed periventricular calcifications with a typical stepping stone appearance (figure 1), brain FDG-PET showed hypometabolism frontoparietal and in the basal ganglia. Genetic analysis of the CSF1R-gene revealed a novel mutation (c.2466G>A, p.Met822IIe Mayoclinic, R. Rademakers). Progressive neurological deterioration with a tetraparesis and bedridden state evolved and she eventually died 3 years after symptom-onset. Brain autopsy including electron microscopy of the frontal deep white matter showed axonal spheroids, swollen axons containing neurofilaments and residual bodies and macrophage containing pigmented lipofuscin, hallmark features of ALSP (figure 2).

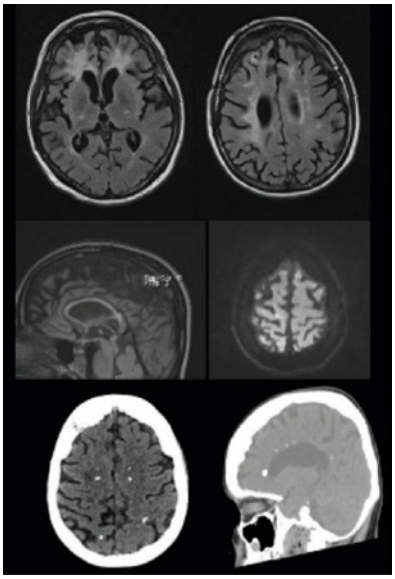

Figure 1: a-d.: Confluent white matter lesions periventricular, corpus callosum atrophy and diffusion-restricted lesions, e-f.: Calcifications, sparing basal ganglia, with stepping stone appearance

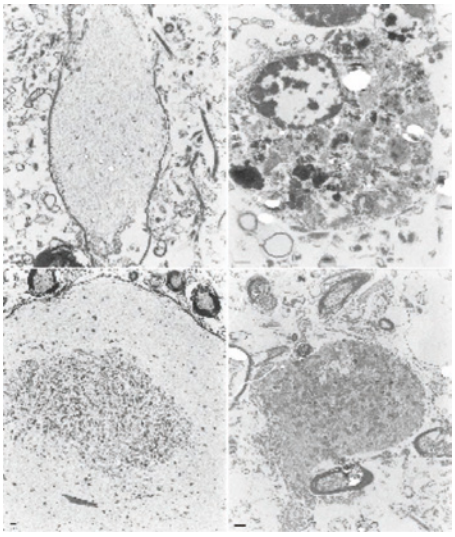

Figure 2: Electron Microscopy of frontal lobe, deep white matter. a. Swollen Axon b. Macrophage containing pigmented lipofuscin c. Swollen axon containing neurofilaments and residual bodies d. Axonal Spheroid

Conclusion: This report highlights the importance of considering ALSP in the differential diagnosis of adult-onset leukoencephalopathy and adds to the growing list of CSF1R-mutations in ALSP.
Disclosure: Nothing to disclose

EPR1118

Utility of Whole Exome Sequencing as a diagnostic tool in different neurologic phenotypes

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Background and aims: Next generation sequencing methodologies, including whole exome sequencing (WES), are transforming the way neurology is practiced. Our aim here was to evaluate the utility of WES in various phenotypes in a cohort of Greek patients.

Methods: Patients presenting with neurological disorders deemed genetic in origin were offered WES based on prespecified criteria. After obtaining informed consent, WES was performed on 109 patients (46 females; mean age=19.5±2.0 years, range 1-73 years). Sequencing was performed at Otogenetics, Norcross, GA, USA, using the Illumina HiSeq2000/25000 platform aiming at a 50X coverage. Variant annotation was performed in the Neurology Laboratory, University of Crete, Greece, using the Ingenuity (Qiagen, USA) software and taking into consideration clinical and bibliographic information.

Results: The most common indications for ordering WES were epilepsy/epileptic encephalopathies (29.3%), muscle disorders (19.3%), developmental disorders (13.8%) and motor neuron disease/spastic paraparesis (8.3%). The overall diagnostic rate of WES was 46.8% (causative genetic defects identified in 51/109 patients). Per diagnostic category, the diagnostic rate was: epileptic syndromes 34.4% (11/32), muscle disorders 66.7% (14/21), developmental disorders 60.0% (9/15), motor neuron disease/spastic paraparesis 55.5% (5/9), cerebellar ataxia 14.3% (1/7), metabolic disorders 66.7% (4/6) and polyneuropathy 50.0% (2/4). In most instances, WES provided final diagnosis after several tedious and expensive diagnostic tests were inconclusive.

Conclusion: In our cohort of neurological and pediatric neurology patients, WES showed high diagnostic efficiency. These data offer support to the value of WES when applied in clinical practice to end the diagnostic Odyssey of patients with heterogeneous neurogenetic disorders.

Disclosure: Nothing to disclose

EPR1119

Novel, likely pathogenic, sequence variants in hereditary neuropathy genes

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Background and aims: Hereditary neuropathy is caused by a large number of genes involved in different cellular mechanisms. Charcot-Marie-Tooth (CMT) disease is the most prevalent inherited neuropathy. Next-generation sequencing (NGS) has during the last five to ten years entered the clinical diagnostics. NGS has proven to be efficient in the diagnostics of disorders where multiple genes can be involved.

Methods: Our NGS-based targeted gene panel consists of 99 hereditary neuropathy genes, i.e. mostly CMT genes. This study is a retrospective study of clinic samples received between May 1 2014 and October 1 2017.

Results: We describe the identified novel likely pathogenic sequence variants, according to International Guidelines. In this period we identified novel, not previously described, likely pathogenic sequence variants in the following genes: AARS, ANO5, BSCL2, FGD4, GAN, GJB1, HINT1, HSPB1, IGHMBP2, LITAF, LRSAM1, MME, MPZ, NEFL, PMP22, POLG, SBF1, SH3TC2 and YARS.

Conclusion: There is now a wide range of genes causing hereditary peripheral neuropathies and many likely pathogenic sequence variants. Likely pathogenic sequence variants are identified in old well established neuropathy genes as well as in the newer genes. The affected in a hereditary neuropathy family share the unique sequence variant causative for the familial disorder.

Disclosure: Nothing to disclose

EPR1120

Genetic analysis of a dementia patients' cohort: experience from Coimbra center in Portugal

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Background and aims: The Dementia outpatient clinic of the University Hospital Center of Coimbra, the largest hospital in the central region of Portugal, is a reference centre on dementia diagnosis and with the support of the Neurogenetics Laboratory has been focused on the genetically mediated dementia forms. We aim to analyse the known causative dementia genes and ApoE genotype in our patient's cohort representative of this region with 2 millions.
Methods: The genetic analysis included: PSEN1 and 2, APP, MAPT, GRN, C9orf72 and SQSTM1 as well as the major genetic AD risk factor, ApoEε4 allele.
Results: A cohort of 2273 patients was recruited: 963 AD, 377 MCI, 248 FTLD, 17 CBD, 11 PSP, 151 LBD, 149 VD or mixed dementia; the remainder have other diagnosis. We identified 4 mutations in PSEN1, PSEN2 and APP in AD patients, 13 C9orf72 expansions, 16 GRN, 3 MAPT and 5 SQSTM1 mutations in FTLD, CBD and LBD patients. In AD patients 45% were ApoEε4 carriers.
Conclusion: In AD patients, the overall low mutation frequency (0.4%) suggests that other yet unknown genes must be involved. ApoEε4 frequency is in accordance with the previously reported. In FTLD cohort, C9orf72 and GRN are the major genetic causes followed by MAPT and SQSTM1 genes. However, mutations in GRN and SQSTM1 genes are also associated with CBD and LBD, respectively. Interestingly, some of the mutations found are novel and are shared by several unrelated patients, reflecting the specific genetic background of the Portuguese population, although we cannot rule out a common ancestor in these families.
Disclosure: Nothing to disclose

EPR1121

Targeted sequencing for the diagnosis of familial dementias

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Background and aims: Genetics is intricately involved in the etiology of degenerative dementia. Indeed, familial occurrence varies between 2% and 50%, depending on the dementia subtype. The current clinical approach is to test a single gene or a limited group of genes using Sanger sequencing, according to specific flow-charts. However, identifying a specific genetic cause of dementia can be difficult due to phenotypic overlap between the different forms of dementia subtypes, locus heterogeneity, and variability in accessibility of genetic tests.
Methods: In this study, we conducted targeted sequencing of 300 heterogeneous patients, mainly with early-onset and/or familial neurodegenerative dementia, using a custom-designed Next Generation Sequencing (NGS) panel covering 27 genes known to harbor mutations that can cause different types of dementia, in addition to the detection of C9orf72 repeat expansions. Novel variants were classified according to the standards and guidelines for the interpretation of sequence variants.
Results: We identified pathogenic and novel likely pathogenic variants in 55 patients (18.33%), in common (presenilin 1, presenilin 2, C9orf72, and granulin) and rare genes (optineurin, serpin family I member 1 and protein kinase cAMP-dependent type I regulatory subunit beta). Additionally, we found one patient with a novel possible risk factor, seven with known genetic risk factors, and ten with previously reported variants of uncertain significance.
Conclusion: Our results support the use of an extended NGS panels as a quick, accurate and cost-effective method for diagnosis in clinical practice. This approach could have a significant impact on the proportion of tested patients, ideally all with early onset disease.
Disclosure: Nothing to disclose

Neuroimaging 1

EPR1122

Functional connectivity changes in relation to dopaminergic decline in Parkinson's over time: a resting-state fMRI and 11C-PE2I PET imaging study

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Background and aims: Resting-state functional magnetic resonance imaging (fMRI) has demonstrated that basal ganglia functional connectivity is altered in Parkinson's disease (PD) as compared to healthy subjects. However, such functional connectivity alterations have not been related to the dopaminergic decline that occurs in PD over time. To evaluate the functional connectivity patterns of basal ganglia subdivisions in relation to dopamine transporter density, as assessed with Positron Emission tomography (PET) and the specific tracer11C-PE2I, and motor features in patients with PD at baseline and over time.

Methods: We assessed functional connectivity of the basal ganglia subdivisions during resting-state fMRI and dopamine transporter density using 11C-PE2I PET in thirty PD patients at baseline. Of these, 15 PD patients were rescanned after 19.9±3.8 months. A seed-based approach was used to analyse resting-state fMRI data. 11C-PE2I binding potential (BPND) was calculated for each participant with the seed regions-of-interest.

Results: At baseline, functional connectivity between striatum and substantia nigra/supplementary motor area (SMA) was significantly correlated with striatal 11C-PE2I BPND. Moreover, substantia nigra-caudate/putamen functional connectivity was significantly correlated with nigral 11C-PE2I BPND. Over time, reduction in posterior putamen functional connectivity with substantia nigra and SMA was significantly correlated with decreases in posterior putamen 11C-PE2I BPND.

Conclusion: Our findings suggest that basal ganglia functional connectivity is related to the integrity of the dopamine system in patients with PD. Application of resting-state fMRI in a large cohort and longitudinal scanning may be a powerful tool to study functional connectivity changes in PD over time.

Disclosure: Nothing to disclose

EPR1123

Natural history of brain inflammatory lesions in multiple sclerosis: a FLAIR and T1w post contrast MRI volumetric analysis

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Background and aims: To characterize the pathology of new MS lesion formation using monthly FLAIR and post contrast T1w scans.

Methods: The volume of brain white matter (WM) lesions was evaluated monthly on FLAIR and T1w after a single (T1wGdSD) and triple (T1wGdTD) dose of gadolinium based contrast agent.A kinetic time course analysis was applied to the post contrast FLAIR and T1w volumes and a two-random-walks model to the FLAIR volume kinetic.

Results: RRMS patients(n=26) underwent a monthly MRI follow-up. The highest volume recordered on FLAIR images was superior to the T1wGdTD one that in turn was superior to the one observed on T1wGdSD, showing similar bell shape profiles. The FLAIR volume kinetic was described by two two-random-walks curves: a rapid onset one, with similar shape compared to the T1wGdSD-TD curves and a second one beginning at the same time but slowly increasing and decreasing. Both nodular(n=84) and ring enhancing lesions(n=16) were described by this model with high fitting quality.

Conclusion: FLAIR MRI resulted to be sensitive to both acute and later stages of lesion pathology: the rapid onset random walk curve, similar in shape to the T1wGdSD-TD ones, describing the acute inflammatory phase marked by overt BBB disruption and the second random walk curve, slowly increasing and decreasing, mirroring the demyelinating process. The mathematical analysis of FLAIR volume kinetic (second random walk curve) may help to monitor remyelinating treatments efficacy in MS. This biological model was valid for both nodular and ring enhancing lesions suggesting a similar physiopathological substrate.

Disclosure: Nothing to disclose

EPR1124

Brain glucose metabolism and connectivity support current diagnostic criteria for Lewy Body Dementia

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Background and aims: Dementia with Lewy bodies (DLB) is a common neurodegenerative condition characterized by a prevalent neurodegeneration of occipital brain regions. Although a posterior brain hypometabolism, as assessed by [18F]FDG-PET, is a supportive feature in the DLB diagnostic criteria, the relationship with clinical features are yet to be elucidated. We aimed to characterize [18F]FDG-PET brain metabolism alterations in a large cohort of patients, in conjunction with detailed clinic-neuropsychological evaluations.
Methods: In a cohort of probable DLB patients (N=72), we applied to [18F]FDG-PET data: i) a validated voxel-wise analysis to obtain brain hypometabolism maps in single-cases, ii) hierarchical cluster analysis to investigate the presence of brain dysfunctional subtypes within our group, iii) seed-based interregional correlation analysis to assess the resting-state networks.
Results: The temporo-parietal and occipital hypometabolism was highly consistent in each included single-case. According to the hierarchical cluster analysis, the severity of occipital hypometabolism varied among patients: a more severe occipital hypometabolism was associated with worse global cognitive status, in particular visuo-perceptual performances, and presence of visual hallucinations.
Network analysis revealed local and long-distance connectivity alterations converging to the posterior brain networks. We found an association between presence/amount of hallucination and alterations in the attentional and visual resting-state networks, and between rapid eye movement sleep behavior disorder and alterations of the subcortical networks.
Conclusion: The disease-specific brain metabolism signature in single-subject supports the FDG PET role in the current consensus criteria for DLB diagnosis. The underlying connectivity dysfunction and network-level alterations, differentially associated with the core clinical manifestations, may promote clinical heterogeneity within the disease.
Disclosure: This work was supported by EU FP7 INMIND Project (FP7-HEALTH-2013, grant agreement no. 278850), and the IVASCOMAR project "Identificazione, validazione e sviluppo commerciale di nuovi biomarcatori diagnostici prognostici per malattie complesse" (grant agreement no. CTN01_00177_165430).

EPR1125

Globus pallidus and red nucleus T2 signal differences in idiopathic and LRRK2-related Parkinson's disease

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Background and aims: In both idiopathic and some monogenic forms of Parkinson's disease (PD), increased iron deposition in the substantia nigra has been described, resulting in lower signal intensity in T2-weighted magnetic resonance (MR) images. In other areas of the brain findings are controversial. Our aim was to characterize signal changes in the globus pallidus (GP) and red nucleus (RN) in PD patients with LRRK2 gene mutations (LRRK2-related PD) and idiopathic PD (iPD), using T2-weighted MR imaging.
Methods: Comparative cross-sectional study including iPD and LRRK2-related PD patients and healthy controls with no known family history of neurodegenerative disorders. Imaging data was acquired using a 3.0 Tesla MR scanner. Regions of interest were manually drawn in the GP and RN and semi-automatically delineated. Mean signal intensity was obtained for each group and used for non-parametric analysis. A p-value below 0.05 was considered significant.
Results: Eleven iPD patients, 12 LRRK2-related PD patients (9 G2019S; 3 R1441H) and 9 healthy controls were included. Using manual segmentation, we identified significantly higher signal intensity in the posterior segment of the GP of the iPD group (462±82) compared to controls (404±76) and significantly higher signal intensity in the RN of the LRRK2-related PD (509±80), compared to controls (450±88). Using semi-automatic segmentation methods, a similar trend was noted. No significant differences were found when comparing iPD and LRRK2-related PD.
Conclusion: T2 signal differences found between iPD and LRRK2-related PD may indicate decreased iron deposition in the GP in iPD and in the RN in LRRK2-related PD.
Disclosure: Nothing to disclose

EPR1126

From minimally conscious state minus to minimally conscious state plus: A multiple case study

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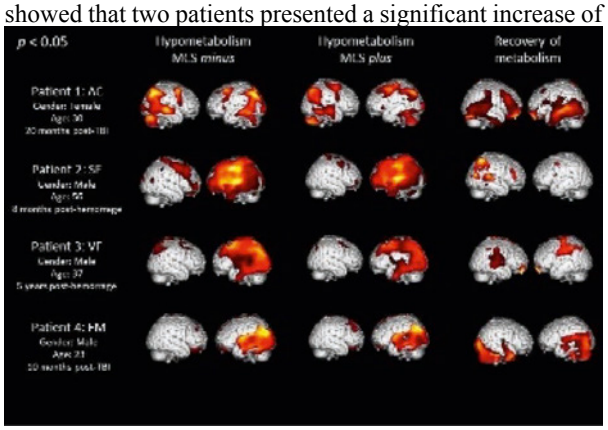
Background and aims: The minimally conscious state (MCS) has been sub-categorized in MCS minus and plus, based on language-related behaviors (i.e., command-following, intelligible verbalization or intentional communication [Bruno et al., 2011]). We here aim to describe behavioral and neuroimaging data of severe brain-injured patients who evolved from MCS minus to MCS plus.

Methods: Four patients (23-56 years old, 2 TBI, time since onset: 8 months to 5 years) were assessed at two time points using the Coma Recovery Scale-Revised. During their first week of assessments, they were diagnosed as MCS minus. They later recovered language-related behaviors (i.e., MCS plus), when reassessed during their second week of evaluations. All patients underwent a positron emission tomography (PET-scan) and magnetic resonance imaging (including voxel-based morphometry – VBM) exams during both assessments. We here compared the neuroimaging differences between the two exams in these four patients.

Results: PET-scan results showed that all patients presented partial recovery of metabolism in temporal lobules, reflecting compensation either from left-sided language areas or from their contralateral regions. VBM results showed that two patients presented a significant increase of



Brain metabolism of the four patients who evolved from MCS minus to MCS plus. Results are significant at $p<0.05$.

Conclusion: The clinical evolution of patients from MCS minus to MCS plus suggests the reappearance of language-based behavioral signs, but also the partial recovery of metabolism and grey matter structure in cerebral regions that were previously associated to language processing. These neuroimaging results highlight the remaining neuroplasticity in chronic MCS.

Disclosure: Nothing to disclose

EPR1127

Association between abnormal functional connectivity of thalamic sub-regions and clinical disability in CIS patients: a longitudinal study

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Background and aims: No study has explored thalamic connectivity abnormalities in early stages of multiple sclerosis (MS). We investigated sub-regional thalamic resting-state (RS) functional connectivity (FC) abnormalities in patients with clinically isolated syndrome (CIS) suggestive of MS and their correlation with disability.

Methods: Structural and RS fMRI data were acquired from 59 CIS patients and 13 healthy controls (HC) at baseline (within 3 months from first attack), year 1 and year 2. Five thalamic sub-regions (frontal, motor, postcentral, occipital, temporal) were parcellated according to their cortico-thalamic structural-connectivity, and used for seed-based RS FC analyses. Thalamic RS FC abnormalities were assessed and correlated with EDSS at follow-up.

Results: Forty-nine (83%) patients developed MS at year 2. At baseline, compared to HC, CIS patients had reduced thalamic RS FC with frontal cortices and cerebellum, for the frontal and motor sub-regions. During follow-up, there was a progressive reduction of thalamic RS FC with: 1) the cerebellum, for the whole thalamus, motor, postcentral, occipital, and temporal sub-regions; 2) some areas of the default-mode network, for occipital and postcentral sub-regions; and 3) temporal cortices, for the whole-thalamus, frontal and temporal sub-regions. Sub-regional thalamic RS FC abnormalities correlated with higher EDSS at follow-up.

Conclusion: Dynamic alterations of thalamic sub-regional connectivity abnormalities with frontal, temporal, default-mode and cerebellar regions characterized CIS patients. Regional thalamic connectivity abnormalities with the frontal cortex and cerebellum at baseline contributed to explain disability after two years, highlighting the role of thalamic involvement in the first stages of the disease for subsequent clinical outcome.

Disclosure: Partially supported by a grant from the Ministry of Science, Republic of Serbia (# 175031).

EPR1128

What does clinical language fMRI look like? Results from a survey of 63 analysts

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Background and aims: Functional MRI is validated for lateralizing language areas in pre-surgical planning, but anecdotally the protocols used across sites vary markedly. Here we report the first comprehensive survey of analysts undertaking clinical fMRI for presurgical planning in epilepsy.

Methods: Respondents included 63 analysts completing language fMRI and were primarily from the US (44%), Europe (32%), and Australia (11%). They were typically from programs in academic centers (82%) treating primarily adults (42%), adults and children (36%), or children alone (22%).

Results: Over 18 cognitive tasks were reported as being in use, with the most frequent including noun-verb generation, verbal fluency, and object naming. Over 75% of programs complete three or more protocols, with runs having a modal duration of 5 minutes. Nearly all aspects of the tasks used differ among programs, including stimulus modality and control conditions, and fMRI has been adapted formally and informally to a range of languages. A de-facto standard data processing stream is evident, with analysis most often using open-source analytic software SPM.

Conclusion: While language fMRI is well established for presurgical language mapping in epilepsy, the protocols used across sites vary markedly and some of the best-validated protocols appear to be rarely used. There is a strong need for comprehensive, accessible guidelines for clinical fMRI and for open, freely available, replicable approaches that can be adopted at any site. Key points for successful use of fMRI in the clinic are noted.

Disclosure: This work was supported by Yale CTSA [UL1TR000142] from the National Center for Advancing Translational Science (NCATS), National Institutes of Health USA; and the Swebilius Foundation.

Neuroimmunology 1

EPR1130

Neurological complications of antiTNF therapies: 16 years tertiary University Hospital experience

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Background and aims: AntiTNF therapies (infliximab, etanercept, adalimumab, golimumab) are widely used in Rheumathology (rheimatoid arthitis, RA, ankylosing spondylitis, AS, psoriatic arthritis, PA), and Gastroenterology (inflamatory bowel disease, IBD). Increased risk of infection and malignancy are common concerns, but neurological complications are considered rare.
Methods: Retrospective analysis of the electronic database of our tertiary university hospital Neurology Department, from 2002-2017, with the search terms antiTNF, infliximab, etanercept, adalimumab, and golimumab. Patients with neurological complaints while on active treatment with these agents were included, clinical variables analysed with appropriate statistical tests.
Results: 15 episodes of 14 patients, 53.4% female with a mean age of 53 years (±8.1DE), on treatment with infliximab (9), adalimumab (6) and golimumab (1) because of IBD (7), RA (5), SA (4), PA (1) and pyoderma gangrenosum (1) were included. No neurological complications related to etanercept were found. Clinical diagnosis was stroke or TIA in 9, demyelinating central nervous system disease in 3, cerebral venous thrombosis in 1, and other diagnoses in 3. Symptoms were deemed unrelated to antiTNF treatment in 5 cases (31%): 2 patients with stroke (atherothrombotic and cardioembolic stroke), 1 patient with psychogenic neurological symptoms and 2 patients with secondary headache (to calcium blockers and aseptic meningitis respectively). Neurological complaints prompted antiTNF discontinuation in 4 (30.7%)
Conclusion: In our experience, neurological complications of antiTNF therapies are rare, being infliximab the most commonly involved. Demyelinating disorders and venous thrombosis, previously described, are represented. A posible association with stroke of undetermined etiology should be assessed with prospective studies.
Disclosure: Nothing to disclose

EPR1131

Establishment of a high-throughput microELISA screen for naturally occurring human tau autoantibodies

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Background and aims: Currently, treatment strategies for tauopathies are scarce and there is a need for specific treatment options. A new approach striving towards the development of novel disease-modifying strategies for neurodegenerative diseases is the of use naturally occurring monoclonal antibodies as therapy. To interrogate the human immune repertoire, a high-throughput screen for naturally occurring tau antibodies will be performed to explore the potential value of tau antibodies as diagnostic biomarkers and therapeutics.
Methods: The Institute of Neuropathology has developed a high-throughput screening platform that allows for screening of 20,000 patients for naturally occurring antibodies against multiple antigens. Recombinant monomeric and aggregated tauK18 as well as full-length tau441 will be absorbed to 1536-well plates and heparin plasma samples will be serially diluted using acoustic dispensing technology. Tau autoantibodies will be detected using an indirect microELISA that runs in a fully-automated robotic platform.
Results: Preliminary data from an initial 953-patient screen showed distinctly reactive patients (negative logarithmic EC50 $\geq$ 2) for tauK18 monomers (corresponding to the 4-repeat sequence of the aggregation domain of tau). To confirm these, competitive ELISAs were performed.
Conclusion: The initial 953-patient screen served as proof-of-feasibility for the microELISA screen for naturally occurring human tau autoantibodies. We will continue to screen 20,000 patients and perform an epidemiological study of tau autoantibodies correlating patient reactivity with clinical data. This will enable us to explore the potential of tau autoantibodies as diagnostic biomarkers of tauopathies and elucidate on the current controversy about the occurrence of anti-tau autoantibodies in healthy vs. diseased subjects.
Disclosure: Nothing to disclose

EPR1132

Soluble factor profile in Natalizumab treated MS patients: increased Th1 promoting factors and sHLAg

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Background and aims: Natalizumab, a humanized monoclonal antibody targeting the cell adhesion molecule a4-integrin, is an effective treatment in multiple sclerosis (MS) preventing inflammatory blood cells from transmigration into the brain. The rare association of the development of progressive multifocal leukoencephalopathy (PML), due to reactivation of JCV polyomavirus, during natalizumab treatment limits its safety. The risk to develop Natalizumab associated PML is evaluated by the detection of JCV-Abs in serum, previous use of immunosuppressant and Natalizumab treatment for more than 24 months.
Methods: In the present study we analyzed serum soluble factors, cytokines and chemokines, soluble (s)HLA-G expression and its genotype (insertion/deletion 14base pairs, +3142 C>G), immunophenotype in order to understand if these factors are associated with PML risk. 19 RRMS were included and analyzed before therapy, 12 and 24 months after therapy.
Results: CXCL10 decreases between T0 and T24, while IL2, IL12p40, IL12p70, TNFa and IL23 increased. IFNg, GM-CSF, IL17, IL10, IL4, IL1, IL6 and CXCL13 do not vary. sHLA-G level divides the patient group into low (ins/ins; G/G), medium (ins/del; C/G) and high (del/del; C/C) producers depending on the HLA-G genotype and is stable in medium and low producers during therapy whereas increases in high producers.
Conclusion: In conclusion Natalizumab therapy seems to shape the inflammatory profile of patients increasing factors that promote Th1 differentiation and is increasing sHLAg production only in a sub group of patients. If this correlates with previous therapies, MS relapses after drug discontinuation or detection of PML risk factors is under investigation.
Disclosure: Nothing to disclose

EPR1133

Modulation of c-Jun N-terminal kinase as target in Multiple Sclerosis treatment

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Background and aims: Multiple Sclerosis (MS) is an inflammatory and degenerative pathology, thus far incurable, of the central nervous system. c-Jun N-terminal kinase (JNK), a mitogen activated kinase (MAPK), is involved in regulation of cytokine gene-expression, immunecell differentiation, neuronal-death-pathways and regulation of astrocyte inflammatory genes and might therefore influence pathomechanisms of MS. In an animal model of MS (experimental autoimmune encephalomyelitis, EAE), and in peripheral leukocytes of MS-patients upregulation of JNK was shown during active disease.
We aimed at investigating the influence of JNK-inhibition on the clinical EAE-course and its effect on T-cell viability in vitro.
Methods: Chronic EAE was induced by active immunization with MOG35-55 in female C57BL/6 wildtype mice. SP600125, a reversible ATP-competitive inhibitor of JNK 1-3, was given orally (30mg/kg, 15mg/kg or vehicle; n=6) on 9 successive days after individual disease onset (10 point scale EAE-Score ≥2).
Jurkat T-cell (T-ALL cell line) apoptosis in vitro by SP600125 (10μM) compared to control (DMSO) was analysed by FACS (AnnexinV/PI; 24h; n=5).
Results: In vivo treatment with 30mg/kg SP600125 significantly reduced disease-severity ($p<0.0001$) compared to controls (mean cumulative EAE-scores ±SD: control=3.5 ±0.8), 15mg/kg=2.9 ±0.5), 30mg/kg=2.2 ±0.4). SP600125-treated Jurkat T-cells exhibited increased apoptosis compared to control (mean±SD: 2.7-fold ±0.8; $p<0.01$).
Conclusion: Functional relevance of JNK-inhibition is indicated by a therapeutic effect on EAE-disease course. Upregulated apoptosis in an immortalized immune cell line in vitro could indicate potential mechanisms of action via depletion of T-cells. Detailed underlying mechanisms are currently under investigation.
Disclosure: This study is supported by SNF (Nr. 310030_172957) MBr: travel grants from Merck KG: former employee of Biogen, not related to this work. AS: speaker honoraria and/or travel compensation for activities with Almirall Hermal GmbH, Biogen, Merck, Novartis, Roche, and Sanofi Genzyme; none related to this work. AC: personal compensation as a Speaker/ consultant for Bayer, Biogen, Genzyme, Merck, Sanofi, Roche, and Teva Neuroscience RH: Research/travel grants from Novartis and Biogen Idec. speaker's honoraria from Biogen, Novartis, Merk and Almirall. LS: travel grants from Novartis and Genzyme Sanofi.

EPR1134

Neuromyotonia in thymoma-associated myasthenia gravis: a clinico-serological study

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Background and aims: Acquired Neuromyotonia (NMT) is an autoimmune condition frequently associated with anti-contactin-associated-protein-like-2 (Caspr2) antibodies. NMT can occur as a paraneoplastic disorder in patients with thymoma, alone or in combination with Myasthenia Gravis (MG). Recently, antibodies against netrin-1-receptors (DCC and UNC5A) have been reported as predictors of thymoma in 6/9 patients with concomitant NMT and MG. We aimed to clinically characterize a large cohort of patients with thymoma-associated MG, and to explore serological correlation of NMT symptoms.

Methods: 268 consecutive patients with thymoma-associated MG were retrospectively collected. NMT was defined as muscle twitching/cramps in at least 2 skeletal districts. Patients with NMT(23) were screened for anti-neuronal antibodies by immunohistochemistry on rat brain and cell based assay.

Results: 23/268 patients developed NMT symptoms (muscle twitching, 3; cramps, 3, or both, 17). Overall, 33/268 patients with thymoma had a tumor recurrence, which was more frequent in those with (8/23) vs those without NMT (25/245, p=0.003). NMT onset preceded the tumor recurrence in 5/6 patients. In univariate analysis predictors of thymoma recurrence were younger age at thymectomy (odds ratio-OR:0.95, confidence interval-CI:0.93-0.97), Masaoka staging (OR:10.73, CI:2.38-48.36) and NMT (OR:4.69, CI:1.76-12.46). 6 patients with NMT had anti-neuronal antibodies (patient#1: Caspr2; patient#2: AMPAR; patient#3: DCC; patient#4: LGI1; patient#5: Caspr2+LGI1+DCC+UNC5A; patient#6: Caspr2+LGI1+DCC). Thymoma recurrence was found less frequently in negative (3/17) vs positive patients with NMT (4/6, #1, #2, #5 and #6; p=0.045).

Conclusion: The occurrence of NMT symptoms in patients with thymoma-associated MG can predict tumor recurrence, and warrants a closer oncologic follow-up. Anti-neuronal surface autoantibodies may be useful to further stratify the recurrence risk.

Disclosure: This work was funded by the 'Ricerca finalizzata ministeriale 2015-2017' provided by the Italian ministry of health

EPR1135

Prognostic impact of MOG antibodies titres in adults with an acquired demyelinating syndrome.

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Background and aims: Myelin oligodendrocyte glycoprotein antibodies (MOG-Ab) have been detected in adult patients with acquired demyelinating syndromes (ADS). Whether MOG-Ab titres predict relapse risk and disability is, currently, unknown.
We evaluate the usefulness of MOG-Ab titres to predict disease course and prognosis in adult patients with MOG-Ab-associated diseases.

Methods: Retrospective nationwide study including 62 MOG-Ab-positive patients aged ≥18, whose samples were obtained within 3 months after the first ADS. MOG-Ab were tested using a cell-based assay. MOG-Ab titres were categorized as low (≤1/1280), intermediate (1/2560-1/5120), and high (≥1/10240) levels. First, we studied association between clinical characteristics and MOG-Ab titres. Second, we investigated, with Cox regression models, the risk of relapse according to categorical MOG-Ab titres. Finally, we used a logistic regression model to investigate the association between disability (EDSS≥3.0 at last follow-up) and categorical MOG-Ab titres.

Results: Patients were mainly Caucasians (91.9%) with a median age at onset of 38.5 years and 54.8% were females. The only epidemiological/clinical features associated to MOG-Ab titers was ethnicity, and Caucasians had lower titers (median 5120) than other ethnicities (median 2560), p =0.030. No association was observed with clinical phenotype at onset or at last follow-up. Categorical MOG-Ab titers did not predict risk to a further relapse (figure1). Finally, categorical MOG-Ab titres were not related to further disability.

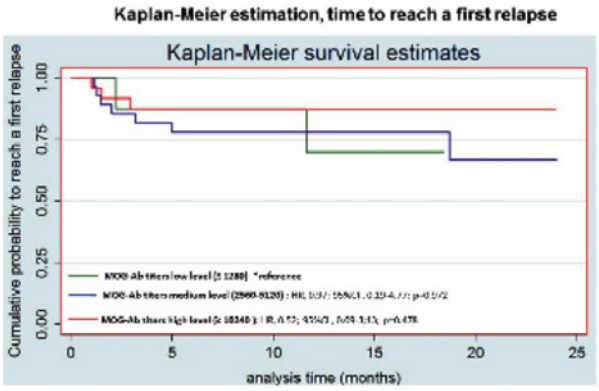

Figure 1.

Conclusion: In the present cohort of adults with MOG-Ab-associated diseases, MOG-Ab titres at onset of disease were not associated with a specific clinical phenotype, and do not predict neither disease course nor prognosis. Caucasians displayed higher MOG-Ab titres than other ethnicities.
Disclosure: Nothing to disclose

EPR1136

Proinflammatory MAIT (mucosal-associated invariant T-cells) cells react to gut flora yeasts and infiltrate multiple sclerosis CNS.

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Background and aims: The ability of intestinal microbiota to sustain an inappropriate immune reaction, such as in autoimmunity, at distant sites has been recently shown in animal models of disease. Similarly, the possibility to generate protective immune responses through the inoculation of selected commensal bacteria which induce regulatory cells has also been shown.
Methods: We have found that a distinct population of cells named MAIT (mucosal-associated invariant T) cells is expanded in individuals with Multiple Sclerosis (MS). These cells are IL-17 producers, they preferentially home to the intestine but can gain access to the brain. Here, we studied the gut microbiota in MS patients and in homozygotic twin pairs discordant for disease; we then studied the response of MAIT cells to yeast strains isolated from faecal samples from MS patients.
Results: We find that the frequency of MAIT cells is significantly increased in the peripheral blood of MS patients and that these cells are equipped with the array of molecules necessary for migration in the CNS. We show that in MS patients the gut mycobiota profiles are different compared to those of healthy volunteers. Furthermore, our immunological in vitro studies consistently show a higher reactivity to yeast extracts in cells of the innate arm of the immune system isolated form MS patients. CD8+ MAIT cells produce proinflammatory cytokines in response to yeast extracts obtained from MS patients.
Conclusion: In conclusion, we show for the first time that proinflammatory MAIT cells respond to yeasts that are more represented in the feces obtained from MS patients.
Disclosure: Nothing to disclose.

Neurological manifestations of systemic diseases

EPR1137

Progressive trigeminal neuropathy, limbic encephalitis and abdominal ganglionitis without primary cancer: an atypical case of anti-Hu auto-immune encephalitis

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Conclusion: Anti-Hu antibodies (Hu-Abs) are the most frequent onconeural antibodies associated with paraneoplastic neurologic syndromes (PNS). PNS include a variety of neurological syndromes, affecting less than 1/10,000 patients with cancer. In the majority of cases, PNS will occur before the malignancy is diagnosed. PNS can affect different levels of the central, peripheral en autonomous nervous systems. Multifocal involvement is common. Patients typically develop sensory neuropathy, cerebellar degeneration, limbic encephalitis and autonomic disfunction. The clinical course is monophasic and progressive with a poor prognosis. We present a case of 58-year-old man who developed a progressive trigeminal neuropathy over a period of 5 years, in combination with cerebellar degeneration, asymmetrical brainstem and limbic encephalitis. Serum showed repeatedly high positive anti-Hu antibodies. Repeated whole body FDG-PET-CTs could not demonstrate any primary malignancy. Patient was treated with corticosteroids and plasma exchange, without beneficial effect. Patient died after 5 years of the complications of an intestinal obstruction. Post-mortem autopsy revealed ganglionitis probably due to anti-Hu syndrome. Post-mortem autopsy revealed no primary malignancy. Brain autopsy showed gliotic changes in brain stem, hippocampus, amygdala and cingulate gyrus. Auto-immune anti-Hu encephalitis cases associated with SCLC or other primary neoplasms are described in literature, but this case is the first in which a progressive multifocal neurological syndrome occurs in the presence of positive anti-Hu antibodies, but without any primary neoplasm.
Disclosure: Nothing to disclose

EPR1138

Outcomes of Patients with Hereditary Transthyretin-Mediated Amyloidosis with Early Onset V30M versus all other Mutations in APOLLO, a Phase 3 Study of Patisiran

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Background and aims: Hereditary transthyretin-mediated (hATTR) amyloidosis is a multi-systemic, life-threatening, autosomal dominant disease caused by transthyretin gene mutations resulting in neuropathy and cardiomyopathy. Patisiran, an investigational RNAi therapeutic, resulted in statistically significant improvement in neuropathy (mNIS+7) and Norfolk Quality of Life for Diabetic Neuropathy (Norfolk QOL-DN) measures compared to placebo in hATTR amyloidosis patients and was generally well tolerated in the Phase 3 APOLLO study. We evaluated patisiran efficacy and safety in patients with early onset V30M versus all other mutations.
Methods: APOLLO was a multi-centre, 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 with multiple secondary endpoints including Norfolk QOL-DN. Pre-specified subgroup analyses were conducted to evaluate patients with early onset V30M (≤50 years of age at onset) and those with all other mutations including late onset V30M (>50 years of age at onset).
Results: APOLLO enrolled 225 patients with 39 different TTR mutations including 42.7% with V30M mutations with 10.2% considered to have early onset V30M disease. Similar to the overall patient population, patisiran demonstrated improvement in mNIS+7 and Norfolk QOL-DN compared to placebo in early onset V30M and as well as in all other mutations at 18-months (Tables 1, 2). Efficacy and safety data to be presented.

Disease characteristics	Placebo		Patisiran	
	N	LS Mean (SEM)	N	LS Mean (SEM)
mNIS+7				
Overall	77	74.6 (37.0)	148	80.9 (41.5)
Early onset V30M	10	68.9 (15.8)	13	81.1 (13.0)
All other mutations	66	75.5 (4.3)	135	80.9 (3.5)
Norfolk QOL-DN				
Overall	76	55.5 (24.3)	148	59.6 (28.2)
Early onset V30M	10	46.0 (7.6)	13	61.7 (9.9)
All other mutations	66	57.0 (3.0)	135	59.4 (2.4)

Table 1. mNIS+7 and Norfolk QOL-DN Baseline Values (Means)

Analysis	Disease Characteristics	Number of Patients (Placebo)	Number of Patients (Patisiran)	Treatment Difference (Patisiran-Placebo)	95% Confidence Interval
mNIS+7	Overall	77	148	-44.0	-59.9, -28.1
	Early Onset V30M	8	13	-22.3	-35.9, 8.5
	All Other Mutations	57	128	-36.1	-42.6, 29.6
Norfolk QOL-DN	Overall	77	148	-23.1	-37.5, -15.1
	Early Onset V30M	8	13	-21.1	-45.1, 2.9
	All Other Mutations	57	128	-21.5	-28.2, -14.9

Table 2. mNIS+7 and Norfolk QOL-DN Results at 18-months

Conclusion: Patisiran, investigated in patients with early and late onset V30M as well as a wide range of non-V30M genotypes, demonstrated consistent benefit over placebo in mNIS+7 and Norfolk QOL-DN.

Disclosure: This research was supported by Alnylam Pharmaceuticals.

EPR1139

Population Pharmacokinetic (PK)/ Pharmacodynamic (PD) Model of Serum Transthyretin (TTR) following Patisiran-LNP Administration in Healthy Volunteers and Patients with Hereditary TTR-Mediated (hATTR) Amyloidosis With Polyneuropathy

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Background and aims: hATTR amyloidosis is a rapidly progressive disease induced by deposition of TTR protein in multiple organs leading to morbidity and mortality. The PK/PD relationship between plasma ALN-18328 concentrations (siRNA) and serum TTR reduction following administration of patisiran-LNP was investigated.

Methods: Longitudinal PK and PD data were pooled from 5 clinical studies following single and multiple-dose administration of placebo and patisiran-LNP in healthy volunteers and patients over a wide dose range (0.01 to 0.5mg/kg). Non-linear mixed effects modelling was used to characterize the PK/PD relationship, quantify intra- and inter-individual variability, and evaluate covariate effects.

Results: PK and PD data from 283 subjects (84 placebo and 199 patisiran-LNP) were pooled. An indirect response model linking ALN-18328 plasma concentrations to inhibition of synthesis rate of TTR best described serum TTR reduction, with an IC50 of 9.45ng/mL. Average steady state ALN-18328 plasma concentrations from 0.3mg/kg q3w patisiran-LNP administration yields 80% to 90% reduction in serum TTR. Covariate analysis indicates similar TTR lowering across all subgroups including baseline age, body weight, sex, race (Caucasian/non-Caucasian), TTR genotype (V30M mutation/non-V30M mutation), mild hepatic impairment, and mild and moderate renal impairment. A 30mg dose for patients >or=100kg was predicted to have similar TTR lowering to 0.3mg/kg in patients up to 100kg.

Conclusion: Patisiran-LNP dose of 0.3 mg/kg q3w in patients up to 100 kg and 30 mg q3w in patients ≥100kg is supported by results from PK/PD modelling and simulation. No dose adjustment is required for any subgroups.

Disclosure: This research was supported by Alnylam Pharmaceuticals.

EPR1140

withdrawn

EPR1141

Long-term follow-up of patients with Neuro-Behçet's disease

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Background and aims: Neuro-Behçet's disease (NBD) is the most debilitating organ involvement of Behçet's disease. In this study, we present long-term follow-up of a large group of patients with Neuro-Behçet's disease.

Methods: We included all patients with NBD who had been followed up in our institution since 1973 in our study. We collected data including clinical and laboratory features, clinical course, and the effect of treatment. A new neurologic disability scale called the Neuro-Behçet's Disability Score (NBDS) devised for patients with NBD was employed to quantify patients' disabilities.

Results: We collected clinical data of 430 patients (291 males, 139 females). The mean follow-up period of patients was 5.2±6.5 years. Patients with parenchymal NBD (p-NBD) had more relapses (41.4% vs. 13.5%; $p<0.001$), more frequent uveitis (60.3% vs. 46.1%; $p=0.012$), and a longer interval between the onset of NBD and BD (8.0±7.8 vs. 6.2±6.1; $p=0.006$). The most frequently involved region in p-NBD was mesencephalon (59.0%), followed by diencephalon (31.9%). Only the presence of uveitis and the time of onsets between BD and NBD predicted relapses in p-NBD.

Conclusion: Herein, we present an extensive series of patients with NBD. We employed a novel and quick assessment disability scale that fills a gap in this area. The presence of uveitis and the time between NBD and BD are prognostic factors for future relapses in p-NBD.

Disclosure: Nothing to disclose

EPR1142

The "face of the giant panda" sign on magnetic resonance imaging in adult onset of Leigh syndrome

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Background and aims: Mitochondrial diseases are a vast group of disorders with a broad of clinical expression related to the system or tissue affected. It presents primarily during infancy, but cases of adult onset have been described. The ''face of the giant panda'' sign on magnetic resonance imaging (MRI) is traditionally considered to be characteristic of Wilson disease. However it has also been reported in other metabolic and mitochondrial disorders.
Methods: Case Report
Results: A 25-year-old male presented with a four-month progressive vision loss and diplopia, associated with gastric pain. The neurological exam revealed bilateral internuclear ophthalmoplegia, upgaze palsy and abnormal vertical oculocephalic reflex. MRI revealed midbrain abnormalities, characteristic of the "face of the giant panda'' sign, with a hyperintensity caudal asymmetric extension of dorsal pons and medulla oblongata in T2. Systemic autoimmune diseases, serologies, metabolic and neoplastic investigation were negative in blood, urine and in CSF. Abdominal echography showed a hepatosplenomegaly. Genetic studies disclosed a homozygous mutation of SURF1 gene. Patient has started antioxidant medication. At a 6 month follow-up there was a clinical and neuroradiological improvement, with no other new symptoms.
Conclusion: Leigh syndrome is a progressive neurodegenerative mitochondrial disorder. It is a genetically heterogeneous disease characterised by a diverse spectrum of phenotypes with a variable neuroimaging findings and disease course. Although the survival rate in Leigh syndrome is generally poor, SURF1-deficient has been described as having a more favourable survival outcome. This patient is a rare case of Leigh syndrome, with limited clinical manifestations, misleading MRI findings and a clinical improvement with treatment.
Disclosure: Nothing to disclose

EPR1143

Partially reversible parkinsonism as an initial manifestation of brain vasculitis: an atypical case of polyarteritis nodosa with neurological involvement.

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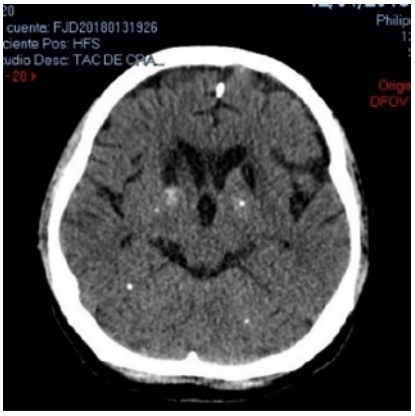
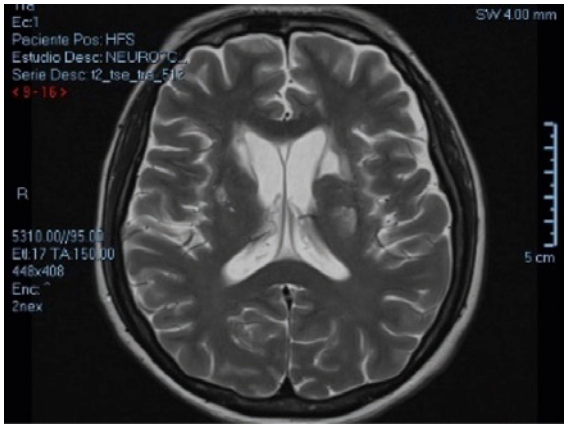
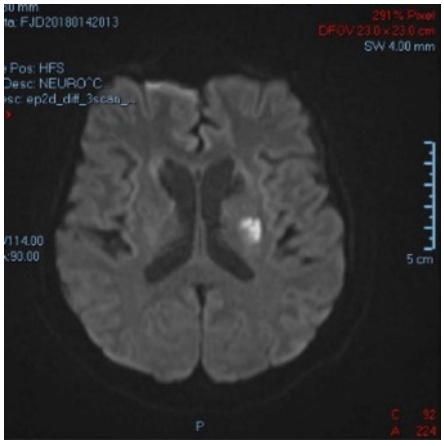
Background and aims: Polyarteritis nodosa (PAN) is a rare inflammatory necrotizing vasculitis in which direct brain vascular damage is rare, occurs lately in the course of the disease and it usually presents as diffuse encephalopathy or multifocal deficits.
Methods: We describe an atypical form of brain vasculitis in a patient previously diagnosed with PAN. We then review current literature about brain involvement in PAN and related diseases.
Results: A 49-year-old woman with an established PAN diagnosis with skin complications and sensitive polyneuropathy presented at the emergency department with a rapid progressing akinetic-rigid syndrome consisting of hypokinesia, hypophonia, dysarthria, postural instability and gait disorder. Brain MRI showed multiple bilateral ischemic lesions affecting basal ganglia and subcortical white matter. Further studies discarded thrombophilia and other connective tissue diseases. Cerebrospinal fluid was normal except for mildly increased protein count. With the suspicion of brain vasculitis, we started high-dose methylprednisolone treatment observing a rapid improvement of the neurological symptoms.



Initial CT



T2 FLAIR



Diffusion

Conclusion: This case report constitutes an extremely atypical form of neurological involvement in PAN. While other atypical forms of CNS involvement have been associated with PAN, parkinsonism cases as the presenting form of PAN are scarce in literature. To our knowledge most parkinsonism syndromes associated with autoimmune diseases appear in the context of systemic lupus erythematosus and are also considered rare. Proposed pathophysiologic mechanism in SLE parkinsonism consists of multiple inmmune-mediated microinfarcts involving basal ganglia and subcortical white matter. As in the case we present here, usually there is a rapid and even complete response to steroid therapy.
Disclosure: Nothing to disclose

EPR2143

A difficult case of Immunoglobulin G4-Hypertrophic Pachymeningitis - Rituximab as part of the solution

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Background and aims: Immunoglobulin G4 (IgG4)-related disease is a recently recognized fibro-inflammatory condition. Its spectrum encompasses hypertrophic pachymeningitis (HP) which is often a challenging neurological manifestation.
Methods: n.a.
Results: A 70-year-old man developed progressive right ptosis and vision loss during the previous year, associated with frontal headache. Brain MRI depicted right frontal lobe hypersignal with homogeneous enhancement and meningeal thickening with dural enhancement along the falx and right frontal area; brain CT showed ethmoidal and frontal bone erosion.
An exhaustive serum and cerebrospinal fluid study for autoimmune, neoplastic and infectious causes was unremarkable. A cerebral biopsy was performed revealing a lymphoplasmacytic infiltrate, storiform fibrosis, and more than 10 IgG4-expressing plasma cells per field, consistent with IgG4-related HP.
The patient initiated oral corticotherapy which was tapered as the symptoms improved, but the patient started bilateral progressive deterioration of visual acuity with increased meningeal thickening on MRI. He received a 5-day course of intravenous methylprednisolone, followed by prednisolone, but there was no clinical improvement. Subsequently, he was treated with two infusions of rituximab with a slight improvement of visual acuity, but brain and orbits MRI remained unchanged and intrathecal rituximab administration was attempted.
Conclusion: Intravenous rituximab is emerging as a promising therapeutic strategy in patients with IgG4-related HP who respond poorly to steroids. Recent literature advocates intrathecal administration of rituximab in patients who fail to improve after its intravenous administration based on poor blood-brain barrier penetration of the drug.
Disclosure: Nothing to disclose

Neuro-ophthalmology/neuro-otology; Spinal cord and root disorders

EPR1144

Thalamic exotropia from paramedian thalamic infarction

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Background and aims: The supranuclear pathways for vergence eye movements are still not fully understood. It has been proposed that loss of vergence control can be caused by interruption of supranuclear pathways. Thalamic infarction might lead to such an interruption, as cortico-mesencephalic fibers traverse the paramedian thalamus. It is well established that unilateral lesions of the posterior thalamus may cause 'thalamic esotropia'(1). Likewise, convergence excess has been reported in a patient with bilateral paramedian thalamic-infarctions(2)and contralateral convergence paresis in unilateral thalamotectal haemorrhage(3). We here report a patient with thalamic exotropia from ipsilateral paramedian thalamic infarction.

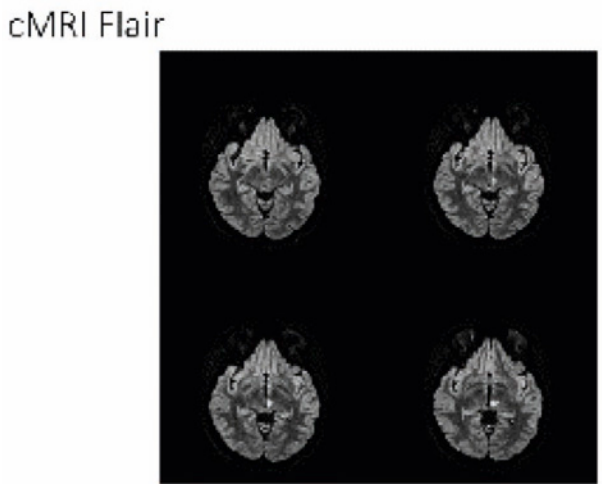
Methods: Case presentation:

A 26-year-old female patient presented with horizontal diplopia and exotropia of the left eye in primary-gaze; upward-gaze was slowed bilaterally.

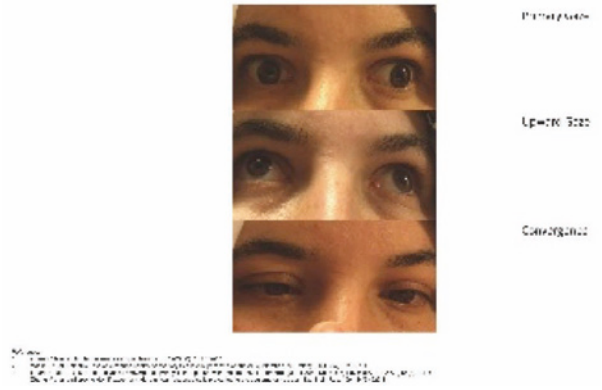
cMRI and neuro-ophthalmologic testing performed, inluding computer perimetry, test of skew and assessment of cyclorotation of the eyes and the subjective visual vertical. Detailed ocular motor and vestibular examination was performed by means of videooculography and rotational chair testing.

Results: Vergence testing revealed slowed convergence movement of the left eye, whithout other symptoms. Pupillary-light-reaction was normal.

cMRI disclosed unilateral left sided paramedian thalamic-infarction.



cMRI Flair



Gaze

Conclusion: The findings suggest that the syndrome of thalamic exotropia -not yet been described in the literature- is secondary to unilateral interruption of supranuclear fibers to midbrain vergence neurons, our findings support prior suggestions that descending cortical pathways pass the paramedian thalamus and exert an input to premotor vergence neurons in the midbrain. It is likely that this unilateral lesion has selectively interrupted projections to 'near-response-cells' to the medial rectus motoneurons on a supranuclear level(4).

Disclosure: Nothing to disclose

EPR1145

Pharmacological treatment of acquired pendular nystagmus: a case series

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Background and aims: Acquired pendular nystagmus (APN) is a rare but debilitating type of central nystagmus. Main causes include vascular lesions and multiple sclerosis. APN is attributed to brainstem and cerebellar dysfunction and almost always requires treatment due to severe oscillopsia. So far memantine and gabapentin have proven somewhat effective although often therapy efforts can be frustrating. In this study we evaluated the effect of acetyl-DL-leucin, a modified amino acid, on APN, as this drug has emerged in recent years as therapeutic option in cerebellar dysfunction, in comparison to standard therapies with gabapentin and memantine.
Methods: We evaluated nine patients with APN of different aetiology before and after therapy with memantine, gabapentin and acetylleucin. Eye movements were evaluated by performing a thorough neuro-opthalmological examination and videooculography, including testing of smooth pursuit, saccade, optokinetic nystagmus and gaze holding. The clinical examination was also documented with video recordings.
Results: Four out of nine patients responded to acetyl-DL-leucin 5g/d therapy. In those patients optimal results were achieved when acetyl-DL-leucin was combined with memantine 20-40mg/d. Other two patients responded partially to gabapentin monotherapy, whereas the remaining three patients did not respond to pharmacological treatment
Conclusion: Acetylleucin provides a new therapeutic alternative to APN therapy and should be tested individually on these patients, since its side effects are negligible.
Disclosure: Nothing to disclose

EPR1146

Response to eslicarbazepine in patients with vestibular paroxysmia

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Background and aims: Vestibular paroxysmia (VP) is a neurovascular compression syndrome characterized by recurrent spontaneous spells of dizziness/vertigo. Excellent response to carbamazepine has been referred and indeed, it has become a diagnostic criteria for this entity. Other antiepileptic drugs have been tried with different results. The aim of this studio was to describe safety and effectivenes of eslicarbazepine in a case series of patients from a tertiary hospital in Spain.
Methods: Descriptive retrospective study of a case series of 10 patients with VP treated with eslicarbazepine
Results: Nine out of ten patients were female, with a mean age of 54.5 years (range 38-84 years) an a mean age at onset of 49.8 years (range 36-64 years). All had paroxismal spells of dizziness/vertigo of less than 60 seconds. All patients had spontaneous spells and 62.5% had episodes triggered by cephalic movements. There was no evidence of other ear or neurological diseases that could explain the symptoms. MRI revealed a vascular compression of the estatoacoustic nerve in 55%. The response with eslicarbazepine was complete in 80% of patients and partial in the rest. Two patients had to withdraw treatment due to adverse effects (skin rash n=1, hyponatremia n=1). Other mild adverse side effects was reported by two patients.
Conclusion: Eslicarbacepine could be an effective therapeutic option in vestibular paroxysmia. Drug treatment is usually safe and well-tolerated.
Disclosure: Nothing to disclose

EPR1147

Intramedullary tuberculosis in the Neurology department at the University Hospital Center of Conakry

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Background and aims: The diagnostic certainty of the medullar tuberculosis without Pott disease is difficult to establish in the tropical environment with the large group of infectious, parasitic and systemic myelopathies.
We report 13 cases of tuberculous myelopathies without Pott disease for the purpose of a reevaluation of this pathology from the clinical, neuroradiological and evolutionary point of view.
Methods: We retrospectively analyzed the files of 186 patients hospitalized in the Department of Neurology and Neurosurgery of the University Hospital Center of Conakry between 2008 and 2016 for the management of non-compressive and compressive myelopathy. Biological evidence of tuberculous infection was demonstrated for 13 patients (6.9%).
Results: Infectious clinical picture prior to the installation of neurological signs was reported in 11 patients (84.6%). The neurological signs were summed up by the existence of a sensitivomotor semiology of progressive evolution (100% of cases) with sphincter disorders in 11 patients (84.6%) and a medullary compression symptomatology with a lesion and under lesion syndrome from the outset in 4 patients (30.8%). Medullary MRI revealed an extensive intramedullary hyper signal in 9 patients with non-compressive myelopathy and in 4 cases, the lesions appeared in T1 hyper signal and T2 isosignal localized.
Lumbar puncture revealed lymphocytic pleocytosis, hypoglucorrhage (0.3 to 0.5 g / l) and leukocytosis.
Conclusion: The avenue of Magnetic resonance imaging has revolutionized the diagnostic management of pathology. The biopsy remains the essential element to make the diagnosis, but the therapeutic response, is not left behind.
Disclosure: Nothing to disclose

EPR1148

Spinal-cord Stimulation in Pain Relief

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Bucharest, Romania

Background and aims: Patients with painful diabetic peripheral neuropathy of the lower extremities can reduce their pain with spinal-cord stimulation(SCS).
Methods: From an initial 136 painful diabetic peripheral neuropathy patients screened, 50 met the inclusion criteria and started trial stimulation. The results are the conclusion of a 4-year multicenter prospective study.
The mean age was 49.3, and 39% were female. The majority(90%) of patients had type 2 diabetes. They underwent test implantation with the SCS under local anesthesia. The patients had been experiencing pai for 4.5 years. The scor from numerical rating scale(NRS) for pain at baseline was 6.5.
Results: The results were evaluated after 1 year and every year until 4 years. Success of treatment defined as pain relief was >50% after 4 years. The NRS score during the day was 3.8 and during the night was 3.9 after 12 months. After 4 years, the mean day score was 4.3 and the mean night score was 4.6.
Of the patients, 85% had treatment success at 1 year, falling to 69% at 2 years, 75% at 3 years, and 55% at 4 years; 75% were still using their devices after 4 years.
Two patients had SCS device infection, eight needed battery replacement until the end of study period.
Conclusion: In conclusion, the SCS is reserved for patients with severe pain due to the high costs. Unfortunately, in our country the device is currently in the experimental stage.
Disclosure: Nothing to disclose

EPR1149

Electromyography in acute abdominal wall paresis

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Background and aims: Acute abdominal wall paresis caused by thoracic radiculopathy is very rare entity. The first clinical symptom is usually pain irradiating to the lower chest or abdomen. Patients are visiting general practitioner, internist or surgeon; however, final diagnosis is often determined with a long delay.
Methods: Needle electromyography (EMG) of obliguus abdominis and rectus abdominis muscles was performed in 8 subjects (4 females, 36 - 78 years), accompanied by conduction study on the lower limbs. Magnetic resonance imaging (MRI) of spinal cord was performed in all subjects. Routine blood tests and cerebrospinal fluid (CSF) assessment was obtained, too.
Results: In all subjects, spontaneous abnormal activity (fibrillation, positive sharp waves) was present in abdominal muscles. In two patients, diabetic mixed sensorimotor neuropathy was found. Four patients had acute neuroborreliosis proved by blood and CSF tests. MRI revealed disc protrusions at the level Th12/L1 in one patient, and foraminal herniation at Th10/11 in the other one.
Conclusion: Spontaneous deep abdominal pain manifested by unilateral or bilateral partial paresis of the abdominal wall is a rare condition. Except routine cerebrospinal fluid assessment and MRI of spinal cord we recommend to add needle EMG where findings of spontaneous activity confirmed an acute thoracic axonal root lesion. After final diagnosis, therapy according to main cause has to be performed (surgery, antibiotics, etc.).
Supported by the Research project of Charles University, Progress Q35.
Disclosure: Nothing to disclose

EPR1150

Cervical Spinal Cord Gray Matter Atrophy in Post-Polio Syndrome

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Background and aims: Post-polio syndrome (PPS) is defined by progressive persistent new muscle weakness or fatigability occurring after a stable interval, decades after the initial viral infection of spinal cord (SC) motor neurons. The precise mechanisms underlying PPS are unknown. Recent advances in MR sequence development now allow for reliable quantitation of SC gray matter (GM) in vivo. The aim of this study was to quantitate SC GM in PPS patients.
Methods: 20 patients with PPS (mean age 66.5 years [SD 4.53], 12 men) and 20 age and sex-matched healthy controls (HC) were investigated at 3T by axial 2D-AMIRA imaging (in plane resolution 0.5x0.5mm) (Weigel & Bieri 2017) at the intervertebral disc levels C2/C3, C3/C4, C4/C5, C5/C6 and C6/C7. SC GM areas were segmented manually.
Results: Compared to HC, PPS patients showed significant SC GM atrophy at all levels (C2/C3 $p=0.0405$, C3/C4 $p=0.0002$, C4/C5 $p<0.0001$, C5/C6 $p=0.0006$, C6/C7 $p=0.0356$). In multivariable regression analysis GM area at C2/C3 (with age and sex as covariates) explained 56% of neck flexor strength variance.
Conclusion: AMIRA imaging is a sensitive method to quantitate SC GM atrophy in vivo. Cervical SC GM areas were reduced in PPS compared to HC, and correlated with muscle strength in the corresponding myotome in PPS. Longitudinal studies are necessary to investigate atrophy over time, its relation to symptom evolution and possible prognostic value. The methodology used here is promising for the development of novel imaging surrogates not only for PPS, but also for other neurodegenerative, genetic or autoimmune mediated diseases of the SC.
Disclosure: Nothing to disclose

EPR1151

Cervical musculoskeletal disorders: occupational and individual risk factors

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Background and aims: Cervical musculoskeletal disorders (CMSD) represent a common cause of morbidity, including absenteeism, as well as change/loss of employment. As the characterization of CMSD as occupational diseases remains debated. our objective was to evaluate the prevalence of CMSD in a cohort of employees, assessing potential personal and occupational risk factors.
Methods: The sample included a total of 473 employees from 31 private companies in the meat processing industry (2012-2013; Northern Italy). Participants were evaluated by two occupational physicians, who also personally analyzed the specific occupational risks. Working definition of CMSD is described. Associations between CMSD and current working conditions, as well as psychosocial factors were analyzed by means of Poisson regression models and calculation of corresponding proportional rate ratios (PRR).
Results: CMSD were identified in 49 out of 397 employees (12.3%) who completed the survey. Among the assessed occupational factors, only exposure to temperatures <17 ° C was actually associated with CMSD (PRR 2.510 95% CI 1.152-5.469). Among individual risk factors, a significant association was found for sedentary lifestyle (PRR 2.583 IC95% 1.173-5.687) and a personal history of low back pain (PRR 2.003 IC95% 1.006-3.986).
Conclusion: Workers from the meat processing industry are usually recognized as exposed to the highest levels of professional constraints. Although our study confirms a high prevalence (12.3%) of cervical pain, our data confirm the lack of a sound association between CMSD and occupational risk factors.
Disclosure: Nothing to disclose

Neurorehabilitation 1

EPR1152

Effect of treadmill training on challenging walking in people with Parkinson's Disease

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Background and aims: Impaired walking ability is one of the important motor symptoms in patients with Parkinson's Disease (PD). Walking ability under challenging conditions, such as dual-task walking, can predict the risk of falls. Treadmill training is commonly used in gait rehabilitation, but its effects on over-ground challenging walking in patients with PD are not clear. The purpose of this study is to investigate effect of treadmill training on walking ability under cognitive loads in patients with PD.
Methods: Eight individuals with PD received 8 weeks of treadmill training. Temporal spatial gait parameters were evaluated in single task over-ground walking with comfortable and fast speeds. The evaluations were also performed under challenging walking conditions which were dual task walking under cognitive loads of spatial memory, stroop, and calculation tasks. The evaluations were performed before training and after 4 and 8 weeks of training.
Results: The walking speed and step length increased ($p=.012$) after 4 weeks in single task comfortable speed walking but not in fast speed walking ($p>.05$). It took eight weeks for the walking speed and step length to improve in walking under cognitive loads of spatial memory and calculation tasks ($p<.05$). The cognitive performance did not change after training.
Conclusion: The effect of treadmill training can be translated to over-ground walking and walking under challenging conditions. Longer time of training is required for PD patients to obtain benefits of walking under challenging conditions.
Disclosure: Nothing to disclose

EPR1153

Computational Analysis of Movement for Evaluation of Motor Function Impairment after Stroke.

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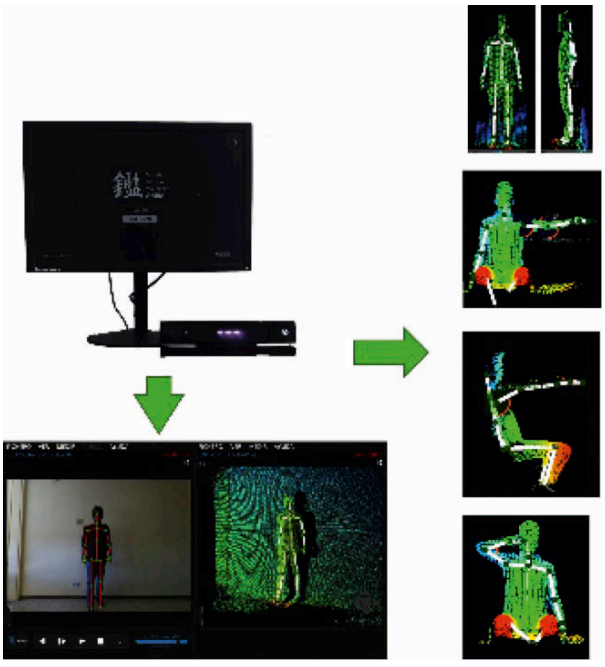
Background and aims: Motion capture systems are used in neurological rehabilitation. We aimed to explore the usefulness of MCS to obtain an objective measurement of functional status after stroke.
Methods: Prospective observational case-control pilot study. Acute stroke patients and controls performed a battery of exercise in front of the camera Microsoft Kinect® and the movement were analyzed in the three-dimensional space with the software Akira®. The differences in performance before and after each exercise and between both sides of the body were compared between groups. The correlation between the NIHSS score and the mRS score were analyzed. The patients also were evaluated at 3 months.



Microsoft Kinect with Software Akira. Exercises included in the study: balance, abduction of arm and flexion of shoulder and elbow.

Results: 72 controls and 37 patients were analyzed. The median NIHSS score was 2 (rank 0-12), and the median mRS was 0 (rank 0-4). The measurements that showed better discrimination capacity were those obtained from the

abduction of the arm: the shift of the joint angles was different between groups in the frontal plane of the elbow, shoulder, and forearm; all in pronation and supination ($p<0.001$). Those differences were independent of the NIHSS score, but were moderately correlated to the mRS score at the moment of the evaluation: elbow in supination (Rho=0.41, P=0.01); shoulder in pronation (Rho=0.45, P=0.006) and supination (Rho=0.64, P<0.001). There were no significant differences in those angles at 3 months.

Conclusion: Computational analysis of movement could be a useful tool for evaluation of upper limb function in stroke patients with slight deficit underestimated using current clinical scales, but correlated with outcome.

Disclosure: The research group of Cerebrovascular diseases of La Paz University Hospital has a collaboration agreement with System Friend Inc, an enterprise that provides the software and hardware used in the study.

EPR1154

Structural and Functional MRI Correlates of Motor Performance in Patients with Multiple Sclerosis

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Background and aims: Motor impairment affects a large proportion of multiple sclerosis (MS) patients. We applied voxel-wise methods and an independent component analysis in a large cohort of MS patients to evaluate correlations between abnormalities of brain gray matter (GM) volumes, white matter (WM) architecture and resting state functional connectivity (RS FC) and clinical and functional measures.

Methods: From 134 HC and 366 right-handed MS patients, brain 3D T1-weighted, diffusion tensor and functional MRI scans were acquired and used to perform an analysis of correlations with Expanded Disability Status Scale (EDSS), manual dexterity [9 Hole Peg Test (9HPT) and Finger Tapping (FT) test] and mobility [Timed 25 Foot Walk Test (T25FW)] tests.

Results: Compared with HC, MS patients showed a widespread pattern of GM atrophy. The analysis of WM architecture showed a distributed reduction of fractional anisotropy and an increased axial, radial and mean diffusivity in MS patients. RS FC was decreased in MS patients compared to HC, both in sensory-motor and cognitive networks. In MS patients, worse performance at 9HPT and higher EDSS correlated with atrophy of putamen, insula and cerebellum, whereas worse FT and T25FW performances correlated with atrophy in temporal areas. Several correlations between altered diffusion indexes and worse motor performances were found. Finally, correlations between lower RS FC and worse motor performances were found in all investigated networks.

Conclusion: Structural and functional abnormalities of cerebellum and deep GM structures contribute to explain motor dysfunction in MS patients.

Disclosure: Partially supported by Fondazione Italiana Sclerosi Multiple (FISM2013/S/1).

EPR1156

Methodology Matters: Comparing Approaches for Defining Persistent Post-Concussion Symptoms

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Background and aims: Post-concussive symptoms (PCS) such as headache, dizziness, fatigue, sleep disturbance, poor concentration, forgetfulness, irritability, and/or mood changes are common after mild traumatic brain injury (mTBI). The symptoms are not specific to mTBI, they are frequently experienced by other patient groups and healthy individuals. To complicate matters further, the tests used in research and clinical practice, and the definitions of persistent symptoms, vary considerably. The purpose of this study is to evaluate how the methodology used to define persistent PCS can influence the outcome of a study.
Methods: We included 221 patients who sustained mTBIs according to the WHO criteria, 64 age- and sex-matched trauma controls, and 74 community controls. The patients completed the Rivermead Post Concussion Symptoms Questionnaire (RPQ) and the British Columbia Postconcussion Symptom Inventory (BC-PSI) three months after injury. We compared and contrasted 11 methods for evaluating persistent PCS, including ICD-10 postconcussional syndrome diagnostic criteria as well as other commonly used criteria for defining persistent symptoms.
Results: The prevalence of persistent PCS ranged between 10% to 47% in the mTBI group, 2% to 34% in the trauma controls, and 0% to 32% in the community controls depending on the different classification methods used.
Conclusion: The methods used to define persistent PCS yield dramatically different results and are highly relevant for outcome research following mTBI. Researchers and clinicians should consider carefully which methods to use when evaluating persistent PCS.
Disclosure: This project is financed by the Norwegian ExtraFoundation for Health and Rehabilitation and The Liaison Committee for Education, Research and Innovation in Central Norway.

EPR1157

Effects of two types of dual-task balance interventions on gait and cognitive performance under single- and dual-task conditions in patients with stroke

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Background and aims: Functional ambulation requires an ability to divide attention between concurrent tasks while walking. Interference between gait and cognition indicates that diminished dual-task abilities, which may impede functional mobility and community participation for stroke patients. The objective of this study is to investigate the effects of motor and cognitive dual-task training [MCDTT] and cognitive dual-task training [CDTT]) on gait and cognition under single- and dual-task conditions in patients with stroke.
Methods: Twelve subjects with stroke were randomly allocated to either MCDTT or CDTT group. Both groups received 12-session programs at progressively increasing task difficulty (5-min warm-up, 20-min standing balance, 10-min sitting-to-standing, 20-min treadmill walking, and 5-min cool-down). MCDTT group undertook balance and gait training while concurrently performing both motor and cognitive tasks. The CDTT group trained balance and gait while simultaneously performing cognitive tasks only (verbal fluency tasks, calculation tasks, and visual discrimination tasks). All participants were examined walking and cognition under single- and dual-tasking at pretreatment and posttreatment. Primary outcome measures of walking and cognition were gait speed and composite score of Stroop task under single- and dual-tasking. Cognitive-motor-interference was calculated.
Results: Both groups significantly improved gait speed under single- and dual-task walking after training. The MCDTT group was significantly less cognitive-motor-interference on cognition under dual-task fast walking at posttreatment. There was a trend that only MCDTT group improved cognitive costs under comfortable walking with Stroop at posttreatment.
Conclusion: The preliminary results showed a favorable trend toward motor and cognitive dual-task training with less cognitive-motor-interference and cost on cognition.
Disclosure: This work was supported by the Ministry of Science and Technology (104-2314-B-182-035-MY3) and Chang Gung Memorial Hospital (CMRPD1G0621) in Taiwan.

EPR1158

Simplified Evaluation of CONsciousness Disorders (SECONDs): A new tool to assess consciousness in severely brain-injured patients

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Background and aims: The Coma Recovery Scale-Revised (CRS-R) is currently the gold standard behavioural tool to assess patients with disorders of consciousness. However, the time needed to complete an assessment limits its use in intensive care and rehabilitation settings. Recent literature suggests that focusing on the five most frequent responses allows detecting 99% of conscious patients. We aim at developing a scale to assess consciousness within a short time-period, the SECONDs.
Methods: A group of experimenters (OB SW CA HC) assessed 12 patients with disorders of consciousness within two consecutive days. On day A, one CRS-R and one SECONDs were randomly administered one hour apart. On day B, two SECONDs were performed one hour apart. The order (A-B) was randomized. We compared the diagnoses based on the CRS-R vs. the SECONDs (same day), and the diagnoses based on the CRS-R vs. three SECONDs.
Results: Nine out of 12 patients had the same diagnosis with the CRS-R and the SECONDs performed on the same day. Globally, the three SECONDs gave the same diagnosis as the CRS-R in 10 patients. No diagnostic mismatch could be explained by the presence of a behavioural response not assessed by the SECONDs. Assessments using the SECONDs were faster than with the CRS-R [Z=-3.059, p=0.002218; median time (IQR) : 9 (6) vs. 22 (8.25) minutes].
Conclusion: Our preliminary results suggest that the SECONDs could be a useful, fast, alternative tool to detect consciousness in severely brain-injured patients when time is limited.
Disclosure: CA is research fellow, and SL research director, at the FRS-FNRS.

EPR1159

Perilesional Induction of Sleep Slow Waves improves Motor Recovery after Ischemic Stroke

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Background and aims: Clinical and experimental studies suggest a positive role for sleep in brain plasticity during stroke recovery. Here, we investigate the role of Slow Waves (SW) oscillations during sleep on motor recovery following ischemic stroke using optogenetic techniques and in vivo electrophysiology in mice.
Methods: Ischemic stroke was caused in wild type mice via middle cerebral artery occlusion (MCAO). Following injections of CamkII-ChR2-EYFP (ChR2), CamkII-ArchT-EYFP (ArchT) and CamkII-mCherry (control) adeno-associated viruses (AAV) within the peri-lesional primary somatosensory forelimb (S1FL) cortex, SW-like oscillations were induced by optical stimulations of transfected pyramidal neurons. Starting from post-stroke day 5, and consecutively every day until post-stroke day 15, animals underwent 2 h of stimulation session. Behavioural tests at post-stroke days 4, 7, 10 and 15 were used to assess the effect of optogenetically evoked SW on motor outcomes.
Results: MCAO induced an increased amount of NREM sleep and reduced wakefulness following ischemic stroke. Specifically, ipsilateral SWs showed longer duration compared to contralateral sleep slow waves. We showed that optogenetic activation (ChR2) and silencing (ArchT) of pyramidal neurons in the per-lesional S1FL cortex successfully induced SW sleep-like responses in both ipsilateral and contralateral EEG traces. Moreover, chronic optogenetic induction of SW-like, predominantly during NREM sleep, improved recovery of fine motor movements as compared to control mice.
Conclusion: Our results, in line with previous observations, suggest a positive role of sleep in motor recovery following ischemic stroke. Optogenetically-induced SW-like oscillations, targeting the activity of pyramidal neurons in the peri-lesional cortex, significantly promote functional outcomes after stroke.
Disclosure: Nothing to disclose

Peripheral nerve disorders 1

EPR1160

Carpal tunnel release follow-up: when do we perform instrumental tests?

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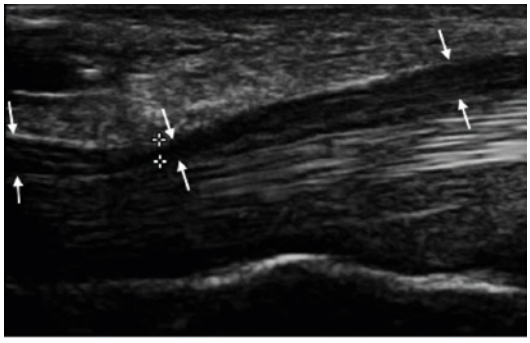
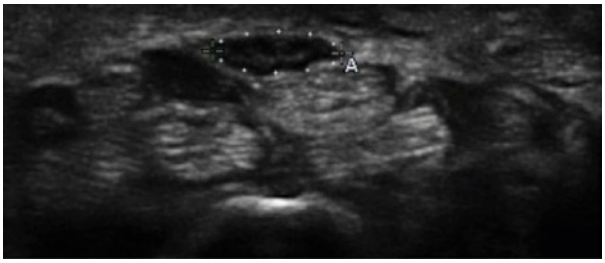
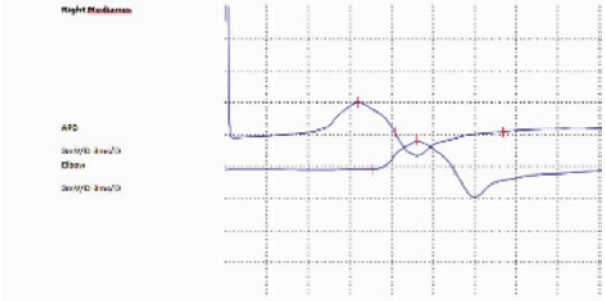
Background and aims: Electrodiagnostic studies (NCS) and high-resolution ultrasound can be used for follow-up after median nerve decompression at the carpal tunnel (CTS).
The study aims to find out the most relevant terms for follow-up tests in patients with idiopathic CTS after the complete ligament dissection.
Methods: 72 patients (or 108 affected hands), 11 men and 61 women, from 37 to 88 years (mean age 62.83±11.74 years) with electromyographic evidence of carpal tunnel syndrome were recruited. The patients were examined before the nerve decompression, after 2 weeks, 1.5 and 6 months after the treatment. 25 healthy gender- and age-matched individuals were recruited as controls. The NCS (n. medianus – motor and sensory portions) was conducted with Dantec Keypoint Focus. The ultrasonography with an assessment of the median nerve cross-section area at the carpal tunnel was performed with Philips IU22. The results were processed in program Statistica 6.0 and Microsoft Excel.



Median nerve entrapment at the carpal tunnel. Arrows - the borders of the nerve, markers - the nerve's narrowing.



Cross-section area (CSA) measurement (markers) of the median nerve at the carpal tunnel. CSA=0,12cm2



Right Medianus Motor			
	Lat	Amp	CV
	ms	mV	m/s
Wrist-APB	6.34	2.8	
Elbow-Wrist	10.7	2.6	57.3

Median nerve compound muscle action potentials (CMAPs) in a patient with CTS. Prolonged distal latency, decreased amplitude, normal conduction velocity at the forearm.

Results: In all cases the release was sufficient.
NCS showed sensory conduction velocity improvement in 2 weeks (p=0.027). Also motor and sensory distal latencies significantly improved in 1.5 months and 6 months accordingly. Such parameter as a nerve cross-section area did not change significantly over the whole period of observation.
Conclusion: The follow-up after the operation is important to assess the effectiveness of the procedure by confirming the complete carpal ligament dissection and visualizing the structures of the carpal tunnel in early post-operative period (2 weeks) already. NCS are already meaningful in 2 weeks after the nerve decompression.
Disclosure: Nothing to disclose

EPR1161

Chronic inflammatory demyelinating polyradiculoneuropathy is not a painless disease

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Background and aims: Recently, some newly recognized clinical features have been noticed in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). We sought to gather new information about frequency, severity and features of neuropathic pain (NeP) in CIDP patients and to assess the association between NeP and other disease features.
Methods: We included 106 patients diagnosed with CIDP. PainDETECT questionnaire (PD-Q) was used to assess the presence of NeP. The Medical Research Council (MRC) Sum Score, INCAT disability and sensory scores, and Beck Depression Inventory were also used.
Results: NeP was present in 47 (44.3%) CIDP patients. Half of the patients with NeP had severe pain at testing. The most common neuropathic symptoms were sensations of sudden attacks of electric shocks, slight pressure triggering pain, and allodynia. Slowly-progressive course of the disease was more frequent in patients with NeP (86.4% vs 59.6, $p<0.05$). Patients with NeP had worse INCAT sensory score ($p<0.001$), INCAT disability score ($p<0.01$) and MRC sum score ($p<0.001$) at time of testing. Depression was more common in patients with NeP (45.5% vs 25.9%, $p<0.01$). More severe weakness (lower MRC score) and higher INCAT sensory score appeared as significant independent predictors of higher score on PD-Q in patients with CIDP.
Conclusion: NeP was very common and often severe in our cohort of CIDP patients. It was associated with worse functional disability, sensory deficit, and depression. Special attention should be paid to these patients since they request additional symptomatic therapy.
Disclosure: Nothing to disclose

EPR1162

Obinutuzumab, a new anti-CD20 antibody, is active and effective in anti-MAG antibody polyneuropathy.

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Background and aims: Rituximab, a chimeric anti-CD20 monoclonal antibody (mAb), has been used in polyneuropathy associated with anti-myelin-associated-glycoprotein (MAG) antibodies with controversial results. Obinutuzumab, a new glycoengineered humanized anti-CD20 mAb, in combination with chemotherapy, induces longer progression-free survival in B-cell lymphomas, as compared with rituximab.
Methods: A 82-yr-old man presented with severe demyelinating sensory-motor neuropathy. At our first evaluation, he used wheelchair to travel outdoors, was incapable of standing and walked few steps only with bilateral support. He had distal weakness at lower limbs (2/5 MRC), tactile hypoestesia and loss of vibration up to knees, areflexia. He had a clonal B lymphocytosis CD5+ CD23+, compatible with chronic lymphocytic leukemia (CLL), IgM lambda paraprotein and anti-MAG titre was >70,000BTU. The presence of favorable CLL prognostic markers (mutated IGHV gene and absent of TP53 deletions or mutations) prompt us to use chlorambucil+obinutuzumab (obinutuzumab iv at 1000mg on day 1, 8 and 15 of cycle 1 and day 1 of cycles 2-6; chlorambucil os at 0.5mg/kg on day 1 and 15 of cycles 1-6).
Results: At cycle 6 the patient was able to stand, gait was possible with monolateral support, tactile hypoestesia was limited to feet, distal strength and vibration improved. M-protein decreased from 15.8g/L to 11.61 at cycle 6. Similarly, IgM level (14.8 vs 8.7g/L), lambda free-light chain (145 vs 59mg/L) and lymphocytes (6,340 vs 900/µl) decreased.
Conclusion: CLL might have had a role in the response to therapy, but a possible role of chlorambucil+obinutuzumab in anti-MAG polyneuropathy, regardless of the associated hematological condition, should be considered in future trials.
Disclosure: Nothing to disclose

EPR1163

Influence of diabetes mellitus on chronic inflammatory demyelinating polyradiculoneuropathy

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Background and aims: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a treatable disease characterized by progressive weakness and sensory abnormalities. Diabetes mellitus (DM) is one of the most frequently reported comorbidities in CIDP. We aimed to analyze association of DM with clinical, paraclinical features and outcome of CIDP.

Methods: Study comprised 194 CIDP patients examined between 2007-2016 in medical centers of Serbia, Bosnia and Herzegovina and Montenegro. Patients were divided in groups with and without diabetes. The degree of disability was assessed by Inflammatory Neuropathy Cause and Treatment score (INCAT) and Medical Research Council (MRC) sum score.

Results: At the time of CIDP diagnosis 21.6% of patients had DM, increasing to 26.3% after 8±6 years follow-up. Those patients had later onset of CIDP ($p<0.01$), more extensive sensory disturbances ($p<0.05$) with worse sensory INCAT score in lower extremities ($p<0.01$). INCAT disability and MRC sum score did not differ between groups. DM patients more frequently had ataxia (48.8% vs. 29.9%, $p<0.05$) and facial nerve palsy (12.5% vs. 4.1%, $p=0.05$). They also less frequently fullfiled definitive electrophysiological criteria (68% vs. 92%, $p<0.01$), while cerebrospinal fluid parameters were similar between groups. Slowly progressive course was present more often in DM patients (97.5% vs. 68.3%, $p<0.01$). No difference in the response to CIDP therapy was noticed between groups ($p>0.05$). However, death occured more frequently in DM group ($p<0.05$).

Conclusion: CIDP patients with DM had specific clinical presentation with more sensory symptoms and ataxia. Response to therapy was similar, but lethal outcome was more frequent in DM positive group.

Disclosure: Nothing to disclose

EPR1164

Benefit-Risk Profile of Intravenous Immunoglobulin (IVIG) and Subcutaneous Immunoglobulin (SCIG) in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): the PATH Study

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Background and aims: PATH investigated efficacy and safety of SCIG (IgPro20, Hizentra®, CSL Behring) as maintenance therapy for CIDP. Before randomisation to IgPro20 or placebo, subjects underwent IVIG withdrawal and, upon clinical deterioration, were re-stabilised with IVIG (IgPro10, Privigen®, CSL Behring). IgPro10 and IgPro20 have the same manufacturing process with the only differences between products being the final immunoglobulin concentration and administration route. The benefit-risk profiles of IgPro10 IVIG and IgPro20 SCIG are evaluated here.

Methods: IVIG re-stabilisation comprised an initial dose of 2g/kg followed by 3–4 doses of 1g/kg at 3 week intervals. Subjects were then randomised to weekly SCIG maintenance therapy (0.2 or 0.4 g/kg) or placebo for 24 weeks. The adverse event (AE) profile and relapse (change in adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] score) were analysed for both products.

Results: A total of 207 subjects received 1894 IVIG infusions and 115 of these subjects subsequently received 4225 SCIG infusions. The most frequent AEs were headache (IVIG) and local reactions (SCIG). The majority of headaches (65%) and local reactions (95%) were mild. With IVIG, 9 haemolysis AEs occurred (all non serious and resolved without transfusion); none occurred with SCIG. No thromboembolic events, renal failures or deaths were reported. A total of 83% of subjects re-stabilised on IVIG; subsequently, 81% of subjects did not relapse on SCIG 0.4 g/kg (0.2 g/kg: 67%; placebo: 44%).

Conclusion: Both IVIG and SCIG had the expected effectiveness reported in literature, while rates of systemic AEs were lower with both SCIG doses.

Disclosure: This study was sponsored by CSL Behring

EPR1165

Focal neurological episodes in Familial Amyloid Polyneuropathy patients – clinical and laboratory features

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Background and aims: Liver transplantation in Familial Amyloid Polyneuropathy (FAP) slows disease progression by replacing the variant TTR by wild-type TTR. However, mutant TTR production in the choroid plexus and in the retina continues. Focal neurological episodes (FNEs) have been described in FAP patients with over 10 years of disease duration. Similarly to amyloid spells, FNEs were divided in negative phenomena (TIA-like and aura-like) and positive phenomena (aura-like and epileptic seizures).
Methods: Descriptive analysis of clinical and paraclinical data of 5 FAP patients with FNEs.
Results: 5 male patients, aged between 42 and 53 years-old, presented with FNEs at a median of 15 (10.19-19.8) years post liver transplant. We describe a total of 12 events, 8 AIT-like, 4 epileptic seizures of which 2 were followed by prolonged focal neurological deficits. The events tended to maintain the same clinical presentation for each patient. 3 patients underwent CSF analysis, which showed elevated protein without pleocytosis. EEG was performed in all patients in the acute phase at least once: findings were variable, ranging from normal (3) to non-convulsive status epilepticus (1).
Conclusion: Our demographic and clinical data are consistent with what has been previously reported by Maia et al., The frequency of abnormalities in the EEG argue in favor of the existence of cortical dysfunction, and elevated protein in CSF could implicate disruption of the blood brain barrier, supporting that amyloid deposition in leptomeningeal vessels is the most likely etiology
Disclosure: Nothing to disclose

EPR1166

A new variant in the WNK1 gene causing Hereditary Sensory and Autonomic Neuropathy type 2

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Background and aims: Hereditary Sensory and Autonomic Neuropathies (HSAN) are a group of rare genetic disorders affecting specifically the sensory and autonomic peripheral nerve fibers. Its classification, created before genetic testing was available, proposes four clinical subtypes. We present a case of HSAN type 2 whose genetic evaluation revealed a novel disease-causing variant in the WNK1 gene.
Results: A 30-year-old African woman born to normal consanguineous parents presented at nine years of age with a painless wound in her left foot, complicated with osteomyelitis and amputation of the fifth toe. The family reported repeated painless injuries, burns and loss of sensation in her distal limbs since three years of age. Neurological examination revealed loss of deep tendon reflexes, sensory ataxia and loss of all sensory modalities in all four limbs. A sural nerve biopsy revealed complete absence of myelinated nerve fibres without onion bulbs. The diagnosis of HSAN type 2 was established. In light of recently reported variants associated with HSAN, a next-generation sequencing panel of 15 genes was ordered. It revealed a novel homozygous variant at the WNK1 gene resulting in a truncated protein [c.2920C>T;p.(Gln974*)].
Conclusion: Variants in WNK1, RETREG1, KIF1A and SCN9A have been associated with HSAN type 2. Our patient presents an unreported variant resulting in a truncated WNK1 protein, a serine/threonine protein kinase, expressed in sensory ganglia neurons, whose exact function in the nervous system is unknown. This work contributes to enlarge the still limited knowledge about the clinical, pathological and genetic features of this group of rare diseases.
Disclosure: Nothing to disclose

EPR1167

A novel Alanyl-tRNA synthetase gene mutation identified in three Charcot-Marie-Tooth families

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Background and aims: Hereditary neuropathy is caused by a large number of genes involved in different cellular mechanisms. Charcot-Marie-Tooth (CMT) disease is the most prevalent inherited neuropathy. Next-generation sequencing (NGS) has proven to be efficient in the diagnostics of disorders where multiple genes can be involved. Alanyl-tRNA synthetase (AARS) catalyzes the attachment of the respective amino acid to the appropriate tRNA. Heterozygous mutations in the AARS gene cause axonal CMT while homozygous mutations cause early infantile epileptic encephalopathy.
Methods: Neuropathy patients from different families have been investigated with a NGS-based targeted gene panel of 99 genes, mostly CMT genes.
Results: We have identified three unrelated CMT families with a shared, novel AARS gene mutation. Mutations in other neuropathy genes better explaining the phenotype in the affected were not found.
Conclusion: The identification of a unique AARS sequence variant in neuropathy patients from three unrelated families makes it plausible that this variant is causative for CMT in these three families. In addition, the NGS analysis of the other hereditary neuropathy genes did not reveal other sequence variants better explaining the phenotype of the affected in these families.
Disclosure: Nothing to disclose

EPR1168

Age-dependent cognitive dysfunction in untreated and liver transplanted ATTRV30M patients

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Background and aims: Central nervous system (CNS) involvement, including cognitive dysfunction, has been recently described in hereditary transthyretin (TTR) amyloidosis. This study aims to explore the effects of age on cognitive dysfunction in TTRVal30Met mutation carriers.
Methods: A series of 547 carriers of the TTRVal30Met mutation (160 asymptomatic, 180 untreated symptomatic, and 207 treated with liver transplant - LT) underwent a neuropsychological assessment, which included the Dementia Rating Scale-2 (DRS-2), Auditory Verbal Learning Test, Semantic Fluency, Phonemic Fluency, and Trail Making Test. Cognitive deficits were identified at the individual level, after adjusting the neuropsychological test scores for demographic characteristics (sex, age, and education), based on large national normative data. The presence of cognitive dysfunction was determined by deficit (≤5th percentile) in DRS-2 and/or multiple cognitive domains (i.e., learning/memory, language, and attention/executive functions). Chi-square (or Fisher's Exact) and Mann-Whitney test were applied for group comparisons.
Results: The frequency of cognitive dysfunction was higher in untreated symptomatic (9%) than in asymptomatic carriers (2%, p=0.003), but similar to patients treated with LT (9%, p=0.798). Cognitive dysfunction in untreated symptomatic participants was associated with older age (≥50 years) at disease onset (p<0.001) and at assessment (p<0.001), and with longer disease duration (p=0.001). Cognitive dysfunction in treated patients with LT was associated with older age at disease onset (p=0.009), but not with older age at assessment (p=0.332) or disease duration (p=0.830).
Conclusion: This cross-sectional study shows that cognitive dysfunction is associated with late onset of ATTRV30M amyloidosis.
Disclosure: Nothing to disclose

Peripheral nerve disorders 2

EPR1170

A Multicenter, Double-Blind, Placebo-Controlled, Pivotal Phase III Study (PLEO-CMT) of a Fixed Combination of Baclofen, Naltrexone and Sorbitol (PXT3003) for Charcot-Marie-Tooth Disease Type 1A (CMT1A)

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Background and aims: Disability and impairment associated with CMT1A improved after 12 months of treatment with PXT3003 in a randomized, placebo-controlled, double-blind explorative phase II study (Attarian, 2014). In December 2015, the PLEO-CMT phase III study (ClinicalTrials.gov: NCT02579759) was initiated, to assess the efficacy and safety of 2 doses of PXT3003 compared to placebo in mildly to moderately affected adult CMT1A patients.

Methods: The primary objective is to assess the effect on disability as measured by the mean change from baseline Overall Neurology Limitations Scale (ONLS) score after 15 month of treatment with PXT3003. Furthermore, efficacy on the proportion of responders (i.e. improvement of ONLS), impairment (CMTNS-V2), functional tests (10-MWT, QMT, 9-HPT), electrophysiological parameters (CMAP, SNAP and NCV) and quality of life are secondary endpoints. Pursuant this study, patients will be eligible for a 9-month extension study, allowing all patients to receive PXT3003.

Results: Randomization of patients was completed (n=323) in December 2016. The screen failure rate was 26%, as expected (437 patients were screened). The independent DSMB recommended to continue the study as planned following a safety analysis on all available data in September 2017. A blind variability analysis and blind futility analysis concluded that the study can continue as planned in November 2017. To date, 34 patients (10.5%) withdrew from the study, 8 (2.5%) due to adverse events possibly related to study treatment. The baseline patient characteristics and demographics, and study status will be presented.

Conclusion: This pivotal study of PXT3003 is expected to be completed in December 2018.

Disclosure: Study is sponsored by Pharnext SA Julie Foucquier: employee Pharnext SA René Goedkoop: employee Pharnext SA

EPR1171

Diabetes-related risk factors for the painful diabetic neuropathy

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Background and aims: Unsatisfactory diabetes control and other factors associated with diabetes have repeatedly shown significant association with the development of diabetic distal symmetrical sensory-motor polyneuropathy (DSPN), while association of these factors with pain related to DSPN is discussed contradictory. We aimed to identify the diabetes-related factors significantly associated with neuropathic pain in a large cohort of well-defined DSPN subjects.

Methods: In this observational cross-sectional cohort study of 400 subjects with non-painful (n=215) and painful (n=185) DSPN associated with diabetes mellitus of type 1 and 2 (median age 62 years, range 21-87 years; 236 men), factors related to diabetes (type, duration, control expressed as HbA1C level, presence of dyslipidaemia and nefropathy, BMI) were analyzed with regard to the presence of neuropathic pain.

Results: In painful DSPN subgroup, significantly higher number of patients showed abnormally increased serum creatinine levels and abnormally decreased estimated glomerular filtration rate as markers of possible diabetic nephropathy in comparison with non-painful DSPN patients. We were not able to confirm an association of painful neuropathy with any other of the diabetes-related parameters. Diabetes control expressed as HbA1c levels showed only unsignificant trend towards better control in non-painful DSPN.

Conclusion: The only diabetes-related factor, confirmed by our study as being significantly associated with the presence of pain in DSPN, was diabetic nefropathy, as another microvascular complication of diabetes. Other metabolic factors, relevant for the presence or severity of polyneuropathy, did not showed any significant difference between painful and painless patients.

Disclosure: Nothing to disclose

EPR1172

Feasibility of Switching from Intravenous to Subcutaneous Immunoglobulin Therapy in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): Comparison of PATH Trial Results with Clinical Experience

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Background and aims: In chronic inflammatory demyelinating polyneuropathy (CIDP), immunoglobulin (Ig) therapy is typically administered intravenously (IVIG). Subcutaneous Ig administration (SCIG) enables independence from hospitals and increased convenience. The phase 3 PATH study showed efficacy of SCIG in CIDP. Here we evaluate the feasibility of switching from IVIG to SCIG in CIDP patients by comparing PATH data with clinical experience.

Methods: In PATH, subjects with CIDP were switched to SCIG (0.2 or 0.4 g/kg/week) or placebo after IVIG induction. Adverse events (AEs), quality of life (QoL; EuroQol - 5 Dimension questionnaire) and patient preference were assessed. Observational studies of switching from IVIG to SCIG in CIDP and multifocal motor neuropathy (MMN), with assessment of safety, QoL (Life Quality Index [LQI] questionnaire) and patient preference are detailed.

Results: The percentage of PATH subjects who experienced ≥1 AE with IVIG was 48% (rate: 0.175/infusion). Corresponding percentages for SCIG-0.2 and SCIG-0.4 were 58% and 52% (0.08 and 0.05/infusion). The most common AE was headache for IVIG (16%, 0.033/infusion), and local infusion site reactions for SCIG (19% [0.03/infusion] for SCIG-0.2; 29% [0.02/infusion] for SCIG-0.4). Most subjects (88%) felt SCIG was easier to use versus IVIG. Significantly more subjects (P-values <0.005) improved/maintained QoL health status with SCIG versus placebo. In observational studies, switching from IVIG to SCIG was associated with increased QoL and reduced systemic AEs.

Conclusion: The randomised PATH study and observational studies comprising large cohorts of subjects have documented the feasibility, safety and efficacy of SCIG therapy in CIDP.

Disclosure: This study is sponsored by CSL Behring

EPR1173

Clinical and Magnetic Resonance Imaging features of a series of 11 Spanish patients who carry mutations in the BICD2 gene

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Background and aims: Mutations in the BICD2 gene are a cause of dominant spinal muscular atrophy. We report 11 Spanish patients (five families) carriers of mutations in the BICD2 gene.
Methods: Patients underwent neurological examination and electrophysiological studies with standard techniques. Muscle magnetic resonance imaging (MRI) of lower limbs (LL), including pelvis and feet, was performed in seven patients. Genetic diagnosed was reached using a gene panel for genetic testing of inherited neuropathies. Punch skin biopsy for the study of Epidermal Nerve Fiber Density (ENFD) was performed in two patients.
Results: Three novel mutations (p.Val485Gly; p.Tyr557His and p.Ser681Leu) and the already described p.Ser107Leu mutation were identified. The most frequent clinical phenotype consisted in mild weakness in proximal muscles of LL combined with foot deformities. In one patient, nerve conduction studies (NCS) showed reduced sensory and motor nerve action potentials. In the rest of patients, NCS were normal and electromyography showed chronic denervation predominantly in LL. In muscle MRI the most affected muscles were rectus femoris, vastus lateralis, medial gastrocnemius, gluteus medius and gluteus minimus. There was fatty infiltration in intrinsic muscles of feet in two patients. There was a reduction of ENFD in one patient with normal NCS.
Conclusion: We report three new pathogenic mutations in the BICD2 gene. In our study we include MRI findings at the level of pelvis and feet, which allow us to better define the pattern of muscle involvement related with this gene. Our results also raise the subject of a possible sensory involvement in the disease.
Disclosure: Study funding: grants IIS La Fe 2015/0085, ISCIII (PI12/00946), PI Fundación Grupo ERESA 2013.

EPR1174

Effects of alpha lipoic acid on loss of myelin sheath of sciatic nerve in experimentally induced diabetic rats

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Background and aims: Diabetic neuropathy is the most frequent chronic complication of diabetes. It may attack to sensory, motor or autonomous fibers. Varied mechanisms account for the development of diabetic neuropathy such as metabolic disorders, microvascular damages, neurotrophic support deficit, alternation in neuro-immune interactions, neural and glial cell apoptosis, and inflammation. Alpha lipoic acid (ALA) is a potent lipophilic antioxidant in vitro and in vivo conditions, which plays a main role as cofactor in many mitochondrial reactions, easily absorbed from gastointestinal tract and can easily cross the blood brain barrier (BBB). Apoptosis is an important mechanism of degenerative diseases, which is induced by some factors like hyperglycemia toxicity. In vivo and in vitro studies showed that hyperglycemia affected the cell survival and induced apoptotic changes in dorsal root ganglion neurons and Schwann cells.
Methods: In this experiment we used a total of 28 rats. 14 rats were given 180mg/kg streptozotocin (STZ) dissolved by single intraperitoneally (i.p.) injection. Rats are divided into 4 groups; Control (group I), DM (group II), ALA (group III) and DM+ALA (group IV). Myelin sheaths of sciatic nerves were examined histologically for each group.
Results: In the results of the histological examination, showed that loss of myelin sheath in sciatic nerves of rats while the group treated with ALA showed less myelin loss.

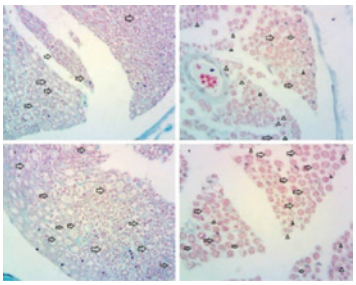

Figure 1.1 shows sciatic nerve control group, figure 1.2 is sciatic nerve DM group, figure 1.3 is sciatic nerve ALA group, figure 1.4 is sciatic nerve DM+ALA group. Tissue was stained with hematoxylin-eosin. Arrows show normal myelin sheath, arrowheads show myelin obliteration in histological imaging of sciatic horizontal section of groups.

Conclusion: This study might be suggested that ALA has a protective effect on peripheral neuronal cell damage generated with Diabetes mellitus (DM).
Disclosure: This study was supported by a grant from Firat University.

EPR1175

Baseline characteristics of patients with hereditary transthyretin (hATTR) amyloidosis with polyneuropathy enrolled in the phase 3 study NEURO-TTR demonstrate significant disease burden

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Background and aims: hATTR is a rare, progressive, and fatal disease, caused by systemic accumulation of transthyretin (TTR) protein that significantly impacts patient quality of life (QOL). We evaluated QOL at baseline in patients with hATTR with polyneuropathy (hATTR-PN) in the NEURO-TTR study (NCT01737398).
Methods: Adults (n=172) with hATTR-PN (stage 1 or 2) were randomized (2:1) and received 300-mg weekly subcutaneous inotersen, an antisense oligonucleotide inhibitor of TTR protein production, or placebo. At baseline, neuropathy was assessed using the modified Neuropathy Impairment Score+7 (mNIS+7), and QOL was assessed using the patient-reported questionnaires Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QOL-DN) and the SF-36v2 Health Survey (SF-36v2). For these analyses, baseline QOL scores from patients in this study were reported relative to healthy controls.
Results: At baseline, 69% of patients were male; 67.4% stage 1 and 32.6% stage 2 disease; and 63% of patients had cardiomyopathy. Mean baseline QOL scores were significantly worse for patients with hATTR than healthy controls. The baseline mean (standard deviation [SD]) scores in QOL measures for patients with hATTR vs healthy controls was 48.4 (27.2) vs 2.6 (5.0) for Norfolk QOL-DN total score (higher scores reflect worse QOL) and 36.3 (9.1) vs 50.0 for SF-36v2 Physical Component Summary score (lower scores reflect worse QOL). The mNIS+7 and Norfolk QOL-DN total score showed strong correlation with each other and with disease severity.
Conclusion: The significantly impaired QOL observed in patients with hATTR compared with healthy controls confirms the unmet medical need for effective treatments that can reduce disease burden.
Disclosure: This study was sponsored by Ionis Pharmaceuticals (Carlsbad, CA, USA).

EPR1176

Inotersen improves quality of life and neuropathy in patients with hereditary transthyretin (hATTR) amyloidosis with polyneuropathy: results of the phase 3 study NEURO-TTR

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Background and aims: hATTR is a rare, progressive, fatal disease caused by systemic accumulation of transthyretin (TTR) amyloid, causing significant morbidity and progressive decline in quality of life (QOL). We report safety and efficacy of inotersen, an antisense oligonucleotide inhibitor of TTR protein production, in patients with hATTR with polyneuropathy (hATTR-PN).

Methods: NEURO-TTR (NCT01737398) is a global, randomised, double-blind, placebo-controlled phase 3 study. Adults (n=172) with hATTR-PN (stage 1 or 2) were randomised (2:1) and received 300-mg weekly subcutaneous inotersen or placebo for 15 months. Primary endpoints were change from baseline to week 66 in the Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QOL-DN) total score and modified Neuropathy Impairment Score+7 (mNIS+7).

Results: At baseline, 69% of patients were male; mean age was 59 years. Compared with placebo, inotersen treatment resulted in significant improvement in primary endpoints based on the difference in mean change from baseline to week 66 [95% CI] in mNIS+7 (–19.73 [–26.43, –13.03], P<0.0001) and Norfolk QOL-DN (–11.68 [–18.29, –5.06], P=0.0006) total score. 50.0% and 36.5% of inotersen-treated patients improved from baseline to week 66 in Norfolk QOL-DN total score and mNIS+7, respectively. Most adverse events were mild or moderate. Key safety findings of thrombocytopenia and renal events were easily managed and monitored with routine testing. 80% of patients completed the 15-month treatment period, and >95% of patients who completed treatment entered the open-label extension study.

Conclusion: Inotersen demonstrated highly significant benefits in QOL and prevention of neurological disease progression in patients with hATTR-PN.

Disclosure: This study was sponsored by Ionis Pharmaceuticals (Carlsbad, CA, USA).

EPR1177

Changes of nerve conduction velocity and ultrasound characteristics in cidp over time. a three-year prospective study in seventeen patients

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Background and aims: About 50% of nerve segments in CIDP patients shows quantitative and qualitative ultrasound (US) changes, which correlate with neurophysiological findings, disease duration, MRC sum-score and INCAT score.

Methods: During a three-year F-U, we evaluated changes of clinical, neurophysiological (EDX), and US characteristics in 17 CIDP patients. The nerve cross sectional area (NCSA) in 236 nerve segments was evaluated with US by the same examiner, while EDX study was performed in 136 nerve segments by another examiner, at baseline and FU-end. The EDX data in each segment were stratified in normal, axonopathic and myelinopathic.

Results: Both at baseline and FU-end, MCV, NCSA, MRC-80 and INCAT score were all significantly correlated each other ($p=0.001$). Mean MCV was 43.04+13.73 m/s at baseline and 42.29+13.68 at FU end ($p=0.34$). At baseline EDX was normal in 34% of segments, axonopathic in 22% and myelinopathic in 44%; at FU-end it was normal in 22%, axonopathic in 46% and myelinopathic in 32% ($p<0.0001$). US was abnormal in 104/235 (44.5%) at baseline and in 116/235 (48.7%) segments at FU-end. In 102/235 (43%) segments US was normal at baseline and didn't change during FU. NCSA decreased significantly in 97 (41%) segments and increased in 104 (44%) (paired data t-test. $p<0.0001$) during the FU; it remained unchanged in 34 (14%) segments. MCV decreased ($p=0.024$) in segments with increased NCSA.

Conclusion: This prospective study confirms the correlation between clinical, electrophysiological and US characteristics in CIDP both at baseline and at FU-end. US could be a useful tool to follow nerve morphological changes over time.

Disclosure: Nothing to disclose

Sunday, June 17 2018

Ageing and dementia 2

EPR2001

Physical activity as a moderator of AD pathology: a systematic review of observational studies

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Background and aims: Physical exercise has been shown to reduce Alzheimer's disease (AD) pathology in animal models, and is associated with reduced risk of cognitive decline in humans. The objective was to carry out a systematic review of observational studies on the possible association between physical activity (PA)/physical fitness (PF) and AD pathology.
Methods: The systematic review was carried out according to the PRISMA guideline. Observational studies of physical activity or physical fitness with AD biomarkers as outcome measures (Beta-amyloid, total-tau, phosphorylated-tau in cerebrospinal fluid (CSF); 18F-FDG-PET, Amyloid-PET, hippocampal atrophy on MRI) in healthy subjects, patients with mild cognitive impairment and patients with AD, were included.
Results: A total of 55,114 studies were identified and screened. Fifty studies were included. Nine studies reported results on amyloid PET, 5 on CSF, 4 on 18F-FDG-PET and 32 on hippocampal volume. Three studies were longitudinal. Twelve studies reported a significant association between hippocampal volume and either PA or PF, 2 studies reported a significant association between total-tau and phosphorylated tau and PF/PA and 1 study for beta-amyloid, in a favourable direction, whereas 2 studies found an association between amyloid tracer uptake and PF/PA, in a similar direction. Lastly, 2 studies reported increased metabolism in parietal and temporal areas to be correlated with PF/PA.
Conclusion: The findings do not support a physically active lifestyle being associated with less detrimental AD related biomarkers. However, the number of studies was limited apart from studies utilising MRI in healthy subjects, thus limiting a final conclusion. Further studies are needed.
Disclosure: Nothing to disclose

EPR2002

Rapidly progressive Alzheimer's disease and sporadic Creutzfeldt-Jakob disease: comparison of clinical and neuropathological features

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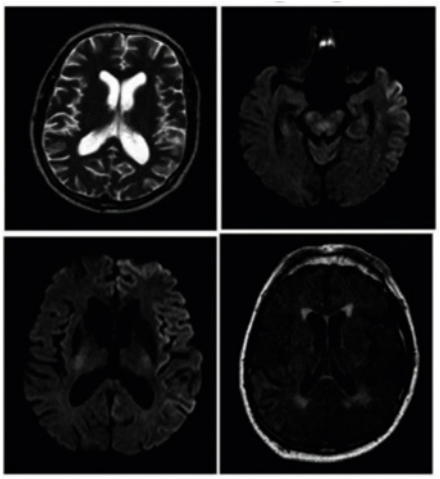
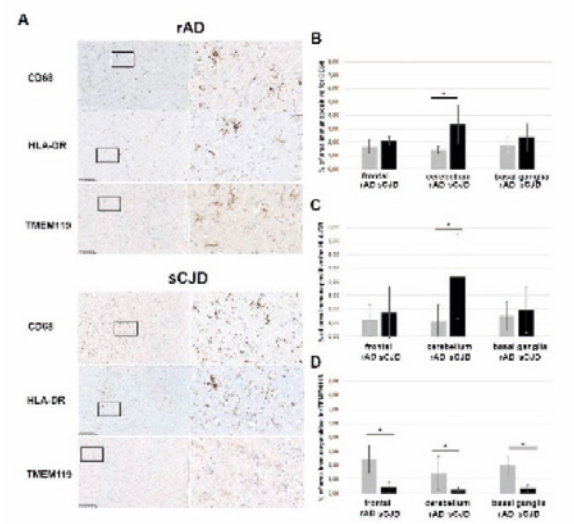
Background and aims: Rapidly progressive forms of Alzheimer's disease (rAD) with a rapid cognitive decline and an early occurrence of focal neurological symptoms, mimicking prion diseases, appear to exist.
Methods: We performed immunohistochemical analysis of brain autopsy tissue samples and compared clinical characteristics of 8 patients with rAD and 8 matched patients with sporadic Creutzfeldt-Jakob disease (sCJD). Survival time did not differ significantly between two groups. In all patients, sCJD was clinically suspected and included in the differential diagnosis at the time of death.
Results: All patients experienced a progressive cognitive deterioration as a main clinical symptom. Magnetic resonance imaging (MRI) lesions characteristic for sCJD could be observed in five sCJD patients, but in none of rAD patients. sCJD typical electroencephalographic (EEG) findings could be seen in two cases with sCJD; none of rAD patients displayed those changes. Cerebrospinal fluid proteins 14-3-3 were positive in seven sCJD cases; four of rAD cases were also positive.
Immunohistochemical stainings with markers that do not discriminate between resident microglia and monocyte-derived macrophages (MDM) (HLA-DP, -DQ, -DR antibody and CD68 antibody), and with the astrogliosis marker (GFAP antibody), did not reveal any significant differences in immunopositivity. TMEM119 (a marker unique to brain resident microglia) immunopositivity was significantly increased in rAD patients in comparison with sCJD patients.



Typical MRI lesion patterns in rAD and sCJD patients



Immunohistochemical stainings with HLA-DP, DR, DQ, CD68 and TMEM119

Conclusion: rAD should be considered in the differential diagnosis in patients presenting with a rapidly progressive multifocal neurological syndrome. Future studies of microglial activation may provide new insight into the pathogenesis of AD in general and a possibility to modulate disease progression.
Disclosure: Nothing to disclose

EPR2003

Association between Tau haplotype and Frontotemporal Lobar Degeneration

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Background and aims: Frontotemporal lobar degeneration (FTLD) have been associated with the microtubule-associated tau protein since tau gene mutations have been demonstrated to be the cause of FTLD and parkinsonism linked to chromosome 17. The objective of this study was to determine whether genetic variability in tau gene is associated with the development or modulation of FTLD.
Methods: Retrospective study from different Tissue Banks and pathological diagnosis of FTLD. Molecular data: H1/H2 MAPT gene polymorphism. Clinical data: Age of onset and death, average time of disease, personal history and cardiovascular risk factors, clinical diagnosis, first clinical symptom and evolution of the disease. Pathological data: FLTD diagnosis – PiD, PSP, CBD, FTLD-Tau, TDP and FUS. Other - TDP43 inclusions, Braak stage, CERAD and vascular pathology.
Results: Fifty-one cases were analyzed. The most frequent haplotype for the MAPT gene was H1/H1 (48.6%). Regarding neuropathological diagnosis, H1/H1 was related to PSP cases and H1/H2 to TDP-43 cases. Supranucelar gaze palsy (64.7%; p=0.037), parkinsonism (59.5%; p=0.005) and gait disturbance (58.1%; p=0.065) was related to H1/H1 cases (75%) and behavioral disturbances to H1/H2 (38:9%) as the most frequent initial symptom. There were no statistically significant differences in age of onset / death and time of disease. No mutation was found in MAPT gene.
Conclusion: Phenotypic clinical characteristics were different in H1/H2 haplotype in MAPT gene and they were related to specific FTLD diagnosis. These findings support a role of tau protein in modulating disease phenotype in these FTLD cases.
Disclosure: Nothing to disclose

EPR2004

Prion protein codon 129 polymorphism modifies progression but not age at onset in Alzheimer's disease

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Background and aims: Recent studies have proposed a role for cellular prion protein (PrPc) in neuronal death induced by amyloid-β (Aβ) oligomers. Therefore, PrPc appears to be closely linked to the pathogenic process in Alzheimer's disease (AD). Our goal is to determine whether the PRNP codon 129 polymorphism (M129V) could influence the occurrence of AD and/or modify age at onset or progression of the disease in a sample of Spanish subjects.
Methods: In this case-control study, we compared the genotype frequencies of the PRNP M129V polymorphism in 200 sporadic AD patients (median age 79.7±6.7 years, 66.5% women) and 201 healthy controls older than 75 years (median age 71.0±4.9 years, 51.7% women). The PRNP M129V polymorphism (rs1799990) was analyzed using qQRT-PCR technique. We also determined age at onset and rate of cognitive decline in AD patients (rapid progression, MMSE decay/follow-up time [years]>4.5).
Results: Subjects carrying the M129V genotype were not significantly more susceptible to AD [MV vs MM: OR=1.50; CI95%=0.95-2.35; p=0.081]. However, a direct association between AD and M129V genotype was present in APOE ε4 non-carriers [OR=1.93; CI95%=1.16–3.20; p=0.011]. Moreover, the M129V genotype displayed consistent effects on disease progression (25.0% MV vs 11% MM and 9.1% VV rapid progression, p=0.027), but not on age at onset (p=0.413).
Conclusion: Our data show that the PRNP M129V genotype increases the speed of progression in AD. Further research is needed about the potential role of APOE4 for the oligomers of PrPc and PrPsc in the development of the disease.
Disclosure: Nothing to disclose

EPR2005

Impairment of basal forebrain projections contributes to hippocampal atrophy in subjects at risk of Alzheimer's disease

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Background and aims: Basal forebrain (BF) degenerates early in Alzheimer's disease(AD) and is a major source of acetelcholine in brain cortical areas including hippocampus. The aim of this study was to assess, if impairment of basal forebrain projections to hippocampus contributes to hippocampal atrophy in cognitively normal elderly(CN) subjects with subjective memory complaints(SMC) or mild cognitive impairment(MCI).
Methods: 85 subjects from ADNI2 cohort were selected - CN(n=30), SMC(n=32) and MCI(n=23). The diffusion and structural images were obtained from ADNI website. Fornical projections from basal forebrain (BF) to hippocampus were reconstructed using probabilistic tractography and diffusion tensor-based tract integrity measures were derived (mean diffusivity(MD), fractional anisotropy(FA), radial diffusivity(RD), axial diffusivity(AxD)). Pearson correlation coefficient was used to assess correlation of BF and hippocampal volumes. Causal mediation analysis was performed in 2 directions (1.BF to hippocampus, 2. hippocampus to BF) to evaluate the mediation effect of tract integrity measures while controlling for intracranial volume, sex, age, education and APOE status.
Results: We found significant correlations between hippocampal and BF volume (r2=0.251, p=0.02), BF volume and MD, RD, AxD (r2=(-0.37)-(-0.41), p=0.001-0.005), FA(r2=0.26, p=0.013) and hippocampal volume and MD, RD, AxD(r2=(-0.40)-(-0.50), p<0.0001), FA (r2=0.45, p<0.0001). We found significant mediation effect (ME) and total effect (TE) in first direction in MD, RD and AxD (ME.p=0.006-0.03, TE.p=0.042-0.049). There was no significant TE in second direction.
Conclusion: Track integrity of BF projections to hippocampus mediates association of BF and hippocampal volumes, but only in BF to hippocampus direction. This supports the hypothesis that atrophy of BF contributes to hippocampal atrophy.
Disclosure: Nothing to disclose

EPR2006

Serum BDNF levels in patients with vascular cognitive impairment (VCI): association with MoCA

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Background and aims: The association between the levels of brain derived neurotrophic factor (BDNF) and Mini Mental State Examination (MMSE) scores has been previously documented in Alzheimer's disease and aging, however there is a lack of studies on BDNF as a biomarker in VCI, where MoCA is the more suitable instrument for evaluation of cognitive function.
Methods: 104 patients with VCI (mean age 66.7±8.4 years, 65 women) were assessed using the Hachinski ischemic scale, MMSE and Montreal Cognitive Assessment (MoCA). Serum BDNF was measured using Quantikine ELISA kits (RnD Systems). BDNF data in VCI patients was compared with values from 20 healthy controls without significant cognitive impairment.
Results: In VCI patients (MoCA 22.2±2.5) serum BDNF levels were lower compared to controls (24.1±7.1 ng/ml vs. 27.5±7.4 ng/ml; p=0.03; Mann–Whitney U test). When we tested the association of MMSE and MoCA with age, gender and BDNF using multiple linear regression, the impact of age (beta= -0.32, p= 0.0009) and BDNF (beta=0.31, p=0.002) on MMSE, as well as the association between MoCA and BDNF (beta=0.31, p=0.00047) were revealed.
Conclusion: Our study demonstrated an association between MoCA scores and BDNF levels that opens new avenues in the studies of VCI.
Disclosure: Nothing to disclose

EPR2007

Cerebrospinal fluid neurofilament light chain illustrates that semantic dementia is a distinctive neurodegenerative disease

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Background and aims: Semantic dementia (SD) is a homogeneous neurodegenerative disorder characterized by progressive language problems that falls within the

frontotemporal dementia (FTD) spectrum. Its relative homogeneity facilitates the development of disease-modifying agents, wherefore robust biomarkers are required. We aimed to investigate the utility of cerebrospinal fluid (CSF) neurofilament light chain (NfL) as a biomarker in SD.

Methods: This large retrospective multicenter study compared CSF NfL levels of 162 SD patients with 44 controls. CSF NfL levels of patients were correlated to clinical parameters (including survival), neuropsychological test scores, and regional gray matter atrophy.

Results: CSF NfL levels were significantly higher in SD patients (median: 2326 pg/mL, interquartile range: 1628-3535 pg/mL) than in controls (989 [682-1362]). Higher CSF NfL levels associated with more severe language impairment, as measured by the Boston Naming Test, and with smaller gray matter volume of the parahippocampal gyri. However, CSF NfL levels did not associate with progression of gray matter atrophy, and were not able to predict survival. In addition, age at onset influenced total survival after onset, but we did not identify different factors influencing survival.

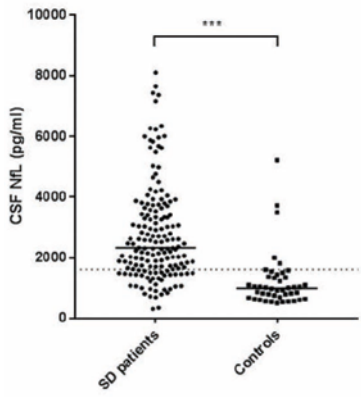

Figure 1. CSF NfL concentrations in SD patients and controls.

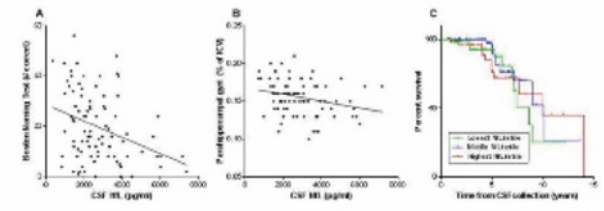

Figure 2. Relationship of CSF NfL to language impairment, parahippocampal atrophy, and survival in SD patients.

Conclusion: These results suggest that CSF NfL has the potential to serve as a biomarker for disease staging and monitoring of disease severity. However, unlike other FTD subtypes, NfL does not predict progression of atrophy or survival in SD, which illustrates the distinctiveness of SD within the FTD spectrum.

Disclosure: Nothing to disclose

EPR2008

Comparison of sulcal opening in posterior cortical atrophy and typical Alzheimer's disease

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Background and aims: Calculate the discriminating power of sulcal opening in the differentiation between Posterior Cortical Atrophy (PCA) and typical Alzheimer disease (tAD).

Methods: MRI of twelve PCA patients were compared to 27 tAD patients and to 14 matched controls. All patients fulfilled the current clinical criteria: Cruth 2017 for PCA, Dubois 2014 for tAD. For each subject, 6 cortical areas (olfactory sulcus, temporal pole, medial temporal, posterior cingulate sulcus, precuneus, parieto-occipital sulcus, both sides) were analysed using Brainvisa software. Moreover visual rating scales for each area were scored by two raters. Results were compared among PCA, tAD and controls using Mann-Whitney U-test. Pearson correlation was calculated between the two methods.

Results: Using Brainvisa, PCA compared to controls showed more atrophy in right olfactory, right temporal pole, right precuneus, medial temporal and parieto-occipital both sides, while compared to tAD showed more atrophy in medial temporal both sides and right parieto-occipital. Likewise, visual rating scales showed more sulcal opening in right olfactory, temporal pole, medial temporal and parieto-occipital both sides in PCA compared to controls, while only right parieto-occipital sulcus was wider than tAD. The correlation between the two methods was significant for all the areas.

Both methods have demonstrated the utility of sulcal opening in the differentiation between PCA, tAD and controls, showing that atrophy particularly affects the right hemisphere in PCA, especially around the parieto-occipital sulcus. The results obtained in visual rating have been validated using Brainvisa.

Conclusion: Opening of right parieto-occipital sulcus can differentiate between Posterior cortical atrophy and typical Alzheimer disease.

Disclosure: Nothing to disclose

Autonomic nervous system; Sleep disorders

EPR2011

Vagomimetic Fingolimod effects are compensated by central up-regulation of cardiovagal withdrawal upon rapid blood pressure decrease

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Background and aims: Fingolimod, an oral disease modifying drug used in relapsing-remitting multiple sclerosis (RRMS) has vagomimetic cardiac effects which might compromise the ability to quickly withdraw cardiovagal-activity which might impose the risk of syncope. We aimed at assessing whether Fingolimod-initiation alters the ability to withdraw cardiovagal-activity in patients with RRMS.
Methods: We tested 26 RRMS patients (mean age 33.5±1.8 years, 13 women) before and 0.5, 1, 2, 3, 4, 5, 6 hours after Fingolimod-initiation. We recorded heart rate (HR), RR-intervals (RRIs) and systolic blood pressure (BPsys) at rest to monitor HR slowing and during Valsalva maneuver (VM) to assess rapid cardiovagal-withdrawal as the baroreflex cardiovagal-gain (BRG) which is calculated from the slope of the regression between RRIs and BPsys during early VM phase II. Parameters were compared by ANOVA for repeated measurements and post-hoc paired t-tests (significance: $p<0.05$).
Results: In 15/26 patients, HR decreased while BRG increased (3.9±2.02 ms/mmHg vs. 5.4±3.5ms/mmHg; p=0.03) until 5 hours after Fingolimod-initiation, and then HR re-increased and BRG decreased at the 6th hour (3.92±2.023 ms/mmHg vs 3.90±4.53 ms/mmHg; p=0.98). In 11/26 patients, HR decrease beyond 5 hours while BRG showed a tendency to increase till the 6th hour (3.3±1.2 ms/mmHg vs 5.9±1.1 ms/mmHg; p=0.05).
Conclusion: As long as Fingolimod slows HR, central autonomic regulation compensates the vagomimetic effects during situation associated with a rapid BP-decrease requiring swift cardiovagal-withdrawal and assures higher BRG as long as HR-slowing prevails. This central compensation prevents cardiovascular instability with the risk of syncope.
Disclosure: Nothing to disclose

EPR2012

Comparison of polysomnographic parameters of RLS patients with and without augmentation

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Background and aims: Augmentation can frequently occur in restless legs syndrome (RLS) patients treated with dopaminergic agents. Video-polysomnographic (PSG) data from augmented RLS patients are scant. The aim of this study was to evaluate PSG findings in augmented RLS patients and compare them with those of non-augmented RLS patients.
Methods: Valid PSG data from 99 augmented and 84 non-augmented insufficiently treated RLS inpatients with severe RLS who underwent one-night PSG were analysed and compared.
Results: Both patient groups showed a high subjective burden of RLS symptoms. The mean scores on the IRLS in the group with augmentation were 31.75±4.66, higher than in the group without augmentation (29.63±7.57, p=0.02). The PLM index (PLMI) was increased in both groups (54.09±43.09 vs 53.86±51.97, p=0.973), mostly on the account of the PLM in wakefulness (PLMW: augmentation 93.11±60.07 vs non-augmentation 78.75±58.92). Both groups presented a reduced sleep efficiency (70.60±14.55 vs 72.27±13.22) and an increased sleep latency (28.45±33.83 vs 29.21±28.93). The Levo-dopa equivalent dose (LED) was significantly higher in the augmented group (74.24±165.83mg vs 29.46±44.42mg, $p< 0.0001$).
Conclusion: Our study confirms that RLS patients with augmentation have subjectively and objectively disturbed sleep with a high amount of PLM and sleep fragmentation. Overall, however, polysomnographic characteristics were not different between insufficiently treated RLS and severely augmented RLS patients, implying that augmentation could represent a severe form of RLS in the night and not a distinctive sleep pattern.
Disclosure: The statistical analysis was supported from a grant from UCB Pharma

EPR2013

REM sleep behavior disorder in the diagnosis of neurodegenerative diseases: Retrospective analysis of polysomnographic records at Hospital Egas Moniz between 2012-2017

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Background and aims: REM sleep behavior disorder (RBD) is prevalent in the early stages of alpha-synucleinopathies. Video-polysomnography (V-PSG) assessment may be relevant in the differential diagnosis of neurodegenerative diseases. We aim to describe the impact of RBD detection on V-PSG in the diagnosis and therapeutic approach of neurodegenerative syndromes

Methods: Retrospective analysis of clinical and polysomnographic records of all patients submitted to V-PSG at the Egas Moniz Hospital Neurology Department between July 2012 and March 2017. We selected cases of neurodegenerative syndromes without a defined clinical diagnosis and recorded whether the result of V-PSG was useful 1) to define the diagnosis (Lewy Body Dementia); 2) as a diagnostic clue in cases clinically confirmed as alpha-synucleinopathy (Multiple System Atrophy and Parkinson's Disease; 3) in the therapeutic decision

Results: 325 patients were submitted to V-PSG. 61 exams were requested for neurodegenerative syndromes without definitive clinical diagnosis: 60.6% were cases of dementia, 31.3% of parkinsonism and 8.1% of ataxia. The detection of RBD generated definitive criteria for LBD in 13 patients (72.2%), modifying therapy in 61.5%. Of the 7 patients in whom this diagnosis would be possible without V-PSG, the mean time for diagnosis without and with V-PSG would be 24.7 and 14.3 months, respectively. In the study of parkinsonian/ataxic syndromes, V-PSG served as a diagnostic clue in 14 patients (60.9%), changing therapy in 35.7%

Conclusion: RBD detection by V-PSG is an important diagnostic aid in alpha-synucleinopathies, with potencial impact on therapeutic approach and diagnostic time reduction

Disclosure: Nothing to disclose

EPR2014

Effect of CPAP therapy on neurographic features in male OSA patients with and without sensomotor polyneuropathy

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Background and aims: So far, the effect of CPAP therapy on neurographic features of peripheral nerves in OSA patients has not been sufficiently investigated.

Objectives: The aim of this study was to determine the effect of CPAP therapy on neurographic features of peripheral nerves in male OSA patients with (n=5) and without (n=5) peripheral polyneuropathy.

Methods: We conducted a cohort study on 10 male OSA patients confirmed by the whole - night polysomnography (PSG).

All subjects underwent neurological examination and standardised electroneurographic testing of peroneal and sural nerves, before and one year after CPAP therapy. For statistical analysis a paired t-test test was used. Level of significance was set at $P<0.05$

Results: The one-year application of CPAP therapy resulted in the improvement of neurographic features in terms of a significant increase in CMAP and SNAP amplitude values, but also of sensory conduction velocities.

Averaged peroneal nerve CMAP amplitudes were 4.64±2.53 mV before and 6.56±1.65 mV after therapy, p=0.001.

Averaged SNAP amplitudes were 9.96±5.78 μV at baseline and 15.6±7.28 μV after therapy, p=0.0015.

Sensory conduction velocities were 43,36±3,90 m/s at baseline and 45.99±5.44 m/s after therapy, p=0.0048.

Conclusion: These results confirmed that CPAP therapy is effective in OSA patients with and without peripheral polyneuropathy in terms of an increase in CMAP and SNAP amplitude values and sensory conduction velocities.

Disclosure: Nothing to disclose

EPR2015

Biomarkers of alphasynucleinopathies in REM sleep behavior disorder: a pilot cross-sectional study

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Background and aims: REM sleep behavior disorder (RBD) is a parasomnia related to loss of muscle atonia during REM sleep phase manifesting with abnormal behavior. It has been shown that great majority of patients with RBD develop alphasynucleinopathies. Among these Parkinson's disease (PD) is most common. We wanted to evaluate the occurrence of various biomarkers of prodromal alphasynucleinopathies in idiopathic RBD.
Methods: In this pilot cross-sectional study we evaluated six patients (age 66.7±11.3, three female) with polysomnographically confirmed RBD. They underwent neurological and cognitive examination, University of Pennsylvania Smell Identification Test (UPSIT), Beck Depression Inventory (BDI), MRI, dopamine transporter imaging (DaTSCAN) and 18F-FDG-PET. PD related metabolic and cognitive patterns (PDRP, PDCP) expressions were calculated and compared to 20 PD patients and 20 normal controls (NC). Alpha-synuclein (αS) in cerebrospinal fluid (CSF) was measured for three of them.
Results: Neurological examination and DaTSCAN were normal in all cases. MoCA score for RBD patients was 25.7±1.6, UPSIT (20.3±2.1/40) confirmed hyposmia (anosmia in one patient), five were depressed and one constipated. PDRP and PDCP expressions in RDB patients were above the average of NC, but below the PD average. In two cases expressions were in the range of PD patients. CSF αS was higher in RBD patients compared to PD, LBD and MSA patients.
Conclusion: All RDB patients had multiple signs of prodromal alphasynucleinopathy including changes in brain metabolism, similar to those in PD, although presynaptic dopaminergic integrity was still normal. Metabolic brain changes may develop earlier in the course of alphasynucleinopathies then presynaptic dopaminergic dysfunction.
Disclosure: Nothing to disclose

EPR2016

Validation of Wearable Sleep Monitoring Device Based on Cardiopulmonary Coupling and Accelerometer with Comparison to Polysomnography in Adults

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Background and aims: Long-term monitoring of sleep with wearable devices is getting increasingly popular, but the accuracy of most devices tracking movements with accelerometers is poor. New products combining actimeters and autonomic markers like heart rate variability are being developed. We compare the accuracy of a novel smart watch classifying sleep and wakefulness based on cardiopulmonary coupling (CPC) and actimetry with video-polysomnography (PSG).
Methods: 59 PSGs from 32 volunteers (f: 20; age: 18-54; no self-reported sleep disorder) were collected while wearing a smart watch (Huawei FIT, Huawei Device (Dongguan) Co., Ltd, China). Four males had sleep apnea syndrome and one female (measured twice) had bruxism, so 53 out of 59 PSGs were from healthy population. The PSGs were manually scored by experienced somnologists. The wearable data were analyzed by the company blinded to the PSG results.
Results: Epoch-by-epoch (1-min) comparison with all PSGs revealed that Huawei FIT showed sleep detection sensitivity, specificity, accuracy and Cohen's kappa of 96.3%, 73%, 93.5% and 0.7, respectively. Values from the 53 healthy PSGs were 96.8%, 76.4%, 94.2% and 0.74, respectively. In the 59 PSGs the sleep duration highly correlated to the one measured by the watch, and Bland–Altman analysis suggested good agreement in measuring sleep length and efficiency using PSG and Huawei FIT.
Conclusion: Wearable devices measuring CPC and actimetry are promising tools for sleep detection at home. They may be valuable for studying sleep related epidemiology and its impact on public health. Whether they can assess sleep architecture needs to be further studied.
Disclosure: This study is supported by Clinic Barmelweid research foundation and Huawei European Research funding.

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EPR2018

Cervical Artery Dissection : Risk Factors, Clinical Features and MRA Manifestations

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Background and aims: In cervical artery dissections(CAD), which are the most common etiologic cause of young stroke group, clinical suspicion and appropriate radiologic examination increase the accuracy of diagnosis and reduce morbidity and mortality. Our aim in this study is to retrospectively evaluate the clinical and radiological findings of the patients who were diagnosed with dissection.
Methods: Demographic and referral clinical characteristics of patients were recorded. Parenchymal and vascular views were analyzed in the application. Localization of dissection, risk factors and clinical evaluation were noted. Patients were treated with anticoagulation/antiplatelet therapy. Vascular imaging was used to confirm the diagnosis of CAD. Angiographic findings of the dissection include a string sign (Figure 1), stenosis, occlusion (Figure 2b), intimal flap, dissecting aneurysm (Figure 2a), pseudo/double lumen.

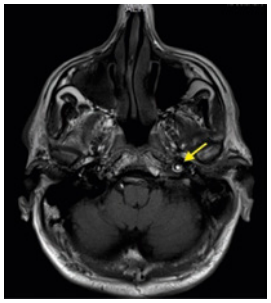

Figure 1. Fat-SE T1 axial cranial MRI, Subacute dissection appearance of the left ICA with 'crescent sing' intramural hematoma (yellow arrow)

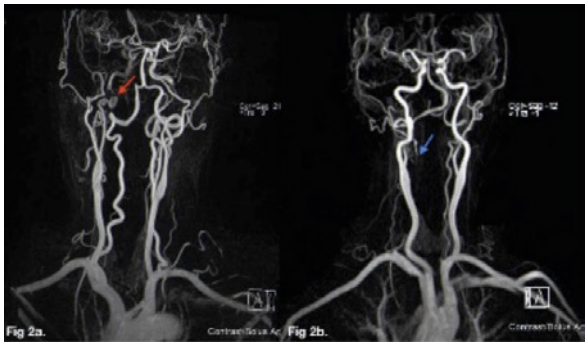

Figure 2a. MRA oblique projection right ICA dissection, pseudoaneurysm (red arrow) Figure 2b. MRA coranal projection, right VA V1 segment occlusion (blue arrow)

Results: A total of 45 patients (28 male, 17 female) with a mean age of 44.17 (± 13.8) with the diagnosis of CAD were enrolled. Hypertension (24.4%) is the most common risk factor in the history (Table 1). In the etiology 40% of cases had minor/major trauma. The most common cause of minor trauma was drop/crash (38.9%) (Table 2). The most common clinical presentation was stroke (46.7%). Headache/neck pain (42.3%) is the most common local symptom. The most common vascular findings on angiographic imaging were intaramural hematoma (31.3%).
Conclusion: Multimodal CT or MRI assessment is crucial for defining vessel wall abnormalities. Recognition of CAD are highly important in the presence of localized symptoms, TİA/stroke, especially in the young adults with clinical suspicion.
Disclosure: Nothing to disclose

EPR2019

Would intravitreal bevacizumab injection increase risk of cerebral infarction?

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Background and aims: Although studies have evaluated the relationship between intravitreal bevacizumab (IVB) injection and cerebral infarction(CI), the effects of IVB on CI are still not clear. The aim of this study was therefore to investigate the effects of IVB injection on CI patients with age-related macular degeneration (AMD).
Methods: We retrospectively reviewed patients with AMD who received IVB injections for 1 year and determined the incidence of CI within 60 days after IVB injection to analyze the possible association between IVB and CI.
Results: Over a 12-month period, 263 patients were enrolled. Six patients (2.28%) were diagnosed with CI within 2 months after receiving an IVB injection. The incidence of CI in patients 75–84 years of age was 6.38%. These results showed a higher incidence of patients with IVB injections than the results of previous epidemiological studies (0.13% for all age groups, 1.68% for patients 75–84 years of age). All CI occurred 21–53 days after the IVB injection (mean: 39.33±14.65 days). Logistic regression analyses showed that age and a history of previous CI were factors associated with CVA. However, the total number of IVB injections and the number of IVB injections over 1 year were not associated with CI.
Conclusion: Treatment with IVB might be an independent risk factor for CI. These results are useful for planning treatment strategies for patients with AMD and for prevention of CI.
Disclosure: This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (grant number: 2017R1E1A1A01074324)

EPR2020

Free fatty acid and pro-BNP as predictors of atrial fibrillation in acute ischemic stroke patients

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Background and aims: Atrial fibrillation (AF) is a common arrhythmia and a major risk factors for stroke. A recent study has shownthat AF relate to some biomarkers such as free fatty acid (FFA) and pro-brain natriuretic peptide (pro-BNP) have been reported. The purpose of this study is to investigate the useful blood biomarkers to predict AF in acute ischemic stroke.
Methods: Total 195 consecutive patients (mean age, 66.7±12.4 years; 39.5% women; 16.9% AF group) with acuteischemic stroke within 72 hours of onset were retrospectively enrolled. We analyzed the biomarkers such as hs-CRP, FFA, pro-BNP, D-dimer, myoglobin and eGFR between stroke with and without AF.
Results: Age, heart rate, FFA, pro-BNP, D-dimer, myoglobin and the frequency of woman were significantly higher in AF group ($p < 0.05$). eGFR was significantly lower in AF group ($p < 0.05$). hs-CRP was no significant difference. The respective cut-off value of FFA, pro-BNP and D-dimer level for prediction of the AF were 1235.5 μEq/ml, 287.5pg/ml and 1.105 μg/ml (sensitivity 58%, specificity 91%, AUC 0.80 for FFA; 88%, 83%, 0.93 for pro-BNP;39%, 82%, 0.73 for D-dimer). The combination of FFA, pro-BNP or D-dimer for the prediction of the AF had a sensitivity of 94% and and a specificity of 66%. Multivariate logistic regression analysis demonstrated that female gender, FFA and pro-BNP were independently associated with the presence of AF.
Conclusion: The combination of FFA or pro-BNP can be a strong biochemical marker for the prediction of AF on admission in patients with acute ischemic stroke.
Disclosure: Nothing to disclose

EPR2021

Diagnostic workup and aetiologic diagnosis of ischemic stroke in young adults: a two-centre comparison

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Background and aims: Identifying the aetiology of ischemic stroke in young adults is often a difficult task. Strategies for diagnostic assessment vary between a comprehensive approach, a staged workup emphasizing local prevalence of potential causes and a clinical hints-based approach.
This study attempts to compare the workup strategy of ischemic stroke in young adults between two stroke units in Europe, ultimately aiming to investigate the influence of workup variations in aetiologic classification.
Methods: This study included patients aged 18 to 55 years admitted for ischemic stroke or transient ischemic attack to the stroke units of Santa Maria Hospital in Lisbon, Portugal, and Innsbruck State Hospital in Innsbruck, Austria, between 2014 and 2016. Aetiology and diagnostic procedures were compared between centres.
Results: This study enrolled 156 patients from Innsbruck State Hospital and 110 patients from Santa Maria Hospital. CT (computed tomography) and MR (magnetic resonance) angiography ($p<0.01$), transoesophageal echocardiography ($p<0.05$) and ophthalmologic and dermatologic evaluation ($p<0.01$) were more commonly performed in Innsbruck, whereas patients in Lisbon were more frequently submitted to transcranial Doppler ($p<0.01$) and screening for thrombophilia ($p<0.05$), autoimmune disorders ($p<0.01$) and other causes. No significant differences in aetiology were found.
Conclusion: The variations in the diagnostic workup between both centres did not influence aetiologic diagnosis. Extensive laboratory testing not guided by clinical hints does not seem to influence diagnosis of stroke of other determined cause, thereby emphasizing the importance of a clinically-oriented diagnostic approach.
Disclosure: Nothing to disclose

EPR2022

Predictors for timely arrival in hospital and effect on clinical outcome in patients with acute stroke in Germany

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Background and aims: Even though effect of recanalization therapies for acute stroke has been proved to be highly effective, most of stroke patients still reaches hospitals outside the time window.
We aimed at identifying factors decisive for timely arrival at the hospital of patients with acute stroke within the therapeutic time window.
Methods: In two regional stroke units in North-Rhine-Westfalia, Germany 895 consecutive patients with ischaemic stroke or TIA were surveyed after admission to hospital and 3 months later.
Results: Only 44.9% of subjects reached the hospital within 4 hours and 54% within 6 hours, respectively. 12.3% received rTPA, 3.1% thrombectomy. Patients who notified emergency service were more likely to arrive in due time (OR 2.3 95% CI [1.1-4.9]). Knowledge of stroke symptoms (OR=1.2 95% CI [1.1-1.4]) and private health insurance (OR=3.9 95% CI [1.1-13.9]) were associated with a timely arrival.
At discharge 46.8% of timely arrived patients were symptom free compared to 30.9% of those who arrived late (Chi-Quadrat= 27.8, df =6, p=0.001). Three months later, clinical outcome of timely arrived patients still was better (Chi-Quadrat= 3.66, df=6,p= 0.72).
Conclusion: Despite free access to medical care the acute treatment of stroke in Germany is still insufficient. More than a half of stroke victims arrive too late and do not receive adequate treatment. The results call for public awareness campaign in order to increase the number of timely arriving stroke patients.
Disclosure: Nothing to disclose

EPR2023

Dexamethasone Therapy versus Surgery for Chronic Subdural Haematoma, a clinical randomised controlled trial (DECSA - trial)

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Background and aims: Chronic subdural haematoma (CSDH) is a common neurological disease with rapidly rising incidence due to increasing age and widespread anticoagulant use. Current treatment for symptomatic patients is mostly surgical intervention by burr hole craniostomy (BHC). However, dexamethasone (DXM) therapy is used increasingly as a non-surgical alternative. Randomised controlled trials comparing both therapies are lacking, leaving beneficial effects of DXM unsettled.
Objective: To compare the effect of primary DXM therapy versus BHC on functional outcome in symptomatic patients with CSDH in a multicentre randomised controlled trial.
Methods: CSDH patients with Markwalder Grading Scale (MGS) grade 1-3 are randomised to either BHC or DXM-treatment. The latter contains 16 mg DXM per day on day 1 to 4, after which the dose is halved every three days and stopped on day 20. Primary outcome is functional outcome assessed with the modified Rankin Scale (mRS) at three months. Secondary outcomes include mRS and MGS at discharge, two weeks and six months, Extended Glasgow Outcome Scale score at three months, quality of life and haematoma recurrence at six months, haematoma thickness on follow–up CT at two weeks, complications and mortality. Assuming a treatment effect of 80% in the BHC treatment arm compared to 60% for DXM, 170 patients are required to test our hypothesis of BHC superiority over DXM.
Results: Results are expected in 2019.
Conclusion: This study aims to demonstrate whether BHC is superior to DXM on functional outcome in symptomatic patients with CSDH. Ultimately it will provide a basis for future guidelines on CSDH management.
Disclosure: Nothing to disclose

EPR2024

Clinical characteristics of ischemic stroke in patients treated previously with direct oral anticoagulants

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Background and aims: Clinical guidelines recommend direct oral anticoagulants (DOACs) for secondary prevention of ischemic stroke (IS) in atrial fibrillation (AF). Optimal management of recurrent IS on DOAC therapy is controversial.
Methods: Prospective registry (2010-2015) of patients with AF treated with DOACs in secondary prevention of IS. Demographic, clinical variables, IS recurrence and its management were analyzed.
Results: We included 425 patients, 53.4% women, with a mean age of 77.1±10.2 years, mean CHA2DS2VASc 5± and HASBLED 2±, treated with dabigatran (57.7%), rivaroxaban (24.7%), and apixaban (17.6%), with a mean follow-up of 20±18.1 months. Thirty-four incidental IS (7.95%) were registered in a median time of 7 months from treatment onset (1-52); 14 (41.2%) were transient ischemic attacks. Annual rate of IS was 0.05 cases/person-years. All recurrent IS patients were receiving the correct dose of DOACs according to the label, and mean glomerular filtration rate in the event was similar to baseline (61.8±31ml/min). Reperfusion therapies were performed in 5 patients (4 intravenous thrombolysis and 1 mechanical thrombectomy). Twenty patients (58.8%) were independent (mRS $\leq$2) at three months, while one patient died (2.9%). For further IS prevention, 21 patients retained the same DOAC, 7 were switched to a different DOAC, and 1 to acenocoumarol. Two patients underwent left appendage closure in addition to DOAC therapy.
Conclusion: In our experience with patients treated with DOACs in secondary IS prevention, rate and clinical features of recurrent IS was similar to the pivotal trials. Clinical decisions following recurrent IS were individualized, in the absence of formal guidelines.
Disclosure: Nothing to disclose

EPR2025

Inhibiting aquaporin 4 modulates the perivascular drainage of amyloid Aβ peptide in the brain.

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Background and aims: The absence of aquaporin 4 (AQP4) in mice with APP/PS1 overexpression has a negative effect on Aβ paravascular drainage, leading to its deposition especially as cerebral amyloid angiopathy. In this pilot study, we aimed to assess the influence of direct AQP4 inhibition on the diffusion and paravascular drainage of Aβ.

Methods: We have injected 1µl of fluorescently Aβ40 peptide into the cortex of TgN(hGFAP-mRFP1) mice exhibiting endogenous fluorescent astrocytes, under a two-photon microscope, and visualizing in the same time the blood vessels (fluorescently labelled Dextran). We imaged the lesion site continuous for 90 min after the injection. We utilized non-injected animals (N=6), Aβ40 injected animals (N=6), and animals injected with Aβ40 after a single intraperitoneal administration of the AQP4 inhibitor TGN-020 (100mg/kg) (N=6). Image datasets were interpreted in order to measure the diffusion of Aβ40.

Results: Our data confirmed first that, after slow injection, Aβ40 diffuses around the site of injection in the parenchyma and slowly clears around small and medium-sized blood vessels, dissecting between the blood vessels lumina and the astrocytes end-feets. Next we showed for the first time that after AQP4 temporal inhibition, Aβ40 diffuses in the parenchyma at comparable speeds as without AQP4 inhibition, but it tends to remain located in the perivascular perimeter longer than in animals without TGN-020 treatment.

Conclusion: Altogether, these findings support the hypothesis that functional AQP4 deficiency that appears with age-related vascular changes (hyalinization of the basement membranes, increased rigidity, etc.) favors Aβ accumulation in these patients.

Disclosure: Acknowledgments. This work was supported by a grant of the Romanian National Authority for Scientific Research and Innovation, CNCS – UEFISCDI, project number PN-III-P2-2.1-PED-2016-0803, within PNCDI III (contract number 143PED/2017).

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EPR2026

Risk of recurrent ischemic stroke in young patients with a cryptogenic cause

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Background and aims: The cause of ischemic stroke (IS) remains often cryptogenic, despite of an extensive diagnostic setting and especially in younger patients. Thus secondary preventive treatment does not have to be adequate. Our aim was to assess the risk of recurrent IS (RIS) in young cryptogenic IS (CIS) patients.
Methods: The study set consisted of young acute IS patients<50 years enrolled in the prospective HISTORY (Heart and Ischemic STrOke Relationship studY) study registered on ClinicalTrials.gov (NCT01541163). In all patients, the brain ischemia was confirmed on CT or MRI. Admission ECG, serum specific cardiac and thrombophilia markers, neurosonology, TEE, 24-hour and 3-week ECG-Holter were performed in all patients to assess CIS according to the ASCOD classification.
Results: Of 220 enrolled young IS patients<50 years, 161 (74%) patients were identified as cryptogenic (90 males, mean age 41.3±7.4 years). All patients were on antiplatelet therapy during the follow-up (FUP) with a median of 35 months. Six (4%, 2 males, mean age 46.8±1.2 years) CIS patients suffered RIS during FUP with a median of 13 months after first IS (median of admission NIHSS was 4 points). Median of 3-month clinical outcome was 1 point in modified Rankin Scale. One-year risk of RIS was calculated as 0.021 (95% CI: 0-0.044) using Kaplan-Meier analysis.
Conclusion: The risk of RIS in young CIS patients seems to be very low and with good outcome despite unclear cause.
Disclosure: Supported by the grant of Ministry of Health of Czech Republic nr. 17-30101A, and by the grant IGA LF UP_018_2018.

EPR2027

Predictors of readmission after acute ischemic stroke in a tertiary care center

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Background and aims: Stroke is one of the leading causes of disability both in developing as well as developed nations. Among those who survive the acute period, there remains a risk of recurrent vascular events or other stroke related non vascular complications leading to re-hospitalizations and increasing economic and health care related burden, especially in a country with limited availability of health insurance schemes.
Methods: We performed the study to evaluate the frequency and factors affecting readmission within one month of discharge among patients with acute ischemic stroke who were admitted to the stroke unit of the Aga Khan University Hospital, Pakistan, from January to December 2016. Retrospective review of data was performed on 1109 patients who fulfilled the inclusion criteria. Logistic regression was performed to evaluate for factors associated with readmission.
Results: Of the 1109 patients discharged after acute stroke, 115 (10.3%) were readmitted within one month. The most frequent causes for readmission were found to be recurrent strokes, infections particularly chest and urinary tract, seizures, electrolyte imbalances and cardiovascular events. Older age, higher MRS score at discharge and multiple underlying stroke risk factors were independent predictors of readmission.
Conclusion: Survivors of acute stroke are a vulnerable population with a higher likelihood of requiring readmission from certain stroke or non stroke related complications. Recognition of these factors and cautious monitoring may help develop strategies for quality of care improvement in these patients.
Disclosure: Nothing to disclose

EPR2028

Comparison of short longitudinal and transverse skin incision for carotid endarterectomy

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Background and aims: Nerve injuries, wound complications and poor cosmetic results still have an important impact on patient's outcome after carotid endarterectomy (CEA). The study aimed to compare 30-day morbidity and cosmetic outcome between patients undergoing CEA using short longitudinal incision (SLI) and transverse skin incision (TSI).
Methods: All consecutive patients with ICA stenosis >70% indicated for CEA were screened in this monocenter prospective study and randomly allocated to SLI or TSI group. Physical and neurological examinations were performed 30 and 90 days after surgery. Cosmetic results were evaluated using the Patient and Observer Scar Assessment Scale (POSAS) 90 days after surgery.
Results: Out of 189 enrolled patients, SLI was used in 102 patients (71 males; mean age 64.0±7.1 years) and TSI in 87 patients (58 males; mean age 66.4±7.2 years). Stroke or transient ischemic attack occurred during 30 days in 4 (3.9%) patients in SLI group and in 2 (2.3%) patients in TSI group (P=0.689). The scar quality assessed using POSAS was higher in TSI than in SLI patients (12.4 vs. 16.6 points; P<0.01). Patients in TSI group evaluated better than SLI patients the scar pigmentation, thickness, relief, pliability and surface area (P<0.01 in all cases). No significant differences were found in the occurrence of local complications (8.0% in TSI and 8.8% in SLI group; P=1.00).
Conclusion: Better cosmetic results were observed in patients after CEA using TSI than SLI. No differences in morbidity and in the occurrence of local complications were observed.
Disclosure: Supported by MHCR grants No. 17-31016A, 16-30965A, 16-29148A.

EPR2029

Illicit substance use as a cause of stroke in young adults: a case control study

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Background and aims: Illicit drug use is a potential cause of stroke in young adults. The concomitant role of conventional cardiovascular risk factors and other co-morbidities in young adult stroke associated with illicit drug use is unclear.
Methods: We retrieved from the Stroke registry of an acute stroke unit (SU) of a tertiary care hospital all young adult patients admitted between 2005 and 2016 with a history of illicit drug use (cases). Controls (3:1) were consecutive stroke patients admitted to the SU during the same period, matched by age and gender. We compared cardiovascular risk factors, co-morbidities, type of stroke and outcome.
Results: We identified 42 stroke patients with illicit drug use (opioids-48%, cocaine-43%, cannabinoids-38%, LSD-7%, multiple drugs-43%). Smoking and other comorbidities (viral hepatitis, HIV and chronic renal disease) were statistically significant more frequent among drug users (X2=9.20, p=0.002; X2=7.8, p=0.005, respectively). All drug users had at least a cardiovascular risk factor or comorbidities potentially predisposing to stroke, while 8.5% of stroke in controls were not associated to other conditions (X2=2.49, p=0.115).
Both groups had comparable rates of ischemic vs hemorrhagic stroke. The anterior circulation territory was the most often affected in both groups (69.2% and 68.4%). The posterior circulation territory was frequently involved in cannabis users (42.9%).
The clinical outcome at hospital discharge was similar in both groups.
Conclusion: Stroke type and outcome were similar between drug users and non-users. Illicit drug users had cardiovascular risk factors and other comorbidities, which may have a synergistic effect with illicit drug use in causing stroke.
Disclosure: Nothing to disclose

EPR2030

Comparison of transcranial Doppler and echocardiogram for patent foramen ovale diagnosis

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Background and aims: Patent foramen ovale (PFO) is an interatrial septum defect present in about 25% of adults, and a possible cause of cryptogenic stroke. Recent studies suggest the benefit of its closure in embolic strokes of undetermined origin. Therefore, PFO presence is frequently searched, especially in young adults with stroke, either by echocardiography or transcranial Doppler (TCD) with IV gaseous contrast for left-right shunt detection. TCD results are interpreted according to the number of detected microembolic signals (MES), with and without Valsalva maneuver (VM): 0-negative; 1-10; >10 without curtain; curtain (not individualized MES).
Our objective is to compare the results of TCD and echocardiogram for PFO detection.
Methods: Analysis of TCD exams for left-right shunt detection at our center in the last 2 years, and comparison with echocardiogram results.
Results: Fifty-seven PFO studies were performed, 34 early positive. One acute stroke patient, unable to perform Valsalva manouver, had negative TCD, while a later transesophageal echocardiogram (TEE) was positive. Of the patients with PFO on TCD, 9 were confirmed by TTE (transthoracic echocardiogram) and 16 by TEE. Three positive TCD were not confirmed by echocardiogram; of these, one was positive only with VM (7 MES), another had 3 MES without VM and >10 with VM, and another had >10 MES without VM. Six positive DTC had negative TTE and wait for TEE. Regarding the echocardiogram, TCD had 96% sensitivity, 87% specificity, 89% PPV and 95% NPV.
Conclusion: In our series, TCD showed great accuracy compared to echocardiogram, currently considered the gold standard for PFO diagnosis.
Disclosure: Nothing to disclose

EPR2031

Intravenous trombolysis for ischemic stroke in pregnancy and puerperium – case series

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Background and aims: Pregnancy and puerperium have been reported to be associated with an increased risk of ischemic stroke with higher risk in puerperium. Reported incidence is from 11 to 34 per 100 000 pregnancies. Standard recanalization therapy with intravenous thrombolysis (IVT) in pregnant women is not verified by large clinical trials. Although there are number of reported cases showing safety of thrombolysis in pregnant women and postpartum period, there are still doubts for use of IVT in common practice.
Methods: Case series of 5 ischemic stroke patients from Motol comprehensive stroke centre treated in 2014 -2017 when pregnant or postpartum.
Results: Three patients were pregnant (1st and 2nd trimester), two were in puerperium. Mean age was 34 (29-38 years), mean NIHSS at admission was 7.4 (5-15). Affected territory was twice middle cerebral artery, twice posterior cerebral artery and in one patient vertebral and basilar artery. We have not seen any bleeding complications – intra or extracranial. One patient was complicated with infratentorial decompressive craniectomy for cerebellar ischemia with oedema. Modified Rankin scale at 3 months was good in all patients (0-1 points). Outcome of pregnancies was also good, 2 women delivered healthy child, 1 is still pregnant with no complications. 1 from 2 at puerperium had another safe pregnancy after the stroke.
Conclusion: Thrombolysis during pregnancy and the puerperium in our experience is safe and has good efficacy and should be considered in therapy of stroke in pregnant women.
Disclosure: Nothing to disclose

EPR2032

Emergent carotid artery stenting in internal carotid artery atherosclerotic disease with tandem intracranial occlusion

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Background and aims: Several randomized trials have proven the safety and efficacy of mechanical thrombectomy (MT) in large vessel occlusions; nonetheless, there is still no consensus concerning hyperacute management of tandem occlusions. Recent studies have proposed emergent carotid artery stenting (eCAS), along with MT, as an effective and safe treatment option.
Aims: To characterize safety and short-term outcome of patients treated with eCAS during endovascular treatment of acute ischaemic stroke.
Methods: Review of the prospective patient registry submitted to MT for anterior circulation acute ischaemic stroke in a single referral centre and selection of patients treated with eCAS for atherosclerotic occlusion/near-occlusion of cervical internal carotid artery between January/2015 and July/2017. Clinical data was collected and assessment of procedure safety and 3-month-outcome were performed.
Results: Among 252 patients submitted to MT, 24 patients (9.5%) underwent eCAS. Most patients were male (23/24), median age was 65.2 years (IQR=57.3-73.8), median admission NIHSS was 14 (IQR=11-17) and 14/24 patients had been submitted to intravenous thrombolysis. Successful recanalization was obtained in 95.8% of patients. Two patients (8,3%) experienced symptomatic intracranial haemorrhage, one patient experienced early intra-stent thrombosis and one patient developed cerebral hyperperfusion syndrome. At 3-month follow-up, 17 patients were independent (70.8%) and 1 patient died (4,2%).
Conclusion: Overall, positive results were obtained using emergent carotid stenting (eCAS). Although an optimal intervention for this type of occlusions has not yet been formally established, eCAS has been surging has a feasible and safe treatment option.
Disclosure: Nothing to disclose

EPR2033

Early transcranial color-coded Doppler in the prediction of cerebral edema post-thrombectomy

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Background and aims: Recanalization of a large vessel occlusion (LVO) has a dramatic impact on patients' outcome, however it also increases the risk of reperfusion injury and devastating clinical consequences, such as cerebral edema and hemorrhagic transformation. We aimed to assess the accuracy of the hemodynamic status post-thrombectomy, evaluated by transcranial color-coded Doppler (TCCD), in the prediction of cerebral edema.
Methods: Cohort study of acute stroke patients with LVO in the anterior circulation, who achieved effective arterial recanalization (TICI 2b/3 post-thrombectomy) and were evaluated by TCCD in first 24 hours. We analyzed the mean velocity in the M1 segment of the symptomatic and asymptomatic middle cerebral arteries (MCAs), and the symptomatic/asymptomatic MCAs ratio (MCAsRa). Cerebral edema was classified in the 24 hours CT scan by blinded-Neurorradiologist. Statistical analysis included univariate analysis and logistic regression adjusted for age, initial NIHSS and previous arterial hypertension.
Results: One-hundred patients were enrolled, mean age 67.69 (±13.86) years, 59 males (59.0%). The mean velocity in the symptomatic MCA was not statistical different in patients with (60.55±22.31cm/sec) vs. without cerebral edema (54.55±17.09cm/sec),p=0.173; MCAsRa were also similar between groups (1.04±0.359 vs. 1.00±0.32;p=0.608). Neither mean velocity or MCAsRa were predictors of cerebral edema: OR 1.020 (0.996-1.045,p=0.105) and OR 1.594 (0.431-5.895,p=0.484).
Conclusion: Cerebral reperfusion injury has a complex mechanism with multiple pathologic processes and cerebral edema is frequent. Nevertheless, early TCCD does not seem to identify predictors of cerebral edema post-thrombectomy.
Disclosure: Nothing to disclose

Child neurology/developmental neurology

EPR2034

Basal Ganglionic Lesions in Egyptian Children: Radiological Findings in Correlation with Etiology and Clinical Manifestations

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Background and aims: In childhood, the metabolic activity of the basal ganglia is greater and they are particularly prone to injury, that causes problems controlling movement, muscle tone and cognition.
Aim of work: to determine the etiology of basal ganglionic disorders in a sample of Egyptian children.
Methods: A cross-sectional observational study was utilized on 34 patients attended at the Pediatric Neuro Outpatient Unit of Neurology department at f Al-Azhar University Hospitals during a period of one year from November 2014 to November 2015. A specialized pediatric neurological sheet, Cognitive assessment using Stanford-Binet Intelligence Scale and Laboratory investigations were performed. The included patients were classified according to MRI into two groups; ganglionic (included patients with isolated basal ganglionic lesions) (n=23) and para-ganglionic (included patients with combined ganglionic and para-ganglionic lesions) (n=11).
Results: Frequency of male was higher than female patients in both groups without significant difference (13 (56.5%) versus 6 (43.5%) and 10 (54.5%) versus 5 (45.5%), in ganglionic and para-ganglionic groups, respectively). acute ischemic stroke was the most frequent cause, which was found in 12 (35.3%) cases, followed by 10 (29.4%) had metabolic and infectious causes, and lastly 2 (5.9%) had toxic causes. The incidence of toxic causes (CO poisoning) was higher among ganglionic group compared to para-ganglionic group (2(8.7%) versus 0(0.0%), respectively).
Conclusion: Acute ischemic stroke was the most frequent cause of basal ganglionic lesion in a sample of Egyptian children.
Disclosure: Nothing to disclose

EPR2035

The concentration of Doublecortin in the cerebrospinal fluid from human infants is developmentally regulated

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Background and aims: Doublecortin (DCX) is specifically expressed in neuronal precursor cells and migrating neurons. DCX is neurodevelopmentally regulated, and its concentration in the rodent cerebrospinal fluid (CSF) and in rodent and human brain declines during early postnatal stages. In this study, we analyzed the concentration of DCX in the CSF (DCX-CSF) from human infants.
Methods: CSF was collected from pediatric patients requiring neurosurgical treatment. DCX concentration was measured with the Mesoscale platform. Clinical data was retrospectively collected from individual patient charts. Chronological age was adjusted for premature birth.
Results: A total of 52 CSF samples from 35 patients (18 females) were collected between February 2013 and June 2016. The patients' age was from 0.3 years before due date to 18 years (median 2.9; interquartile range 0.3-7.3). DCX-CSF could be quantified in 21 samples from 12 patients ranging from 13 to 21,568 pg/ml (1065; 150-3,495). All 11 patients younger than 4 months had detectable DCX-CSF that decreased with age. Only one 5-year-old with a grade III astrocytoma also had detectable DCX-CSF (331 pg/ml).
Conclusion: Our results show an age-dependent downregulation of DCX-CSF from humans until 4 months of age, similar to that observed in rodent neonates. This time window for the detection of DCX in human CSF strikingly coincides with the recently described migration of DCX+ cells to the frontal lobe in the human brain that persists for 5 months after birth. Further investigations are warranted to understand the clinical significance of DCX-CSF in humans.
Disclosure: Nothing to disclose

EPR2036

The role of monoamine oxidase A mutation in a boy with neurodevelopmental and behavioural problems – a new family with Brunner Syndrome?

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Background and aims: Monoamine oxidase A (MAOA) gene polymorphisms have been associated with various behavioural and psychiatric phenotypes. Brunner Syndrome was first described in 1993 as a recessive X-linked disorder characterized by altered behaviour with impulsive aggressiveness and mild mental retardation associated with MAOA deficiency. Only more recently, after two decades since the first Brunner Syndrome description, three more families have been identified, indicating that this entity should be more frequently suspected.
Methods: Case report.
Results: We present a case of a 9-year-old boy followed in neurology consultation since 2 years of age due to epilepsy, behaviour problems, sleep disturbance with night terrors, attention deficit and hyperactivity symptoms and a borderline intellectual disability with important language delay. He had a history of impulsivity, frustration intolerance and heteroaggressiveness with anger outbursts. Due to the complexity of the clinical picture, together with a family history of male individuals (two brothers and one nephew) with similar neurodevelopmental and behavioural problems, the suspicion of a recessive X-linked disorder was raised. Accordingly, a disease-focused exome sequencing was performed and a MAOA mutation c.617G>A(p.Arg206Gln) was identified in hemizigoty in the clinical proband.
Conclusion: We describe a new genetic MAOA variant, associated with a severe behavioural phenotype, in a family with several male elements affected with psychiatric symptoms, suggesting an X-linked pattern of disease inheritance. Further biochemical and genetic studies are now being performed. If confirmed, this corresponds to the fifth family identified with this syndrome worldwide.
Disclosure: Nothing to disclose

EPR2037

Imaging of the Mechanisms of Thalamic Damage in Pediatric Multiple Sclerosis

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Background and aims: Thalamic damage occurs in pediatric multiple sclerosis (MS) patients. Thalamus location exposes this structure to different pathobiological processes: Wallerian degeneration for its extensive cortical and subcortical white matter (WM) connections and neuroinflammation due to cerebrospinal fluid (CSF) mediated immune-cytotoxic factors. This study is aimed at characterizing thalamic volumetric abnormalities according to their distance from CSF and their correlation with WM lesions in pediatric MS patients.
Methods: Dual-echo and 3DT1-weighted images were acquired from 70 pediatric MS and 26 age and sex-matched healthy controls (HC). To assess thalamic shape differences a vertex-analysis was performed using the FMRIB Integrated Registration and Segmentation Tool. Cortical surface reconstruction and mean cortical thickness measurement were performed using FreeSurfer. Correlations with clinical and conventional MRI variables were also explored.
Results: Global thalamic volume did not differ between HC and pediatric MS patients ($p=0.06$). The vertex analysis revealed significant differences in thalamic shape with a prominent inwards displacement of thalamic ependymal surface and a relative sparing of ventrolateral thalamic surface ($p<0.05$). No correlation was found between thalamic surface inwards displacement and T2 and T1 lesion volume, cortical thickness, disease duration and clinical disability.
Conclusion: In pediatric MS, the absence of correlations between thalamic volumetric abnormalities, focal WM lesions and clinical variables supports the hypothesis of an early damage, linked to acute inflammatory processes occurring close to disease onset rather than to Wallerian degeneration. Thalamic inward surface displacement could represent an early neurodegenerative process, potential target for monitoring disease progression from the earliest stages of disease.
Disclosure: Partially supported by grants from Italian Ministry of Health (GR-2009-1529671) and Fondazione Italiana Sclerosi Multipla (FISM2011/R/19, FISM 2012/R/8, FISM-2016-R-23)

EPR2038

Headaches in preschoolers: are "red flags" predictive of positive neuroimaging in Emergency Department? Preliminary data.

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Background and aims: Headache at preschool age can frequently be secondary. An emerging problem is to establish the role of neuroimaging in children suffering headaches, but to date in literature we do not have clear evidence concerning when neuroimaging study is necessary, mostly in this age group, rather than clinical follow-up to limit repeated visits to Emergency Department (ED). Aim of this study is to explore and verify the relationship between the presence of red flags and neuroimaging abnormalities in a preschool population.
Methods: We collected clinical data of children aged from 1 to 7 years old admitted in ED from October 2015 to September 2016. We used a predetermined list of red flags (acute onset, associated symptoms, abnormal neurologic examination and others) and we evaluate the number of children underwent computed tomography (CT).
Results: We found that 128/400 (32%) children admitted in ED are preschoolers, 58 males and 70 females. Seventy-nine of these (61.7%) showing one or more red flags at the access, 57/79 (72.15%) were investigated with CT. Thirty-eight of them showed positive TC for incidental benign abnormalities, while just one patient, with more than one red flags (acute onset, occipital localization and paresis) at the access, showed altered TC for dangerous anomalies.
Conclusion: These is the first study on a selected preschool population with headache. Preliminary results confirm literature data about the poor specificity of undifferentiated red flags in identifying which patients need neuroimaging, underlying that in the setting of a normal neurologic examination neuroimaging can be deferred in most pediatric patients.
Disclosure: Nothing to disclose

EPR2039

ELAC2 mutation and phenotypic spectrum, a case report

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Background and aims: ElaC Ribonuclease Z 2 (ELAC2) encodes the long form of RNase Z, an endonuclease responsible for the removal of the 3-prime extensions from tRNA precursors, which is an essential step in tRNA biogenesis both in nucleus and mitochondria. Primarily the ELAC2 gene was regarded as a heritable prostate cancer susceptibility factor.However, ELAC2 mutations also cause a mitochondrial RNA processing defect associated with hypertrophic cardiomyopathy and combined oxidative phosphorylation deficiency. In some instances symptomatology such as encephalopathy, microcephaly, muscular hypotonia, seizures and growth retardation as well as early death have been reported. Next-generation sequencing (NGS) has proven to be efficient in the diagnostics of disorders where multiple genes can be involved. NGS-based exome trio analysis of proband and parents detects recessive, X-linked and de novo genetic disorders.
Methods: A twelve year old girl with ataxia, deafness and scoliosis was primarily referred for NGS ataxia testing. However, due to growth retardation and mixed developmental disorder NGS exome was performed.
Results: A homozygous sequence variant in ELAC2 was identified. The identified sequence variant probably explains her symptomatology.
Conclusion: NGS is versatile tool when investigating probable genetic causes of undiagnosed child neurology or developmental delay cases. Due to the ELAC2 finding an echocardiogram was performed. The ELAC2 symptomatology is probably more diverse than originally suspected.
Disclosure: Nothing to disclose

EPR2040

Visual cortical excitability in pediatric migraine: a study with sound-induced flash illusions

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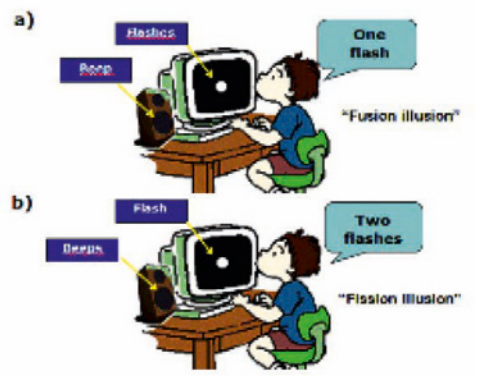
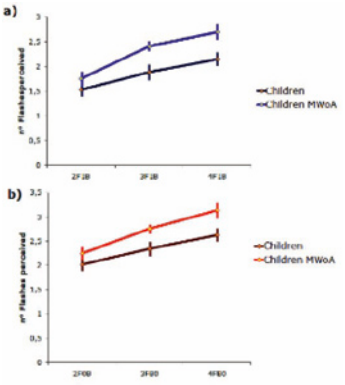
Background and aims: Sound-induced flash illusions (SIFI) are related with the level of visual cortex(V1) excitability(1). In adults migraineurs, in response to SIFI, V1 is hyperexcitable(2). Susceptibility to SIFI in children is increased because during childhood acoustic dominance switch to a visual(3). We evaluate by SIFI the V1 excitability in children with migraine to assessing also age-related differences in audio-visual perception. Twenty-six migraine children (examinated interictally), fifteen children and twenty-four adult healthy with no familiarity for migraine were tested.

Methods: Visual(flash) and sound(beep) stimuli are presented with different combinations: multiple flashes with a single beep causes perception of less flashes (fusion illusion) while multiple beeps and single flash, induce perception of more flashes (fission illusion). Each combination was randomly presented and the subject had to indicate the number of the flashes seen.



Results: Children see more illusions than adults. Children with migraine do not differ from age matched control in the illusory percept, but they perceive more flashes in multiple flash trials.



Flash seen with (a) and without beep (b).

Conclusion: Children see a greater number of SIFI than adults, this is due to the higher propensity of visual stimulation to be driven by auditory stimulus. Even if no difference in the illusory percept between controls and patients emerge, the migraine children have an increased ability to perceive flashes, even outside migraine attack, that reveal a hyper-functional visual cortex in migraine also in pediatric age. The SIFI can be used in pediatric migraine for testing the responsivity of V1.

Disclosure: Nothing to disclose

Clinical neurophysiology

EPR2041

Effects of 10- and 20-Hz transcranial alternating current stimulation (tACS) over motor cortex on blink reflex excitability. A blink reflex recruitment curve study

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Background and aims: Brain oscillations play a pivotal role in motor function. Pathological increase of beta-band oscillations has been associated with motor dysfunction in Parkinson's disease. Transcranial alternating current stimulation (tACS) may modulate brain oscillations in a non-invasive fashion. As a way to understand the role of brain oscillations is to study their effects on reflex circuits, we wished to explore the result of 20-Hz and 10-Hz tACS sessions over M1 on blink reflex excitability.
Methods: Fifteen healthy volunteers (age:27.4±2.7;11F) underwent 10-minutes tACS sessions (active/reference:C4/Pz; intensity: 1 mA; three conditions: 1) 20-Hz tACS; 2) 10-Hz tACS and 3) sham tACS). Blink reflex recruitment curves were obtained for interstimulus intervals (ISI) of 100, 150, 200, 300, 400, 500 and 750 milliseconds before (T0), at the end of each stimulation (T1) and 30 minutes from onset of each tACS session (T2).
Results: Repeated measures of ANOVA showed a significant effect of ISI ($F=62.610$, $p=0.0000$) and type of stimulation ($F=3.5917$, $p=0.01627$). R2 responses were significantly increased at T2 after 20-Hz stimulation whether compared to baseline ($F=7.8102$, $p=0.00927$) and sham sessions ($F=5.4862$, $p=0.02651$). 10-Hz tACS didn't differ from baseline and sham sessions.
Conclusion: This is the first study exploring a modulatory effect of tACS on trigemino-facial reflex circuits. In our study, 20-Hz tACS determines a late increase of blink reflex excitability. At beta-band frequency, tACS was able to determine a larger effect than at alpha-band frequency, supporting a driving role of beta band- oscillations of motor cortex on exciting subcortical structures such as basal ganglia and brainstem circuits.
Disclosure: Nothing to disclose

EPR2042

PCI & Auditory ERPs for the diagnosis of disorders of consciousness: an EEG-based methods comparison study.

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Background and aims: Diagnosing the level of consciousness in patients suffering from severe brain lesions is still a major challenge. EEG-based systems can help discriminate conscious from unconscious patients. This study aims to confront the results from two of the most reliable methods: the Perturbational Complexity Index (PCI) which is based on Transcranial Magnetic Stimulation (TMS-EEG), and a recent machine learning approach using EEG-extracted markers from a standardized oddball auditory stimulation paradigm (EEG-ERP).
Methods: Patients presenting either an unresponsive wakefulness syndrome (UWS), a minimally conscious state (MCS) or an emergence of MCS (EMCS) underwent both TMS-EEG and EEG-ERP. We computed PCI value by compressing the spatiotemporal pattern of cortical responses to the perturbation of the cortex with TMS. For EEG-ERP, we extracted 60 markers corresponding to quantification of power spectrum and complexity in individual EEG sensors and information sharing between them. Using machine-learning, we predicted the individual probability of being (minimally) conscious.
Results: PCI and EEG markers, when considered categorically (i.e. UWS vs MCS), were consistent for all UWS and EMCS patients, whereas the results for MCS patients showed less consistency. Nevertheless, we found a significant correlation between PCI values and the probability of being conscious with the multivariate classifier.
Conclusion: PCI correlated positively with the combination of EEG markers in severely brain-injured patients. These findings imply that EEG signatures of consciousness can be reliably extracted from different contexts and combined into coherent predictive models, encouraging future efforts in large-scale data-driven clinical neuroscience.
Disclosure: Nothing to disclose

EPR2043

Relationship between EEG and psychophysical responses to perception of contact heat stimuli

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Background and aims: Only a few indirect methods allow for the assessment of sensory processing and conscious perception of nociceptive inputs in humans.
Methods: In 12 healthy subjects, we obtained contact-heat evoked potentials (CHEPs) to thermoalgesic stimuli of two intensities (lowT-42ºC and highT-52ºC) while subjects assessed stimulus perception time through the Libet's clock (AW). In test trials, they were requested to do the same but also hitting a switch at stimulus perception (React). We compared the timing of CHEPs, React and AW in the two stimulus intensities.
Results: Stimulus intensity was more effective to modulate CHEPs (472ms±40ms for highT and 748ms±47ms for lowT) than RT (486±74 vs 649±72) but it did not show a significant effect on AW (337±83 vs 384±83). At both stimulus intensities, task complexity did not affect CHEPs but prolonged RT and AW. Temporal profiles induced by changing stimulus intensity and task complexity were non-linear for CHEPs, React and AW.
Conclusion: Our findings support the dissociation between CHEPs, React and AW in the assessment of nociceptive stimulus processing. AW brings valuable information on conscious perception of painful stimuli.
Disclosure: Grant ESPY-112/18 from Instituto de Salud Carlos III to J. M. Castellote

EPR2044

Early Transient Dysphagia in Acute Pontin Infarctus

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Background and aims: Early transient dysphagia in stroke patients with pontin infarctus has not been studied by electromyographical methods. This study aims to evaluate the presence of swallowing abnormalities and some pathophysiology of dysphagia in the patients with acute pontine infarctus using electrophysiological methods.
Methods: A prospective study of 30 patients with pontin infarctus within 9 days after the onset of stroke and 20 age-matched healthy adults were investigated. Electrophysiological methods included dysphagia limit (DL) and sequential water swallowing (SWS) tests.
Results: 58% of the patients who are not suffering from dysphagia clinically have been found to be pathological in terms of both DL and SWS tests. Among pathological patients with DL; 77.8% of them were also pathologic in SWS test. Among non-pathological patients with DL; 35.3% of them were pathological in SWS test.
Conclusion: The electrophysiological methods presented here are non-invasive, easy to apply, and very simple to complete. They can be used in patients with neurogenic dysphagia of any kind, including the acute stroke patients. We recommend electrophysiologic methods to detect oropharyngeal dysphagia in stroke patients even if they have no overt swallowing complaint.
Disclosure: Nothing to disclose

EPR2045

withdrawn

EPR2046

Cognitive impairment in MRI-negative epilepsy: Relationship between neurophysiological and neuropsychological assessments.

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Background and aims: Epileptic patients frequently develop cognitive impairment due to seizures and antiepileptic drugs. The aim of the current study is to evaluate the cognitive status of epilepsy patients using neurophysiological and neuropsychological measures and seek for possible correlations.

Methods: The study sample consisted of twenty MRI-negative epilepsy patients (mean age±SD: 30.3±12.56 years; average disease duration: 13.95 years) and ten age-matched controls. Auditory ERPs were elicited and latencies and amplitudes of the major late ERP waves (N200, P300 and Slow Wave) were determined. EpiTrack, a brief screening tool for measuring cognitive impairment was administered to all patients.

Results: Latencies of P300 and Slow wave were prolonged in patients compared to controls ($p<0.05$). Moreover statistical significant difference was evident in the subtests Trail-Making A,B of the EpiTrack test. Significant negative correlations were observed between P300 latency and all Epitrack subtests (all p's<0.05) AED load and the performance of the patients' in the maze subtest were the most significant predictors of P300 latency

Conclusion: A decline in the memory, attention and speed of mental processing of MRI-negative epileptic patients compared to age matched controls which is also corroborated by P300 latency and the Epitrack scores was observed and seems to be mostly due to antiepileptic drug load.

Disclosure: Nothing to disclose

EPR2047

Peripersonal space in Autism Spectrum Disorder: an electrophysiological study

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Background and aims: People with Autism Spectrum Disorder (ASD), characterized by impaired social functioning, fail to adjust a normal peripersonal space (PPS) with others, either keeping the distance too far or disturbingly close.
The features of PPS in healthy subjects has been delineated by using hand-blink reflex (HBR). Our aim was to assess its spatial and electrophysiological properties in people with ASD compared to controls.
Methods: A total number of 16 patients diagnosed with ASD and 12 healthy volunteers, (14-30 years) were included in the study. The blink reflex responses elicited by stimulating the median nerve was recorded in three positions of the stimulated hand: far, medium and near (Table1). The data were entered into SPSS 20 programme and statistical significance was analysed with t-test, chi-square and Friedman tests.

Table 1: Three positions of the stimulated hand in hand blink reflex; far, medium and near (from left to right)

Results: HBR responses resembled in latency between the two groups, but the amplitudes were 1.5-4 times higher in the ASD group in all positions. Though the near position elicited the highest amplitude in controls, it was still lower than the minimum response in ASD group (Table2). While the HBR responses are expected to intensify as the hand approaches to face, ASD patients showed a decrease in amplitude in the medium position; and the near-far responses did not show a significant difference (Table3).

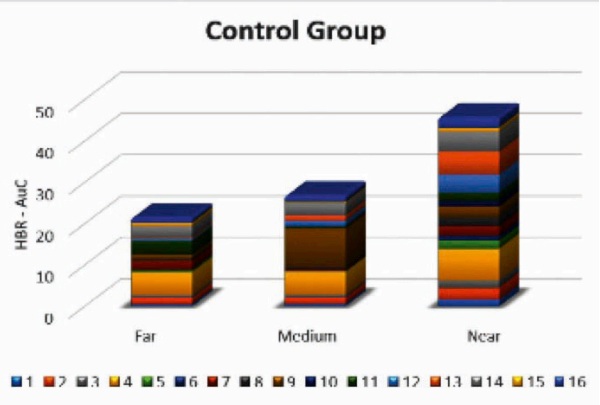

Table 2: This table shows the cumulative hand-blink reflex responses of the control group, seperated by the far, medium and near positions of the stimulated hand. HBR: Hand blink reflex, AuC: Area under the curve

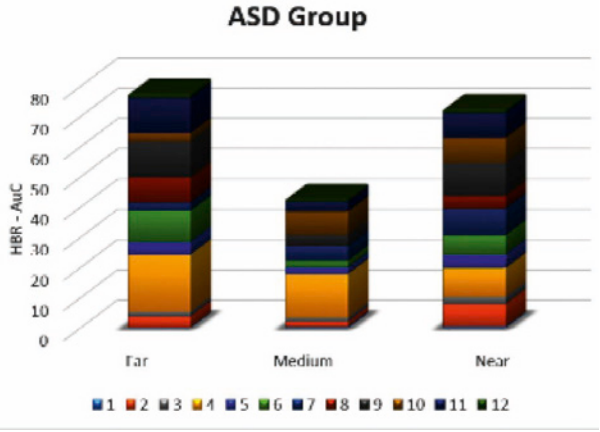

Table 3: This table shows the cumulative hand-blink reflex responses of the ASD group, seperated by the far, medium and near positions of the stimulated hand. HBR: Hand blink reflex, AuC: Area under the curve ASD: Autism spectrum disorder

Conclusion: This is the first study to investigate the electrophysiological and spatial properties of PPS in ASD, which revealed a marked qualitative and quantitative difference in patients compared to controls, in correlation with odd choices of personal space use in people with autism.
Disclosure: Nothing to disclose

EPR2048

Gender differences in Parkinson's disease: transcranial magnetic stimulation study of newly diagnosed and drug-naive PD patients

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Background and aims: Demographic studies of Parkinson's disease (PD) found that women are almost twice less affected than men, implying protective effect of female sex. It is not known, once the symptoms develop, if disease course differs between genders, which would suggest differences in pathophysiology. In early PD, functional changes may be detected in primary motor cortex (M1) using transcranial magnetic stimulation (TMS). We hypothesised that, if pathophysiology differ between genders in PD, this will be reflected in differences of M1 TMS measurements.
Methods: Thirty-nine newly diagnosed and untreated PD patients (23 males, 16 females) were assessed using UPDRS. Motor thresholds, input/ output curve (IO), short interval intracortical inhibition (SICI), cortical silent period (CSP) and intracortical facilitation (ICF) were measured over both hemispheres, corresponding to less and more affected side, using TMS. Plasticity was probed using paired associative stimulation (PAS) protocol. Twenty-three healthy controls were studied for comparison.
Results: There were no gender differences in UPDRS. Female patients had less steep IO curve on the less affected side. Females also had more preserved SICI and trend toward better response to PAS protocol in both hemispheres, compared to male PD patients, while there were no differences in motor thresholds, ICF and CSP. Healthy controls showed no gender differences in any of the TMS parameters.
Conclusion: Less steep IO curve, preserved SICI and tendency toward preserved cortical plasticity in female compared to male patients with early PD suggest gender differences in disease pathophysiology. We provide first neurophysiological evidence that sex is an important factor in heterogeneity of PD.
Disclosure: Nothing to disclose

EPR2049

A comparison of the P300 and PET in patients with disorders of consciousness in absence of response to command

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Background and aims: Diagnosis of patients with disorders of consciousness (DOC) has become more accurate by using standardized behavioral assessment and objective measures of consciousness derived from neuroimaging. Another major challenge is the assessment of covert response to command in patients who do not present overt response to command, in order to ultimately find a means of communication.
Methods: We assess the passive (auditory and tactile) and active (tactile) P300 ERP in twelve patients without behavioral command following to test its sensitivity for the detection of residual consciousness and confront it to cerebral metabolism as measured with glucose PET, the most sensitive objective diagnostic tool.
Results: For the passive paradigms we have found that the accuracy of the discrimination of the standard and deviant stimuli in the auditory paradigm is higher for UWS than for MCS patients, while for the tactile paradigm the accuracy is slightly higher for MCS than UWS patients. There was no correlation between percentage of glucose metabolism reduction and P300 accuracy. One patient reached a high accuracy during the active tactile paradigm, suggestive of covert command following, even if behavioral command following was absent, and no discernable difference between the PET of this and other patients could be observed.
Conclusion: Our results suggest that the passive P300 is not a good marker for consciousness or overall brain metabolism. On the other hand, the active P300 might probe covert command following in patients without behavioral response to command and therefore could be a valuable addition in the clinical assessment of DOC patients.
Disclosure: The authors declare that the hard- and software was made available by Gtec.

Epilepsy 2

EPR2050

Parkinson's disease and the risk of epileptic seizures

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Background and aims: To assess the association between incident Parkinson's disease (PD) and subsequent incident epileptic seizures.
Methods: Retrospective cohort study with nested case-control analysis using data from the UK Clinical Practice Research Datalink. We identified patients aged ≥40 years with an incident diagnosis of PD between 1995 and 2016 and a matched comparison group of PD-free individuals. We calculated crude incidence rates (IRs) with 95% confidence intervals (CIs) of epileptic seizures in PD patients and the PD-free comparison group, and corresponding crude incidence rate ratios (IRRs). In the nested case-control analysis, we calculated adjusted odds ratios (adj. ORs) of incident PD among cases with incident epileptic seizures and seizure-free controls overall and stratified by various, seizure-provoking comorbidities.
Results: Among 23,086 incident PD patients and 92,343 PD-free individuals, we identified 898 patients with incident epileptic seizures. The crude IR of epileptic seizures in PD patients was 266.7/100,000 person years (95% CI 235.6-297.7), and in PD-free individuals 112.4/100,000 person years (95% CI 103.5-121.3) [IRR: 2.37, 95% CI 2.06-2.37]. The adj. OR of epileptic seizures was 1.68 [95% CI 1.43-1.98]) in PD patients compared with PD-free individuals. PD patients with comorbid brain disorders (adj. OR 12.36 [95% CI 8.74-17.48]) or with >1 seizure-provoking comorbidity (adj. OR 13.24 [95% CI 10.15-17.25]) were at the highest risk of epileptic seizures compared with PD-free individuals with no seizure-provoking comorbidities.
Conclusion: This study suggests that incident PD is associated with an increased risk of incident epileptic seizures.
Disclosure: Nothing to disclose

EPR2051

Abnormal visual connectivity in Eyelid Myoclonia with Absences: evidences from Electrocortical Connectivity and Non-linear Quantitative Analysis of EEG Signal

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Background and aims: Eyelid myoclonia with absences (EMA) is an epileptic syndrome characterized by eyelid myoclonia with or without absences, eye-closure sensitivity and photosensitivity. The objective of our study was to analyze the electrocortical networks of visual sensitivity in EMA.
Methods: Data of 10 EMA patients and 10 controls were analyzed. EEG networks were computed using independent components analysis LORETA. Moreover, the power law exponent β was obtained. β values ~ 1 imply self-similarity, property of fractal phenomena.
Results: A reduction of alpha activity over the occipital lobe and of beta activity over the frontal lobe during the resting state and an increase of beta activity over the frontal lobe after eyes-closure was found in patients. A significant increase of the beta index over the frontal regions was found in patients (F3: 2.89±0.28, vs 2.61±0.24, p=0.03; F4: 2.88±0.26 vs 2.62±0.28, p=0.05; F7: 2.64±0.33 vs 2.28±0.31, p=0.02) and, among patients, significant differences were found between the resting state and the eyes-closed task with an increase of beta index over the parieto-occipital regions after eyes-closure (P3: 2.86±0.35 vs 3.01±0.37, p=0.03; P4: 2.86±0.37 vs 3.02±0.38, p<0.01; O1: 2.76±0.42 vs 2.98±0.43, p<0.01; O2: 2.81 ±0.37 vs 3.01±0.36, p<0.01).
Conclusion: The findings of our study confirm the role of an intrinsic abnormality of the occipital cortex with an altered occipital-frontal network in determining the visual sensitivity in EMA.
Disclosure: Nothing to disclose

EPR2052

Influence of "epilepsy school" on the quality of life of patients with epilepsy

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Background and aims: To study the effect of "epilepsy school" on the quality of life of patients using QOLIE-31 questionnaire.
Methods: 100 patients with epilepsy were divided into 2 groups randomly. The main group consisted of 50 patients who later visited "epilepsy school" combined with optimized pharmacotherapy to improve their compliance. "Epilepsy school" was held once in a month during 6 month. The comparison group included 50 patients with epilepsy, only with optimized pharmacotherapy. Both groups were comparable ($p<0.05$). Quality of life was checked twice by using QOLIE-31 questionnaire at the beginning and after 1 year.
Results: In the comparison group (without attending "epilepsy school") after 12-month follow-up, most (58%) patients had rare seizures, 2% - achieved clinical remission, and 40% had high-frequency seizures. During analysing QOLIE-31 subscales after 12 month (2nd visit) the highest scores were obtained for the subscales "Overall Quality of Life" (59.2±6.56), "Emotional Well-Being" (53.36±9.23), "Medication Effects" (46.98±7.98).
In the main group after attending "epilepsy school" half of patients (50%) had rare seizures, only 14% had high-frequency seizures, and 36% of patients achieved control over seizures. When analyzing the QOLIE-31 subscales, after 12 months, most of QOLIE-31 subscales were increased. The highest scores were obtained for the subscales "Overall Quality of Life" (72.76±12.20), "Emotional Well-Being" (64.51±10.12), "Social Functioning" (62.34±11.46).
Conclusion: Thus, optimized pharmacotherapy in combination with the school of epilepsy can reduce the incidence of side effects, improve the effectiveness of treatment and improve the emotional, social and physical state of patients with epilepsy.
Disclosure: Nothing to disclose

EPR2055

Autonomic Cardiovascular Dysfunction in Patients with Temporal Lobe Epilepsy (TLE)

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Background and aims: Impaired autonomic function is considered to be one of the possible mechanisms of sudden unexplained death in epilepsy. The aim of the study was to evaluate the level of autonomic cardiovascular regulation in patients with TLE.
Methods: Twelve adult patients (mean age 36.83 ± SD 7.33 years, 6 males) with TLE and twelve gender- and age-matched healthy controls were included in the study. We performed the time and frequency domain analysis of heart rate variability (HRV) and systolic blood pressure variability (sBPV) was investigated. The following parameters were recorded: standard deviation of normal-to-normal RR intervals (SDNN), root mean square of successive differences (RMSSD), total power (TP) of HRV and sBPV, the range of high frequency (HF) of HRV, the range of low frequency (LF) of HRV and sBPV. We also estimated the sensitivity of spontaneous arterial baroreflex (BRS) and parasympathetic reactivity (RRmax/RRmin). Data are presented as median [interquartile range].
Results: People with epilepsy (PWE) had decreased level of cardiovascular autonomic modulation as revealed by significantly lower SDNN (17 [15;22] vs 53 [39;58] msec [p=0.001]) and TP of HRV (331 [228;490] vs 2448 [976;3275] $msec^2$ [p=0.001]) compared to healthy controls. Significant difference between PWE and controls was revealed for RMSSD and HF of HRV, reflecting decreased parasympathetic activity and for LF of HRV and sBPV, indicating lower sympathetic activity. BRS and parasympathetic reactivity were also reduced in patients with epilepsy.
Conclusion: Patients with TLE have impaired autonomic cardiovascular function, especially in the domain of parasympathetic regulation.
Disclosure: Nothing to disclose

EPR2056

Morphology of noninvasive ictal electroencephalographic recordings in patients with intractable focal epilepsy

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Background and aims: Morphology of noninvasive electroencephalographic (EEG) recordings is influenced by connections, size, location and orientation of the epileptogenic zone and epilepsy etiology. The aim of this investigation was determining the morphology of ictal EEG recordings in patients with intractable focal epilepsy and a magnetic resonance imaging (MRI) evident remporal (TL) or extratemporal (ETL) lesion.
Methods: We retrospectively analyzed 125 consecutive patients at The Neurology Clinic, Clinical Center of Serbia with intractable focal epilepsy who were evaluated for epilepsy surgery between 2014. and 2016. and who had at least one seizure registered and a MRI evident EL confound to either the temporal (TL) or extratemporal (ETL) region (82 and 43 patients respectively). Morphology of ictal EEG recordings was classified as 1. Attenuation (A) of amplitude of baseline activity ≥50%; 2. Rhythmic activity (RA) comprised of waves of uniform frequency, 3. Irregular activity (IRA) comprised of waves of mixed frequency, 4. Paroxysmal fast activity (PFA) frequency ≥13Hz, and 5. Repetitive epileptiform activity (REA) comprised of 3 or more successive epileptiform discharges. Seizures with no ictal EEG changes or obscured ictal patterns were not analyzed. Statistical difference was determined using $\chi 2$-test.
Results: Seizures that initiated with A (41.5% vs. 16.5%, $p<0.001$), RA (38.5% vs. 14.9%, $p<0.001$) i IARA (15.8% vs. 8.0%, $p=0.008$) were statistically more frequent in patients with TL, while PBA (0.0% vs. 33,0%, $p<0.001$) i REA (4.2% vs. 27.7%, $p<0.001$) were statistically less frequent in patients with TL.
Conclusion: Morphology of ictal EEG recordings is significantly different in patients with TL and ETL.
Disclosure: Nothing to disclose

EPR2057

Physician Adherence to EEG Guidelines and Prognostic Factors for Obtaining EEG in Patients Admitted to Intensive Care Unit for Intracranial Hemorrhage

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Background and aims: Electroencephalography (EEG) aids seizure detection in intracerebral hemorrhage (ICH). However, physician adherence to EEG guidelines for assessing electrographic seizures in ICH patients is uncertain. We sought to determine physician adherence to EEG guidelines and assess potential clinical confounders that impact guideline adherence.
Methods: Retrospective analysis of 330 patients with ICH (49% women, 42% lobar hemorrhage) admitted to a neurological intensive care unit at a single tertiary care academic center between 01/2013-12/2015. Multivariable logistic regression models were constructed to determine clinical confounders for physician adherence to guidelines for obtaining EEG. Model fit was compared using C-statistics (area under the curve [AUC]).
Results: Overall, 83 (25.2%) underwent EEG. 190 (57.6%) of included patients fulfilled criteria for obtaining EEG per existing guidelines, 78 (41.1%) of whom underwent EEG (sensitivity 94.0%). Of 140 patients not fulfilling criteria, 135 (96.4%) did not have an EEG (specificity 54.7%). The C-statistics of guideline adherence to predict EEG in unadjusted analyses was 0.74 (95%-CI 0.69-0.80). After adjustment for age, admission Glasgow coma scale score, and presence of a clinical seizure during hospitalization the C-statistics of guideline adherence to predict EEG was 0.85 (95%-CI 0.81-0.90). Model performance was similar when forcing withdrawal of care / in-hospital death into the model.
Conclusion: Our data suggest that physicians based their decision to obtain EEG in patients with ICH on clinical criteria beyond those recommended for the routine EEG criteria. Ongoing analyses are aimed at understanding the impact of physician non-adherence to EEG guidelines on patient care.
Disclosure: Nothing to disclose

Headache and pain 2

EPR2059

Interictal mismatch between neuronal activation and resting metabolism in the visual cortex of migraine patients: a study comparing FDG-PET and visual evoked potentials

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Background and aims: Migraine attacks might be triggered by a disruption of cerebral homeostasis. Between attacks, migraine patients are characterized by abnormal sensory information processing, but this functional abnormality may not be sufficient to disrupt cortical equilibrium unless it is accompanied by a reduction in energy reserve.
The aim of this study was to compare resting cerebral metabolism using 18fluorodeoxyglucose-positron emission tomography (18FDG-PET) and visual cortex activation using visual evoked potentials (VEP) between interictal migraineurs and healthy volunteers.
Methods: Twenty episodic migraine without aura patients and twenty healthy volunteers were studied. 18FDG-PET and VEP recordings were performed on separate days. PET scans were compared between groups using area under the VEP as regressor. For case-wise analysis, eigenvalues from the cluster exhibiting significantly different FDG-uptake in the visual cortex were extracted. Standardized metabolism and VEP values from each subject were coupled and compared between groups.
Results: The mean area under the curve (AUC) of VEP was greater in migraine patients than in healthy controls. In patients, cortical metabolism in relation to VEP's AUC was significantly reduced in a cluster extending through Brodmann's areas 7, 19, and 18. A visual Z-score exceeding the metabolic Z-score was found in 90% of migraine patients, but in only 15% of healthy volunteers.
Conclusion: Comparing FDG-PET and visual evoked potentials, our study identifies an area of mismatch between neuronal activation and glucose uptake in the visual cortex of migraine patients between attacks. This observation supports the concept that activity-induced rupture of cerebral metabolic homeostasis may be a cornerstone in migraine pathophysiology.
Disclosure: Nothing to disclose

EPR2060

Are there clinical differences in episodic and chronic cluster headache patients? Results from the Danish Cluster Headache Survey

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Background and aims: Episodic (eCH) and chronic (cCH) cluster headache are defined by the duration of the symptom-free interval between the bouts. However, it remains unclear whether there are other differences between the two phenotypes. Therefore, we aimed to describe differences in the clinical presentation of eCH and cCH in a large and well-characterized CH population.
Methods: CH patients from the Danish Headache Center, aged 18–65 years, diagnosed with CH according to International Classification of Headache Disorders-II completed questionnaires followed by a semi-structured interview. The clinical presentation in eCH and cCH was compared. Pain intensity was rated on a Likert scale from 0-4.
Results: A total of 400 patients participated (cCH: 154 eCH: 246) with a higher prevalence of women with cCH than with eCH (41% vs. 28%, $p<0.05$). Age of CH onset was comparable (32.7 vs. 30.6 years, $p=0.16$). cCH patients reported more attacks/day (4.07 vs. 3.33, $p<0.01$) and longer treated attack duration (47 vs. 34 minutes, $p<0.05$), however untreated attack duration (106 vs. 103 minutes, $p=0.72$) and pain intensity were comparable (3.51 vs. 3.59, $p=0.21$) between eCH and cCH. Accompanying symptoms as ptosis, eyelid edema, feeling uneasy and flushing were more frequently reported in cCH than in eCH.
Conclusion: cCH patients were more severely affected than eCH patients in relation to attack frequency and treated attack duration, which indicate a significant need for more awareness and more effective acute and preventive treatment of this highly disabling neurological disease.
Disclosure: Nothing to disclose

EPR2061

A Multicenter, Prospective, Randomized, Open-Label Study to Compare the Efficacy, Safety, and Tolerability of OnabotulinumtoxinA and Topiramate for Headache Prevention in Adults with Chronic Migraine: The FORWARD Study

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Background and aims: To compare effectiveness and tolerability of onabotulinumtoxinA and topiramate for chronic migraine (CM).

Methods: The FORWARD Study (ClinicalTrials.gov, NCT02191579) is a multicenter, randomized, parallel-group, open-label prospective study. Adults with CM were randomized to receive either 155U of onabotulinumtoxinA for 3 treatment cycles or 50-100 mg/day of topiramate administered daily up to week 36. Patients who discontinued topiramate could cross-over to onabotulinumtoxinA no earlier than 12 weeks. The primary efficacy outcome was the 50% headache day responder rate weeks 29-32. Analyses were performed on the ITT dataset using logistic regression with baseline carried forward to impute missing data. Adverse events (AEs) were monitored.

Results: 282 patients were enrolled (onabotulinumtoxinA, n=140; topiramate, n=142); mean(SD) baseline headache days (onabotulinumtoxinA, 22.1[4.6]; topiramate, 21.8[4.8]) were similar. 148 patients completed treatment as randomized (onabotulinumtoxinA, 85.7%; topiramate, 19.7%). Primary reasons for withdrawal were ineffective treatment (onabotulinumtoxinA, 5.0%; topiramate, 19.0%) and AEs (onabotulinumtoxinA, 3.6%; topiramate, 50.7%). 80 topiramate patients crossed-over to onabotulinumtoxinA. OnabotulinumtoxinA demonstrated significantly higher proportion of patients with ≥50% reduction in headache frequency compared to baseline vs topiramate (40.0% vs 12.0%, respectively; adjusted OR, 4.9 [95% CI, 2.7-9.1]; P<0.001). All secondary endpoints were met including: change in headache day frequency, HIT-6 scores, and ≥70% responder rate (P<0.001). Treatment-related AEs were reported by 17.3% of onabotulinumtoxinA-treated patients and 69.7% of topiramate-treated patients.

Conclusion: OnabotulinumtoxinA had a more favorable tolerability profile versus topiramate based on treatment-related AEs and overall discontinuations. When using imputation methods accounting for discontinuation differences, onabotulinumtoxinA was more effective than topiramate.

Disclosure: The funding source for this study is Allergan plc (Dublin, Ireland)

EPR2062

Safety of Erenumab among Patients with Migraine using Triptans or With Cardiovascular Risk Factors

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Background and aims: Erenumab is a fully human anti-CGRP receptor antibody in development for migraine prevention. As CGRP can mediate vasodilation, inhibiting the CGRP pathway may carry a theoretical cardiovascular risk. Here, we assess the safety of erenumab in patients with cardiovascular risk factors and in those using triptans/ergotamines.

Methods: A 12-week, integrated safety analysis of patients in phase 2/3 studies (NCT02066415, NCT01952574, NCT02456740 and NCT02483585) who received ≥1 dose of placebo or erenumab (7, 21, 70 or 140 mg).

Results: Overall, 66.2% (n=690/1043) of placebo-treated and 65.5% (n=1056/1613) of erenumab-treated patients used migraine medications (primarily triptans [>99%]). AE incidence in placebo- and erenumab-treated patients was 49.6% and 47.4% among triptan/ergotamine users and 47.9% and 47.2% among non-users, respectively. Serious AE (SAE) incidence in placebo- and erenumab-treated patients was 1.9% and 1.7% among triptan/ergotamine users and 0.8% and 0.5% among non-users, respectively. At baseline, 29.7%, 40.6% and 29.7% of placebo-treated and 28.2%, 41.7% and 30.1% of erenumab-treated patients had 0, 1 or ≥2 cardiovascular risk factors, respectively. AE incidence for 0, 1 or ≥2 cardiovascular risk factors was similar between placebo-treated (47.4%, 46.3% and 54.2%, respectively) and erenumab-treated patients (44.8%, 46.4% and 51.1%, respectively). Cardiac (<2.0%) or vascular AE incidence (≤2.3%) was similar among the cardiovascular risk subgroups and the treatment groups, as was SAE incidence (<2.0%). No dose relationship was observed with triptans/ergotamines or cardiovascular risk factors.

Conclusion: AEs, including cardiovascular AEs, were similar between erenumab and placebo in triptan/ergotamine users and in those with cardiovascular risk factors.

Disclosure: This study was supported by Amgen Inc., USA

EPR2063

Patient–Reported Outcomes in Chronic Migraine Patients with Prior Prophylactic Treatment Failure Receiving Placebo or Erenumab: Subgroup Analysis of a Pivotal Randomised Study

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Background and aims: Erenumab, a fully human monoclonal antibody, selectively targets the CGRP receptor. A pivotal 12-week randomised, double-blind study demonstrated efficacy and safety of erenumab (70mg and 140mg monthly) in patients with chronic migraine (CM). We report here the patient–reported outcomes (PROs) in subgroup of patients with prior prophylactic treatment failure (TF) (≥1 and ≥2 medication-categories) due to lack of efficacy and/or poor tolerability.

Methods: 667 adults with CM were randomised (3:2:2) to receive monthly subcutaneous placebo or erenumab 70mg or 140mg. Exploratory-endpoints included: headache impact measured by the Headache Impact Test (HIT–6), migraine–related disability measured by the Migraine Disability Assessment Test (MIDAS), and person-centred evaluations of physical, mental, and social health measured monthly by the Patient-Reported Outcome Measurement Information System (PROMIS). No formal hypothesis was tested; p–values (erenumab dose-groups vs placebo) are descriptive.

Results: For both subgroups with ≥1 and ≥2-TF, treatment with erenumab (both doses) resulted in greater reduction (improvement) in HIT-6 total-scores, MIDAS total-score, absenteeism and presenteeism-scores as compared with placebo at Week 12. For both TF-subgroups, erenumab (both-doses) resulted in greater reduction (improvement) in PROMIS scores as compared with placebo at Weeks 4, 8 and 12–except for erenumab 70mg at Week 4. Week 12 results are shown below. Treatment-corrected differences exceeded established minimal-intergroup differences where applicable (eg. for HIT-6 of -2.3 points).

Conclusion: Erenumab–treated-CM patients with prior-TF experienced consistent and clinically meaningful improvements in PROs as compared with placebo starting from first month of treatment. Improvement was particularly visible among patients with ≥2 TF, hard-to-treat population.

Disclosure: This study was supported by Amgen Inc., Thousand Oaks, California, USA and Novartis Pharma AG, Basel, Switzerland.

EPR2064

Effect of Erenumab on Patient-Reported Outcomes in Episodic Migraine Patients with Prior Prophylactic Treatment Failure: Results from a Post-Hoc Analysis of the STRIVE study

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Background and aims: There is a high unmet need for new prophylactic treatments for migraine, especially for patients who have failed existing migraine therapies or have contraindications. In the STRIVE study (NCT02456740), erenumab 70 mg and 140 mg QM led to significant improvement of patient-reported outcomes (PROs) in patients with episodic migraine. We report results from a subgroup analysis assessing the effect of erenumab (70 mg and 140 mg) on PROs in patients with ≥1 prior prophylactic treatment failure(s) due to lack of efficacy and/or poor tolerability.

Methods: PRO endpoints were change from baseline in mean monthly scores over months 4–6 for modified monthly Migraine Disability Assessment Questionnaire (MIDAS; total score, absenteeism, and presenteeism), the Headache Impact Test (HIT–6TM) and the Migraine–Specific Quality of Life Questionnaire (MSQ; -role function restrictive, -role function preventive, and -emotional function), based on eDiary calculations. P-values comparing erenumab vs placebo are nominal without multiplicity adjustment.

Results: At baseline, mean values for all measures were similar between groups. Clinically meaningful improvements were observed in the total MIDAS (greater reduction), HIT-6TM (greater reduction) and MSQ scores (greater increase) in patients treated with erenumab (70 mg and 140 mg) vs placebo.

Conclusion: Erenumab 70 mg and 140 mg showed robust treatment effects on migraine-related disability, functional impact and quality of life in episodic migraine patients with ≥1 prior prophylactic treatment failure(s) showing the benefit of treatment with erenumab in this subgroup of patients. Numerically better or equal scores were observed for the 140 mg dose compared with 70 mg for all PROs.

Disclosure: This study was supported by Amgen Inc., Thousand Oaks, California, USA and Novartis Pharma AG, Basel, Switzerland.

Infectious diseases

EPR2066

Prolonged upregulation of C5a is associated with unfavorable outcome in bacterial meningitis

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Background and aims: The uncontrolled inflammatory response in patients with bacterial meningitis is associated with complications and unfavorable outcome. Complement component 5a (C5a), an anaphylatoxin critical in upregulating the inflammatory response, emerges as a promising treatment target in bacterial meningitis. We aim to assess the concentration of C5a in the acute phase of bacterial meningitis and the associated clinical outcome.
Methods: Patients (≥16 years old) with suspected community-acquired bacterial meningitis and typical findings in the cerebrospinal fluid, who present at one of the 12 participating hospitals in the Netherlands, undergo serial blood sampling at day 0, 1, 2, 7 and 3 months of presentation. Patients are also included in a prospective nationwide clinical cohort study. We performed C5a ELISAs (BD) of all serially-collected EDTA samples which were handled and stored according to manufacturer's protocol.
Results: A total of 155 samples of 39 patients (17 male, median age 57 years, 12 unfavorable outcome (Glasgow Outcome Scale score 1-4), 3 death) were analysed. C5a concentration during bacterial meningitis was significantly elevated compared to controls and patients with a history of bacterial meningitis, even at 3 months (median 47 (IQR 15) vs. 30ng/ml (IQR 12), p<0.001, Figure 1). Median C5a concentration was highest at day 1 (median 68ng/ml, IQR 26). Increase of C5a after day 1 was significantly associated with an unfavorable outcome (44% vs 8%, p=0.05, Figure 2).

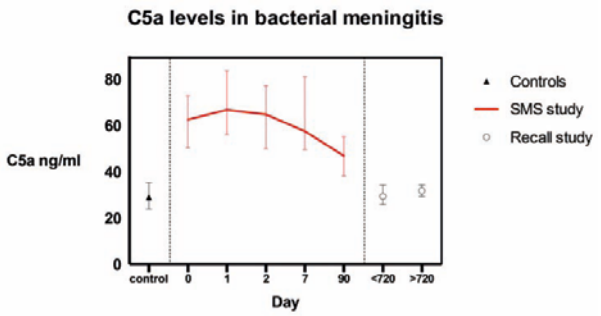

Figure 1

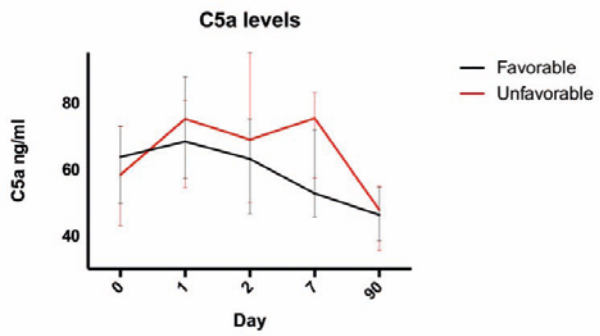

Figure 2

Conclusion: C5a is significantly upregulated during bacterial meningitis and a prolonged upregulation is associated with unfavorable clinical outcome. These findings further confirm the rationale for C5a antibody therapy.
Disclosure: Nothing to disclose

EPR2067

Early diagnosis of five cases of Gerstmann–Sträussler–Scheinker

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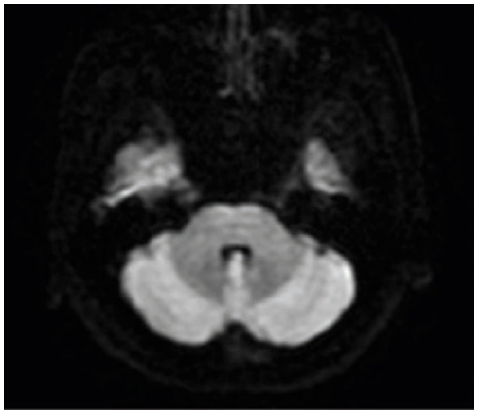
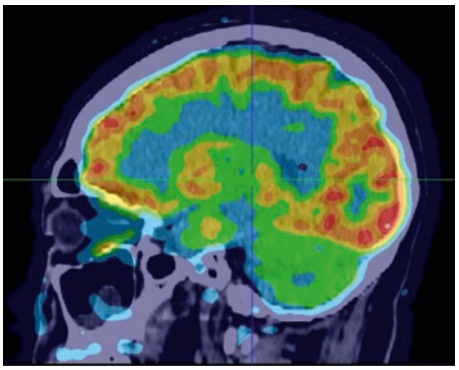
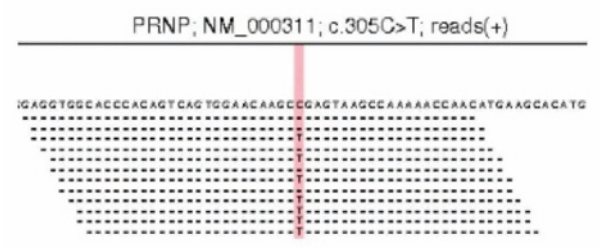
Background and aims: This article summarised 5 GSS cases in terms of clinical manifestation, electrophysiology, imaging and gene, providing the experience in the early diagnosis of GSS.
Methods: Retrospective analysis of 5 GSS cases that had been diagnosed by gene or clinically manifestation in the General Hospital of People's Liberation Army from 1 December 2015 to 31 December 2017.
Results: This article collected 5 GSS cases, 2 males (40%) and 3 females (60%). The average age was 47.40±8.59 years. All cases were chronic progressive aggravation, 1 died within 3 months due to complications, the others' course of disease averaged 30.00±10.55 months. All cases had cerebellar ataxia, cortical sensory disturbance and cognitive impairment as early core symptoms. 4 cases had insomnia, nystagmus or myoclonus in advanced stages. 1 case had a positive family history. The sensitivity of 14-3-3 protein was 40% and abnormal electroencephalogram appeared in 4 cases but only 1 had triphasic wave. Diffusion weighted imaging abnormally signals appeared in 5 cases but only 2 in cerebella. 4 cases who completed positron emission tomography-computed tomography were found having hypo-metabolism in cerebella. 4 cases were diagnosed by gene (3 cases were P102L mutation and 1 case was T188K mutation), and 1 case was clinically probable case. 4 cases were misdiagnosed of somatic disorder or spinocerebellar ataxia.



Diffusion weighted imaging abnormally high signals in cerebella.



Low metabolism in cerebella of PET-CT.



P102L gene mutution.

Conclusion: The GSS should be considered when cerebellar ataxia, cortical sensory disturbance and cognitive impairment are identified. The electroencephalogram and 14-3-3 protein have low sensitivity in GSS. PET-CT and gene examination play a critical role in this disease.
Disclosure: Nothing to disclose

EPR2068

Histopathology of listeria meningitis

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Background and aims: Listeria monocytogenes meningitis is the third most common cause of bacterial meningitis in adult patients and has a high mortality and morbidity rate. In this study, we describe the clinical course and brain pathology results of 5 patients who died of listerial meningitis.
Methods: The cases were identified from two nation-wide prospective cohort studies and the neuropathology database in Amsterdam. Clinical course and results from diagnostic tests were derived from a chart review. Severity of vascular, parenchymal and ventricular damage and inflammation was scored according a pathology scale previously used in pneumococcal meningitis.
Results: All patients were immunocompromised and age ranged between 48-76 years. Three cases were cerebrospinal fluid culture confirmed, one brain culture confirmed and one diagnose was based on a positive blood culture and findings at neuropathological examination. Mild inflammation of meningeal arteries was found in 3 of 5 cases (60%), moderate to severe ventriculitis in 4 cases with available material (100%) and abscesses were found in 3 of 4 cases (75%). The inflammatory cells present in the meninges were a mix of monocytes/macrophages and neutrophils and frequent presence of efferocytosis. A moderate infarct was found in 1 of 4 cases (25%), mild to moderate hemorrhage in 2 of 4 cases (50%) and mild/moderate thrombosis of meningeal artery in 3 cases (60%).
Conclusion: Pathological examination of five listeria cases was characterised by presence of moderate to severe ventriculitis, abscesses and abundant efferocytosis which previously has been suggested to be exploited by L. monocytogenes for cell-to-cell spread.
Disclosure: Nothing to disclose

EPR2069

Complement factor H deficiency increases mortality in experimental pneumococcol meningitis through C3 depletion

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Background and aims: Complement factor H (CFH) inhibits alternative pathway activation and genetic variation influences susceptibility and outcome of bacterial meningitis. The aim of this study was to determine the role of CFH in pneumococcal meningitis.
Methods: CFH-deficient (n=28) and C57BL/6 wild-type (n=33) mice were inoculated intracisternally with 1µl of 10^7 CFU/ml Streptococcus pneumoniae. Animals were observed for 50 hours in a survival analysis and sacrificed after 5 and 20 hours in a time-point experiment. Bacterial outgrowth, complement component 3 (C3), interleukin-1beta (IL-1b) and macrophage inflammatory protein-2 (MIP-2) were determined. In a treatment model wild-type mice received adjuvant treatment with intraperitoneal human CFH (n=11) or PBS (n=12) at 16 hours after infection.
Results: CFH-deficient mice showed an increased mortality compared to wild-type mice, median survival 23 vs. 32 hours (Log-rank, p=0.0028). CFH deficiency was associated with decreased plasma C3 levels at both time points and increased bacterial outgrowth at 20 hours. CFH-deficient mice showed reduced brain levels of IL-1b (median 13 vs. 30 pg/ml, p=0.013) and MIP-2 (median 61 vs. 193pg/ml, p=0.009) at 5 hours and increased brain levels of IL-1b (median 754 vs. 532pg/ml, p>0.05) and MIP-2 (median 1556 vs. 748pg/ml, p=0.023) at 20 hours. The 72-hours mortality rates were similar between human CFH and PBS treated mice (45% and 50%, respectively).
Conclusion: CFH deficiency is associated with decreased bacterial clearance and increased mortality in experimental pneumococcal meningitis due to secondary C3 depletion. Treatment with human CFH did not influence outcome.
Disclosure: Funding: EU-FP7 EUCLIDS project

EPR2070

Performance of meningitis prediction rules in the at-risk population

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Background and aims: Community-acquired bacterial meningitis is a severe disease that needs immediate medical attention. Various prediction models have been developed to assess the likelihood of bacterial meningitis in suspected patients. Although they have been validated externally, it is necessary to look at the value of these models in a different, at-risk population.
Methods: We prospectively included patients who underwent a lumbar puncture for suspected meningitis or encephalitis. We performed a literature search for various prediction models for bacterial meningitis and applied them to this cohort. We calculated sensitivity and specificity for all models.
Results: From 2012 to 2015 we included 363 episodes of suspected meningitis or encephalitis. A total of 89 (24%) patients received a final diagnosis of an infection of the central nervous system, of whom 27 had bacterial meningitis. Ten prediction models for bacterial meningitis were identified. In seven of them all required parameters were available to use the model in our cohort. Sensitivity ranged from 12% to 96%, in which the highest sensitivity was reached with the model of Hoen et al. Specificity ranged from 32% to 99%, in which the highest specificity was reached with the model of Bonsu et al.
Conclusion: None of the models showed both high sensitivity and specificity. None of the existing scores performed well enough to recommend routine use in individual patient management.
Disclosure: Nothing to disclose

EPR2071

Community acquired Group B Streptococcal meningitis in adults

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Background and aims: Streptococcus agalactiae (GBS) is an uncommon cause of bacterial meninigitis in adults. We describe the clinical features, complications, treatment, and outcome of adults with GBS meningitis in a two nationwide surveillance study in the Netherlands.
Methods: In two prospective nationwide cohort studies performed between 1998-2002 and 2006-2017 we evaluated adults with community-acquired bacterial meningitis caused by GBS in the Netherlands.
Results: We assessed 33 patients with GBS meningitis with a median age 58 years of whom 22 were male (67%). The calculated annual incidence was 0.17 per 1.000.000 adults. Eleven patients (33%) had an immunocompromised status and in twelve patients (36%) an infectious focus outside the central nervous system was found, consisting of endocarditis in 4 patients (13%) and otitis/sinusitis in 4 patients (12%). The most common serotype was serotype III (n=12 [41%]). Patients with GBS meningitis more frequently had endocarditis (13% vs 1%, P=0.001) and alcoholism (18% vs 6%, P=0.01) while otitis or sinusitis occurred less frequently (12% vs 35%, P=0.008) compared to patients with meningitis due to other pathogens. Seven patients (21%) died and seven survivors an unfavorable outcomes such as blindness (n=2), cerebral infarction with neurological deficits (n=2). Nineteen patients (58%) made a full recovery. Serotype 5 was associated with death (mortality 3 of 4 [75%] serotype V vs 4 of 28 [14%] other serotypes P=0.025).
Conclusion: GBS is associated with concomitant endocarditis and alcoholism. Patients with GBS meningitis should receive cardiac ultrasound to rule out endocarditis. Mortality is associated with bacterial serotype.
Disclosure: Nothing to disclose

EPR2072

The contribution of variation in coagulation and fibrinolysis genes to cerebrovascular complications in community-acquired bacterial meningitis

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Background and aims: Bacterial meningitis is a severe infection of the brain often resulting in poor outcome due to cerebrovascular complications. Our aim was to determine whether genetic variation in coagulation and fibrinolysis genes contributes to cerebrovascular complications in bacterial meningitis.

Methods: We performed a nationwide prospective genetic association study in adult community-acquired bacterial meningitis patients. The exons and flanking regions of 16 candidate genes involved in coagulation and fibrinolysis pathways were sequenced. We analysed whether genetic variation in these genes resulted in a higher risk of cerebrovascular complications, unfavorable outcome and differences in thrombocyte count on admission. We used linear and logistic regression to compare genotype frequencies.

Results: From 2006 to 2011 a total of 1101 bacterial meningitis patients were included of which 752 (68%) supplied DNA for genotyping. After quality control, data of 622 patients of European ancestry could be used for further analyses. In 139 patients (22%) the episode of bacterial meningitis was complicated by cerebral infarction, and 188 (30%) had an unfavorable outcome. We identified the rs494860 variant in the protein Z (PROZ) gene as our strongest association with occurrence of cerebral infarction (odds ratio [OR] 0.49 [95% confidence interval 0.33-0.73]). The rs494860 variant is an expression quantitative trait locus contributing to variation in the PROZ protein mRNAs expression. No genetic variants were significantly associated with cerebral infarction, outcome or thrombocyte count after correction for multiple testing.

Conclusion: Our study does identify a genetic variation in the PROZ gene, effecting its transcription, as the strongest association with cerebral infarctions during bacterial meningitis.

Disclosure: Nothing to disclose

Movement disorders 4

EPR2073

A novel TMEM240 variant in SCA21 without cognitive impairment

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Background and aims: Variants in the transmembrane protein 240 (TMEM240) gene were described in French families with autosomal dominant, early-onset, slowly progressive ataxia, and cognitive impairment (SCA21). We characterised clinically and genetically a Portuguese family with SCA21.
Methods: Files review/patients observation through structured protocol.
Results: A1 is a 76y-old woman who developed dysarthria and gait ataxia, by age 15y. Diplopia and upper limbs incoordination were noticed in her 50s and dysphagia in her 70s. By age 66y, she needed a walking stick. On examination, she had dysarthria, fragmented pursuit, hypermetric saccades, upper/lower limbs dysmetria, brisk deep tendon reflexes, ataxic gait (SARA=18.5). Neuropsychological assessment (by age 76y) was normal. MRI disclosed marked cerebellar atrophy, more in the upper part, with anterior pons atrophy. Her youngest daughter (B1), 43y, developed gait ataxia by age 22y. In her 30s, handwriting deteriorated and speech became slurred. She has no cognitive deterioration. On examination, she has dysarthria, postural hand tremor, upper/lower limbs dysmetria, brisk deep tendon reflexes, ataxic gait (SARA=7). MRI showed mild upper cerebellar atrophy. Both bare a novel variant on TMEM240: c.486_487del (p.(Tyr163Profs*69)), resulting in a frameshift and extension of the reading frame. Another daughter of A1, 49y, is said to be affected. A daughter of B1, 22y, complains of disequilibrium and is under investigation. Neither is said to have cognitive impairment.
Conclusion: Both patients present a SCA phenotype, with minor pyramidal signs, but no cognitive deterioration. This is the first variant resulting in a larger protein. These cases contribute to enlarge the clinical spectrum of SCA21.
Disclosure: Nothing to disclose

EPR2074

Sex-specific pattern of sensori-motor network connectivity in de novo Parkinson's disease patients

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Background and aims: Clinical and epidemiological evidences support the presence of sex-specific expression of Parkinson's disease (PD), from the early to the late stages. In the present study, we aimed to investigate the potential sex-difference effect on the spontaneous neuronal activity within the sensori-motor network (SMN) in early untreated PD patients, using the amplitude of low-frequency fluctuation (ALFF) and its correlation with baseline and longitudinal clinical features.
Methods: 56 de novo PD patients and 23 matched healthy controls (HC) were enrolled in the study. Whole brain structural and functional imaging was performed on a 3T GE MR scanner. Functional data were analysed using BrainVoyager QX software. Linear logistic regression was used to investigate whether functional imaging data at baseline were predictors of motor impairment over a 2-year follow-up period.
Results: Compared with female PD patients and HC, male PD patients showed an increased ALFF connectivity within the SMN in the 5-slow band. No ALFF differences were detected between male and female HC and within female PD patients and HC. Male PD patients showed a higher risk to develop axial symptoms at 2-year follow-up. Functional abnormalities within the SMN at baseline showed to be an independent predictor of axial impairment overtime in the PD group.
Conclusion: Our findings revealed that the organization of the intrinsic functional connectivity within the SMN in PD differs between genders. We hypothesise that this specific pattern may be related to the presence of a gender-specific nigro-striatal dopaminergic pathway and might predict PD progression and development of motor complications over the disease course.
Disclosure: Nothing to disclose

EPR2075

Impaired motor planning in PD patients with fatigue: a seed-based RS-fMRI study

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Background and aims: Previous studies have consistently demonstrated that fatigue in Parkinson's Disease (PD) is associated with a dysfunction within brain areas involved in the motor planning, suggesting a pivotal role played by the supplementary motor area (SMA).

We aimed to investigate the functional connectivity of the SMA in de novo PD patients with and without fatigue, by using a seed-based resting-state functional MRI.

Methods: 20 PD patients with fatigue (f-PD), 20 PD patients without fatigue (nf-PD), and 20 age and sex-matched healthy controls (HCs) were enrolled. Presence and severity of fatigue was assessed with the Parkinson Fatigue Scale. Structural and functional imaging was performed on a 3T MR scanner. Statistical analysis was completed using BrainVoyager QX software. A seed-based approach was used to compare f-PD and nf-PD patients, selecting the SMA and the pre-SMA as regions of interest. Voxel-based morphometry (VBM) was used to exclude structural differences.

Results: Compared with nf-PD patients, f-PD patients showed a decreased connectivity within the left SMA and the left middle frontal gyrus as well as an increased connectivity within the left pre-SMA and the left post-central gyrus ($p<0.05$). VBM analysis showed no significant volume difference between all groups ($P<0.05$).

Conclusion: In the present study f-PD patients showed the presence of a disrupted connectivity between the SMA and several cortical areas involved in motor planning and executive attention. This aberrant functional connectivity may rely on an impairment during both programming and controlling the motor execution, likely leading to the difficulty in performing self-initiated movements which characterised f-PD patients.

Disclosure: Nothing to disclose

EPR2076

Spectrum of symptoms in prodromal synucleinopathy and their relation to the degeneration of nigrostriatal pathway

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Background and aims: Idiopathic REM sleep behavioral disorder (RBD) is a prodromal synucleinopathy. It is frequently associated with several motor and non-motor symptoms such as hyposmia, constipation, and orthostasis along with gradual loss of dopaminergic neurons in substantia nigra. Our aim was to compare prevalence and severity of degenerative symptoms in RBD and control group. Additionally, we investigated whether these symptoms are associated with the degree of nigrostriatal degeneration.

Methods: 75 RBD (5f, mean age(SD) 67.5(6.2)) and 41 control subjects (4f, mean age 65.3(8.4) were examined using Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III), Montreal Cognitive Assessment (MoCA), University of Pennsylvania Smell Identification Test (UPSIT), Scales for Outcomes in PD-Autonomic (SCOPA-AUT), and orthostatic test. In 65 RBD patients, 123I-Ioflupane (DaTscan) SPECT was performed, putaminal indices were calculated using the BASGAN_V2 software and subsequently classified as normal, borderline, or abnormal.

Results: RBD patients had significantly more severe mean scores in MDS-UPDRS-III ($p=0.01$), MoCA ($p=0.001$), UPSIT ($p=0.0001$), and SCOPA-AUT ($p=0001$) compared to controls (Table1). Orthostatic test was positive in 33% RBD patients vs 0% controls ($p=0.05$). RBD patients with abnormal DaTscan had significantly higher MDS-UPDRS-III ($p=0.01$) and lower UPSIT ($p=0.03$) scores compared to patients with borderline/normal DaTscan result while no differences were found for age, symptom duration, MoCA, and SCOPA-AUT scores (Table2).

Comparison of RBD patients and control group

	RBD (total)	Controls	P value*
Number (females)	75 (6)	41 (4)	
Age in yrs*	67.5 ± 6.2	65.3 ± 8.4	0.12
MDS-UPDRS III	6.2 ± 5.6	3.5 ± 4.1	**0.008**
MoCA	23.7 ± 2.7	25.4 ± 2.0	**0.001**
UPSIT	22.6 ± 8.1	30.9 ± 4.6	**<0.0001**
SCOPA-AUT	11.8 ± 7.8	6.1 ± 4.2	**<0.0001**
Orthostatic test + (%)	33	0	**0.05**

*values reported as mean ± SD unless stated otherwise
Student t-test

Table 1

Stratification of RBD cohort according to DaTscan results

	DaTscan normal	DaTscan borderline	DaTscan abnormal	P value*
Number (females)	25 (3)	27 (2)	13 (1)	
Age in yrs*	68.4 ± 6.7	67.2 ± 6.5	67.2 ± 6.1	0.76
Symptoms duration in yrs	6.8 ± 6.3	5.4 ± 4.3	7.2 ± 7.1	0.57
MDS-UPDRS III	5.4 ± 5.1	5.6 ± 4.1	10.8 ± 8.3	**0.01**
MoCA	23.6 ± 2.2	24.5 ± 3.1	22.8 ± 2.5	0.16
UPSIT	25.4 ± 8.2	22.5 ± 7.8	17.3 ± 4.6	**0.03**
SCOPA-AUT	10.8 ± 6.9	14.4 ± 8.1	11.2 ± 8.9	0.21

*values reported as mean ± SD
ANOVA test

Table 2

Conclusion: RBD is associated with hyposmia, autonomic dysfunction, cognitive decline, and motor impairment indicating diffuse alpha-synuclein pathology. Subtle parkinsonian motor symptoms and hyposmia along with abnormal DaTscan are likely biomarkers of imminent conversion to manifest neurodegeneration.

Disclosure: Supported by Czech Science Foundation, 16-07879S, and Czech Ministry of Health, 15-25602A, 16-28914A.

EPR2077

How to diagnose and manage progressive ataxia: guidelines for professionals

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Background and aims: The progressive ataxias are a group of rare, heterogeneous and complicated neurological disorders, knowledge of which is often poor among healthcare professionals. The patient support group Ataxia UK, recognising this lack of awareness, has developed guidelines for their diagnosis and management, focusing especially on hereditary ataxia (including Friedreich's ataxia and autosomal dominant spinocerebellar ataxia), cerebellar variant multiple system atrophy and "idiopathic" progressive ataxia.

Methods: 30 UK health professionals contributed to the production of the guidelines, their inputs reflecting diverse clinical experience in various aspects of ataxia diagnosis and management. After review of the published literature in their respective spheres, they provided summaries on "best" practice- including grading of evidence available for interventions, using the Guideline International Network (GIN) criteria. Where no specific published data existed, recommendations were based on data related to similar conditions and/or expert consensus.

Results: The guidelines comprise 128 recommendations, organised into four main sections (on diagnosis, medical interventions, allied health professional interventions and palliative care). By the GIN criteria, 6 recommendations are graded B, 7 graded C, 10 graded D and 105 graded GPP (Good Practice Points).

Conclusion: The guidelines aim to assist healthcare professionals when caring for patients with progressive ataxia, indicate evidence-based (where it exists) and best practice, and, overall, provide a useful resource for those managing ataxia patients. They also highlight the urgent need to develop effective disease-modifying therapies, and, given the large number of recommendations based on GPP, emphasise the need for further research to provide evidence for effective symptomatic interventions.

Disclosure: Nothing to disclose

EPR2079

Activities of daily living and quality of life in patients with advanced Parkinson's disease who are treated with or planning to use device-aided treatments

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Background and aims: To correlate activities of daily living (ADL) and quality of life (QoL) in advanced Parkinson's disease (APD) patients with ongoing or planned device-aided treatment (DAT) and to identify characteristics that may predict ADL and QoL response to DATs. ADL influences QoL in patients with APD. However, it is unknown how disease characteristics (eg, motor fluctuation/PD duration) affect ADL and patient QoL.

Methods: This was a post-hoc analysis of OBSERVE-PD, (a global, multicenter, cross-sectional, observational study). ADL was assessed using the Unified PD Rating Scale (UPDRS) Part II; QoL was assessed using PD 8-item questionnaire (PDQ 8). DATs included deep brain stimulation, levodopa-carbidopa intestinal gel infusion, and continuous apomorphine subcutaneous infusion. ADL and QoL correlation was assessed in APD patients eligible for DAT (planned and ongoing) using Pearson correlation coefficients.

Results: This analysis included 384 patients with ongoing DAT and 164 patients planning to initiate DAT. Despite greater disease duration and age [Table1], patients receiving DAT generally had better ADL/QoL scores than patients planning to initiate DAT [Table2]. Patients receiving DAT with >4 years motor fluctuation and >10 years since PD diagnosis also demonstrated slightly better ADL/QoL scores. ADL and PDQ-8 scores were strongly correlated for patients with ongoing DAT (r=0.54722;P<.0001) and planned DAT (r=0.55487;P<.0001).

Conclusion: Patients with planned DAT vs. ongoing DAT generally had worse ADL and QoL, suggesting DAT improves long-term patient-reported outcomes. ADL and QoL were strongly correlated in patients with ongoing and planned DAT. These data demonstrate the importance of assessing ADL/QoL in APD.

Disclosure: AbbVie Inc, participated in the study design, study research, collection, analysis, interpretation of data and writing, reviewing, and approving of this abstract for submission.

EPR2080

Abnormal α-synuclein deposits in skin nerves: inter and intra-laboratory reproducibility

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Background and aims: Phosphorylated α-synuclein at serine 129 (p-syn) in skin nerves is a promising test for the in vivo diagnosis of synucleinopathies. Here we aimed to establish the intra and inter-laboratory reproducibility of intraneural p-syn positivity in two laboratories (Würzburg, Germany and Bologna, Italy) with a major expertise in this analysis.

Methods: We enrolled 42 patients (26 from Würzburg and 16 from Bologna) affected by Parkinson's disease (PD: 21 patients), REM sleep behavior disorder (RBD: 11), Multiple System Atrophy (MSA: 4) and small fiber neuropathy (SFN: 6). Skin biopsy was performed in C7 paravertebral spine region and distal leg. The analysis was standardised in both laboratories and made blinded on a single skin slide double stained with p-syn and PGP 9.5 (pan-neuronal marker). 50 skin slides were analysed. Slides differently classified were re-evaluated to understand the reasons of the discrepancy.

Results: The intra-laboratory analysis showed an excellent reproducibility both in Würzburg (concordance of classification 100% of slides; K=1; p<0.001) and Bologna (96% of slides; K=0.92; p<0.001). Inter-laboratory analysis showed a reproducibility in 45 slides (90%; K=0.8; p<0.001) and a different classification in 5 slides which was mainly due to fragmented skin samples or weak PGP 9.5 signal.

Conclusion: 1) p-syn analysis showed an excellent inter and intra-laboratory reproducibility supporting the reliability of this technique as in vivo biomarker for synucleinopathies; 2) the few ascertained discordances were important to further improve the standardisation of this technique.

Disclosure: Nothing to disclose

Movement disorders 5

EPR2081

Quantitative gait analysis in idiopathic normal pressure hydrocephalus using instrumental timed up and go test

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Background and aims: Gait disturbance is the most frequent symptom in idiopathic normal pressure hydrocephalus (iNPH), and it is characterised by a short-stepped, magnet-like and broad-based gait. The timed up and go test (TUG) is widely used to assess gait and balance. In this study, quantitative measurements were performed twice, using iPhone speed sensors and free "SENIOR QUALITY " software. Herein, we report the characteristics of gait in iNPH compared with those in controls.
Methods: 33 patients with suspected iNPH and 86 control subjects were recruited. Data were automatically collected during TUG and 6 components of gait (Standing, Go, Turn, Back, Backturn and Sitting) were automatically computed. Statistical comparisons were performed to compare those with iNPH and controls.
Results: Correlations of total time between first and second TUGs were high (>0.9) in both the iNPH and control groups. In comparing first and second TUGs, statistically significant shortening of time was noted in Go, Backturn and Sitting in the controls. In those with iNPH. mean values were decreased in the second TUG in all components except for Turn, but these results were not statistically significant. Comparison between the iNPH with control groups revealed that all components of iNPH were slower in the first TUG, while only the Go, Back and Backturn components were slower in the second TUG.
Conclusion: The instrumental TUG enables quantitative measurements of six components of TUG. This provides further insight into the pathophysiology of gait disturbances in various disorders.
Disclosure: The first author, MI, received honoraria from Johnson & Johnson, Japan and Medtronic Japan.

EPR2082

Impact of infusion-based therapies initiation on levodopa equivalent daily dose in advanced Parkinson's disease patients: a 2-year retrospective study in a french expert center

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Background and aims: In Parkinson's disease (PD), cumulative levodopa equivalent daily dose (LEDD) is associated with the onset of motor complications. Subthalamic deep brain stimulation (STN-DBS), subcutaneous apomorphine infusion (Apo) and intrajejunal levodopa-carbidopa infusion (IJLI) are the treatment options for patients with refractory motor complications. While cumulative LEDD is dramatically reduced after STN-DBS, its evolution after infusion-based therapies initiation is unclear. Thus, the aim of our study was to assess the evolution of cumulative LEDD after initiation of Apo or IJLI in PD patients.
Methods: We conducted a retrospective study in a movement disorders unit, between January 2015 and July 2017. LEDD was calculated before initiation and after the titration period necessary to reach the optimal clinical state, and included the LEDD of the injected drug.
Results: 68 patients were included: 21 received IJLI and 46 received Apo. Cumulative LEDD significantly increased after IJLI initiation (1483±788mg/d vs 1224±582mg/d before; $p<0.01$) and after Apo initiation (1571±579mg/d vs 1203±444mg/d before; $p<0.001$). The L-dopa daily dose did not significantly decreased after Apo initiation (865±513mg/d vs 984±425mg/d before; $p=0.23$). The increase in LEDD after Apo initiation is comparable to IJLI (+33.5±42.3% vs +32.6±76.1%; NS).
Conclusion: IJLI and Apo induced an increase in LEDD when the dosage of the injected drug was included in the evaluation, what was not done in most of previous studies. These results suggest that infusion-based therapies allow to reach higher LEDD than pulsatile oral conventional treatment, and that STN-DBS is the only option to decrease LEDD.
Disclosure: Nothing to disclose

EPR2083

Foot clearance pattern: a distinctive gait variable in vascular Parkinson's disease

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Background and aims: Foot clearance (height's foot above ground during swing phase and foot angles before and after swing phase, Figure 1) has been related to the risk of falling in people with Parkinson's disease PD). The literature on foot clearance is scarce, especially in Vascular PPD (VPD).
Objective: To investigate foot the clearance pattern of patients with VPD and IPD patients, and levodopa response.
Methods: Physilog sensors (GaitUp®) were used to measure the clearance variables of each stride during 60-meter continuous course in a self-selected pace in 15 healthy subjects, 15 IPD patients and VPD patients in (Off phase) and 1 h after (On phase) the acute administration of suprathreshold morning levodopa dose. Two features (mean and coefficient of variation) of each time series were statistically compared using Mann-Whitney test (comparison between groups) and using Wilcoxon signed ranks test (intragroup) (significant P-values <0.05).
Results: VPD patients presented lower lift-off angle, strike angle, maximum heel and toe height, all of these refractive to levodopa. Patients with IPD and VPD, particularly VPD, presented higher variability at the beginning (lift-off angle, maximum heel) and the end (maximum toe 2, strike angle) of swing phase.

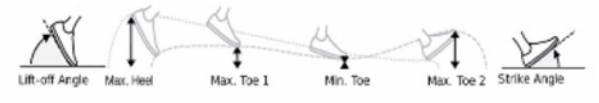

Figure 1: Illustration of clearance variables. (Adapted from Gait Up®)

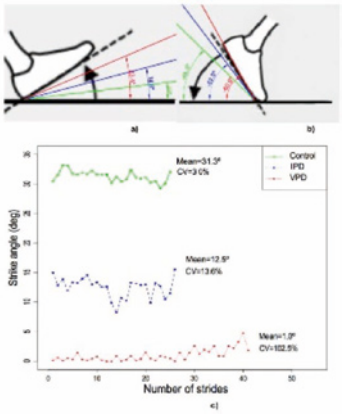

Figure 2: Strike angle (panel a)) and lift-off (panel b)) of foot clearance in VPD (green line), compared to a healthy subject (red line) and an IPD patient (blue line). Panel; c) Representative times series of strike angle over a continuous course of 30 meters, showing higher variability over the mean (CV=102.5%) in VPD.

Conclusion: Foot clearance analysis allowed to identify unique foot and heel patterns, potentially less amenable to be identified on clinical examination, with VPD patients displaying difficulty lifting the foots from the ground.
Disclosure: Nothing to disclose

EPR2084

The prevalence of dystonic tremor and tremor associated with dystonia in patients with cervical dystonia

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Background and aims: Link between dystonia and tremor has been known for decades, but at present question arises whether they are two separate illnesses or just different manifestations of one disease. We distinguish two types of tremor in dystonia: dystonic tremor, which appears on body part affected by dystonia, and tremor associated with dystonia (TAWD) in locations where dystonia does not occur. Dystonia has always been considered a basal ganglia disease. However, theory of neuronal network dysfunction, involving many areas of brain, currently prevails. Role of cerebellum seems especially important, which promotes theory, that TAWD might not be just a coincidence of essential tremor and cervical dystonia, but one of symptoms of cerebellar dysfunction in dystonia.
Methods: Prevalence of different forms of tremor was determined in a group of patients with cervical dystonia, treated with regular local injections of BoNT-A.
Results: In total, 123 patients with CD were included in the pilot study, 28 men (22.76%) and 95 women (77.24%). Mean age of patients was 59.8 years. Dystonic tremor of the head was present in 70 patients (56.91%). TAWD was in all 14 cases (11.38%) observed on upper limbs as static or intentional tremor.
Conclusion: In this pilot study, we point out the presence of TAWD as one of the clinical signs of cervical dystonia, occurring in 11.38% of patients in the studied group. Dystonic tremor occurred in more than half of the patients and appears to be a relatively common part of clinical picture in patients with cervical dystonia.
Disclosure: This pilot study was supported by grant AZV of the Ministry of Health of the Czech Republic no. 16-30210A and Institutional Support of the Research Organizations of the Ministry of Health of the Czech Republic RVO FNOL 2017.

EPR2085

Accelerometric evaluation of motor performance in PD patients before and after STN-DBS treatment

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Background and aims: Conventional assessment of motor fluctuations and dyskinesia in Parkinson's disease (PD) patients relies on subjective self-reporting and patient diaries. We have used wrist-worn accelerometers to objectively monitor motor symptoms in PD patients before and after STN-DBS.
Methods: We studied 13 advanced PD patients (6 women, mean age 61±10.5) in the period 1 year before and again 4-12 months after bilateral STN-DBS, when the patients were considered stabilised on DBS. Patients were wearing a wrist-worn accelerometric device (Parkinson's Kinetigraph-PKG) over a period of 6 consecutive days. The percentage of daily time spent in moderate to severe dyskinesia and in bradykinetic state were recorded, and the fluctuation and dyskinesia score (FDS) was calculated as a measure of fluctuation, derived from variations of dyskinesia and bradykinesia scores produced by the PKG. These were compared before and after STN-DBS surgery using Wilcoxon Signed-ranks Test.
Results: The pre-DBS rank was significantly higher than the post-DBS one for the time spent with dyskinesia (Mdn=0.41 vs. Mdn=0.1, $Z=2.97$, $p<0.01$). However, there was no significant difference in bradykinesia (Mdn=0.35 vs. Mdn=0.49, $Z=0.85$, $p=0.064$). The FDS was significantly lower after STN-DBS (Mdn=17.5 vs. Mdn=9.2, $Z=2.97$, $p<0.01$).
Conclusion: Our study shows an objective statistically reliable reduction of dyskinesia. No change in bradykinesia was probably due to l-dopa overdose before the operation to avoid "off" periods at the cost of dyskinesia. The improvement of FDS score after operation suggests more stable daily motor performance. PKG offers a reliable and objective measure of patient's motor condition.
Disclosure: Nothing to disclose

EPR2086

Probable novel presenilin 1 mutation (p. Arg41Ser) as cause of early-onset Parkinsonism

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Background and aims: Although Alzheimer's disease (AD) and Parkinson's disease (PD) are multifactorial neurodegenerative disorders having distinct genetic risk factors, studies have revealed a possible genetic links between them. Mutations in presenilin-1(PSEN1) accounts for the majority of cases of early-onset autosomal dominant AD as well as sporadic forms. Atypical presentations have been reported including extrapyramidal signs (parkinsonism, myoclonus, dystonia). In the last years, mutations involving the PSEN1 and PD genes such as PARK2, PINK1 and LRRK2 have been demonstrated.
Objective: Report a case of PSEN1 mutation presenting with early-onset Parkinsonism (EOPD) phenotype.
Methods: A 46-year–old Argentinian woman with a remarkable medical history of chronic iron deficiency anemia,and a positive family history of psychiatric disorders started at age 35 with progressive asymmetric left resting tremor, bradykinesia and rigidity. Wilson's and Niemann-Pick type C disease resulted negative. EOPD was diagnosed. L-dopa/carbidopa (LD/C) and rotigotine were slowly titrated, with clinical improvement. Two years later, she reported mild difficulties with memory and attention during the last two years.
Results: Neuropsychological examination showed a predominant frontal subcortical cognitive decline. Brain MRI showed moderate signs frontal atrophy and 18FDG-PET reduced metabolism in frontal cortex. PiB-PET (Pittsburgh compound) image was amyloid negative. Because of EOPD and family history a Next Generation Sequencing-NGS was performed on DNA extracted from whole blood. NGS analysis revealed a novel missense PSEN1 mutation position 14:73637540, A>T, p.Arg41Ser. Parental DNA analysis could not be examined.
Conclusion: This missense PSEN1 was considered a potential causative mutation, given the phenotype and the occurrence of the mutation in a very conservative region
Disclosure: Nothing to disclose

EPR2087

(Dys)prosody in Parkinson's disease: effects of medication and disease duration on different prosodic functions

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Background and aims: Sentence modality and speech chunking are two prosodic functions crucial to communication. It is currently unknown whether/how the expression of these linguistic functions is impaired in Parkinson's disease (PD), and how disease duration and medication affect prosodic functions in PD.
Methods: 20 PD patients were compared to 20 controls during the production of sentences eliciting various prosodic patterns (Table1). Patients fell in two groups according to disease duration (G1: 1-5 years; G2: ≥10 years), and medication (OFF: no medication; ON: one hour after a dopaminomimetic drug intake). Prosodic analysis was done with PRAAT, using the P-ToBI system to annotate nuclear contour types and phrasing breaks. A deviance scale from '1' to '-1' was computed by subject, with the language target prosody as '1' and the most deviant prosody in the data as '-1'. Group performance was examined by a One-Way ANOVA. A mixed ANOVA assessed the effects of disease duration and medication.

Table 1. *Participants' mean age, age range and gender, by group.*

Participants	Mean age	Age range	Females
Controls (n=20)	60	43 - 74	10
PD – G1 (n=10)	66	40 - 82	6
PD – G2 (n=10)	64	41 - 79	6

Table 1. Participants' mean age, age range and gender, by group.

Results: Both the expression of sentence modality and speech chunking were disturbed in PD, as patients overall performed significantly worse than controls (Fig.1). However, medication improved the expression of modality, while no effects of disease duration were found (Fig.2, left). Differently, for speech chunking there was no main effect of medication, or of disease duration, but a significant interaction between medication and disease duration: G1 chunking improved in ON, unlike G2 chunking (Fig.2, right).

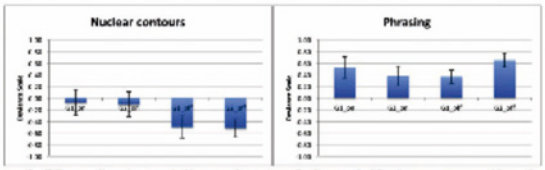

Figure 2. *PD: medication and disease duration. Left panel: Nuclear contours (data for all sentence types); Right panel: Phrasing (expected speech chunking).*

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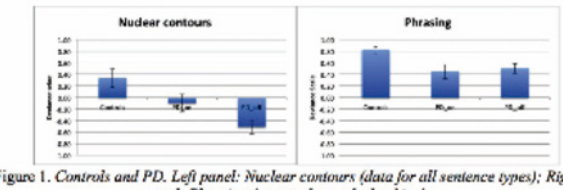

Figure 1. *Controls and PD. Left panel: Nuclear contours (data for all sentence types); Right panel: Phrasing (expected speech chunking).*

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Conclusion: These findings are the first to demonstrate that different prosodic functions are affected differently in PD, with implications for PD neurophysiology and therapy.

Disclosure: Research developed within the project Dysarthria in Parkinson's disease: Lusophony vs. Francophony comparison (FCT-ANR/NEU-SCC/0005/2013), funded by FCT-ANR, within the Program Blanc Accords Bilatéraux France/Portugal. Additional support was provided by CLUL (Grant UID/LIN/00214/2013).

EPR2088

The diagnostic accuracy of the hummingbird and morning glory sign in patients with neurodegenerative parkinsonism

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Background and aims: The hummingbird (HB) and morning glory flower signs (MGF) reflect midbrain pathology on MRI. Therefore, we aimed to determine diagnostic accuracy and reproducibility of midbrain atrophy patterns in a large cohort of patients with neurodegenerative parkinsonism and healthy controls (HC).

Methods: Retrospective analysis of midbrain atrophy patterns on T1-weighted MRI by at least two independent experienced and two junior raters.

Results: 95 patients with progressive supranuclear palsy (PSP), 289 with Parkinson's disease (PD), 97 with multiple system atrophy (MSA) and 79 HC were included. Presence of the HB sign had a specificity of 99.5% and a PPV of 96.1% for a diagnosis of PSP, while sensitivity was suboptimal (51.6%). Presence of the MGF sign yielded a specificity of 97.7% for a diagnosis of PSP, but sensitivity was only 36.8%. Cohen's kappa revealed almost perfect agreement between both experienced rater (HB: k 0.945; MGF: k 0.918;$p<0.001$), strong agreement in the assessment of the HB sign (k 0.871;$p<0.001$) and moderate agreement in the assessment of the MGF sign (k 0.651;$p<0.001$) between the two junior raters. There was also an almost perfect agreement for the comparison of consensus rating of the HB sign between the junior and the experienced raters (k 0.901;$p<0.001$), for the MGF sign only a strong agreement could be achieved (k 0.719;$p<0.001$).

Conclusion: Midbrain atrophy patterns are useful in the differential diagnosis of neurodegenerative parkinsonism but both the HB and MGF sign suffer from low sensitivity.

Disclosure: Nothing to disclose

Movement disorders 6

EPR2089

Variability of presynaptic nigrostriatal dopaminergic function and clinical heterogeneity in a Dopa-responsive dystonia family with GCH-1 gene mutation

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Background and aims: Mutation of guanosine triphosphate cyclohydrolase 1 (GCH-1) is the most common and best characterized condition that manifests as Dopa-responsive dystonia (DRD). Since the gene product is related to tyrosine hydroxylation, impairment of dopamine production in the nigral cell seems to be responsible for DRD. However, results of the functional imagings were still controversial. The aim of this study was to evaluate presynaptic nigrostriatal dopaminergic function by brain TRODAT SPECT imaging in a Taiwanese DRD family.
Methods: Three of five members of the DRD family were found to have a heterozygous T241C mutation in exon 1 of GCH-1. We studied TRODAT SPECT imaging in those three members. We further analyse the correlation between the phenotypic presentation of DRD and the nigrostriatal dopaminergic function
Results: There was presentation of intrafamilial variability in the DRD family; one was a classic DRD (proband), one presented with parkinsonism which was distinguishable from typical PD, and the other one was an asymptomatic gene carrier. The proband was a 10-year-old girl with classic DRD and normal presynaptic nigrostriatal dopaminergic function. Her grandmother, a 79-year-old woman, presented with slowly progressive PD and excellent response to dopaminergic therapy for 21 years. Her brain TRODAT imaging revealed a markedly and asymmetrically reduced uptake of dopamine transporter at the bilateral striatum. Her father, a 54-year-old man, was an asymptomatic gene carrier and his brain imaging revealed asymmetrically reduced nigrostriatal dopaminergic transmission in the bilateral striatum.
Conclusion: We conclude variability of presynaptic nigrostriatal dopaminergic function in patients with DRD is related to their clinical heterogeneity.
Disclosure: Nothing to disclose

EPR2090

Quantitative assessment of postural instability by measuring minimal weight load for stepping reaction in pull test

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Background and aims: We developed an apparatus for quantitative assessment of pull test in Parkinson's disease (PD). Before applying this apparatus to PD patients, we investigated whether several physical parameters in healthy subjects might affect the amount of minimal weight load for inducing backward stepping in pull test.
Methods: 26 adult healthy subjects (23±3.7 y.o., male : female=10 : 12) participated in the experiment. The subject wore a vest, in which a lope was connected at the back. A basket was attached at the other end of the lope. By putting a heavy bob into the basket, the subject at standing position was pulled backwards unexpectedly (Fig. 1). A minimal weight for inducing stepping reaction (MWS) was measured. During the experiment, EMGs of both tibialis anterior muscle (TA) and soleus muscle (SOL) were recorded. All the experiment process was recorded with a video camera.

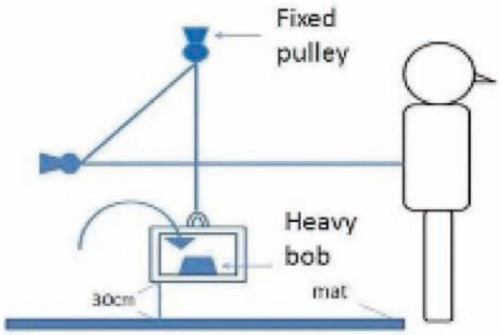

Fig 1: Apparatus Mimicking Pull Test

Fig. 1
Results: Mean MWS was 1.73±0.73kg. Among several physical parameters investigated, grasp power had a significant correlation with the MWS ($r=0.408$, $p<0.05$) (Fig. 2). Other physical parameters including height, weight, foot size etc. had no statistical correlation with the MWS. The large variations among each subject were observed in the latency of TA EMG activity after weight load.

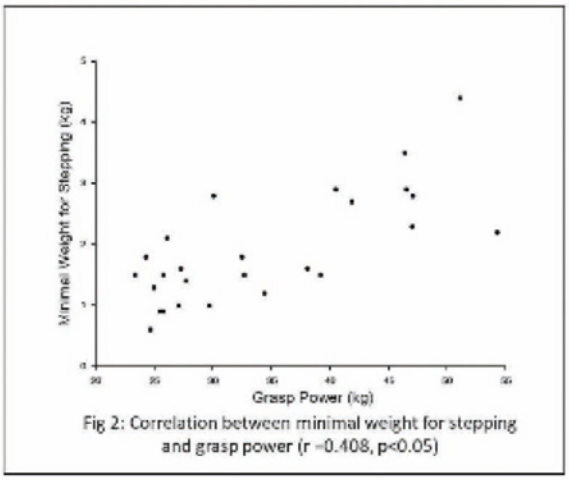

Fig. 2

Conclusion: Considering that mean grasp power represents whole body muscle strength, whole body muscle strength may affect the result of pull test.

Disclosure: JSPS KAKENHI Grant Grant-in-Aid for Scientific Research C Number JP16K01510.

EPR2091

Genotype-phenotype correlation in ADCY5-related movement disorders

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Background and aims: Mutations in ADCY5 gene might derive in different phenotypes: benign hereditary chorea (BHC), facial dyskinesia and paroxysmal dyskinesia with hypotonia. Our aim is to describe the variability in clinical manifestation among patients with different mutations in ADCY5.

Methods: We report a family clinically affected with BHC and a sporadic case with paroxysmal dyskinesia and hypotonia. Our family index case is a 34-year-old woman with a childhood onset chorea and facial dyskinesia with mild dystonia and myoclonus. Some of her relatives had been studied in our Movement Disorders Unit for BHC, suggesting an autosomal dominant pattern of inheritance. The sporadic case was an eighteen-year-old male without delivery problems. He developed hypotonia with six months and nocturnal paroxysmal dyskinesia during the first two years of life, increasing frequency of these events among childhood.

Results: Cerebral MRI were normal in all patients. Neurophysiological studies showed myoclonus in both, family index and sporadic cases. Genetic tests for the most common causes of dystonia, paroxysmal dyskinesia and myoclonus were performed with negative results. In the familiar index case a pathogenic mutation c.2176G>A (p.Ala726Thr) in gene ADCY5 was found. In the sporadic case a de novo mutation c.1252C>T (p.Arg418Trp) in ADCY5 was demonstrated.

Conclusion: We described two mutations in gene ADCY5 causing different phenotypes: BHC and paroxysmal dyskinesia with hypotonia and myoclonus. Facial dyskinesia or nocturnal exacerbations of dyskinesia are clinical features that help through the diagnosis. De novo mutations in ADCY5 can be present, this etiology should be considered even without positive family history.

Disclosure: Nothing to disclose

EPR2092

The overlap syndrome of three neurodegenerative diseases – a case report

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Background and aims: Progressive supranuclear palsy (PSP), frontotemporal dementia (FTD) and corticobasal syndrome (CBS) are neurodegenerative diseases classified as tauopathies. Clinical and/or histopathological features of these diseases may coexist in one patient within an overlap syndrome. In such cases, mutations or polymorphism of genes attributed to different neurodegenerative diseases are often found. The concomitance of features of PSP, FTD and CBS is observed in 10-30% of overlap syndromes.
Methods: A 51-year-old man had four years history of progressive psychomotor slowness, reduction of spontaneous activity, deficits in memory and attention, behavioural disorders (hygiene neglect, binge eating), dysarthria, excessive salivation, frequent falls and uncontrolled laughter. The symptoms have become a burden for the patient at home and in the workplace. Neurological examination revealed psychomotor slowness, difficulties in performing complex tasks, pseudobulbar features, oculomotor abnormalities (bradykinesia, limited vertical movements), oromandibular and truncal dyskinesias, extrapyramidal symptoms (hypomimia, postural reflexes disturbance, rigidity of right limbs with foot dystonia and "alien" lower limb phenomenon), right-sided pyramidal symptoms and cerebellar features.
Results: Brain magnetic resonance imaging displayed moderate frontal, temporal and mesencepahlic atrophy with signs of neuronal necrosis. Neuropsychological testing confirmed disturbances in cognition, visuospatial organization, executive functions, impaired impulse control and stiffness of emotional reactions. The patient was diagnosed with an overlap syndrome comprising progressive supranuclear palsy, frontotemporal dementia and corticobasal syndrome.
Conclusion: We presented a rare case of an overlap of three tauopathies. The concomitance of clinical features typical for different neurodegenerative diseases may generate diagnostic difficulties and is usually associated with a poor prognosis.
Disclosure: Nothing to disclose

EPR2093

The effect of bilateral subthalamic stimulation on postural sway and its correlation with disease-related factors in Parkinson's disease

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Background and aims: The effect of bilateral subthalamic stimulation (STN-DBS) on the postural instability in Parkinson's disease (PD) is not unequivocal in different studies. We aimed to analyse it and explore its influencing factors.
Methods: 24 PD patients treated with STN-DBS and 18 age-matched healthy subjects performed Instrumented Clinical Test of Sensory Organisation and Balance test while wearing an Opal motion sensor on the lumbar region. Sway area (m2s4) of the trunk (Table1) was calculated with Mobility Lab software (APDM Inc.) during stimulation-off state (NON) and with optimal bilateral stimulation (BON) after 12 hours medication withdrawal. Pre- and postoperative clinical data were collected and compared.
Results: The age of the patient group was 65(10) years [median (interquartile range)], the elapsed time since operation: 19(27) months. The preoperative UPDRS III. scores in MED-OFF state were 30(29) points; its postoperative improvement was 81(51)%. Sway values in PD, in NON state were higher than that of controls (Table1). PD group was divided into Group1 (sway decreased with neurostimulation) and Group2 (sway increased in BON state). Sway values in these groups were not different in NON state, but Group2 had higher values in BON state (Table2). Age and the elapsed time since the operation were not different in the two PD groups. However, Group2 had higher preoperative UPDRS III. scores (24(13.5) and 48(33); p=0.004).

Table1. Sway values of the PD group in NON state compared to control values

	Sway (m^2s^4) [median (IQR)]				
	Eyes opened Ground	Eyes closed Ground	Eyes opened Foam	Eyes closed Foam	Combined Sway
Patient group	0.036 (0.04)	0.048 (0.04)	0.089 (0.091)	0.249 (0.19)	0.116 (0.07)
Control group	0.015 (0.01)	0.024 (0.02)	0.045 (0.04)	0.167 (0.17)	0.068 (0.07)
p	**0.006**	**0.029**	**0.006**	0.127	**0.036**

Table 1.

Table2. Sway values of the NON and BON state in the two patient groups

	Sway values (m^2s^4) [median (IQR)]									
	Eyes opened Ground		Eyes closed Ground		Eyes opened Foam		Eyes closed Foam		Combined sway	
	NON	BON	NON	BON	NON	BON	NON	BON	NON	BON
Group 1.	0.027 (0.04)	0.014 (0.01)	0.033 (0.05)	0.027 (0.02)	0.075 (0.11)	0.046 (0.03)	0.181 (0.16)	0.13 (0.12)	0.09 (0.08)	0.06 (0.04)
Group 2.	0.045 (0.04)	0.061 (0.06)	0.056 (0.04)	0.08 (0.13)	0.093 (0.08)	0.13 (0.15)	0.301 (0.15)	0.33 (0.25)	0.13 (0.07)	0.17 (0.11)
p	0.44	**0.001**	0.06	**0.01**	0.32	< **0.001**	0.1	< **0.001**	0.13	< **0.001**

Table 2.

Conclusion: Our data suggest that worse preoperative motor performance is a risk factor for stimulation-induced postural instability after STN-DBS in PD. Further predictive factors should be explored.
Disclosure: Nothing to disclose

EPR2094

Eyes that are both quick and slow: three patients with PSP syndrome and gaze evoked nystagmus – new observation.

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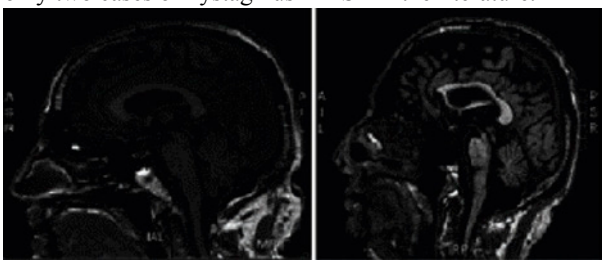
Background and aims: Nystagmus is an atypical finding in progressive supranuclear palsy (PSP). In fact, presence of nystagmus in patient with parkinsonism points toward multiple systemic atrophy. Since the diagnosis of different parkinsonian conditions is primarily clinical, it is important to determine phenotypic spectrum of the disease. We present three patients with PSP syndrome and horizontal, gaze-evoked nystagmus (GEN).
Methods: Patients were clinically examined, video recorded and followed-up up to 5 years. Extensive diagnostic work up, including brain MRI and FDG PET, spinal tap and genetic testing was performed. Pub Med was searched for articles describing GEN in PSP patients.

PATIENT SEX AND AGE	MAIN CLINICAL FEATURES	TYPE OF NYSTAGMUS	BRAIN MRI	BRAIN FDG - PET CT
Male. 66	-Early falls -Parkinsonism, unresponsive to levodopa - Axial rigidity -Postural instability -Eyelid apraxia – Vertical gaze palsy -Slowing of saccades in all directions	Gaze evoked, horizontal nystagmus in both directions	Mesencephalic and frontal lobe atrophy	Decreased activity in basal ganglia and frontal lobes. Normal activity in cerebellum.
Male, 68	-Postural instability -Symmetrical parkinsonism, unresponsive to levodopa – Vertical gaze palsy - Slowing of saccades in all directions	Initially vertical, gazed evoked nystagmus on looking up and gazed evoked horizontal nystagmus in extreme positions. At last follow up, gaze evoked horizontal nystagmus, more prominent on looking to left.	Mesencephalic atrophy	Slightly increased activity in basal ganglia. Normal activity in cerebral cortex and cerebellum.
Male, 61	-Postural instability with early falls -Dysarthria -Parkinsonism unresponsive to levodopa --Axial rigidity -Vertical gaze palsy - Slowing of saccades in all directions	Gaze evoked horizontal nystagmus in both direction, present only in some head positions (and no vertigo)	Mesencephalic atrophy	Decreased activity in the pons and both frontal lobes. Normal activity in cerebellum.

Table 1: Patient information regarding sex, age, PSP symptoms, head MR and PET CT.

Results: All three patients (Table) had parkinsonism poorly responsive to levodopa and vertical gaze paresis with slowing of vertical and horizontal saccades, indicating PSP syndrome. The atypical finding was horizontal GEN, with no other cerebellar signs. Imaging results were characteristic for PSP and alternative diagnosis were excluded. We found only two cases of nystagmus in PSP in the literature.



Picture 1: Head MR of the second patient (on the left) and of the third patient (on the right).

Conclusion: The same pontine structures are responsible for voluntary saccades and the fast phase of nystagmus, thus the co-occurence of nystagmus and gaze paresis might be contraintuitive. However, in our PSP patients, it might be explained by gradual neurodegenerative process, which first affects voluntary saccades causing saccadic slowing as an early manifestation of gaze paresis. At the sime time, reflex saccades responsible for the fast component of nystagmus, are relatively unaffected. With disease progression, reflex saccades become impaired and the nystagmus fades away. GEN may frequently be overlooked in PSP, as it appears only temporarily.
Disclosure: Nothing to disclose

EPR1078

Dopaminergic adverse-events in patients that switched from entacapone to opicapone: the BIPARK-I open-label experience

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Background and aims: Assess the occurence of dopaminergic adverse-events (AEs) in levodopa-treated Parkinson's Disease (PD) patients that switched from entacapone (ENT) to opicapone in the BIPARK-I open-label part.
Methods: After completing the BIPARK-I double-blind part, ENT-patients switched to a 1-year open-label extension, in which all subjects received OPC. This post-hoc analysis investigated the occurence of dopaminergic AEs, namely, dyskinesia, nausea, vomiting, hallucinations (including delusion, illusion and disturbance in attention), and orthostatic hypotension on those entacapone 'switchers'. Dopaminergic AEs were defined as new or worsening post-treatment from baseline or double-blind.
Results: 100 patients switched from ENT to 1-year OPC open-label extension. By the end of double-blind, 4% of ENT-patients reported at least 1 dopaminergic AE. After switching to OPC, cumulatively, 22% of ENT switched-patients reported at least 1 dopaminergic AE. Most common AE was dyskinesia (20% cases) that presented an earlier onset. About 45% of ENT switched-subjects with dopaminergic AEs had a levodopa daily-dose reduction of ~25%. By the end of the 1-year OPC open-label extension, actual (by-day) frequency reported was 4% and 1%, respectively for dyskinesia and nausea. One case each of dyskinesia and orthostatic hypotension led to patient withdrawal.
Conclusion: After switching to OPC, we observed an increase in the rate of dopaminergic AEs by ENT switched-patients. This was largely due to worsening or new emergence of dyskinesia, which appeared to be controlled by levodopa reductions. These observations support an enhanced dopaminergic efficacy of OPC and an early follow-up may be warranted to perform any required levodopa adjustments in a timely manner.
Disclosure: Nothing to disclose

EPR2096

Effects of probiotic bacterial strains on peripheral inflammation in Parkinson's disease

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Background and aims: Parkinson's disease (PD) is characterised by loss of dopaminergic neurons and intraneuronal accumulation of alpha-synuclein, both in the basal ganglia and in peripheral sites, such as the gut. Recent findings demonstrate that PD patients display a pro-inflammatory phenotype. In this context, the present in vitro study was focused on the direct effects of probiotic bacterial strains on inflammatory pathways in PD patients
Methods: We enrolled 40 PD patients and 40 matched controls. Peripheral Blood Mononuclear Cells (PBMCs) were isolated and cultured with the following bacterial strains: Lactobacilli (salivarius, plantarum, acidophilus, rhamnosus) and Bifidobacteria (breve and lactis). The modulation of the in vitro release of the major pro- (Tumor Necrosis Factor-alpha and Interleukin-17A) and anti-inflammatory (Interleukin-10) cytokines by PBMCs was investigated, as well as the production of free oxygen radicals (ROS). To provide a surrogate marker of inflammatory profile, we expressed cytokine data as Th1/Th2 ratio.
Results: All strains were able to inhibit inflammatory cytokines and ROS production in both patients and controls. The most striking results in patients were obtained with L. salivarius: 55 and 94% reduction of Th1/Th2 ratio and ROS compared to baseline. A relevant decrease of Th1/Th2 ratio was provided by L. plantarum and B. breve (39 and 38%), whereas ROS production was reduced of 85 and 77% by L. plantarum and L. acidophilus.
Conclusion: Probiotics exert promising results in modulating the release of cytokines towards an anti-inflammatory profile and in counteracting oxidative stress. Further data are mandatory to confirm the role of bacteriotherapy in PD
Disclosure: Nothing to disclose

MS and related disorders 4

EPR2097

Clinical predictors of long-term outcome in multiple sclerosis patients: a prospective cohort study

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Background and aims: Randomised clinical trials have shown that interferon (IFN)-beta reduced relapse frequency and relapse-related accumulation of disability in multiple sclerosis (MS). The aim of this study is to describe the accumulation of long-term disability in a cohort of IFN-beta treated MS patients and to assess whether clinical data have long-term prognostic value.
Methods: This is a prospective study of 419 (236 IFN-beta-treated, 183 untreated) relapsing-remitting (RR) MS patients recruited consecutively, at the Clinic of Neurology, Belgrade. Out of this original cohort, 10-year follow-up data were available on 364 (233 IFN-beta-treated, 131 untreated) subjects. The median time since recruitment was 9.7 years and 19.1 years since MS onset.
Results: The composite predictor, no evidence of clinical disease activity (NEDA-2), from baseline through second year of the study was detected in 60.9% IFN-beta-treated and 7.6% untreated patients ($p<0.001$). The baseline Expanded Disability Status Scale (EDSS) score ($p<0.001$), baseline to year 2 increase in EDSS ($p<0.001$), annualized relapse rate from baseline to year 2 ($p<0.001$), and NEDA-2 ($p=0.002$) were significant predictors for secondary progressive MS conversion, and likelihood of confirmed EDSS worsening up to scores ≥ 4 and ≥ 6 in IFN-beta-treated group. In untreated group, all those variables were significant predictors for all three end points, except annualized relapse rate from baseline to year 2.
Conclusion: Our observational study showed the necessity of IFN-beta treatment in patients with RRMS, in order to prevent disease progression and permanent disability, and additionally that NEDA-2 was significant predictor for long-term worsening disability.
Disclosure: Nothing to disclose

EPR2098

Dynamic functional network connectivity in CIS patients: a longitudinal study

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Background and aims: Time-varying properties of resting-state (RS) functional network connectivity (FNC) at earliest stages of multiple sclerosis (MS) have never been studied. We investigated the trajectory of longitudinal dynamic FNC (dFNC) changes in patients with clinically isolated syndrome (CIS) suggestive of MS.
Methods: RS fMRI data were acquired from 50 CIS patients and 13 healthy controls (HC) at baseline (within 3 months from first attack), year 1 and year 2. Independent component analysis identified 41 relevant networks, which were subsequently classified according with their functional system. Between-group differences of dFNC strength and dynamism measures were analysed.
Results: 47 (94%) patients developed MS at year 2. HC and CIS patients presented 2 dFNC states: State1 (frequency=69%), characterised by low FNC, and State2 (frequency=31%) characterised by high FNC. At baseline, compared to HC, CIS patients showed increased dFNC mainly for sensorimotor and default-mode networks in State 2, which was maintained at follow-up. Reduced dFNC for executive and visual networks that decreased over time, mainly in State 1, was also observed. FNC dynamism tended to increase over time in CIS patients vs HC, with: a) an increasingly higher distance travelled through meta-states at year 1 and year 2, and b) higher number of meta-states and more frequent switches between meta-states at year 2.
Conclusion: The analysis of time-varying RS FNC patterns in CIS patients highlights the relevant role that sensorimotor, default-mode, executive, and visual networks play at the first stages of MS, while helping to establish a potential target for MS early diagnosis.
Disclosure: Partially supported by a grant from the Ministry of Science, Republic of Serbia (# 175031).

EPR2099

Long-term fingolimod treatment in patients with RRMS: MRI outcomes from the LONGTERMS study

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Background and aims: Assessment of long-term efficacy of disease-modifying therapies for multiple sclerosis (MS) is an important aspect of MS disease management in routine clinical practice. We assessed the radiological stability in patients with relapsing-remitting MS treated with fingolimod for up to 120 months.

Methods: LONGTERMS is an open-label, single-arm, extension study evaluating the long-term safety, tolerability and efficacy of fingolimod in patients who previously participated in phase 2/3/3b studies. The full analysis set included all patients randomised to fingolimod 0.5 mg. The selected MRI endpoints were annualised rate of new or newly enlarging T2 lesions (ARneT2), the proportion of patients free from gadolinium-enhancing (Gd+) T1 lesions, percent brain volume change (PBVC) from the first dose of fingolimod by visit, and the annualised rate of brain atrophy (ARBA; an average annual percentage change in brain volume).

Results: At baseline, 3168 patients (women, 71.2%; age [mean± standard deviation (SD)], 38.0±9.1 years; median exposure to fingolimod, 528.5 days [range, 75–3805]; Expanded Disability Status Scale [mean±SD], 2.4±1.5) were included. ARneT2 gradually decreased from 1.362 at Month (M) 0–12 to 0.922 at M0–60 to 0.71 at M0–120. Of the 924 evaluable patients, 48.3% remained free from Gd+ T1 lesions up to M60. PBVC remained low from the first dose of fingolimod (least squares mean: M12, -0.38; M60, -1.57; M120, -3.28). Change in brain volume, as assessed by ARBA, was stable throughout the study (mean: M12, -0.37; M60, -0.33; M120, -0.32).

Conclusion: These results support the long term efficacy of fingolimod in maintaining low disease activity.

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

EPR2100

International consensus on quality standards for multiple sclerosis care: results from a modified Delphi process

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Background and aims: The importance of prompt intervention in multiple sclerosis (MS) was described in the widely endorsed report, Brain health: time matters in multiple sclerosis.1 The present study aimed to define standards for the timing of key steps in the care pathway.

Methods: An international group of 29 MS neurologists was recruited to participate in a Delphi process. Across five rounds, they defined 'core', 'achievable' and 'aspirational' standards (to reflect a minimum, good and high standard of MS care, respectively). A Reviewing Group of 31 MS nurses, experts with MS and allied healthcare professionals reviewed the results and provided feedback.

Results: Consensus was reached (≥75% agreement; n=21) on core, achievable and aspirational standards for 21 steps in the MS care pathway, covering symptom onset, referral, diagnosis, treatment decisions, lifestyle, monitoring, and managing new symptoms. For example, the panel agreed that MS teams should complete a diagnostic workup for MS within 2 months of referral to a neurologist as a core standard, and that completion within 4 weeks of referral should be achievable for most MS teams, with completion within 7 days as an aspirational standard. Here, we will present core, achievable and aspirational standards for key steps in the MS care pathway.

Conclusion: These standards will inform tools for clinics and people with MS and act as a future benchmark for established and developing MS clinics across the globe aiming to deliver the highest quality care.

Reference

1. Giovannoni G et al. Mult Scler Relat Disord 2016;9 Suppl 1:S5–S48.

Disclosure: JHobart has received consulting fees, honoraria, support to attend meetings or research support from Acorda, Asubio, Bayer Schering, Biogen Idec, F. Hoffmann-La Roche, Genzyme, Merck Serono, Novartis, Oxford PharmaGenesis and Teva. ABowen has nothing to disclose. LEberhard is an employee of PharmaGenesis London. GPepper has received consulting fees from Biogen, Novartis, Oxford PharmaGenesis and Teva. GGiovannoni has received consulting fees from AbbVie, Atara Biotherapeutics, Almirall, Biogen, Celgene, GlaxoSmithKline, MedDay Pharmaceuticals, Merck and Company (US), Merck Group (Europe), Novartis, Oxford PharmaGenesis, Roche, Sanofi Genzyme, Synthon, Takeda, Teva Pharmaceutical Industries Ltd., UCB; and grant/ research support from Biogen, Sanofi Genzyme, Takeda.

EPR2101

Prespecified subgroup analyses of ocrelizumab efficacy in patients with primary progressive Multiple Sclerosis from the Phase III ORATORIO Study

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Background and aims: The Phase III ORATORIO study (NCT01194570) demonstrated the efficacy of ocrelizumab versus placebo on a broad range of clinical and imaging outcomes in patients with primary progressive multiple sclerosis.
Methods: The effect of ocrelizumab (600mg) versus placebo on 12-week CDP was analysed in prespecified subgroups (age, sex, region, BMI, body weight, EDSS score, T1 gadolinium-enhancing lesions, prior MS disease-modifying treatment, duration of MS since symptom onset) by Cox proportional hazard models including treatment-subgroup interaction effects. Additional analyses of outcomes were performed for subgroup comparisons that showed a trend for differences in treatment effect (nominal interaction $p<0.3$ on 12-week CDP). The study was not powered to demonstrate efficacy within, or differences between, subgroups.
Results: No differences in the magnitude of ocrelizumab treatment effect on 12-week CDP between all prespecified subgroups were statistically significant (all interactions $p>0.05$; ocrelizumab n=487; placebo n=244). Numerical differences in treatment effect were observed within subgroups based on sex, baseline T1 gadolinium-enhancing lesions and age (interaction $p<0.3$). On 12-week CDP, males seemed to derive more benefit; however, male and female patients benefited from ocrelizumab on key clinical and imaging secondary and exploratory endpoints. Although the effect of ocrelizumab was generally larger in patients with baseline T1 gadolinium-enhancing lesions and/or at a younger age, older patients and those with no baseline T1 gadolinium-enhancing lesions also derived benefit across key endpoints.
Conclusion: Directionally consistent point estimates favouring ocrelizumab versus placebo were seen across all clinical and MRI endpoints in prespecified subgroups of the ORATORIO study.
Disclosure: Sponsored by F. Hoffmann-La Roche Ltd.

EPR2102

Case report of a fingolimod treated patient with possible progressive multifocal leucoencephalopathy, without prior immunosuppression

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Background and aims: Progressive multifocal leukoencephalopathy (PML) is rarely encountered in MS patients as a potential side effect of treatment with some disease modifying drugs, notably natalizumab and more recently fingolimod and dimethyl fumarate, usually in immunocompromised or priorly immunosuppressed patients.
Methods: Herein, we report a case of a fingolimod-treated multiple sclerosis (MS) patient with no lymphocytopenia and no prior exposure to immunosuppressants, who developed possible PML.
Results: A 36-year-old woman, with relapsing-remitting MS previously treated with interferon b-1β, was switched to fingolimod due to breakthrough disease activity. After three years she presented with right pyramidal weakness, right inferior quadrantanopia, progressive cognitive dysfunction, apathy and mixed aphasia. Absolute white blood cell count was 10,51K/μl and absolute lymphocyte count was 1,93 K/μl (>30% from baseline). Fingolimod was discontinued and methylprednisolone was initiated. Brain MRI revealed a left frontal and temporal lobe lesion with no contrast enhancement. She tested negative for HIV and DNA PCR for JC virus was repeatedly negative. Proton magnetic resonance spectroscopic imaging revealed evidence of PML. A course of plasmapheresis followed and mirtazapine was also administered. Repeated brain MRIs showed improvement along with clinical improvement.
Conclusion: Even patients without previous immunosuppressive therapy or low lymphocyte count, may be at risk for developing PML. In fingolimod treated patients no guidelines exist for PML surveillance and the clinical course of PML in naïve-immunosuppressed patients, may be different compared to patients receiving natalizumab. Vigilant clinical and radiologic monitoring is needed in order to timely diagnose this possibly critical side effect.
Disclosure: Nothing to disclose

EPR2103

Siponimod improves cognitive processing speed in patients with SPMS: Results from Phase 3 EXPAND Study

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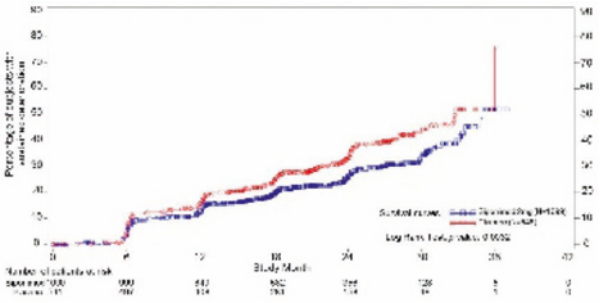
Background and aims: Symbol Digit Modalities Test (SDMT) and Paced Auditory Serial Addition Test (PASAT) are commonly used in clinical trials to assess cognitive processing speed (CPS). The SDMT is more reliable and sensitive than the PASAT. A 4-point change in the SDMT is proposed to define a clinically meaningful change. The Brief Visuospatial Memory Test-Revised (BVMTR) evaluates visual/spatial memory and is valid in MS patients. We report the effect of siponimod on CPS and visual/spatial memory in secondary progressive multiple sclerosis (SPMS) patients.

Methods: Patients from the EXPAND study (siponimod, 1099; placebo, 546) underwent SDMT, PASAT and BVMT-R at 6-month intervals with flexible follow-up per patient. Between-group comparisons for change from baseline were performed using a repeated measures model, adjusted for treatment and baseline scores. Subgroup analyses were performed for patients with/without relapses (rSPMS/nrSPMS) in 2 years before baseline. Cox models assessed the time to 6-month sustained 3 and 4 points change on SDMT.

Results: Siponimod reduced the risk of 3- and 4-point-confirmed worsening on SDMT versus placebo by 28.6%(p=0.0002) and 21.3%(p=0.0157) respectively (Figure 1).Month 24-SDMT scores improved (3points/4points) in 44.8%/40.8% of patients receiving siponimod versus 38.8%/30.2% receiving placebo (Figure 2A&B). Difference in mean change from baseline (2.48) favoured siponimod (p=0.0004). Between-group scores for PASAT/BVMTR were similar. Compared with baseline, SDMT scores improved with siponimod in both rSPMS and nrSPMS patients; for PASAT a difference was only seen in



CI, confidence interval; SDMT, Symbol Digit Modalities Test

Figure 1. Percentage of patients with sustained deterioration based on SDMT score (cut-off 4 points)

a) With superimposed relapses in the 2 years before the study start				
Time point-parameter	Adjusted means (SE) Siponimod (n=388)	Placebo (n=202)	Difference	p value
M24-SDMT	0.996 (0.6504)	1.847 (0.8527)	2.57	0.0151
M24-PASAT	3.20 (0.653)	0.70 (0.878)	2.42	0.0275
b) Without superimposed relapses in the 2 years before the study start				
Time point-parameter	Adjusted means (SE) Siponimod (n=388)	Placebo (n=202)	Difference	p value
M24-SDMT	1.700 (0.5266)	0.740 (0.8185)	2.442	0.0699
M24-PASAT	2.83 (0.514)	3.56 (0.773)	-0.74	0.4281

PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digit Modalities Test; SE, standard error; SPMS, secondary progressive multiple sclerosis

Table 1. Change from baseline in the SDMT and PASAT scores by visit in patients a) with superimposed relapses (rSPMS) and b) without superimposed relapses (nrSPMS) in the 2 years before the study start

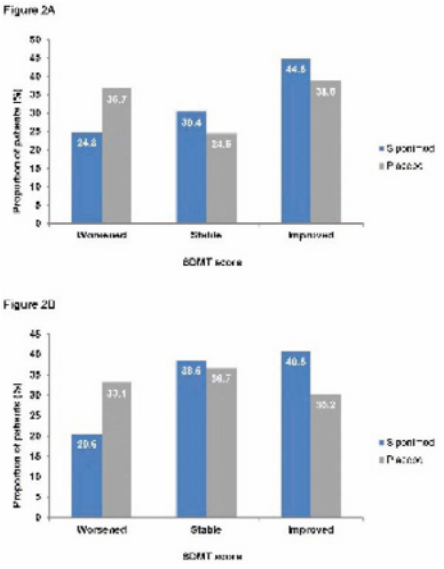


Figure 2. Proportion of patients with deteriorated, improved and stable SDMT scores with cut-off 3 points (A) and 4 points (B) at Month 24

Conclusion: Siponimod demonstrated a significant and clinically meaningful positive effect on CPS as measured by SDMT in SPMS patients with/without relapses.

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

EPR2104

Effect of Teriflunomide on substantial disability worsening in patients with relapsing forms of MS in a Pooled Analysis of the phase-3 TEMSO and TOWER studies

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Background and aims: In 2 phase-3 studies (TEMSO, NCT00134563; TOWER, NCT00751881), teriflunomide 14mg significantly reduced the risk of 12-week confirmed disability worsening (12wCDW) vs placebo in patients with relapsing forms of MS. In a post-hoc analysis of the pooled TEMSO/TOWER dataset, the effect of teriflunomide 14 mg on more substantial disability worsening using 3 exploratory definitions of 12wCDW was assessed.

Methods: In TEMSO and TOWER, 12wCDW, defined as a ≥1.0-point increase in Expanded Disease Severity Status Scale (EDSS) score from baseline (≥0.5 point when baseline was >5.5), was a key secondary endpoint. We assessed 12wCDW using both the original definition (OD) and the following exploratory definitions: D1: ≥1.5 points (baseline ≤5.5) or ≥0.5 point (baseline >5.5); D2: ≥2.0 points (baseline ≤5.5) or ≥0.5 point (baseline >5.5); D3: ≥2.0 points (baseline ≤5.5) or ≥1.0 point (baseline >5.5). Risk of 12wCDW was assessed using a Cox proportional hazards model.

Results: For the pooled TEMSO/TOWER dataset, risk of 12wCDW by OD was reduced for teriflunomide 14 mg (n=728) vs placebo (n=751): hazard ratio (HR) (95% confidence interval [CI]), 0.695 (0.542, 0.892), P=0.0037. The effect of teriflunomide was maintained using higher thresholds of EDSS increase (D1: HR 0.600 [95% CI 0.415, 0.868], P=0.0055; D2 and D3: HR 0.613 [95% CI 0.380, 0.988], P=0.0436).

Conclusion: Teriflunomide significantly reduced the risk of 12wCDW when more-stringent exploratory definitions were used. These observations are consistent with primary analyses in both studies and provide further insight into the positive impact of teriflunomide on disability worsening in patients with relapsing MS.

Disclosure: Study supported by Sanofi.

MS and related disorders 5

EPR2105

Decreased cerebrospinal fluid antioxidative capacity is associated with disease severity and progression in early Multiple Sclerosis (MS)

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Background and aims: Oxidative stress (OS) is a major feature of multiple sclerosis (MS) and promotes cell damage and neuronal death. The antioxidative capacity (AOC) acts as an important defence mechanism and may limit OS-induced toxic effects. An imbalance of OS and AOC may facilitate tissue damage in MS. Various OS species have been investigated so far; however, the role of AOC in MS remains inconclusive. We therefore aimed to compare AOC in serum and cerebrospinal fluid (CSF) between MS patients and controls, and assess its relation with clinical measures.

Methods: We included serum and CSF of 69 patients (clinically isolated syndrome (CIS)/MS) and 67 controls (other non-inflammatory neurological diseases) (Table 1). AOC was determined as the sample's ability to inhibit 2,2'-azobis(2-amidinopropane) dihydrochloride-induced oxidation of dihydrorhodamine. Clinical follow-up was available in all patients.

Table 1. Demographic and clinical data & AOC results

	CIS/MS *n*=56/13	Controls *n*=67	*p*-value
n Female	47 (68.1)	45 (67.2)	n.s.[a]
Age (years)	32.2 (26.6-39.8)	32.7 (25.2-44.9)	n.s.[b]
Disease duration (months)	0.5 (0.3-4.9)	N/A	
n CSF OCB positive	66 (95.7)	N/A	
EDSS	1.5 (0.0-3.0)	N/A	
n DMT	1 (1.4)	N/A	
Time FU (years)	4.3 (1.8-7.0)	N/A	
EDSS last FU (remission)	0.0 (0.0-1.5)	N/A	
n DMT last FU	34 (53.6)	N/A	
Serum AOC (%)	46.4 (41.3-49.9)	47.0 (43.0-50.0)	n.s.[b]
CSF AOC (%)	29.0 (19.6-40.8)	32.8 (23.0-41.4)	n.s.[b]

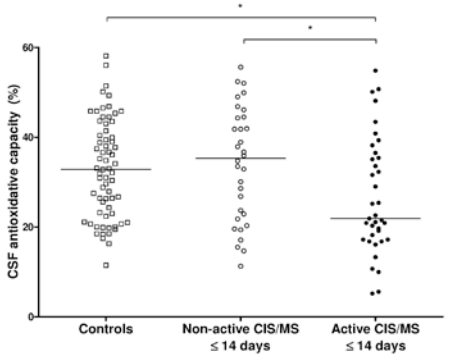
***AOC**=antioxidative capacity; **CSF**=cerebrospinal fluid; **CIS**=clinically isolated syndrome; **DMT**=disease modifying treatment; **EDSS**=Expanded Disability Status Scale; **FU**=follow-up; **MS**=multiple sclerosis; **n**=number of subjects; **N/A**=not applicable; **n.s.** = not significant; **OCB**=oligoclonal bands.*

Unless otherwise indicated, data are given for time at sampling. Values are given as number (%) or as median (interquartile range). Significance ($p<0.05$) was assessed by chi-square test[a] or Mann-Whitney *U* test[b].

Table 1. Demographic and clinical data & AOC results

Results: AOC did not differ between CIS/MS patients and controls in serum and CSF, respectively. CSF AOC was lower in patients with active disease (clinical relapse ≤14 days before sampling, n=37) vs. non-active disease or controls (Figure 1), and correlated with Expanded Disability Status Scale at sampling (Figure 2). CIS patients who later converted to clinically definite MS (n=21) had lower CSF AOC compared to non-converters (p=0.01).

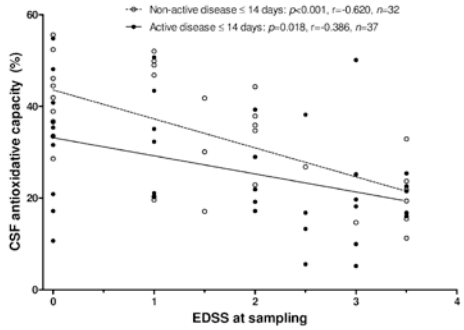
Figure 1. Lower CSF antioxidative capacity in clinical active MS



Cerebrospinal fluid (CSF) antioxidative capacity was significantly decreased in CIS/MS patients who were in an active state of disease (clinical relapse within 14 days prior to sampling) compared to non-active CIS/MS and controls. Significance was assessed by Kruskal-Wallis test and post-hoc Dunn's multiple comparison test. Horizontal bars indicate median values. * $p<0.05$.

Figure 1. Lower CSF antioxidative capacity in clinical active CIS/MS

Figure 2. Lower CSF antioxidative capacity correlated with EDSS



Cerebrospinal fluid (CSF) antioxidative capacity significantly correlated with patient's Expanded Disability Status Scale (EDSS) score at sampling ($p<0.001$, $r=-0.492$, $n=69$), also for patients with active disease (clinical relapse ≤ 14 days prior to sampling) and non-active patients separately. Significance was assessed by Spearman's Rank-Order Correlation. Linear regression lines are drawn for both subgroups.

Figure 2. Lower CSF antioxidative capacity correlated with EDSS

Conclusion: Decreased CSF AOC is associated with disease activity and progression in MS patients, and seems to be either a critical factor to counteract MS pathology, or reduced as a consequence of active or progressing disease. Further research is warranted towards the potential of AOC as a treatment target in MS.

Disclosure: This study represents a sub-study supported by the Austrian Federal Ministry of Science, Research and Economics (core-study named 'BIG-WIG MS' [Bildgebung, Immunpathogenese, Gesundungsfaktoren – Wien, Innsbruck, Graz – bei Multiple Sklerose'; 'Neuroimaging, immunopathogenesis and salutogenic factors in MS – a collaborative effort of the universities of Vienna, Innsbruck and Graz']) and the Austrian MS research society (Multiple Sklerose Forschungsgesellschaft). Miss Voortman received funding from the Austrian Federal Ministry of Science, Research and Economics and was trained within the frame of the PhD Program Molecular Medicine of the Medical University of Graz.

EPR2106

Disability improvements in each functional system of the EDSS in active RRMS patients following treatment with alemtuzumab: results from CARE-MS I extension

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Background and aims: In treatment-naïve RRMS patients from CARE-MS I (NCT00530348), alemtuzumab (12mg/day, baseline: 5 days; 12 months later: 3 days) significantly improved clinical/MRI outcomes versus SC IFNB-1a over 2 years (y). Durable efficacy was demonstrated in a 4-years extension (NCT00930553). Alemtuzumab efficacy on disability improvement at the level of functional systems (FS) of the EDSS was assessed over 6 years.

Methods: Assessments: percentage achieving stable/improved EDSS scores (≤0.5-point change/≥1.0-point decrease from baseline [mean±SD, 2.0±0.8]), FS scores (0-point change/≥1.0-point decrease from baseline FS score), and 6-month confirmed disability improvement (CDI; ≥1.0-point EDSS decrease confirmed over 6 months). Assessments in patients with 6-month CDI over 6 years (n=214): percentage with EDSS score (<4; ≥4); number of improved FS/patient; percentage with stable/improved FS scores.

Results: 349 patients enrolled in the extension; 321 (92%) completed Y6. At Y6, 81% showed stable/improved EDSS scores versus baseline, and 77%–88% showed stability/improvement across all FS. Through Y6, 34% achieved 6-month CDI; 100% of these patients had an EDSS score <4; 75% improved in >1 FS. Improvements occurred in each FS; most frequently in the sensory (45%), pyramidal (42%), and cerebellar (38%) FS.

Conclusion: At Y6, the majority (77%–88%) of alemtuzumab-treated patients showed stability/improvement across all FS. The robustness of these results is underscored by the high retention rate (92%) in the extension. Improvements were seen for each of the FS in patients with 6-month CDI, with 75% showing improvements in >1 FS, indicating a broad treatment effect with alemtuzumab in improving multiple aspects of disability.

Disclosure: Study supported by Sanofi and Bayer Healthcare Pharmaceuticals.

EPR2107

Comparison of biodistribution following subcutaneous and intravenous administration of a novel Zirconium-89 labelled anti-CD20 antibody using imaging

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Background and aims: Anti-CD20 therapies have shown clinical efficacy in multiple sclerosis by acting on lymph node resident B-cells that facilitate autoimmune activation. We aim to investigate subcutaneous administration of a novel Zirconium-89 (89Zr) labelled anti-CD20 antibody, and to compare imaging and biodistribution data with that of intravenous administration in control mice.

Methods: Biodistribution of 89Zr-labelled anti-CD20 antibody was examined in healthy mice, following either an intravenous tail vein injection or a subcutaneous right lower flank injection. Biodistribution was assessed using positron emission tomography/computed tomography (PET-CT) and gamma counting of excised organs at early (4–24 hours) and later (72 hours to 7–10 days) time points.

Results: PET-CT data demonstrated that the proportion of 89Zr-anti-CD20 antibody remaining in the whole body at 7 days following intravenous injection (63±5%) is comparable to the proportion remaining following subcutaneous injection (55±4%). In gamma counting experiments at early time points following intravenous injection, the highest levels of 89Zr-anti-CD20 antibody were found in the circulation and in highly perfused organs, while following subcutaneous injection, the highest levels were found in inguinal lymph nodes and circulating blood (Table).

Organ	Mode of administration	Time-points		
		24 h	72 h	7 days
Blood	i.v.	17.0 ± 0.7	11.8 ± 0.7	6.3 ± 1.0
	s.c.	26.5 ± 3.6	24.7 ± 2.8	13.4 ± 0.8
Spleen	i.v.	24.8 ± 9.3	11.4 ± 1.3	28.8 ± 5.5
	s.c.	11.1 ± 1.6	21.4 ± 3.3	21.3 ± 1.2
Lymph nodes	i.v.	7.5 ± 0.5	11.6 ± 3.4	8.3 ± 2.0
	s.c.	25.4 ± 9.0	47.9 ± 0.5	26.8 ± 16.0

ID/g, injected dose per gram; i.v., intravenous; s.c., subcutaneous; SD, standard deviation

Comparison of intravenous and subcutaneous injections of the Zirconium-89 labelled anti-CD20 antibody biodistribution data (% ID/g [mean±SD]) from blood, spleen, and lymph nodes of healthy mice (n=3) using gamma counting

Conclusion: The route of administration affects the distribution of the 89Zr-anti-CD20 antibody. Subcutaneous administration results in effective absorption from the injection site and subsequent distribution preferentially to lymph nodes and to a lesser extent to the spleen as compared to the distribution following intravenous injection.

Disclosure: This study was funded by Novartis Pharma AG, Basel, Switzerland. David Reutens's institution (University of Queensland) has received research support from Novartis, BGI, Innate. The institution (University of Queensland) of Mary-anne Migotto, Rajiv Bhalla and Karine Mardon has received research support from Novartis. Jacqueline Orian received personal compensation for serving as associate editor – Emerging and Evolving Topics in Multiple Sclerosis Pathogenesis and Treatments. Current Topics in Behavioral Neurosciences, Vol 26, Springer De and has received research support from Novartis. Gisbert Weckbecker and Rainer Kneuer are employees of Novartis.

EPR2108

Estimated prevalence of secondary progressive Multiple Sclerosis in the USA and Europe: results from a systematic literature search

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Background and aims: The prevalence of secondary progressive multiple sclerosis (SPMS) has not been widely reported in the literature. We aimed to estimate its prevalence in the USA and EU-5 countries.

Methods: A systematic literature search was conducted using MEDLINE, Embase and the Cochrane Database of Systematic Reviews via the OVID platform to identify publications providing epidemiological data on SPMS. Studies published in English up to September 2017 that reported on the prevalence of multiple sclerosis (MS) or SPMS, or the proportion of patients with SPMS, were included. Articles duplicating data in later publications or from the same patient cohort were excluded. Prevalence per 100,000 people was estimated based on data within included publications and expressed as an unweighted average (range); when MS prevalence was not reported, other sources were used.

Results: In total, 96 of 3487 identified studies were included in the review. Of these, 22 (published 1997–2016) contained information to estimate the prevalence of SPMS in the USA (four studies) or EU-5 countries (18 studies across the UK, Germany, Italy, France, and Spain). The highest estimated prevalence was in the UK, then the USA, Germany, Italy, France, and Spain (Table). Moreover, two of these studies also reported proportion of patients with relapsing SPMS (Germany, 52.7%; France, 39.5%).

Country (Number of studies*)	Prevalence per 100,000 people, unweighted average (range)
UK (2)	57.8 (40.9–74.6)
USA (4)	37.7 (27.0–45.0)
Germany (3)	33.3 (19.1–50.8)
Italy (5)	26.2 (19.4–33.0)
France (1)	25.5 (NA)
Spain (7)	10.9 (2.8–16.7)

*Number of published studies containing information to estimate the prevalence of SPMS (by country).
NA, not applicable; SPMS, secondary progressive multiple sclerosis

Estimated prevalence of SPMS (in decreasing order) in the USA and EU-5 countries

Conclusion: There was wide variation in the estimated prevalence of SPMS within and across countries, and in the proportion of patients with relapsing SPMS. This may be because of differences in SPMS definition, study design or study duration, which should be explored in future studies.

Disclosure: This study was funded by Novartis Pharma AG, Basel, Switzerland. Vivek Khurana and Harsh Sharma are employees of Novartis Healthcare Pvt. Ltd., Hyderabad, India. Jennie Medin was an employee of Novartis Pharma AG, Basel, Switzerland during the conduct of the analysis.

EPR2109

The diagnosis of multiple sclerosis with markers of "better explanation": accuracy of the "central vein sign" in uncovering pathogenic mechansms different from inflammatory demyelination

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Background and aims: In systemic autoimmune diseases with neurological involvement, brain lesions are mainly and periarteriolar and micro-ischemic. In these diseases central vein sign (CVS) frequency in the white matter is lower than 50% (Maggi et al, in press).

In this study differences in the CVS frequency are analyzed in MS and in MS patients with clinical, laboratory or MRi markers of "better explanation" of the diagnosis (MS-plus) not fulfilling the criteria of another diagnosis.

Methods: Relapsing remitting MS (RRMS) patients or MS-plus were included and CVS frequency was evaluated by brain MRI with a T2* sequence. For identifying patients with MS, a treshold frequency below 50% of lesions with the CVS (the 50% rule) was selected for excluding MS, as previously described (Maggi et al, in press).

Results: Patients recruited: 30 definite MS; 34 MS-plus. The CVS frequency was higher in MS than in the MS-plus: 91% vs 17.5% ($p< 0.0001$). A CVS frequency not fulfilling the 50% rule, was observed in 100% the MS and in 40% of the MS-plus patients ($p< 0.0001$). In most of the MS-plus patients above the 50% rule, the CVS frequency was 70-83%, within the range of the definite MS. The most frequent red flags observed in the MS-plus fulfilling the 50% rule, were normal CSF exam and presence of serum autoantibodies.

Conclusion: The low frequency of the CVS observed in most of the MS-plus suggests a non inflammatory-demyelinating underlying pathology. CVS seems a useful marker for increasing the accuracy of the MS diagnostic criteria.

Disclosure: Nothing to disclose

EPR2110

Patient-centred approach in monitoring Dimethyl-Fumarate: data from a real-life experience

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Background and aims: The most frequent side effects (SEs) of Dimethyl-Fumarate (DMF) include flushing and gastrointestinal events (GI). We investigated about the safety issues in a cohort of 120 Relapsing Multiple Sclerosis (RMS) patients treated with DMF 120 mg BID for 7 days (standard titration) or for 2-4 weeks (slower titration), and then increased to 240 mg BID.

Methods: At the time of DMF first prescription, anthropometric measures were assessed. Any SEs were reported immediately upon the occurrence or during the scheduled follow-up.

Results: The observation period was 10.3±5 months. The mean Body Mass Index (BMI) was 23.6±4.38. In our cohort 45% of patients experienced GI and 66.1% flushing. We found a direct correlation between female sex and SEs (r=0.17; p =0.029): GI (r=0.22, p =0.004), nausea/ vomiting (r =0.18, p =0.024), and flushing (r= 0.2; p= 0.011). Multivariate analysis confirmed that male sex was a protective factor against GI (p=0.035; OR=0.287; 95% CI=0.9-0.941) and flushing (p= 0.004; OR= 0.42; 95% CI =0.05-0.365). Stratifying patients according to their "weight category", we found that normal-weight patients (18.5 <BMI <24.99) had higher incidence of AEs (p=0.044), especially GI (p=0.023). A slower titration did not influenced SEs, but among patients with standard titration, a higher BMI was a protective factor for GI (p= 0.003).

Conclusion: Clinicians should evaluate demographic and anthropometric characteristics of MS patients in order to optimize tolerability during MS therapies.

Disclosure: Dr. Paolicelli received honoraria for consultancy and/or speaking from Biogen Idec, Merck-Serono, Almirall, Sanofi-Aventis, TEVA, Novartis and Genzyme. Dr. Manni, Dr. Iaffaldano A, Dr.D'Onghia, Dr. Zoccolella and Dr. Felica have declared that no competing interests exist. Dr. Iaffaldano P. has served on scientific advisory boards for Biogen Idec and Bayer, and has received funding for travel and/or speaker honoraria from Genzyme, Sanofi-Aventis, Biogen Idec, Teva and Novartis. Dr. Trojano received honoraria for consultancy or speaking from Biogen, SanofiAventis, Merck Serono, Novartis, Genzyme, TEVA, and Bayer-Schering and research grants from Merck Serono, Biogen, and Novartis.

EPR2111

A post-marketing observational monocentric study of efficacy and tolerability of Dimethyl fumarate

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Background and aims: Dimethyl fumarate-DMF is a novel oral therapy for multiple sclerosis. Pivotal studies demonstrated a promising clinical and neuroradiological efficacy of DMF but there are still few reports in real life setting.

Methods: Analysis of intention-to-treat was conducted on 298 patients with a follow-up (FU) of at least 24 months; their basal characteristics are shown in Table1. 18% were naïve, 70% switch from 1°line therapy for inefficacy or intolerance, 12% switch from 2°line therapy. All patients had a brain MRI at DMF initiation and once a year and a neurological examination every 3 months. 76 (25.5%) patients discontinued DMF: 10.1% for disease activity, 10.8% for adverse events (shown in Table2) 3.4% for pregnancy, 1.3% for patient's decision.

Table 1. Basal characteristics of 298 pts

Sex	68,8%F F:M=3:1
Mean age at DMF start	37,41 (18,15 - 64,39)
Disease duration at DMF start	10,3 (0,04 – 42,18)
Mean n° of tretaments	1,63 (0 – 6)
IS	16,1% yes
Mean of relapses in the last year	0,5 (0 – 3)
Median EDSS	1,5 (0 – 7,5)
Mean of new T2 lesions in the last year	0,9 (0 – 18)
Mean of Gd+ lesions at basal RM	0,3 (0 – 7)

Table 2. Discontinuation for adverse events

Flushing	N=2 (0,7%)
GI effects	N=11 (3,7%)
Lymphopenia	N=15 (5%)
Liver enzyme elevation	N=3 (1%)
Allergic reaction	N=1 (0,34%)

Results: After 2 years of FU 61% had NEDA-3. Mean ARR was 0.09 (Wilcoxon; p<0.001) and mean of new T2 lesions was 0.404 (Wilcoxon; p<0.001). ARR and MRI activity were also significantly reduced in subgroups. The analysis of ARR and MRI activity in naïve patients could be biased by higher ARR and MRI activity before DMF. Mild gastrointestinal and flushing symptoms were reported within 12 months in the 9.1% and 32.2% of patients respectively while at 24 months frequency was reduced to 6.04% and 23.5%. Since January 2016 we adopted a slower DMF titration schedule and we noticed a lower rate of drug

discontinuation. Lymphopenia of different grades occurred in 17.4% of patients at 12 months and 6.4% at 24 months of FU.
Conclusion: Our data confirm the efficacy of DMF as 1°line treatment and its good tolerability
Disclosure: I received honoraria for speaking and consultancy activity from: Biogen-Idec Merck-Serono Sanofi-Genzyme Novartis TEVA

EPR2112

Prognostic value of serum neurofilaments in patients with clinically isolated syndromes

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Background and aims: MS is a leading cause of youth disability and axonal damage occurs since the early phases of disease. The aim of this study was to evaluate serum neurofilament light chains (Nfls) in patients with Clinically Isolated Syndromes (CIS) and their prognostic value for the development of Clinically Defined Multiple Sclerosis (CDMS) and McDonald 2017 MS (2017MS).
Methods: We evaluated baseline serum Nfls as well as clinical, MRI, and CSF data on 222 CIS patients (mean follow-up 100.6 months) hospitalised from 2000 to 2015 at San Raffaele Hospital, Italy.
Results: At 2 years 45 patients (20%) developed CDMS and 141 patients (63.5%) developed 2017MS. Serum Nfls (median 22.0, IQR 11.6-40.4 pg/ml) and CSF Nfls (median 839, IQR, 387–1647 pg/ml) were highly correlated ($r=0.58$, $p<0.001$). Nfls were significantly higher in patients with a recent relapse, high T2 lesion load and Gd enhancing lesion at baseline MRI. Serum Nfls were prognostic both for CDMS and 2017MS, with a 3-fold and a 2-fold decrease of CDMS and 2017MS risk respectively in patients with very low and low Nfl levels. The results were unaltered following adjustment for known MS prognostic factors. Nfls were associated with baseline disability by the EDSS but not with disability worsening in the follow-up.
Conclusion: Serum Nfl levels have prognostic value for conversion to MS in CIS patients. Nfls may have a dual role as biomarkers in MS, with measured peak levels being a quantitative marker of acute inflammatory activity, while steady state levels reflecting chronic inflammatory and neurodegenerative processes
Disclosure: Nothing to disclose

MS and related disorders 6

EPR2113

Efficacy of cladribine tablets 3.5mg/kg added to interferon-beta in patients with SPMS or relapsing-RRMS: a post-hoc analysis from ONWARD

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Background and aims: In the CLARITY study, treatment with cladribine tablets 3.5mg/kg (CT3.5) significantly improved clinical outcomes vs. placebo in patients with RRMS. The ONWARD study showed similar benefits for CT3.5 administered as add-on therapy to interferon-beta (IFN-beta) in patients with SPMS or RRMS.

Methods: ONWARD was a 2-year, randomised, double-blind study in patients aged 18–65 years, with EDSS scores 1.0–5.5, who experienced ≥1 relapse during the 48 weeks prior to the study while receiving IFN-beta therapy. At baseline, there were 26 patients with SPMS (placebo+IFN-beta, N=9; CT3.5+IFN-beta, N=17) and 171 with RRMS. The effect of treatment with CT3.5 on key outcomes during ONWARD was examined in the SPMS and RRMS subgroups in this post hoc analysis.

Results: At baseline, there were no clinical differences in relapses in the prior year between the subgroups. Mean EDSS was higher in the SPMS vs. the RRMS subgroup. CT3.5 demonstrated a significant reduction in ARR vs. placebo in both subgroups: 89% and 50% for SPMS and RRMS respectively (Figures 1 and 2). Time to 3- and 6-month confirmed EDSS progression was not significantly different in either subgroup. Treatment with CT3.5 was associated with reductions in mean numbers of T1 Gd+ and T2 lesions vs. placebo in both RRMS and SPMS subgroups.

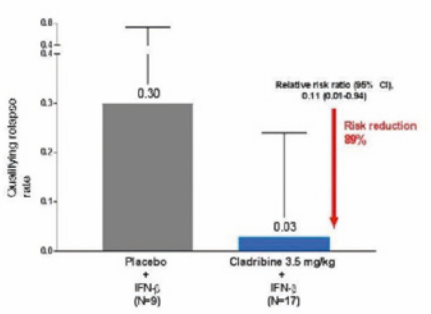

Figure 1: Qualifying relapse rate (annualised, adjusted) in patients with SPMS treated with cladribine tablets 3.5 mg/kg + IFN-beta or placebo + IFN-beta in ONWARD

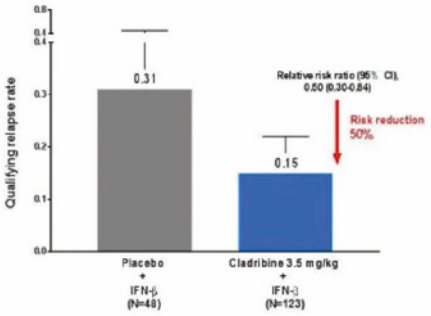

Figure 2: Qualifying relapse rate (annualised, adjusted) in patients with RRMS treated with cladribine tablets 3.5 mg/kg + IFN-beta or placebo + IFN-beta in ONWARD

Conclusion: Despite limitations due to the very low number of SPMS patients, the available data indicate that CT3.5 mg/kg administered with IFN-beta showed evidence of increased efficacy in patients with SPMS and RRMS in the ONWARD study compared to placebo+IFN-beta.

Disclosure: This study was sponsored by EMD Serono Inc, a business of Merck KGaA, Darmstadt, Germany (in the USA), and Merck Serono SA, Geneva, an affiliate of Merck KGaA Darmstadt, Germany (ROW).

EPR2114

Screening for transcription factor binding inside the 200 non-MHC MS susceptibility regions

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Background and aims: In the last decade, genome wide association studies (GWAS) have broadened our understanding of multiple sclerosis (MS) genetic background. The recent MS genomic map has expanded the number of known susceptibility variants outside the major histocompatibility complex (MHC) to about 200. Given the more detailed knowledge of MS genetic architecture, we aimed at defining common upstream regulators by screening for transcription factor (TF) binding inside disease susceptibility regions.

Methods: Non-MHC variants were obtained from the latest MS genomic map. MS regions were defined as the genomic intervals of +/-50 kb around each variant. Experimental data of TF binding (ChIP-seq tracks) in GM12878 cell line were extracted from ENCODE. We analyzed ChIP-seq data against MS regions using Genomic HyperBrowser (http://hyperbrowser.uio.no/hb/). Significant TF were those with a similarity score between TF binding track and MS track>5 as measured by the Forbes coefficient:ratio of observed versus expected overlap, and p-value<0.05.

Pathway analysis on significant TFs was performed using Panther.

Results: NFkB emerged as the main TF binding to MS regions, thus potentially regulating multiple disease susceptibility loci. Other factors include P300, STAT3, STAT5A, NFATC1. The complete list of TFs with Forbes coefficient>5 is presented in Figure1. Panther analysis showed that significant TFs were preferentially involved in immune processes, WNT and JAK-STAT signaling and gonadotropin releasing hormone receptor pathways (Figure2).

Rank	TF	Similarity to MS track	P-value	Overlap between MS and TF binding track (bps)	Genome coverage of TF binding track (bps)
1	NFKB	7.1	0.0196	244676	5581526
2	p300	6.32	0.0196	54038	1384960
3	IKZF1	6.24	0.0196	187456	4861605
4	CEBPB	6.05	0.0196	105571	2826832
5	CHD1	5.51	0.0196	95183	2794092
6	STAT3	5.45	0.0196	88321	2620701
7	WHIP	5.44	0.0196	186585	5546448
8	TBLR1	5.44	0.0196	185993	5538829
9	POL2	5.39	0.0196	379845	11407040
10	MAX	5.35	0.0196	9567	289491
11	BCL11A	5.23	0.0196	145060	4518044
12	STAT5A	5.23	0.0196	125087	3872056
13	MTA3	5.15	0.0196	202361	6360004
14	BHLHE40	5.15	0.0196	141896	4459874
15	YY1	5.1	0.0196	26240	833452
16	CDP	5.09	0.0196	414850	13197610
17	FOXM1	5.02	0.0196	314243	10133142
18	BCL3	5.01	0.0196	153385	4954966
19	NFATC1	5	0.0196	168288	5446547

Significant TF binding tracks overlapping with MS regions (Forbes coefficient>5, p-value<0.05)

Conclusion: MS susceptibility regions are targeted by NFkB and other TFs involved in immune-related pathways. The precise identification of upstream regulators could help better define how MS loci are functionally interconnected in disease-specific networks.

Disclosure: Nothing to disclose

EPR2115

Cesarean delivery and artificial lactation are associated with an earlier age of disease onset in Multiple Sclerosis

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Background and aims: Age at onset (AAO) in multiple sclerosis (MS) is an important marker of disease severity and may have prognostic significance. Understanding what factors can influence AAO may shed light on the etiology of this complex disease, and have applications in the diagnostic process.

Methods: The study cohort consists of 2055 eligible patients followed-up prospectively at San Raffaele Hospital. AAO was defined as the year of the first symptom suggestive of inflammatory central nervous system demyelination. Predictors of AAO were evaluated by linear regression.

Results: In our cohort of patients, the mean age at onset of MS was 28.4 years (SD 8.4 years), and the female:male ratio was 2.2:1. A significant percentage of patients (225 patients, 10.9%) were born from a cesarean delivery, and most of them (1230 patients, 59.9%) received maternal breastfeeding, while the remaining received artificial lactation. Compared with those born from a natural delivery, onset of symptoms was 5.2 years earlier for those with cesarean delivery ($p<0.001$). Also, artificial lactation was associated with an earlier diagnosis (-2.2 years earlier) compared to patients who had been breastfed, in which the duration of the breastfeeding period was directly associated with the age of onset of MS.

Conclusion: An earlier AAO in MS patients born from a cesarean delivery and receiving artificial lactation was observed, and the results suggest that environmental factors which act at the population level may significantly influence disease severity characteristics in genetically susceptible populations.

Disclosure: Marzia Romeo – Received honoraria from Genzyme Gloria Dalla Costa – Reports no disclosures Francesca Sangalli – Reports no disclosures Bruno Colombo – Received honoraria from Biogen Idec, Genzyme e Merck Serono Lucia Moiola – Received honoraria from Sanofi-Genzyme, Biogen Idec, TEVA, Merck Serono and Novartis Marta Radaelli – Received honoraria from TEVA and Genzyme Federica Esposito – Received honoraria from TEVA, Almirall e Genzyme Giancarlo Comi – Received honoraria from Novartis, Teva, Sanofi-Genzyme, Merck Serono, Biogen Idec, Excemed, Roche, Almirall, Chugai, Receptos, Forward Pharma Vittorio Martinelli – received honoraria from Genzyme, Biogen Idec, TEVA, Bayer, Merck Serono and Novartis

EPR2116

No evidence of disease activity achievement over 4 years of peginterferon beta-1a treatment in newly diagnosed patients with relapsing Multiple Sclerosis: subgroup analyses of ADVANCE/ATTAIN

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Background and aims: In the phase-3 ADVANCE study year (Y) 1, relapsing MS (RMS) patients were randomized 1:1:1 to placebo or peginterferon beta-1a every 2 weeks or every 4 weeks; for Y2, placebo patients were re-randomised to peginterferon beta-1a every 2 or 4 weeks. ADVANCE completers entering the ATTAIN extension study (Y3-4) maintained their ADVANCE Y2 dosing regimen. This analysis evaluated attainment of no evidence of disease activity (NEDA) over 4 years in Newly Diagnosed (ND) patients from ADVANCE who continued into ATTAIN.

Methods: The proportion of patients treated with peginterferon beta-1a every 2 weeks in the ATTAIN intent-to-treat population who achieved overall NEDA (no relapses, 24-week confirmed disability worsening, gadolinium-enhancing lesions, or new/newly enlarging T2 lesions) was evaluated over 4 years in ND (diagnosed ≤1 year prior to enrolment and disease-modifying therapy naïve, n=343) and Non–Newly Diagnosed (NND, n=379) subgroups. Annualised relapse rate (ARR) during ATTAIN was analysed based on ADVANCE 2-year NEDA status.

Results: In ADVANCE Y1, both ND and NND patients treated with peginterferon beta-1a every 2 weeks were significantly more likely to achieve NEDA compared to placebo (Table). In Y2–4, yearly NEDA remained consistent for both subgroups. Patients who achieved NEDA in ADVANCE had lower ARR during ATTAIN than non-NEDA patients (ND: 0.057 vs 0.211, P=0.0003; NND: 0.073 vs 0.237, P=0.0001).

Table. Proportion of patients achieving NEDA in the overall population and ND and NND subgroups

	ND		NND		Overall	
% of patients with overall NEDA [total N]	Placebo	Peginterferon beta-1a every 2 weeks	Placebo	Peginterferon beta-1a every 2 weeks	Placebo	Peginterferon beta-1a every 2 weeks
Year 1	18.5 (57/308)	29.3 (92/314)	15.4 (57/370)	46.5 (176/378)	16.7 (114/678)	38.0 (268/692)
	P<0.0010		P=0.0003		P<0.0001	
Year 2	–	55.8 (165/296)	–	54.0 (194/359)	–	54.8 (359/655)
Year 3	–	54.0 (153/283)	–	57.1 (195/342)	–	55.7 (348/625)
Year 4	–	53.0 (132/249)	–	54.4 (146/268)	–	53.7 (278/517)

Conclusion: Both ND and NND patients treated with continuous peginterferon beta-1a every 2 weeks exhibited sustained yearly NEDA rates over 4 years. NEDA achievement in the first 2 years predicted positive long-term clinical outcomes.

Disclosure: This study was supported by Biogen. DLA: equity interest in NeuroRx during the conduct of the study; personal fees from Acorda, Biogen, EMD Serono, Genentech, Genzyme, Hoffman-La Roche, Innate Immunotherapy, MedImmune, Mitsubishi, Novartis, Receptos, Sanofi, and Teva outside the submitted work; grants from Biogen and Novartis. MLN, JY: employees of and may hold stock and/or stock options in Biogen.

EPR2117

Modulation of cortico-subcortical functional connectivity occurs after symptomatic treatment of fatigue in patients with Multiple Sclerosis

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Background and aims: To investigate longitudinal changes of brain resting state (RS) functional connectivity (FC) in multiple sclerosis (MS) patients with fatigue undergoing different symptomatic treatments for this symptom.
Methods: 45 fatigued MS patients were randomly, blindly assigned to treatment with fampridine (n=15), amantadine (n=15) or placebo (n=15) and underwent clinical, neuropsychological and RS fMRI at baseline (T0) and after four weeks (W4) of treatment. 15 matched healthy controls were acquired twice. RS FC analysis of the main brain functional networks was performed using independent component analysis and SPM12.
Results: At T0, compared with controls, MS patients showed increased intra-thalamic RS FC and abnormal fronto-parietal RS FC of several cortical networks. At W4, decreased global, physical and cognitive (p=0.001/0.003/0.01) modified fatigue impact scale (MFIS) scores were found in fampridine patients and, to a lesser extent, in amantadine patients (p=0.04). Placebo patients also showed improved global, physical and psychosocial MFIS (p=0.02/0.01/0.02). At W4, fampridine patients showed increased RS FC of the bilateral precuneus in the default mode and executive control networks, and increased RS FC of the right inferior frontal gyrus in the salience and frontoparietal attention networks. At W4, increased RS FC in frontal regions and decreased RS FC in temporoparietal regions were detected in placebo and amantadine patients. A significant decrease over time of intrathalamic RS FC was found in fampridine and amantadine patients.
Conclusion: Treatment with fampridine (and, to a lesser extent, with amantadine) ameliorates fatigue in MS. Concomitant modifications of RS FC suggest an improved regulation of cortico-subcortical circuits.
Disclosure: Partially supported by grants from Italian Ministry of Healthy (GR-2008-1138784) and Fondazione Italiana Sclerosi Multipla (FISM 2013/S/1).

EPR2118

Patterns of regional gray matter and white matter atrophy in patients starting fingolimod or natalizumab: a 2-year tensor-based morphometry study

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Background and aims: To compare the effects of fingolimod (FTY) and natalizumab (NAT) on preventing regional gray matter (GM) and white matter (WM) atrophy in relapsing-remitting multiple sclerosis (RRMS) after two years of treatment.
Methods: 55 RRMS patients starting FTY (n=25) or NAT (n=30) underwent 3T brain scans at baseline (T0), month-6 (M6), year-1 (Y1) and year-2 (Y2). The longitudinal patterns of regional GM/WM volume changes were assessed using tensor-based morphometry (SPM12, $p<0.05$, FWE-corrected).
Results: At T0, no between-group volumetric difference was found. At M6 vs T0, FTY-patients experienced GM atrophy of bilateral cerebellar cortex and hippocampi, right thalamus and cingulate cortex. At Y1 vs M6 and Y2 vs Y1, a further atrophy of bilateral cerebellar cortex, left thalamus, several fronto-temporo-occipito-parietal regions, and cingulate cortex occurred in FTY-patients. NAT-patients showed a significant atrophy of left cingulate cortex and thalamus and bilateral fronto-temporo-parietal regions only at Y2 vs Y1. At M6 vs T0, both groups showed a significant atrophy in supratentorial WM clusters, while cerebellar WM volume loss occurred in FTY-patients only. At Y1 vs M6 and Y2 vs Y1, supratentorial WM atrophy progressed in both groups, while cerebellar WM atrophy occurred in FTY-patients. Compared to NAT-patients, FTY-patients showed only a significant cerebellar cortical and WM atrophy at M6 vs T0.
Conclusion: The anti-inflammatory effects of NAT and the pleiotropic effects of FTY on the immune system and in the central nervous system differently modified GM/WM atrophy progression in RRMS patients, with NAT having a more significant effect on preventing regional atrophy.
Disclosure: Nothing to disclose

EPR2119

Is it possible to continue a really effective therapy in a patient with a severe hypersensitivity drug reaction?

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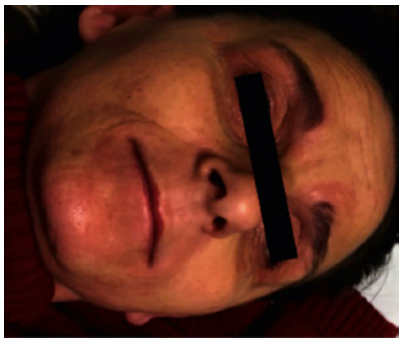
Background and aims: Alemtuzumab (ALEM) is a highly effective monoclonal anti-CD52 antibody approved for patients with active multiple sclerosis (MS). The most common ALEM's adverse events (AE) are infusion reactions (IRs). Three out of 100 IRs are severe and contraindicate treatment prosecution with the traditional schedule.

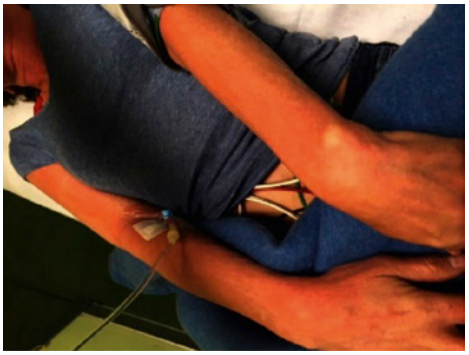
Methods: A case report

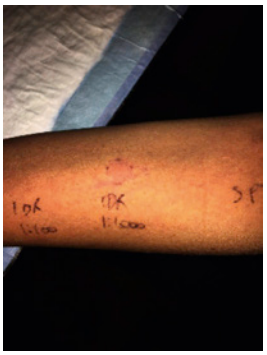
Results: A 45-year-old female, diagnosed with MS in 1998, was treated with several therapies, but only had a complete response to natalizumab. However, natalizumab had been discontinued for a high progressive multifocal leucoencephalopathy risk. After last treatment failure with fingolimod, she was started on ALEM without any AE and with an optimal clinical and neuroradiological response. However, one year later, while she was receiving her second infusion, she suddenly developed severe hypotension, cough, dysphagia and diffuse urticaria/angioedema. She was then treated with intravenous corticosteroids, antihistamines and fluids. Four months later, 1:1000 intradermal tests with ALEM were strongly positive at 20' reading. A diagnosis of IgE-mediated anaphylaxis to ALEM was then confirmed. Since no other effective alternatives were available to treat her MS, ALEM was infused following Castells' desensitization protocol. No mild or severe AE were observed. The treatment was effective with regard to disease activity and quality of life improvement.



Conclusion: This is the first case of ALEM-desensitisation in a MS patient. This procedure allowed a safe administration of the only effective treatment for this highly active patient, despite her previous severe IR to the drug. Desensitisation is a crucial procedure to induce temporary drug tolerance, when no effective alternatives are available.

Disclosure: I received honoraria for speaking and consultancy activity from: Biogen-Idec Merck-Serono Sanofi-Genzyme Novartis TEVA





Neurogenetics 2

EPR2121

European expert consensus recommendations for neurological therapeutic goals for patients with Fabry disease

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Background and aims: In Fabry disease, a hereditary lysosomal storage disease, alpha-galactosidase A deficiency causes globotriaosylceramide accumulation in various organs, significantly reducing life expectancy. Enzyme replacement therapy (ERT) ameliorates symptoms of Fabry disease and slows or reduces organ damage. Cerebrovascular complications (ischaemic stroke, chronic white matter hyperintensities [CWMH]), peripheral neuropathy (predominantly due to small-fibre involvement), and neuropathic pain are the major neurological symptoms. Achieving evidence-based therapeutic goals, individualised to patient characteristics and disease status, can facilitate effective patient management. We formulated consensus recommendations based on expected and achievable responses to ERT and adjunctive therapies administered for neurological disease complications.
Methods: An international multidisciplinary team of 26 experts developed neurological therapeutic goals for Fabry disease based on consensus opinion and evidence obtained from a PRISMA-compliant systematic analysis of literature on ERT published through January 2017.
Results: ERT can be effective in slowing the progression of CWMH and managing neuropathic pain. Amelioration of neuropathy and pain using ERT has been demonstrated in studies utilizing the Total Symptom Score, the Mainz Severity Scale Index, or the Brief Pain Inventory scale. There is also evidence that a higher dose of ERT leads to more substantial pain improvement. We recommend initiating ERT upon pain onset to alleviate pain and to slow CWMH progression. Secondary stroke prevention might reduce the risk of stroke recurrence.
Conclusion: Timely initiation and appropriate dosage of ERT and adjunctive therapies, i.e. personalised and outcome-oriented medicine for patients with Fabry disease, facilitates the achievement of therapeutic neurological goals (Table).

Patient subgroup	Treatment goals
Neuropathic pain due to small-fibre involvement	
Early-stage disease	• Reduce intensity of pain and frequency of pain crises • Slow or stop progression of polyneuropathy
Late-stage disease	• Reduce pain to manageable levels • Slow or stop progression of polyneuropathy
Paediatric patients	• Reduce intensity of pain and frequency of pain crises
Pain due to entrapment neuropathy (large-fibre involvement)	
All patients	• Reduce intensity of pain and manage pain due to nerve compression/entrapment (e.g. carpal tunnel syndrome)
Transient ischaemic attack (TIA)/stroke	
All patients	• Prevent occurrence/recurrence of TIA/stroke and delay age at onset of first TIA/stroke event
CWMH	
Early-stage disease	• Attempt to avoid development of CWMH
Late-stage disease	• Delay progression of number and volume of CWMH

Therapeutic neurological goals in patients with Fabry disease.

Disclosure: Funding (Advisory Board, Abstract): Sanofi Genzyme.

EPR2122

The neuropsychological phenotype of CACNA1A disorders: a retrospective cohort analysis

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Background and aims: The CACNA1A gene encodes the α1-subunit of the neuronal calcium channel P/Q. Autosomal dominant CACNA1A mutations underlie three allelic disorders: familial hemiplegic migraine type 1 (FHM1), episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6). The main clinical features are migraine with hemiplegic aura in FHM1, paroxysmal attacks of ataxia in EA2 and progressive cerebellar ataxia in SCA6. Several case reports suggest that also cognitive and behavioral features belong to the phenotype of CACNA1A disorders, but studies on large case series are lacking.
Methods: Genetically confirmed CACNA1A cases were identified from the database of our Ataxia Unit. Findings from neuropsychological examination, history of psychiatric comorbidities, developmental delay and poor school performance were retrieved through retrospective chart review.
Results: 44 CACNA1A cases were identified. Neuropsychological testing was available in 25 of them (11 FHM1, 10 EA2, 4 SCA6). Diffuse cognitive deficits were documented in 23 cases (92%). Impairments were more evident in figural memory (82,6%, 19/25), visuo-constructive abilities (75%, 16/24), executive functions (100%, 17/17) and attention (68,4% 13/19). Two SCA6 patients had normal neuropsychological tests. Delayed psychomotor milestones were recalled in 8 patients (5 FHM1, 3 EA2). Poor school performance was reported in 8 cases (3 FHM1 and 5 EA2). Psychiatric comorbidities were diagnosed in 8 patients (2 FHM1, 6 EA2).
Conclusion: Diffuse cognitive deficits were documented in our CACNA1A cohort, as well as a high prevalence of developmental delay and psychiatric symptoms. FHM1 and EA2 cases exhibited a neuropsychiatric phenotype while SCA6 patients did not have this comorbidity.
Disclosure: Nothing to disclose

EPR2123

Is it muscle or nerve? - Novel heterozygous variant c.3542G>A; p. Ser1181Asn in POLG explaining a mixed neuro-myopathic phenotype

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Background and aims: Pathogenic variants in POLG can cause a broad variety of central and peripheral nerve symptoms. In one family, we report the novel variant c.3542G>A; p.Ser1181Asn putatively causing a mixed neuro-myopathic phenotype.
Methods: The patients were followed-up at the neuromuscular outpatient clinic of the RWTH Aachen University. An NGS-based diagnostic multigene panel provided by the CeGaT GmbH was analysed in the index patient, a further co-segregation was performed in one unaffected and two affected sisters as well as in the affected father.
Results: With an adolescent onset, the index patient (55) presented with an advanced distal tetraparesis, corresponding atrophies and sensory loss, afferent ataxia, double vision, and a slight bilateral ptosis. One sister (57) showed a Charcot-Marie-Tooth resembling phenotype with calf atrophies and pedes cavi, likewise. A second sister (51) as well as the father (80) predominantly reported exercise-induced muscle pain and proximal weakness. Muscle biopsies obtained from the father and the first mentioned sister showed ragged-red fibers indicating mitochondrial damage. All affected family members were heterozygous for the yet undescribed variant c.3542G>A; p.Ser1181Asn in POLG, whereas an unaffected sister had two wild-type alleles. The mutation spectrum of POLG contains several known pathogenic variants in the vicinity of c.3542G>A; p.Ser1181Asn. The amino acid position is highly conserved lying within the palm-domain. In-silico predictions were indicative for pathogenicity. The allele frequency of 0.02% is compatible with an autosomal dominant inheritance.

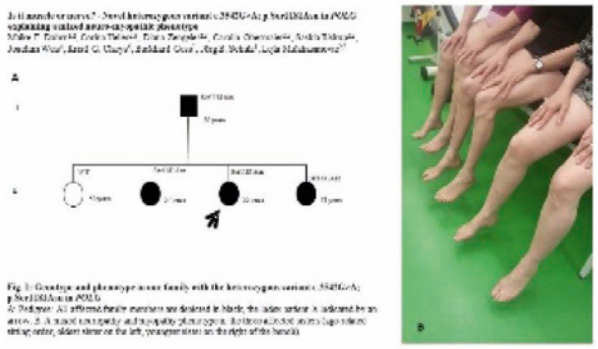

Figure 1: Genotype and phenotype in one family with the heterozygous variant c.3542G>A; p.Ser1181Asn in POLG

Conclusion: The novel heterozygous variant c.3542G>A; p.Ser1181Asn in POLG is likely pathogenic explaining a neuro-myopathic phenotype.
Disclosure: Nothing to disclose

EPR2124

Neurological variants of ataxia telangiectasia - clinical and genetic features

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Background and aims: Variant Ataxia-Telangiectasia is a rare autosomal recessive disorder with a milder phenotype compared to the classic form. Here, we describe the clinical features of the largest cohort of individuals with variant Ataxia-Telangiectasia to date and explore genotype-phenotype correlations.
Methods: Cross-sectional clinical data were retrospectively collected for individuals who have attended the National UK and Dutch Ataxia-Telangiectasia clinics. Patients were classified as variant Ataxia-Telangiectasia based on mutarions with retained ATM kinase activity, or mutations in the initiator methionine codon.
Results: The study includes 57 individuals from 50 families. Mean age at assessment was 37.5 years. Most individuals had their first symptoms by age ten (81%). There was a diagnostic delay of more than 10 years in 68% and more than 20 years in a third of probands.
Three neurological phenotypes were observed, where only a third of included individuals had predominant ataxia and ten probands (18%) a pure extrapyramidal presentation. Individuals with extrapyramidal presentations had milder neurological disease severity. There were no significant respiratory or immunological complications, but fourteen individuals had a history of malignancy.
The presence of missense mutations was associated with milder neurological disease severity and a higher risk of malignancy.
Conclusion: Individuals with variant ataxia atelangiectasia require malignancy surveillance and tailored management. However, our data suggest that the condition is often mis or underdiagnosed. This is likely due to atypical clinical features (including mild severity, exclusive extrapyramidal symptoms, normal eye movements, absent ocular telangiectasia and normal AFP levels) in some individuals, which clinicians may not be aware of.
Disclosure: Nothing to disclose

EPR2125

A study on combined brain positron Emission Tomography (PET) – Magnetic Resonance Imaging (MRI) using Fluorodeoxyglucose (18FDG) (FDG-PET/MRI) in premanifest Huntington's disease gene-expansion carriers

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Background and aims: Huntington's disease (HD) is an autosomal dominantly inherited neurodegenerative disorder, caused by an expansion of a trinucleotide (CAG) repeat in the huntingtin gene. There is no cure and only sparse symptomatic treatment. Structural brain imaging is the most applied and well documented technique to demonstrate longitudinal structural changes in premanifest and manifest HD gene-expansion carriers. Changes in the striatum are registered as far as 15 years before symptom onset with MRI. PET studies have found hypometabolism in the Caudate nucleus, Putamen and the temporal and frontal cortex years before clinical diagnosis along with hypermetabolism in Thalamus prior to symptom onset. By a combined brain PET–MRI using FDG, we wished to simultaneously characterise the structural and metabolic brain changes in premanifest HD gene-expansion carriers.
Methods: We recruited 22 premanifest HD gene-expansion carriers and 17 controls from the Neurogenetics Clinic, Danish Dementia Research Centre, Rigshospitalet, Copenhagen, Denmark. We included individuals with a CAG repeat ≥39 and a Unified Huntingtin's Disease Rating scale-99 total motor score ≤5.
Results: We found significantly reduced volumes of the Putamen bilaterally and the Globus Pallidus in the right hemisphere. Further we found significantly reduced metabolism in the Putamen bilaterally with a significant correlation between CAG age product and the FDG activity which, however, disappeared when correcting for the reduced volume of Putamen.
Conclusion: Our results indicate that the hypometabolism and atrophy of Putamen are evolving simultaneously.
A follow-up study on the cohort will shed more light on the sequential evolution and correlation of structural and metabolic changes.
Disclosure: Nothing to disclose

EPR2126

Cerebral creatine deficiency syndromes: a single-centre experience from diagnosis to treatment

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Background and aims: Cerebral creatine deficiency syndromes (CCDS) are a group of inborn errors of metabolism caused by deficiencies of the creatine transporter SLC6A8 or the enzymes L-arginine:glycine amidinotransferase and guanidinoacetate methyltransferase (GAMT). Typical clinical findings comprise intellectual disability, seizures and movement disorders. Diagnostic workup includes brain MR spectroscopy (MRS) and urinary measurements of guanidinoacetate (GAA), creatine and creatinine. Early creatine supplementation can stabilize symptoms and improve outcome. The aim of this study was to characterize a group of patients with GAMT deficiency regarding clinical, MRS and biochemical findings, as well as treatment response.
Methods: Retrospective review of the medical records of patients with GAMT deficiency followed in our Metabolic Disorders consultation.
Results: We present 7 patients with a mean age of 25 years (9-34) and mean age at onset of 22 months (6-36), with an adult age diagnosis in 2 patients. All patients presented with developmental delay, usually moderate and involving language. Epilepsy was present in 6 patients. Three patients developed behavioural disorders later during childhood. All patients presented low creatine peak in brain MRS and elevated GAA (30-75 times higher than reference values) with low creatine values and normal creatine/creatinine ratio in urine. Creatine supplementation was started in every patient, with clinical stabilisation and normalisation of creatine peak in MRS.
Conclusion: Our patients demonstrate the typical clinical presentation of CCDS. Despite pediatric onset, CCDS sometimes remain undiagnosed until adult age. Since supplementation usually presents good results, neurologists must recognise CCDS and perform an early diagnostic workup with brain MRS and urinary biochemical studies.
Disclosure: Nothing to disclose

EPR2127

L-2-hydroxyglutaric aciduria in a young Greek female with mild mental retardness, pyramidal semiology and ataxia

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Background and aims: L-2-hydroxyglutaric aciduria (L-2-HGA) is a rare neurometabolic disorder with autosomal receive inheritance. Biochemically, is characterised by elevated concentration of L-2-hydroxyglutaric acid (L-2-HG) in plasma, urine and cerebrospinal fluid. This is caused by dysfunction of L-2-hydroxyglutarete dehydrogenase (L2HGDH), an enzyme catalysing the oxidation of L-2-hydroxyglutaric to 2-ketoglutaric, due to mutations of LHGDH gene.
Methods: We evaluated an adolescent female referred to our clinic for mental retardness, gait disorders and dysgraphia. We performed a thorough clinical investigation, complete laboratory work-up and targeted genetic analysis. Patient also had a baseline and a follow-up brain MRI after a 4-year interval.
Results: We present the case of a 24-year-old female with L-2-HGA. Patient reached with delay major neurodevelopmental milestones and presented learning difficulties at school. Mild mental retardness was confirmed after proper paidopsychiatric evaluation. Patient presented with pyramidal semiology, gait disorders, dysmetria, dysarthria and dysgraphia. Brain MRI revealed mild cerebellar atrophy and hyperintense signal in T2-W and FLAIR sequences at subcortical white mater and basal ganglia with sparing of deep white matter and corpus callosum. Strongly elevated exertion of L-2-HG was detected in urine sample. DNA sequencing of L2HGDH gene identified two heterozygous mutations and confirmed the diagnosis.
Conclusion: L-2-HGA is a rare neurometabolic disorder with characteristic clinical, laboratory and neuroimaging presentation. When clinical suspicion is high proper genetic analysis of L2HGDH gene will confirm the diagnosis. Since first described in 1980 by Duran et al approximately 90 patients with L-2HGA have been described worldwide. To our knowledge this is the first report of L-2-HGA in Greece.
Disclosure: Nothing to disclose

Neurogenetics 3

EPR2128

Late-onset leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL): Russian experience

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Background and aims: Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL) is a recently described rare autosomal recessive hereditary disease of the nervous system, associated with DARS2 gene mutations. Clinically it is characterised by progressive pyramidal, cerebellar, and dorsal column dysfunction. MRI is highly specific. Neuroimaging findings are heterogeneous cerebral white matter abnormalities accompanied by a selective involvement of the brainstem and spinal cord tracts and MR spectroscopy shows high lactate level. Usually LBSL manifests in an early childhood, adult-onset forms are extremely rare. We hereby present 9 cases of the disease manifested in the adulthood.

Methods: Nine patients (4 female, 5 male; 29±7.8 years) with the previously made diagnoses of spinocerebellar ataxia, hereditary spastic paraplegia, multiple sclerosis. All the patients received a complete neurologic examination, neuropsychological testing, brain MRI and MR-spectroscopy, DARS2 gene sequencing.

Results: All patients showed different combination of pyramidal, cerebellar and dorsal column symptoms. In six patients different polyneuropathy symptoms were found and in eight patients psychoneurological symptoms were found. MRI and MRS revealed findings typical for LBSL (fig.1, 2). DARS2 gene sequencing revealed a high spectrum of different pathogenic mutations. The frameshift mutation in intron 2 of the DARS2 gene was revealed in all cases (fig.3). The second mutation differed among the patients.

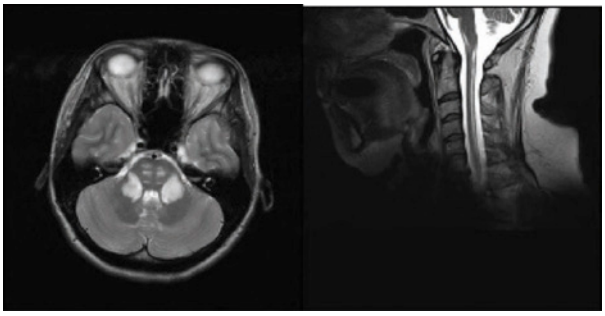

Fig.1. T2 WI showing hyperintense signal from pons, middle cerebellar peducles, spinal cord.

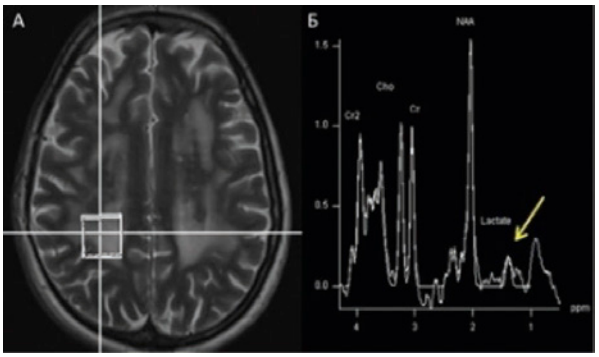

Fig.2. Single voxel MR spectroscopy of the affected white matter showing high lactate level

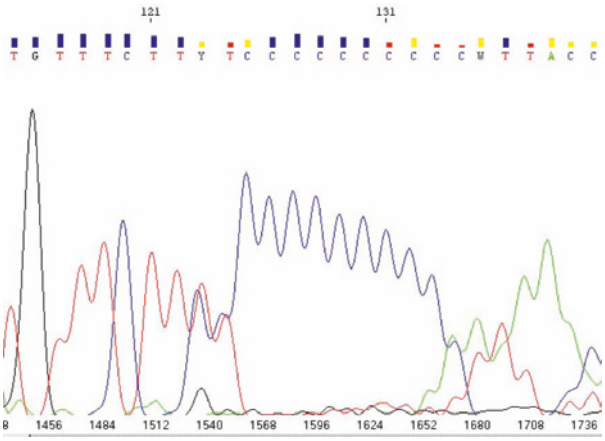

Fig.3. Frameshift mutation c.228-21_20delTTinsCC (rs367543010) in intron 2 of the DARS2 gene

Conclusion: It is deemed to conclude that late onset LBSL is not as rare as it was supposed to be. We reckon LBSL shall be considered to be a possible diagnosis in adult patients with ataxia, pyramidal dysfunction and leukoencephalopathy signs on MRI.

Disclosure: Nothing to disclose

EPR2129

Linguistic characteristics of genetic primary progressive aphasias: a retrospective study of 27 cases carrying GRN and c9orf72 mutations

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Background and aims: Primary progressive aphasia (PPA) is a neurodegenerative disorder characterized by an early and progressive impairment of language. The current classification recognizes three variants: non-fluent/agrammatic (nfaPPA), semantic (svPPA) and logopenic (lvPPA). Genetically determined PPA cases are mainly due to mutations in frontotemporal lobar degeneration (FTLD)-related genes. We aimed at defining the clinical, neurolinguistic and neuroimaging features of a cohort of French PPA patients with a mutation in GRN or c9orf72 genes.
Methods: From 600 patients with genetically determined FTLD included in a French clinical and genetic research network on FTLD, we selected 27 PPA cases who underwent neuropsychological and linguistic evaluation (with Boston Diagnostic Aphasia Evaluation and/or Montreal-Toulouse batteries), CSF biomarkers dosage, structural and functional neuroimaging. Twenty-four PPA patients had a GRN mutation and three a c9orf72 expansion. We described and compared their performances in main language domains at a relatively initial stage (2,2 years from onset) and subsequent disease evolution across PPA subtypes and genotypes.
Results: Among GRN patients, nfvPPA and lvPPA were equally represented (8 cases each), whereas svPPA and mixed phenotypes (5 and 3 cases respectively) displayed the greatest global impairment. In the c9orf72 cohort the age of onset was the earliest (mean 48,3 years) and the progression the slowest. Seven GRN patients later manifested parkinsonism, two of which with CBS phenotype. GRN mutations determined the greatest impairment and the most severe evolution.
Conclusion: This is the largest cohort of PPA cases carrying FTLD mutations described so far. This study allows to define linguistic characteristics of PPA according to their genotype.
Disclosure: Nothing to disclose

EPR2130

Hereditary spastic paraplegia (HSP) type 15 in five Portuguese patients

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Background and aims: Autosomal-recessive hereditary spastic paraplegias (HSP) are typically associated with a complex phenotype. HSP15 is caused by mutations in the ZFYVE26 gene, encoding spastizin. We aim to describe a cohort of five Portuguese HSP15 patients from four different families, further contributing to its genetic and phenotypical characterization.
Methods: Descriptive analysis of the patients' clinical, genetic, imaging and electrophysiological data.
Results: Onset of spastic gait ranged 8-16y. All patients had cognitive dysfunction: three had a delay in cognitive acquisitions; one had cognitive regression by age 6y; the other presented learning difficulties at elementary school and cognitive deterioration by late adolescence. Three were wheelchair bound after a mean disease duration of 14 years. Other non-pyramidal features included neuronopathy/peripheral neuropathy (in 5), levodopa-responsive juvenile-onset Parkinsonism (1), cerebellar syndrome (1). Two patients were born from consanguineous and one from non-consanguineous parents. Parents of the other two patients were from the same small village, though denied consanguinity. All performed brain MRI (4 to 15y after onset), showing a thin corpus callosum (in 4), white-matter abnormalities (4) and cortical atrophy (2). Sequencing revealed four novel and two previously known variants in ZFYVE26; two patients were homozygous and three compound heterozygotes.
Conclusion: We describe five molecularly confirmed cases of HSP15, including four novel genetic variants. Cognitive dysfunction and neuronopathy/peripheral neuropathy were present in all five patients, though the last is a frequent but not universal sign. Levodopa-responsive juvenile-onset Parkinsonism has been described so far in only two HSP15 patients (one of Portuguese ancestry).
Disclosure: Nothing to disclose

EPR2131

Mutations in endocytic recycling protein Rab11FIP3 are associated with ataxia and intellectual disability

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Background and aims: The aim of this work is to identify the genetic cause of disease in two siblings affected with infantile-onset ataxia and intellectual disability.
Methods: Family members were genotyped with Infinium OmniExpressExome-8 v1.4 BeadChip. Two affected brothers and one healthy brother underwent whole-exome sequencing. Linkage analysis was performed with Allegro software. Exomic variants were filtered with Enlis Genome software. A skin biopsy was performed on one affected sibling, from which a fibroblasts culture was derived, in order to study the effect of mutations on patient's cells. Plasmids harboring the two mutations were transfected in HeLa cells.
Results: Using a combined approach of genome-wide linkage analysis and whole-exome sequencing, we found RAB11FIP3 compound heterozygous mutations in two siblings showing infantile-onset ataxia and intellectual disability. Patient's fibroblasts displayed a significant delocalization of Rab11FIP3 protein and morphological anomalies consistent with Rab11FIP3 function. Overexpressed mutated protein showed immunoblot abnormalities in comparison to overexpressed wild-type protein.
Conclusion: In conclusion, the identified RAB11FIP3 mutations are associated with a novel autosomal recessive ataxic syndrome with intellectual disability.
Disclosure: Nothing to disclose

EPR2132

Promoter methylation of full and intermediate C9orf72 expansion in Russian population

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Background and aims: C9orf72 repeat expansion is the most frequent cause of familial frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). It was also identified in some cases of Parkinson's disease (PD). DNA methylation of C9orf72 gene plays a role in the pathogenesis of FTD and ALS, but it is not studied enough.
Methods: We investigated the promotor methylation of full C9orf72 expansions in FTD/ALS patients (n=12), intermediate expansions in PD patients (n=8) and non-expanded alleles in healthy controls (n=8) from a Russian population. The expansion lenght was evaluated by repeat-primed PCR. The full expansion comprised >40 repeats; the intermediate expansion 13-20 repeats. CpG islands of C9orf72 gene were defined using MethPrimer program and the methylation status was determined via sequencing of amplified fragments of bisulfite-converted DNA.
Results: We identified 2 cases with the hypermethylation of C9orf72 promoter in the full expansion group. These patients were sublings from one family. We had detailed information only about a brother (a sister did not visit the clinic due to a disease severity). This patient had an atypical ALS presentation: an onset with parkinsonism, a long duration of ALS symptoms, cognitive impairments with a temporal lobes atrophy and a positive family history. There were no cases of the promoter hypermethylation in the intermediate and control groups.
Conclusion: This is the first data on the C9orf72 promoter methylation in Russian population. The frequency of the promoter methylation among full expansion carriers was 9,1% (1/11) that consistent with previous studies in other populations. The study was supported by RSF 17-75-20211.
Disclosure: RSF 17-75-20211

EPR2133

Mitochondrial ATP6 mutation m.9176T>C leading to mild late-onset manifestation of a neurologic multisystem disorder

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Background and aims: Pathogenic mutations in the ATP6 gene of the mitochondrial DNA (mtDNA) which encodes for a subunit of the mitochondrial ATP synthase (respiratory chain complex V) typically lead to severe early-onset multisystemic diseases such as Leigh syndrome (LS) or to the syndrome of neuropathy, ataxia and pigmentary retinopathy (NARP). In addition, there is increasing evidence for ATP6 mutations causing milder phenotypes with variable age of onset, including adult-onset spinocerebellar ataxia (SCA) or axonal distal hereditary motor neuropathy. More recently, an association between the homoplasmic ATP6 mutation m.9176T>C and acetazolamide-responsive episodic weakness mimicking periodic paralysis as well as hereditary spastic paraplegia-like disorders has been reported.

Methods: Case report including brain pathology, exome sequencing and muscle biochemistry.

Results: This 67-year-old male reported gait disturbance and weakness since age 45 years. Clinical examination revealed cerebellar ataxia, peripheral neuropathy, and mild parkinsonism. Dopamine transporter scan confirmed a presynaptic dopaminergic deficit. Pedigree analysis revealed ten affected maternal relatives. The patient's sister who was symptomatic from age 8 years died at age 66 years. Brain pathology showed age-related findings (Braak I, Thal 3, CERAD 0) and mild gliosis. Exome sequencing identified the known pathogenic ATP6 mutation m.9176T>C in the mtDNA. Respiratory chain analysis in muscle revealed an isolated deficiency of Complex V.

Conclusion: Distinct homoplasmic mutations in the ATP6 gene (m.9176T>C) should be considered as a cause for mild adult-onset multisystemic neurological disorders with spinocerebellar ataxia, neuropathy and parkinsonism.

Disclosure: Nothing to disclose

Neuroimaging 2

EPR2134

The association between patterns of grey matter atrophy and white matter disruption in relapsing-remitting Multiple Sclerosis

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Background and aims: Few recent MRI studies have used source-based morphometry (SBM) to show non-random patterns of either grey matter (GM) atrophy or white matter (WM) disruption in patients with longstanding multiple sclerosis (MS). We used here SBM to assess patterns of both GM atrophy and WM disruption in relapsing-remitting (RR) MS patients with relatively mild disability and explore their relation and relevance to patients' disability.
Methods: We assessed RRMS patients (n=41) with mild disability (median EDSS=1.5). Symbol digit modalities test (SDMT) was abnormal on 8 patients. A 3T MRI was acquired. WM lesion volume was 6.7±11.5 cm3. Patterns of brain changes were assessed on maps of GM volume, fractional anisotropy (FA) and mode of anisotropy (MO) with SBM. Patient data were compared with those of demographically matched normal controls (NC, n=28).
Results: MS patients had GM atrophy in 3/6 patterns ($p \leq 0.01$) and WM disruption (altered FA and/or MO) in 3/4 patterns ($p<0.05$). The three GM patterns in deep GM (DGM), sensorimotor cortex/parancigulate/superior frontal gyrus and temporo-occipital cortex correlated with the WM pattern in the posterior corona radiata (PCR) (r=0.62 to 0.67, $p<0.001$). DGM component also correlated with the two WM components in PCR and callosal splenium (r=0.61 to 0.7, $p<0.001$). Correlations were found between temporo-occipital atrophy and SDMT (r=0.52, $p<0.001$) and between splenium disruption and EDSS (r=-0.55, $p<0.001$).
Conclusion: In RRMS with mild disability, GM atrophy and WM disruption occur in distinct anatomical patterns, which are inter-related and have great relevance for both physical and cognitive disability.
Disclosure: Nothing to disclose

EPR2135

Peak width of skeletonised mean diffusivity (PSMD), a promising imaging marker for white matter diseases: preliminary results in Multiple Sclerosis and CADASIL

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Background and aims: Peak width of skeletonised mean diffusivity (PSMD) is a new, fully automated, MRI-based biomarker, that has shown clinical relevance in cerebral small vessel diseases. We aimed here to explore its relevance in other white matter (WM) disorders such as multiple sclerosis (MS) and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).
Methods: In this ongoing study, we studied thus far 22 MS (age: 43.9±9.3 years, expanded disability status scale: 2 [1-5.5], symbol digit modalities test: 41±11), 13 CADASIL (age: 44.1±8.3 years, mild disability), and 27 normal controls (NC, age: 44.2±11.24 years). MRI data were acquired on a 1.5 T scanner. PSMD was computed from diffusion tensor imaging data through "skeletonisation" of WM tracts and histogram analysis.
Results: No age and sex heterogeneity was found among the three groups. Patients with MS and CADASIL had similar WM lesion volume (LV, 12.4±2.2 cm^3 vs 14.6±10.7cm^3, p=0.54). Both patient groups showed higher PSMD than NC (2.8±0.3 10^-4 mm2/s, $p \leq 0.001$) but in MS PSMD was higher than in CADASIL (4.6±0.6 vs. 3.8±0.9 10^-4 mm^2/s, p=0.008). In both patient groups PSMD correlated with LV (r=0.6, p=0.004 in MS; r=0.7, p=0.007 in CADASIL) whereas no correlations with clinical variables were found.
Conclusion: Our preliminary results showed that, in presence of a similar LV, diffuse microstructural brain damage as detected by PSMD is more pronounced in MS than in CADASIL. PSMD can thus represent a useful marker for a robust quantification of microscopic brain damage in WM disorders.
Disclosure: Nothing to disclose

EPR2136

Automated pipeline to assess clinically relevant white matter lesions (WMLs)

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Background and aims: WMLs reflects vascular damage in Alzheimer's disease, and are often quantified through visual assessment (i.e. Age-Related White Matter Changes Scale-ARWMC, Wahlund et al, 2001). Visual scales require an expert rater clinician, are time-consuming, and showing high intra-rater and inter-rater variability. Therefore, several automated methods have been developed for WMLs quantification, but their clinical relevance has been poorly investigated. The aim of this study is to provide an automated pipeline able to assess clinically relevant WMLs in mild cognitive impairment (MCI) patients.

Methods: We included 134 MCI patients consecutively enrolled in the PharmaCog study (Galluzzi et al., 2016). WMLs visual assessment was performed using ARWMC, automated assessment using in-house pipeline: i) lesion prediction algorithm execution for WMLs segmentation (raw masks), ii) focal and periventricular lesions removal (final masks), iii) WMLs regionalisation as in ARWMC (frontal/parieto-occipital/temporal/infratentorial/basal ganglia). The concordance of ARWMC and WML volumes from raw or final masks was performed using Kendall's rank correlation tau.

Results: At global level, ARWMC showed a moderate concordance with volumes of final masks (tau=0.46-p<.001), higher than that with raw masks (tau=0.35-p<.001). At regional level, the concordance with final masks was higher in frontal (tau=0.51-p<.001) and parieto-occipital regions (tau=0.39- p<.001).

Conclusion: Our pipeline improved the concordance between the widely-used ARWMC scale and raw automated methods, may be useful in research and clinical settings to evaluate vascular damage. These analyses will be replicate on healthy subjects' cohort to provide normative data. PharmaCog is funded by the EU-FP7 for the Innovative Medicine Initiative (grant n°115009).

Disclosure: Nothing to disclose

EPR2137

Detecting whole-brain and gray matter atrophy in Multiple Sclerosis: assessment by MRI

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Background and aims: In this study, the comparison between different available methods for whole-brain and gray matter (GM) atrophy estimation using MRI (ANTs v1.9, CIVET v2.1, FSL-SIENA(X) v5.0.1, Icometrix-MSmetrix v1.7, SPM v12) in multiple sclerosis (MS) was performed, for their potential clinical application.

Methods: The dataset consisted of (1) 8 simulated MR images and longitudinal data (two weeks) from 10 healthy controls to assess cross-sectional and longitudinal accuracy of atrophy measures; (2) test-retest MR images of 29 MS patients acquired within the same day at different scanner field strengths/manufacturers to evaluate precision; (3) longitudinal data (one year) from 24 MS patients to assess the agreement between methods. Tissue segmentation, image registration and white matter (WM) lesion filling were also evaluated.

Results: High values of accuracy (0.87-0.97) for whole-brain and GM volumes were found, with the lowest values for MSmetrix. ANTs showed the lowest mean error (0.02%) for whole-brain atrophy in healthy controls with a coefficient of variation (CoV) of 0.5%. SPM showed the smallest mean error (0.07%) and CoV (0.08%) for GM atrophy. On average, good repeatability ($p>0.05$), but poor reproducibility ($p<0.05$), were found for all methods. The WM lesion filling technique mainly affected ANTs, MSmetrix and SPM results ($p<0.05$).

Conclusion: From this comparison, it would be possible to select software for atrophy measurement, depending on the requirements of the application (research center, clinical trial) and its goal (high accuracy and repeatability or high reproducibility). For clinical application, an improved reproducibility is required for all methods.

Disclosure: Nothing to disclose

EPR2138

Dynamic inter-regional coordination patterns as specific predictors of consciousness

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Background and aims: To date, specific signatures of conscious states in humans remain elusive. Contemporary theories concur that such markers can be traced to temporally evolving brain processes instead of static descriptions of brain activity.

Methods: Dynamic fMRI connectivity patterns (states) by means of clustering of phase-based coherence was estimated on 47 healthy and 112 patients diagnosed in vegetative state/unresponsive wakefulness syndrome (VS/UWS) or in a minimally conscious state (MCS). To validate whether the patterns captured properties of awareness, out-of-sample generalization was performed on patients with cognitive-motor dissociation (i.e. lacking overt conscious behaviour yet evidenced using functional neuroimaging), and on anesthetised patients, under the premise that complex signatures would disappear uniformly across all subjects.

Results: A pattern of long-range positive/negative coherence had a higher probability of occurring in healthy and MCS patients. A pattern of low inter-areal coordination, mostly similar to anatomy, was more likely to occur in VS/UWS. Inter-state transitioning was flexible for healthy and MCS and more rigid for VS/UWS patients. Unconscious patients were more likely to avoid the exploration of the complex connectivity state. The generalisation to cognitive-motor dissociation predicted the occurrence of the complex-connectivity state. The generalisation to propofol anaesthesia showed an equalization of occurrence probabilities of all patterns regardless of clinical diagnosis.

Conclusion: The dynamics of inter-areal coordination contain information specific to conscious awareness. The rigid and less metastable dynamics in VS/UWS could account for the limited mental capacities in these patients. The minute identification of these patterns and their external manipulation could account for non-invasive restoration of consciousness.

Disclosure: Nothing to disclose

EPR2139

Location of T2-W lesions discriminate between radiologically isolated syndrome and preclinical CADASIL

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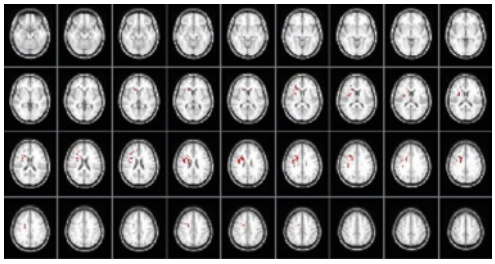
Background and aims: The radiologically isolated syndrome (RIS) refers to asymptomatic subjects who show brain abnormalities on magnetic resonance imaging (MRI) suggestive of multiple sclerosis (MS). Asymptomatic subjects with genetically proven cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) can show brain MRI abnormalties before symptom occurrence, with a pattern similar to that of MS and RIS.
To use lesion mapping to investigate spatial differences in white matter (WM) lesion distribution and frequency between the two groups of asymptomatic subjects with CADASIL and RIS.
Methods: Using T2-W lesions masks a lesion probability map was created and a voxel-wise analysis of lesion distribution and frequency of lesion occurrence was performed in 23 RIS (17F/6M) and 18 asymptomatic CADASIL (8F/10M).
Results: Age- and T2-W lesion load were not different in the two groups ($p>0.1$). Asymptomatic subjects with CADASIL showed significantly higher frequency of lesions in the right external capsule and superior longitudinal fasciculus. The percentage of voxels occupied by lesions in these regions was significantly higher in CADASIL than in RIS (CADASIL: 10.4%±4.2%; RIS: 0.97%±1.37%; $p<0.001$), with a value of 4% that was able to best discriminate between the 2 groups.



Lesion Probability Map
Conclusion: Present results suggest differences in lesion location between asymptomatic subjects with CADASIL and RIS could be of crucial relevance in the differential diagnosis of these conditions.
Disclosure: Nothing to disclose

EPR2140

Cerebellar atrophy patterns in Paraneoplastic Cerebellar Degeneration (PCD) and Spinocerebellar Ataxia type-1 (SCA1)

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Background and aims: Brain and more specifically cerebellar atrophy is a major radiological finding in both Paraneoplastic Cerebellar Degeneration (PCD) with anti-Yo antibodies and Spinocerebellar Ataxia type-1 (SCA1). We sought to analyse the different brain volumetric patterns of cerebellar atrophy in these diseases.
Methods: Patients were recruited in Paris, Lyon and Barcelona reference centres with either anti-Yo PCD (n=16) or SCA1 (n=17). T1 weighted MRI were used. We used 30 MRI from OASIS and IXI databases as controls paired by age. We have applied VolBrain and CEREbellum Segmentation (CERES) algorithms to obtain cerebellar volumetric data. We performed multivariate analysis to compare cerebellar atrophy patterns in the different diseases using R package SCCAN. We also performed whole brain analysis using a Voxel Based Morphometry (VBM) method. All p-values were corrected for multiple testing.
Results: In univariate analysis, most of the atrophic regions ($p<0.05$) were common between PCD and SCA1 patients compared to controls. Lobule IV, and V were atrophic only in PCD patients ($p=0.003$ and $p=0.04$ respectively), whereas atrophy of lobule IX was only found in SCA1 patients ($p=0.009$). Cerebellum cortical thickness was significantly lower in PCD versus controls ($p<0.001$), and versus SCA1 ($p<0.001$). Multivariate analysis using SCCAN and VBM confirmed these results ($p<0.05$) (Figure 1) Interestingly, we identified two complementary patterns of cerebellar atrophy in PCD (Figure 2).

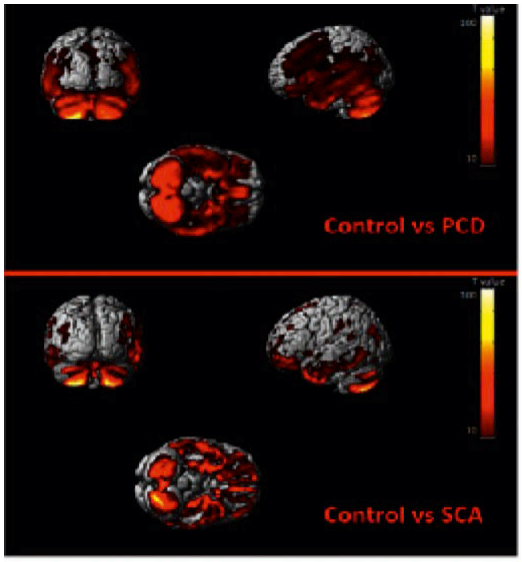

Figure 1: Visualisation of statistically different voxels, using Voxel Based Morphometry (VBM) method through Statistical Parametric Mapping (SPM), between control and both PCD subjects (upper figure) and SCA1 subjects (lower figure). Normalization was made with age and intra-cranial volumes. Family Wise Error Rate correction for multiple testing, p-value set to 0.05 and voxel cluster size set to 10.

Figure 1: Visualisation of statistically different voxels, using Voxel Based Morphometry (VBM) method through Statistical Parametric Mapping (SPM), between control and both PCD subjects (upper figure) and SCA1 subjects (lower figure). Normalisation was made with age and intra-cranial volumes. Family Wise Error Rate correction for multiple testing

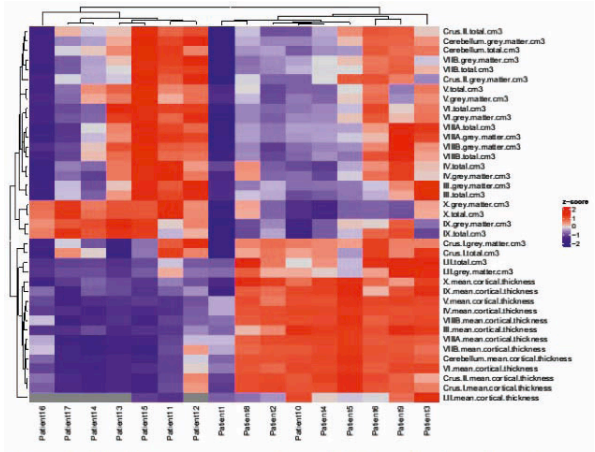

Figure 2. Heatmap representation of PCD cerebellar volumetric features showed two clusters of patients. The volumetric features were transformed using a z-score

Figure 2. Heatmap representation of PCD cerebellar volumetric features showed two clusters of patients. The volumetric features were transformed using a z-score.

Conclusion: The cerebellar atrophy related with PCD is more diffuse and is associated with a broader reduction of cerebellar cortical thickness than in SCA1. These differences can be explained by a differential pathophysiology.
Disclosure: Nothing to disclose

Neurological manifestations of systemic diseases; Neuro-oncology

EPR2141

Impact of Patisiran on Norfolk Quality of Life Questionnaire Diabetic Neuropathy (QOL-DN) in patients with Hereditary transthyretin-mediated Amyloidosis: results from the Phase-3 APOLLO study

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Background and aims: Hereditary transthyretin-mediated (hATTR) amyloidosis is a multi-system, rapidly progressive, life-threatening disease. Clinical manifestations can include polyneuropathy, cardiomyopathy and gastrointestinal symptoms impacting patients' quality of life (QOL). In the Phase-3 APOLLO study, patisiran, an investigational RNAi therapeutic, resulted in a statistically significant improvement in neuropathy (mNIS+7) and quality of life (Norfolk QOL-DN) at 18-months compared to placebo and was generally well tolerated. Here we describe the impact of patisiran on individual domain scores of the Norfolk QOL-DN.

Methods: APOLLO was a multi-centre, international, randomized (2:1), double-blind, study of patisiran 0.3mg/kg or placebo IV q3W in hATTR amyloidosis patients with polyneuropathy (NCT01960348). Norfolk QOL-DN assessed 5 domains: small fibre, large fibre, and autonomic nerve function, symptoms (including walking, arising from a seated position, sensation in extremities and gut motility), and activities of daily living (ADL). Scores range from -4 to 136; lower scores indicate QOL improvement.

Results: APOLLO enrolled 225 patients: mean age 60.5 years (24-83); 74% males; 43% V30M. Patisiran treatment led to significant improvement relative to placebo in the Norfolk QOL-DN overall score LS mean difference (SEM) [95%CI) (p-value) -21.1 (3.1) [-27.2, -15] (p=1.1X10□-10) and improvement within each domain at 18-months (Table 1). Patients on placebo had worsening QOL over time while the patisiran group improved relative to baseline (Table1).

		Placebo n=77	Patisiran n=148
Norfolk QOL-DN Overall (LS Mean Change from Baseline (SE))	-	14.4 (2.73)	-6.7 (1.77)
Individual Domains (Mean Change from Baseline)	Physical Functioning/Large Fibre	9	-1.9
	ADL	5.3	0.5
	Symptoms	2.3	-1.2
	Small Fibre	2.8	0.3
	Autonomic	0.8	-0.3
	Total Score	**20.2**	**-2.6**

Table 1. Norfolk QoL-DN Overall and Domain Scores from Baseline after 18-months of Treatment

Conclusion: Patisiran treated patients reported improvement or preservation in quality of life over 18-months related to strength, digestive health, ability to perform everyday activities, and steadiness on their feet. Those who did not receive patisiran reported a decline.

Disclosure: This research was supported by Alnylam Pharmaceuticals.

EPR2142

Patisiran-LNP Pharmacokinetics (PK), Pharmacodynamics (PD), and Exposure-Response (E-R) relationship in patients with hereditary Transthyretin-Mediated (hATTR) amyloidosis with polyneuropathy

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Background and aims: APOLLO is a global phase-3 study evaluating clinical efficacy, safety, PK, and PD of patisiran-LNP, a first-in-class investigational RNAi therapeutic that inhibits the hepatic synthesis of wild-type and mutant transthyretin (TTR) protein in adult patients with hATTR amyloidosis with polyneuropathy. Here we report PK, PD, anti-drug antibody (ADA), and E-R relationships for TTR reduction, efficacy and safety.
Methods: A total of 148 adult patients received patisiran-LNP 0.3mg/kg intravenously q3W over 18 months (NCT01960348). Sparse PK samples were collected for the determination of plasma concentrations of ALN-18328 (siRNA) and 2 novel lipid excipients (DLin-MC3-DMA and PEG2000-C-DMG). Serum samples were collected for determination of serum TTR concentrations and ADA. Steady-state PK exposures were divided by 4 quartiles and TTR and efficacy (mNIS+7 change from baseline) were summarized by each PK exposure quartile. Similarly, incidence of adverse events (AEs) were analysed by 4 PK exposure quartiles.
Results: Patisiran-LNP exhibited linear and time-independent PK with chronic dosing of 0.3mg q3w over 18 months. There were no differences in PK, TTR reduction or efficacy in any subgroup [age, sex, ADA status, hepatic impairment (mild) and renal impairment (mild to moderate)]. Incidence of ADA was low (3.4%), with no impact on PK, PD, efficacy or safety. Also, TTR reduction, efficacy and incidence of AEs were similar across 4 PK exposure quartiles.
Conclusion: Steady-state PK was similar across subgroups. Intra-subject variability in PK did not affect TTR reduction and clinical efficacy. Incidence of AEs were not associated with patisiran-LNP concentrations.
Disclosure: This research was supported by Alnylam Pharmaceuticals.

EPR2144

Cognitive functioning and health-related quality of life in patients with newly diagnosed primary central nervous system lymphoma: a systematic literature review

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Background and aims: Background: Incidence of primary central nervous system lymphoma (PCNSL) is increasing and prognosis improving due to improved treatment, however, declined cognitive functioning remains a major challenge in the treatment of PCNSL. This cognitive decline, in conjunction with other symptoms caused by the disease and/or its treatment, may compromise health-related quality of life (HRQoL).
Objectives: To give a comprehensive overview of current knowledge on cognitive functioning and HRQoL in PCNSL, including an evaluation of patient- and treatment related factors which can influence cognitive functioning and HRQoL.
Methods: We reviewed literature on cognitive functioning and HRQoL in newly diagnosed adult patients with PCNSL in several electronic resources, including Pubmed and Embase, up to January 4, 2018. Articles were selected using predetermined in- and exclusion criteria.
Results: 42 original articles were included. The tumor itself has a large impact on cognitive functioning and HRQoL. On the short-term, induction chemotherapy resulted in improvement of cognition and HRQoL in most patients. On the long-term only additional Whole Brain Radiotherapy (WBRT) has a negative impact on cognitive functioning, but the magnitude of this impact is not always clinically relevant. HRQoL scores were worse compared to controls. Moreover, scores were worse after chemoradiation when compared to chemotherapy only, particularly on the long-term.
Conclusion: Only chemoradiation seems to have a negative effect on HRQoL and cognition in PCNSL patients. Although prolonged progression-free survival is achieved with combined therapy, information on the impact of treatment on cognition and HRQoL should also be included in clinical decision-making, regarding starting or withdrawing treatment modalities.
Disclosure: Nothing to disclose

EPR2145

Rapidly progressive dementia in an anti-Yo positive patient

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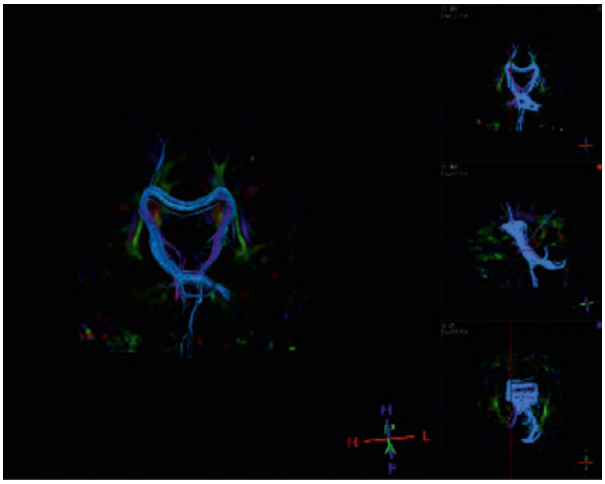
Background and aims: Paraneoplastic cerebellar degeneration (PCD) related to the anti-Yo antibody typically manifests as a subacute pancerebellar dysfunction. Although psychiatric comorbidity is commonly apparent, severe cognitive impairment is rare.

Methods: Case report

Results: A 59-year-old healthy woman, developed a subacute history of apathy and loss of initiative, followed by a progressive gait unsteadiness, with inability to walk within four months. She presented a severe dysexecutive syndrome, characterised by apathy, psychomotor slowing, attention and working memory deficit, ideomotor, oculomotor and constructional apraxia, decreased verbal fluency, speech perseveration, palilalia and agraphia without alexia; primitive signs were present; and a pancerebellar dysfunction with downbeat nystagmus and speech, limb and gait ataxia. The brain MRI revealed small nonspecific hyperintensities in supratentorial white matter. The CSF analysis was normal and bacterial cultures, neurotropic virus PCR and 14-3-3 protein were negative. Screening of prion protein mutations was negative. Body CT scan, upper and lower digestive endoscopy and pelvic, breast and thyroid echographic exams were unremarkable. Whole-body PET-FDG identified two small abdominal hypermetabolic foci, which were biopsied suggesting metastasis of unknown primary tumour, and a right cerebellar hot-spot. Antineuronal antibody anti-Yo was positive. A tractography MRI revealed disruption of the fronto-ponto-cerebellar tract, between the left frontal cortex and the right cerebellar peduncles.



Conclusion: Metabolic changes in PET-FDG along with dysfunction of the ipsilateral cortico-ponto-cerebellar tract suggests a possible mechanism for the cognitive impairment in this patient. A cognitive-affective syndrome has been described in the context of cerebellar lesions. This case supports the development of a Schmahmann syndrome in the setting of PCD.

Disclosure: Nothing to disclose

EPR2146

Primary diffuse large B-cell lymphoma of the dura – a case report

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Background and aims: Primary dural lymphoma (PDL) is a rare subtype of primary central nervous system lymphoma (PCNSL) arising primarily from the meninges without brain or systemic involvement. The most frequent histopathological diagnosis is marginal zone B-cell lymphoma (MZL) and presentation as diffuse large B-cell lymphoma (DLBCL) is extremely rare.

Methods: We report a case of a PDL with skull and epicranial involvement in an immunocompetent patient.

Results: A 43-year-old woman with no previous medical or surgical history, presented to our outpatient clinic with progressive frontal headaches over the last year and two enlarging frontal scalp masses in the past four months. Neurological examination was unremarkable. MRI revealed diffuse pachymeningeal thickening with contrast enhancement, predominantly on the frontoparietal region, with diffuse bone infiltration and soft tissue thickening along the scalp. Partial excision of the epicranial lesions revealed a DLBCL. CSF analysis was negative for malignant cells and bone marrow biopsy was normal. 18F-FDG PET/CT imaging showed avid FDG uptake by the epicranial lesions, but no evidence of systemic involvement. The patient was transferred to a tertiary referral hospital and completed 6 cycles of high dose systemic chemotherapy regimen – R-HCVAD. MRI after four cycles of chemotherapy demonstrated a significative reduction of the pachymeningeal thickening.

Conclusion: Despite being uncommon, PDL should be considered in the differential diagnosis of scalp masses and distinguished from meningiomas. Whether this DLBCL arised de novo or as a transformation/progression from MZL is unknown. Given the scarcity of cases, there is no standard treatment established for PDL.

Disclosure: Nothing to disclose

Neurorehabilitation 2

EPR2147

Effects of gait training using the Hybrid Assistive Limb (HAL®) in patients with spinocerebellar degeneration

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Background and aims: Patients with spinocerebellar degeneration (SCD) are severely disturbed in gait and routine daily activity. The effect of neuro-rehabilitation is usually not enough in SCD. The hybrid assistive limb (HAL®) (the wearable robot suit) assist kinesis during voluntary control of hip and knee joint motion. The aim of this study is to investigate the effect of HAL® on gait disturbance in SCD.

Methods: 15 patients with SCD took part in the experiments (mean age: 59.1±17.4 years old; mean disease duration: 13.7±9.5years). Eight patients with SCA6, one SCA1, two SCA8, one SCA31 were diagnosed. The remaining one patient was cortical cerebellar form. The walking speed and the number of steps were counted to calculate step length. During the 2-minute walk test, the total distance walked was recorded. Evaluation were conducted before treatment (baseline), after training and 2 weeks later. The patients received HAL® treatment for fifteen sessions during three weeks in hospital. Each treatment session lasted 60 minutes per day for three weeks. One therapist operated the walking device and the other operated the computer.

Results: The walking speed was significantly faster from baseline to after training (0.74m/sec vs 0.98m/sec). The total walking distance in the 2-minute walk test were significantly longer observed (71.2m vs 94.8m).

Conclusion: Significant improvements in gait speed, step length, and cadence for the 10-m walk test.

Conclusion: The study showed that gait training using the HAL® in SCD patients can improve gait disturbance and ADL.

Disclosure: Nothing to disclose

EPR2148

Diagnosis and treatment of post-stroke depression in China: a cross-sectional survey of 350 senior clinicians in neurology, geriatrics and rehabilitation department

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Background and aims: Integration incidence rate of post-stroke depression (PSD) in China was very serious. This study aimed to investigate the PSD diagnosis and treatment given by physicians in China.

Methods: A total of 361 physicians working in neurology, geriatrics and rehabilitation medicine departments (8:1:1) at 145 hospitals in 16 cities were selected to answer a PSD questionnaire designed with 41 entries and pre-tested in 29 physicians. The descriptive statistics were used to analyse the 350 feedback PSD questionnaires.

Results: (1) The questionnaire had high reliability (Cronbach's alpha of 0.769) and good structural validity. (2) Physicians (13%) lacked the knowledge of the available screening methods, particularly those who working in geriatrics and rehabilitation departments, would missed diagnosis of PSD. Physicians (87%) would diagnosis less than 30% of their stroke patients with PSD, and another 13% physicians reported it less than 10%. (3) More than half (57%) of physicians agreed that prophylaxis for PSD should be given to patients with stroke, but most (>70%) physicians in these considered non-drug therapy as the first option. 25% of physicians would initiate pharmacology therapy for mild PSD. 79% of physicians would initiate pharmacology therapy (24%) or pharmacologic and non-pharmacologic combination treatment (55%) for moderate-to-severe PSD. (4) The reexamination rate of PSD was not high due to the patients neglect.

Conclusion: This study provides novel insights into the diagnosis and treatment protocol of PSD in China. A general awareness about PSD from neurologists, geriatrics, rehabilitations and also the patients really should be raised.

Disclosure: Nothing to disclose

EPR2149

Rehabilitation after stroke with brain-computer-interface-exoskeleton technology and multimodal cognitive stimulation

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Background and aims: Cognitive dysfunction occurs in more than half of poststroke patients. It reduces the rehabilitation potential and process of adaptation in society. Therefore, comprehensive rehabilitation aimed at restoring motor and cognitive deficits, appears to be most correct you to restore your lost due to stroke functions. The aim of the study: to assess the effect of additional multi-modal stimulation on the recovery of cognitive functions in poststroke patients wich were treated with the brain-computer-interface-exoskeleton technology (BCI-exoskeleton).
Methods: 20 patients treated with BCI-exoskeleton. 10 patients underwent further multimodal stimulation using stabilometric platform using biofeedback and cognitive training (main group). 10 patients of the control group were treated with the BCI-exoskeleton. All patients underwent testing before and after a course of neurorehabilitation using the Frontal Assessment Battery (FAB), memorizing 10 words by AR Luria, Kohs Block Design Test, the Schulte Table, Montreal Cognitive Assessment (MoCA), the Stroop test, The hospital Anxiety and Depression Scale (HADS), The Motivation to Success by T. Ehlers, State-Trait Anxiety Inventory.
Results: After the course of neurorehabilitation in conjunction with multimodal stimulation in main group there was revealed the significantly greater improvement than in the control group of the recovery of impaired cognitive functions on the majority tests ($p<0,05$). There was achieved the trend to improvement of the emotional-volitional sphere in patients of the main group - the reduction of anxiety and depression, and increase of motivation to success.
Conclusion: Additional multi-modal stimulation in neurorehabilitation with using of BCI-exoskeleton improves cognitive functions and emotional-volitional sphere of poststroke patients.
Disclosure: Nothing to disclose

EPR2150

Effect of body-oriented therapy on executive abilities in children with ADD

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Background and aims: It is known that children with ADHD (Attention Deficit Hyperactivity Disorder) and ADD (Attention Deficit Disorder) have deficit in executive abilities. The gaol of this study was to reveal the effect of body-oriented therapy on executive abilities in preschool children with ADD. We compared the efficacy of two methods of treatment (body-oriented therapy for children vs. conventional motor exercises) in a randomised controlled pilot study.
Methods: 15 children with ADD between 5 to 7 years of age were included and randomly assigned to treatment conditions according to a 2×2 cross-over design. The body-oriented therapy included yogas' exercises and breathing techniques. To assess the executive functions and attention in children we used 4 subtests from NEPSY (Tower, Auditory Attention and Response Set, Visual Attention, Statue). Effects of treatment were analyzed by means of an ANOVA for repeated measurements.
Results: The ANOVA has revealed ($p<.05$) that for all 4 subtests on executive functions and attention the body-oriented therapy was superior to the conventional motor training, with effect sizes in the medium-to-high range (0.58-0.89).
Conclusion: The findings from this pilot study suggest that body-oriented therapy can effectively influence the executive abilities in preschool children with ADD. However, it is necessary to further research the impact of body-oriented therapies on the prevention and treatment of ADD in children.
Disclosure: The research was supported by Act 211 Government of the Russian Federation, agreement no. 02.A03.21.0006.

EPR2151

Impact of visuospatial training on preschool children with SLI

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Background and aims: It was shown that children with specific language impairments (SLI) have deficits not only in producing and understanding language but also in visuospatial abilities (Kiselev et al., 2016). We assume that training programmes that are aimed to develop the visuospatial abilities can help children with SLI. The goal of this study was to assess the impact of visuospatial training on the language abilities in children with SLI.
Methods: The participants were 21 children aged 5–6 years (mean age=5.7) with SLI. Children were randomly assigned to the intervention and comparison group. Children from intervention group participated in 36 weeks of visuospatial training. This programme trains the child to do different visuospatial exercises both on motor and cognitive level. This programme is built on the conceptual framework derived from the work of Luria's theory of restoration of neurocognitive functions (Luria, 1963, 1974).
We used the subtests from Luria's child neuropsychological assessment battery to assess language abilities in children before and after the intervention period.
Results: Analysis of covariance tested the effect of visuospatial training programme on five language subtest from Luria's child neuropsychological assessment battery. Group differences ($p<0.05$) were found for subtest that assess understanding prepositions that describe the spatial relations between objects. Posttest mean for the intervention group were significantly ($p<0.05$) greater than the control group.
Conclusion: Visuospatial training in preschool children with SLI benefits specific language abilities for understanding sentences with spatial prepositions.
Disclosure: The research was supported by Act 211 Government of the Russian Federation, agreement no. 02.A03.21.0006.

EPR2152

Efficacy of home-based training in virtual environment in patients with stroke

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Background and aims: The growing level of VR technology allows using portable devices such as Kinect systems for in-home rehabilitation, providing continuous therapy. Studies of Hondori et al. and Capecci et.al showed that Kinect has motion capture accuracy required for clinical appliance and rehabilitation. The aim of our research was to study the efficacy of home-based VR training in patients with stroke.
Methods: 14 post-stroke patients were included in this study (mean age 52 [27; 68], months after stroke 9,5 [2; 23]). Main group (6 patients) received in-home training course on the Rehabunculus system without daily participation of medical personnel. The control group (8 patients) was trained at home without virtual biofeedback. Evaluation methods: Fugl-Meyer Assessment scale (FM), Action Research Arm Test (ARAT), motion capture system. To evaluate dynamics in VR exercise performance in the main group were used Rehabunculus motion analysis statistics of movement trajectories.
Results: FM upper limb scores showed significant increasing of upper limb range of motion, gross upper limb function and tendency to hand movements increasing. Also, patients received in-home Rehabunculus treatment significantly improved gait skills, resulted in increasing of performed steps per minute during "Step forward" exercise, step length with simultaneous decreasing of step height. Control group showed an insufficient tendency to FM increasing of passive range of motion and balance.
Conclusion: Rehabunculus system is the unique tool for in-home rehabilitation which allows providing continuous, self-guided and effective motor rehabilitation for neurological patients.
Disclosure: Nothing to disclose

EPR2153

Non-invasive neuromodulation of neural networks in Alzheimer's disease: cognitive and clinical effects

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Background and aims: There is increasing evidence that human brain is organised into large-scale networks. Among these, the Default Mode Network (DMN) and the Salience Network (SN) show abnormal connectivity patterns in Alzheimer's disease (AD), i.e. reduced connectivity in the DMN and increased connectivity in the SN. In this study, we tested the cognitive/clinical effect of neuromodulation of the above networks in AD through transcranial direct current stimulation (tDCS).

Methods: 20 AD patients participated in the study. Each patient underwent a clinical (neuropsychiatric inventory and geriatric depression scale) and cognitive assessment (memory, language and visuo-spatial functions), before and after ten daily 25-minutes tDCS sessions. Patients were randomized into two groups: anodal DMN stimulation (right parietal cortex), cathodal SN stimulation (right frontal cortex). Clinical and cognitive outcomes were compared by using the Wilcoxon signed-rank test.

Results: Patients were equally randomised to the anodal and cathodal arms (n=10 each). Cognitive assessment revealed significant improvement in memory in both groups (immediate Rey auditory verbal learning test: +20%, $p<0.05$ in the anodal group; +19%, $p<0.05$ in the cathodal group). A significant improvement in tests for visual memory (paired associative learning test; +6%, $p=0.05$), visuo-constructive abilities (clock test; +42%, $p<0.05$) and language comprehension (token test; +9%, $p<0.01$) was observed only in the anodal group. Conversely, improvement in behavioral symptoms (neuropsychiatric inventory: -36%, $p<0.05$) was found only in the cathodal group.

Conclusion: These results suggest that anodal tDCS may be more effective than cathodal tDCS in modulating cognition in AD, while cathodal tDCS may have a specific neuromodulator effect over behavior.

Disclosure: This work was supported by the Italian Ministry of Health (Giovani Ricercatori grant GR2011–02349787 and Ricerca Corrente).

EPR2154

Pilot study evaluating the effects of percutaneous tibial nerve stimulation on sexual symptoms in neurological patients reporting overactive bladder

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Background and aims: The aim of this study is to investigate the effect of Percutaneous Tibial Nerve Stimulation (PTNS) on sexual symptoms in neurological patients receiving this treatment for overactive bladder symptoms.

Methods: This was an open-label pretest-posttest study conducted at the Uro-neurology outpatient clinic of a neurology hospital in London between February and September 2017. Sexually active neurological patients referred for PTNS treatment for overactive bladder symptoms were included in the study. ICIQ-LUTS questionnaire was used to evaluate urinary symptoms and ASEX, FSFI, IIEF-5, SQOL-F and SQOL-M questionnaires were used to assess sexual symptoms. The patients were re-assessed after 12 sessions of PTNS treatment.

Results: The mean age of the 12 patients participating in the study was 51.6±13.5 (mean±SD, range 26-70), 66.6% (n=8) female and most (75%) were ambulatory. Patients' ASEX scores decreased from 20 to 17.5 ($p=0.05$). On the FSFI questionnaire the total score and sub-score scores improved, with a statistically significant improvement in the desire sub-score ($p=0.039$). Improvement was observed in IIEF-5 scores in males (n=4), and sexual quality of life scores and urinary symptoms improved.

Conclusion: PTNS treatment was shown to improve urinary and sexual symptoms and quality of life in neurological patients reporting overactive bladder. This pilot study has shown that good outcomes can be achieved with the continuation of PTSU treatment, and it is suggested to be done in larger sample groups in future studies.

Keywords: Overactive bladder, percutaneous tibial nerve stimulation, sexual function, urinary symptom,

Disclosure: Nothing to disclose

Peripheral nerve disorders 3

EPR2155

The most sensitive test in the diagnosis of carpal tunnel syndrome

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Background and aims: Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. In our study, we compared the sensitivity studies of the sensory nerves of the median sensory nerve with those of the first, second, third finger, palm and superficial radial nerves to determine the early diagnosis of CTS

Methods: For the patient group, 282 hands were included, while for the control group 62 limbs were included. Clinical neurophysiologic evaluation was performed according to the criteria determined by the Italian CTS (ITS) Working Group. Motor and sensory conduction velocities, latencies and amplitudes of unilateral or bilateral median, ulnar and radial nerves, were recorded by superficial electrode recording.

Results: 282 symptomatic hands were examined. Mild CTS in 35.1%, moderate CTS in 37.6% and severe CTS in 3,2% were found. 68 hands had normal electrophysiological findings, even though they had symptoms. This group was defined as the electrophysiological negative CTS group. Electrophysiological negative CTS group and control group were compared. There was no statistically significant difference between median and ulnar nerve motor conduction tests. Second finger and palm-wrist segment sensory latencies were longer in the negative electrophysiological CTS group. It was also observed that the velocities of sensory conduction in the second finger-wrist segment of the electrophysiological negative KTS group were decreased.

Conclusion: Routine electrophysiological studies are not enough in the diagnosis of CTS. In this case, palm-wrist segment sensory conduction study may be useful in addition to second finger-wrist segment examination

Disclosure: Nothing to disclose

EPR2156

Restabilisation treatment after IVIG Withdrawal in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): results from the PATH study

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Background and aims: In patients with chronic inflammatory demyelinating polyneuropathy (CIDP), the dose or frequency of intravenous immunoglobulin (IVIG) administration is recommended to be periodically reduced to assess the need for ongoing therapy. Little is known about the effectiveness of IVIG restabilisation in patients who worsen after IVIG withdrawal.

Methods: In PATH, a randomised, double-blind study of subcutaneous immunoglobulin in CIDP, IVIG therapy was withdrawn before randomisation. Subjects not deteriorating within 12 weeks of IVIG withdrawal discontinued the study as Ig dependency was not confirmed. Upon deterioration (increase in adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] score), subjects received IVIG restabilisation with IgPro10 (Privigen®, CSL Behring): induction dose 2g/kg bw, maintenance doses 1g/kg bw every 3 weeks for up to 13 weeks.

Results: Of 245 subjects in whom IVIG was withdrawn, 28 (11.4%) did not deteriorate within 12 weeks. Another 10 subjects withdrew for other reasons, leaving 207 in the restabilisation phase. Of these 91% improved in at least 1 efficacy measure (improvement: 1 point in adjusted INCAT score, 4 points in RODS score, 8kPa in mean grip strength or 3 points in MRC score). Adjusted INCAT score improved in 72.9% with ~21% of subjects improving beyond their status at study entry. Improvements were seen in all secondary scores (Figure 1). Post-study follow-up of non-improving subjects revealed most subjects had improved.

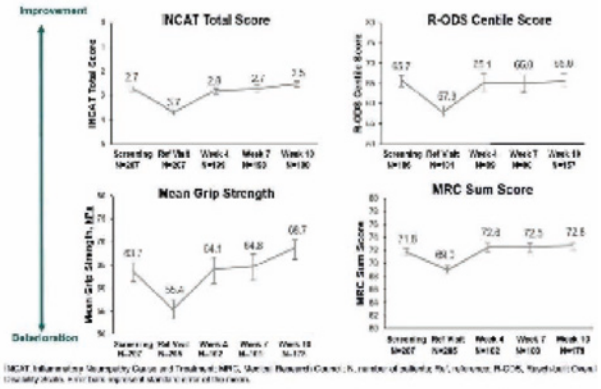

Figure 1. Efficacy of IgPro10 IVIG restabilisation therapy.

Conclusion: IVIG withdrawal was effective in detecting subjects not requiring IVIG therapy. For IVIG-dependent subjects, restabilisation with IgPro10 was effective in reversing observed deteriorations within 12 weeks.
Disclosure: This study is sponsored by CSL Behring

EPR2157

Efficacy and safety of intravenous Immunoglobulin (IVIG) IgPro10 in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): combined analysis of the PRIMA and PATH studies

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Background and aims: Efficacy and safety of intravenous immunoglobulin IgPro10 (Privigen®, CSL Behring) were investigated in CIDP subjects in two studies: PRIMA and PATH.
Methods: PRIMA was a prospective, open-label, single-arm study in 28 CIDP subjects investigating IgPro10 for induction (2g/kg) and maintenance therapy (1g/kg every 3 weeks for 21 weeks). This regimen was also used in 207 IVIG pretreated subjects during the 10–13 week restabilisation period of PATH (before randomisation to subcutaneous immunoglobulin vs placebo). Both studies investigated response (defined as ≥1 point decrease in adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] score), changes in mean grip strength and Medical Research Council (MRC) score, and safety. We analysed separate and pooled results from both studies.
Results: INCAT response rate at last observation was 76.9% (95% confidence interval [CI]: 49.7–91.8) in PRIMA IVIG pretreated subjects (60.7% in all PRIMA subjects) and 72.9% (95% CI: 66.5–78.5) in PATH (Figure 1). In the pooled cohort (n=235), INCAT response rate was 71.1% (95% CI: 65.0–76.5; Table 1). Most responders improved by week 4; additional responses occurred up to week 13 (Table 1). Change from baseline to last observation in efficacy parameters is shown in Table 2. In the pooled cohort, 271 adverse drug reactions (ADRs) were reported in 105 subjects (44.7%), a rate of 0.144 ADRs per infusion.

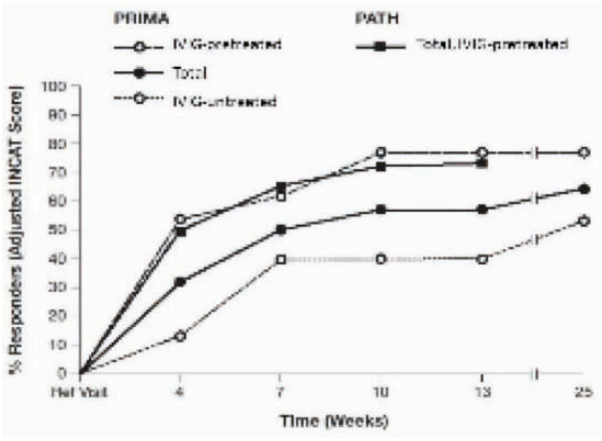

Figure 1. Response rate by INCAT in PRIMA and PATH

Response rate by adjusted INCAT, %	PRIMA IVIG-pretreated (n=13) 76.9	PRIMA IVIG-naïve (n=15) 46.7	PRIMA total (n=28) 60.7	PATH (all pre-treated) (n=207) 72.9	PATH and PRIMA pooled (N=235) 71.1
Number of responders by adjusted INCAT by week, %					
Week 1	0.0	0.0	0.0	n/a	0.0
Week 4	53.8	13.3	32.1	49.8	47.7
Week 7	61.5	40.0	50.0	65.2	63.4
Week 10	76.9	40.0	57.1	72.0	70.2
Week 13	76.9	40.0	57.1	72.9	71.1
Week 16	76.9	40.0	57.1	n/a	n/a
Week 19	76.9	53.3	64.3	n/a	n/a
Week 22	76.9	53.3	64.3	n/a	n/a
Week 25	76.9	53.3	64.3	n/a	n/a

Table 1. Overall INCAT response rate and response rate by week from PRIMA and PATH as separate and pooled cohorts

	PRIMA IVIG-pretreated (n=13)	PRIMA IVIG-naïve (n=15)	PRIMA total (n=28)	PATH (all pre-treated) (n=207)
Adjusted INCAT score	-2.0	-1.0	-1.0	-1.0
MRC score	5.0	6.0	5.0	3.0
Grip strength, kPa (dominant hand)[a]	5.0	5.0	5.0	9.4

Table 2. Median change from baseline to last observation in efficacy endpoints in PRIMA and PATH

Conclusion: Pooled PRIMA/PATH data showed improvement in disability with IgPro10 in a large cohort of CIDP subjects. Improvement was seen at up to 10–13 weeks, suggesting some subjects may need multiple Ig doses to respond.
Disclosure: This study was sponsored by CSL Behring

EPR2158

Blink R1 latency as a sign of primary demyelination of the peripheral nerves in chronic inflammatory demyelinating polyneuropathy (CIDP)

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Background and aims: CIDP is one of the most common forms of autoimmune disease. Diagnosis of CIDP is based on clinical signs, electromyography (EMG) and biopsy.
Methods: The main group (MG) in our study consisted of 59 patients diagnosed with CIDP (mean age: 58.2±17.2 years) based on neurological examination and EMG that meets international criteria for diagnosis of CIDP (INCAT, 2001). The control group (CG) had 31 individuals without any autoimmune disease. All patients underwent EMG, and a blinking reflex was also studied.
Results: 55 patients (93.22%) of MG had an increase of blink R1 latency (> 13ms). 2 people of CG had the blink R1 latency more than 13ms (6.45%). In the MG, the median of blink R1 latency was 15.1ms [13.9; 16.4]. In the CG, the median of blink R1 latency was 10.7ms [10.2; 11.5]. Statistically significant difference in the duration of blink R1 latency was found between the MG and the CG (Mann-Whitney criterion, $p < 0.001$). Direct correlations between the blink R1 latency and the F-wave of the tibial nerve ($r=0.317$, $p=0.023$) and also the F-wave of the ulnar nerve ($r=0.241$, $p=0.037$) were found.
Conclusion: Blink R1 latency may serve as a marker of demyelinating at CIDP. Thus, at difficult clinical cases with the increased blink R1 latency and the simultaneous sharp decrease or absence of the M-response from the peripheral nerves, it is possible to think about the primary demyelinating process.
Disclosure: Nothing to disclose

EPR2159

Functional disability, fatigue and depression as predictors of quality of life in MGUS polyneuropathy

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Background and aims: Monoclonal gammopathy of undetermined significance related polyneuropathy (MGUS-PNP) is a benign paraproteinemic neuropathy. Despite of being benign in nature, it has a chronic and progressive course, and therefore may highly affect quality of life (QoL). The aim of this study was to show how MGUS-PNP affects patients' QoL.

Methods: Our study included 51 patients diagnosed with MGUS-PNP (23.5% IgM, 66.7% IgG or IgA, 7.8% undetermined, 2.0% light chains). QoL was assessed using the SF-36 questionnaire. The Medical Research Council Sum Score for muscle strength, INCAT disability and sensory scores, Krupp's Fatigue Severity Scale, and Beck's Depression Inventory were also used.

Results: Total SF-36 score was 50.0±21.4. Physical domains were somewhat more affected than mental, although both were significantly influenced by the disease (44.4±21.4 vs. 54.5±20.9, respectively). Following factors showed correlation with the SF-36 total score in a univariate analysis: INCAT disability score, INCAT sensory score, Medical Research Council Sum Score, ataxia, fatigue and depression ($p<0.01$). Significant predictors of worse SF-36 total score in our MGUS-PNP patients were depression ($\beta=-0.46$, $p<0.01$), more severe fatigue ($\beta=-0.32$, $p<0.01$), and worse INCAT disability score ($\beta=-0.27$, $p<0.01$).

Conclusion: MGUS-PNP patients with more severe functional disability, with presence of severe fatigue and depression need special attention of clinicians since they could be at higher risk to have worse QoL. This should be taken into account when treating MGUS-PNP subjects.

Disclosure: Nothing to disclose

EPR2160

Regenerative medicine approach for treatment of radix compression syndrome caused by herniated intervertebral discs

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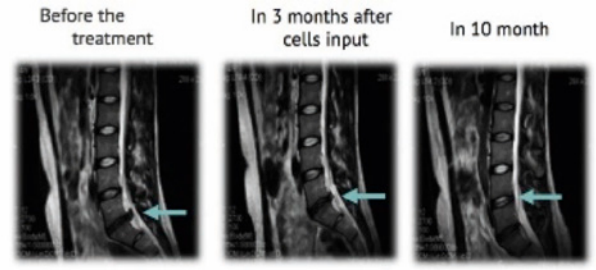
Background and aims: In our clinical practice we applied the regenerative medicine methods with use of autologous cultured adipose-derived mesenchymal stromal cells (MSCs) for neurological patients with herniated discs and made the initial assessment of cell therapy safety and effectiveness.

Methods: Complex treatment of fifteen patients with nerve compression syndrome caused by herniated intervertebral discs in the cervical and lumbar spine level. Cultured stem cells were administered via paravertebral injection technique (20 million MSCs). The clinical application of stem cell therapy carried out on a base of patient's informed consent, MC ilaya Bioethics Committee approval, state licenses for medical practice of cells banking. To evaluate the results of treatment we use MRI and clinical methods. Patients received such an experimental treatment when standard drug therapies were ineffective and/or when patients refused of surgery or had somatic contraindications. The observation terms were 10 months.

Results: The use of cell therapy for the treatment of nerve compression syndrome caused by herniated disc resulted in relief of pain symptoms, disc extrusion reduction and complete regression of neurological deficit within 3-4 weeks. Clinical outcome was excellent or good in 86.7% of patients. At 10 months of observation, the hernia size regressed by an average of 5.3±0.4 mm (95%CI 3.9-5.9). We check reduction in visual analog scale scores of pain for 5.3±1.4 point (95% 3.5-6.7).



Conclusion: Pilot clinical study on cell therapy methods testing for neurorehabilitation of patients with herniated discs demonstrates the safety and effectiveness of chosen cell-based approach. However, it requires further evaluation within the planned clinical trial.
Disclosure: Nothing to disclose

EPR2161

Psychophysical evaluation of small-fibre function in diabetic patients using brief radiant heat and cold stimulation of skin

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Background and aims: Small-fibre neuropathy (SFN) is a common complication of diabetes mellitus. Yet, SFN is often recognised belatedly because routine techniques to assess small-fiber function are lacking. Our study aims to explore the potential of a novel psychophysical procedure based on brief heat or cold stimulation to assess SFN in diabetic patients.
Methods: Brief (100ms duration) temperature-controlled heat and cold stimuli were applied to the skin of the volar wrist and foot dorsum in 15 patients with diabetes mellitus type 2 (6 females; aged 55±4 years) and 15 age-matched healthy controls. Heat stimuli were delivered using a skin temperature feedback-controlled CO2 laser (SIFEC, Ferrière, Belgium). Cold stimuli were delivered using a novel device based on micro-Peltier elements (TCS, Strasbourg, France). A Bayesian adaptive algorithm, the PSI method (Kingdom & Prins, 2010), allowed to estimate the threshold and the slope of the psychometric function for heat and cold detection using only 30 trials per run. Conventional electrophysiological tests were performed to assess large-fiber function.
Results: As compared to healthy controls, patients showed on average a significant reduction in detection performance of heat and cold stimuli, particularly in the lower limbs, even in the absence of large-fibre neuropathy. Higher diagnostic performance was achieved with cold than with heat testing.
Conclusion: This study supports the potential usefulness of this novel psychophysical procedure for the assessment of SFN in diabetic patients. Further studies are needed to assess the advantages over conventional methods for the early diagnosis of SFN.
Disclosure: This study was financially supported by an ERC Starting Grant (336130-PROBING-PAIN).

EPR2162

Impact of central nervous system and ocular phenotypes in ATTR V30M patients

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Background and aims: Central nervous system involvement in ATTR V30M is being increasingly recognised and understanding its natural history and impact on patients is fundamental to implement disease oriented treatment strategies. Ocular involvement is also recognised as a highly disabling feature in ATTR V30M patients, but the inter-action between brain and eye have not been addressed in the same cohort.

Methods: We have evaluated a consecutive and prospective series of 107 liver transplanted ATTR V30M patients. We characterised Focal Neurological Episodes (FNE) due to CNS dysfunction, ATTR ocular stage and neuroimaging findings (Focal brain lesions, brain atrophy and white matter damage).

Results: Over a 5-year period 45% of patients presented at least one FNE. Disease duration was the major determinant. Ocular involvement was present in over 90% of the patients. Ocular phenotype preceded CNS involvement in 70% of the patients. Clinical CNS involvement occurred first in 20%. There was no association between a specific ocular disease stage and CNS involvement. Neuroimaging disclosed 6 cases of non-traumatic intracranial brain hemorrhages with different locations (lobar, subarachnoid or cerebellar) as a feature of CNS involvement. White matter damage and brain atrophy were associated to longer disease duration.

Conclusion: Clinical brain and ocular findings are concomitant and are not prevented by liver transplantation. Disease duration is the major determinant of both phenotypes. Neuroimaging findings support that TTR related cerebral amyloid angiopathy contributes to this new clinical phenotype. The hemorrhagic risk of such vasculopathy, hints caution in acute stroke care or in primary stroke prevention of atrial fibrillation.

Disclosure: Nothing to disclose

EPR2163

Central nervous system complications in ATTR Met30 neuropathy, an epidemiological study in the Cypriot cohort of transplanted patients

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Background and aims: ATTRMet30 neuropathy is a lethal autosomal dominant sensorimotor and autonomic neuropathy. Liver transplantation has been the mainstay of treatment for the last 25 years and complications due to brain involvement are causing concern. Transient focal neurological episodes, seizures and brain haemorrhage signify leptomeningeal involvement. The frequency of brain involvement in transplanted patients is largely unknown.

Aims: To assess the prevalence of brain involvment in the Cypriot cohort of transplanted patients.

Methods: Epidemiological data were collected for all ATTRMet30 neuropathy patients at CING since 1992 . CING is the only tertiary neurology centre in Cyprus where all patients are been followed up. Demographic data on all transplanted patients were analysed including brain and ocular manifestations. Neurological complications included: Transient focal neurological episodes (TFNEs), seizures or strokes.

Results: In Cyprus 48 patients have been transplanted since 1992, 26M/22F. 10 patients out of 48 (20%) have developed CNS complications, 1M/9F. 3 have died as a result of a brain hemorrhage (30%), 8 patients had TFNEs Mean time from disease onset to TFNEs is 16 years (11-22) Onset of TFNEs is rarely sudden TFNEs tend to be stereotyped in any given patient duration is variable from minutes to hours All patients had ocular involvement

Conclusion: CNS complications in the Cypriot transplanted ATTRMet30 cohort in the last 25 years shows a minimum prevalence of 20%.

Mortality due to CNS complications is 30% in those that develop them and is due brain haemorrhage.

Disclosure: Nothing to disclose

Peripheral nerve disorders; Muscle and neuromuscular junction diseases

EPR2165

RCT assessing 2mg bumetanide as a therapeutic agent for a focal attack of weakness in Hypokalaemic Periodic Paralysis (HypoPP)

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Background and aims: HypoPP is a genetic disorder characterised by recurrent attacks of weakness in association with low serum potassium levels. Inhibition of the Na-K-2Cl cotransporter using Bumetanide may be a potential therapeutic strategy based on mouse model studies.
Methods: ClinicalTrials.gov Identifier: NCT02582476
An RCT was performed assessing if bumetanide could abort an episode of focal hand weakness in patients with HypoPP. A focal attack of weakness was induced by hand rest following exercise (McManis protocol). Participants received either placebo or 2mg bumetanide on two different occasions at the attack onset defined as 40% decrement in abductor digiti minimi (ADM) compound muscle action potential (CMAP) amplitude from the maximum response. Electrophysiological measurements assessed the severity and the duration of the attack following 4h of IMP intake.
Results: 9 participants completed both trial visits. There was no statistically significant difference in CMAP amplitude between the treatment groups at 1h ($p=0.27$, primary outcome). Two participants recovered from the attack of weakness ($\leq$35% decrement in ADM CMAP amplitude from the maximum response) within 4 hours following bumetanide intake; none recovered following placebo intake ($\geq$40% decrement). There were no serious adverse events.
Conclusion: 2mg bumetanide was safe but not effective to rescue a focal attack in an immobilised hand in the majority of patients. However, our data supports further studies of this agent. The McManis test used as an objective outcome measure in a clinical trial for the first time was well tolerated.
Disclosure: Nothing to disclose

EPR2166

Oral immunosuppressive treatment of myasthenia gravis in Denmark: a nationwide drug utilisation study, 1996-2013.

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Background and aims: In recent years, several myasthenia management guidelines have been published but population-based studies describing drug utilisation in myasthenia patients are scarce. We aimed in this study to describe the treatment of myasthenia in Denmark in more recent years with emphasis on use of oral immunosuppressant agents.
Methods: Using a validated method, we identified a nationwide cohort of incident myasthenia patients in Denmark in 1996 to 2013 and tracked their use of drugs using data from nationwide registers. Patients with myasthenia were classified according to utilisation of specific immunosuppressants (e.g. prednisolone) as "never user" or "ever user". We used Kaplan-Meier (K-M) and Proportion of Patients Covered (PPC) curves to describe treatment onset and termination.
Results: We identified 928 patients (52% female) with incident myasthenia in the study period. Overall, 638 (69%) were treated with prednisolone and 506 (55%) with azathioprine. Treatment with prednisolone and azathioprine within two years of myasthenia diagnosis was initiated in 462 (56%) and 366 (45%). Only one out of four myasthenia patients (n=231) did not receive oral immunosuppressive treatment at any time in the study period. Prednisolone was stopped in most patients, whereas treatment with azathioprine was often continued throughout follow-up.
Conclusion: Treatment of myasthenia in Denmark in recent years corresponded well to the expected clinical course of myasthenia and was in line with recently published guidelines. Long-term immunosuppressive treatment in the treatment of myasthenia is used extensively in Denmark.
Disclosure: Nothing to disclose

EPR2167

Novel COL6A3 mutation with an autosomal dominant inheritance pattern in a family affected by Bethlem myopathy

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Background and aims: Bethlem myopathy (BM) is one entity of spectrum of collagen VI disorders with autosomal dominant inheritance, which is caused by mutations in the genes COL6A1, COL6A2 and COL6A3. It's characterised by mild fenotype with an early-onset and slowly progressive. We present a family with heterozygous COL6A3 mutation, located in exon 19 c.6360_6322del, not previously reported in collagen VI-related myopathies.

Methods: A 58-year-old male with a history of poliomyelitis without sequels was referred for progressive weakness with difficulty raising his arms above his head, getting up and going up the stairs for 5 years. He needed a unilateral support to walk. Non-consanguineous parents. Neurological examination revealed mild weakness of shoulder girdle and proximal upper limb muscles and slight weakness of hip girdle muscles, mild rigidity of the spine and positive Gower's sign.

Results: Creatine kinase was slightly high. Electromyography showed myopathic pattern (ruled out post-polio syndrome). MRI showed lower limb muscles affectation with peripheral fatty infiltration with sparing of the central part, which is very specific sign of collagen VI-related myopathies. Muscle biopsy without specific pattern. Genetic analysis revealed a heterozygous COL6A3 mutation, located in exon 19 c.6360_6322del not previously reported. Two patient's sisters with clinical manifestations, pathologic neurological examination and MRI presented the heterozygous COL6A3 mutation. One of seven members of next generation presented the same mutation.

Conclusion: This case reports a novel mutation in COL6A3 gene located in exon 19 c.6360_6322del with an autosomal dominant inheritance pattern.

Disclosure: Nothing to disclose

EPR2168

Patient demographics and clinical features of chronic inflammatory demyelinating polyneuropathy – an observational study In Turkey

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Background and aims: Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common treatable chronic neuropathy worldwide. We present the demographic and clinical features of 65 CIDP patients.

Methods: Patient charts of 139 cases with immune mediated demyelinating neuropathy treated at the Neuromuscular Unit between 1993 and 2017 were reviewed for CIDP retrospectively. Cases with an associated paraprotein were excluded.

Results: We identified 65 patients who fulfilled the 2010 EFNS/PNS diagnostic criteria for definite (n=64) or probable (n=1) CIDP. Among 65 patients (43 male, 22 female), 49% typical CIDP, 31% multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy, 18% distal acquired demyelinating symmetric (DADS) neuropathy, 2% pure sensory CIDP were determined. The mean age of symptom onset was 36.95±18.53 years. Twenty percent had juvenile-onset. Patients who had at least one outpatient clinic visit in the past year (n=43) were evaluated using CIDP disease activity status (CDAS), 9% were cured, 19% were in remission, 42% had active stable disease, 9% were improving and 21% had unstable active disease. The majority of the unstable active disease cases had MADSAM(5/9, 56%). Disability was assessed using inflammatory neuropathy cause and treatment disability score(INCAT). The mean INCAT disability score of MADSAM patients was higher than the others (Mean 1.9).

Conclusion: The mean age of onset was younger then literature however the ratio of patients with childhood-onset was higher. MADSAM, the most common clinical phenotype among atypical variants of CIDP in our cohort was more frequent than the literature. MADSAM patients had higher disability scores and were more likely to have unstable active disease.

Disclosure: Nothing to disclose

EPR2169

The first Portuguese kindred with NEFL-related Charcot-Marie-Tooth type-2 disease: a case report

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Background and aims: Charcot-Marie-Tooth disease (CMT) comprises a heterogeneous group of inherited neuropathies clinically characterised by progressive, distal-predominant weakness, amyotrophy, and sensory loss. NEFL-related CMT is a rare form of inherited neuropathy, accounting for less than 1% of all CMT cases, and obvious genotype-phenotype correlations have not been established so far. We describe the first Portuguese CMT2 patient with c.794A>G NEFL mutation.
Methods: Case report
Results: A 67-year-old woman presented progressive weakness and atrophy of distal limb muscles, with hammer toes and pes cavus, stocking-glove pattern of algic hypoesthesia, absent ankle reflexes, mild positional and vibration sensory loss and sensory ataxia. She also presented a mild cerebellar ataxia and pyramidal signs. These symptoms were first noticed by the age of 42 years. No palpably enlarged hypertrophic peripheral nerves were noted. The nerve conduction studies were compatible with sensory-motor axonal neuropathy. The patient's parents were first-degree cousins, and her mother and daughter presented a similar clinical picture.
Mutation analysis of NEFL gene revealed a c.794A>G mutation in heterozygosity. This missense mutation has previously been reported as likely pathogenic, and therefore we performed a co-segregation analysis in her affected daughter, that was also positive for this mutation.
Conclusion: As far as we know this is the first Portuguese case of CMT2E described. This mutation (c.794A>G) was only previously described in another family, in Australia; this family also presented pyramidal signs, but no cerebellar ataxia. We believe this further widens the phenotypic expression associated with this mutation.
Disclosure: Nothing to disclose

EPR2170

Predictive factors of long-term disability in CIDP

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Background and aims: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a disabling disease and about 10% of patients may become persistently disabled over time. Our aim was to identify clinical prognostic factors of long-term disability in a large series of CIDP patients.
Methods: We collected data from 53 CIDP patients with definite diagnosis according EFNS/PNS criteria and positive response to first-line therapies (immunoglobulin or corticosteroids) including sex, age of onset, phenotype, disease duration, course of disease (monophasic/relapsing-remitting, chronic progressive) and disability at the time of diagnosis assessed using the modified Rankin Scale (baseline mRS). All patients had clinical assessment of disability through mRS within the last 6 months (last mRS). Ordinal logistic regression model was applied to evaluate the relationship among the clinical parameters and last mRS, considered as ordinal outcome (0-6). Anova test for repeated measures was applied to test the overall effects of different course on disability accumulation while t-test was performed to evaluate inter-group differences for parametric variables
Results: We found a significant relationship between last mRS and the course of disease [$p<0.000$, $z=4.05$, OR: 14.91]. Disability accumulation was greater in patients with chronic progressive course than those with monophasic/relapsing-remitting course of disease [$p=0.04$]. Moreover, patients with progressive course were older [$p=0.01$].
Conclusion: Our data suggest that chronic progressive course of disease may be a major negative prognostic factor for long-term disability in CIDP patients. To note that a chronic progressive course of disease is also associated with an older age from the beginning and a more pronounced worsening over the course of disease.
Disclosure: Nothing to disclose

EPR2171

EFNS/PNS Guidelines for CIDP and MMN: an international audit of perceived value and usefulness amongst clinicians

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Background and aims: Disease management guidelines have unproven uptake and unconfirmed role in real-life clinical practice. We conducted a prospective web-based international audit on the knowledge about and use of European Federation of Neurological Societies/Peripheral Nerve Society Guidelines for chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) amongst neurologists from a total of nine countries. The project was funded by the EFNS. The global response rate was very low. There was a significantly greater response from by subspecialists in the field. Awareness of the guidelines was higher amongst subspecialists. Although felt helpful, the guidelines did not appear to influence diagnostic and therapeutic management decisions for the majority of subspecialist responders. The guidelines were considered by most to be a useful teaching and training tool and were felt by the majority to represent the most adequate set of criteria and recommendations available for these disorders. We conclude that the clinical value of guidelines for rare disorders such as CIDP and MMN may be limited in general neurological practice. Clinical uptake and usefulness remains incomplete for subspecialists. Further work and research is needed to determine ways of optimising uptake and increasing use as well as interest in the wider neurological community, for future revisions. EFNS/PNS Guidelines are the best known and most used in CIDP and MMN and are of important educational value.

Disclosure: References: EFNS/PNSguideline on management of chronic inflammatorydemyelinating polyradiculoneuropathy: report of a jointTF of the EFNS and the PNS - first revision. Van den Bergh PY, Hadden RD, Bouche P, Cornblath DR, Hahn A, Illa I, Koski CL, Léger JM, Nobile-Orazio E, Pollard J, Sommer C, van Doorn PA, van Schaik IN; EFNS; PNS. EJON. 2010 Mar;17(3):356-63. EFNS/PNS guideline on management of multifocal motor neuropathy. Report of a joint TF of the EFNS and the PNS--first revision. JointTF of the EFNS and thePNS J Peripher Nerv Syst. 2010 Dec;15(4):295-301.

Monday, June 18 2018

Ageing and dementia 3

EPR1155

Event-related cerebral dynamics during mirror movement of hand closing

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Background and aims: Upper extremity mirror rehabilitation is recently used to let a stroke patient induce the movement of affected arm by parallel watching the mirrored movement of unaffected arm. The mirror training has been demonstrated useful in motor improvement but the corresponding neuromuscular processing is less investigated. In this study, event-related cerebral dynamics and corticomuscular coherences during simulated mirror hand movement is investigated.
Methods: 16 healthy adults were included for a movement experiment of right-hand closing then opening but left-hand keeping still under mirror feedback of right-hand movement (MF condition) or watching right-hand movement (non-MF condition). 32-channel electroencephalograms and electromyograms of flexor digitorum profundus and extensor digitorum were parallel recorded.
Results: MF caused significant alpha-band (8-12 Hz) event-related synchronization at CP4 and P4 prior to hand closing than non-MF did and significant weakened beta-band (13-30 Hz) event-related desynchronization at C4, CP4 and P4 compared to their contralateral sites during hand closing. This implies that the MF evoked more somatosensory processing prior to motor execution and reduced cerebral demands during hand closing in the right hemisphere. In addition, MF yielded significant higher peak corticomuscular coherence of F4 and FC4 versus right flexor than non-MF did. The MF may enhance the corresponding association between muscular activity of right-hand closing and right frontal-central operation.
Conclusion: MF is shown to induce a significant enhancement of somatosensory processing and corticomuscular link.
Disclosure: The authors would like to acknowledge the support provided by grants from the Chang Gung Memorial Hospital, Taoyuan, Taiwan under Contract CMRPD1C0203 and from the Ministry of Science and Technology, Taiwan under Contract MOST 105-2221-E-182-035.

EPR3001

Executive dysfunction is a predictive factor of cognitive decline in early onset Alzheimer's Disease

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Background and aims: Alzheimer's disease (AD) is the most common cause of dementia under 65 years. In the absence of curative treatment, the current strategy remains to slow the progression of the disease.
The aim of our study was to identify predictive factors of rapid cognitive in Early Onset Alzheimer's Disease (EOAD).
Methods: We included the first 84 consecutive patients younger than 60 years old at the time of the first symptoms of a probable or certain AD according Mckhann's et al 2011 criteria, with a Mini Mental State Examination (MMSE) greater than 10, included at Lille hospital in the COMAJ cohort between July 2009 and February 2015. For each patient, we reported its clinical, biological, radiological characteristics, the results of the first cognitive screening tests, and their cognitive treatment. Cognitive decline was measured by the difference between MMSE at inclusion and after 2 years of follow-up. We identified three groups of patients declining according to the progression: slow, intermediate or fast.
Results: After 2 years of follow-up, 6 points was the median cognitive decline on the MMSE. After a logistic regression, a low score at the Rapid Battery of Frontal Efficiency at inclusion in the cohort was the only predictor of rapid cognitive decline ($p<0.02$).
Conclusion: In conclusion, severe alteration of executive functions may predict a poor prognosis at 2 years.
Disclosure: Nothing to disclose

EPR3002

Diagnosing frontotemporal dementia: clinico-pathological correlations in the Dutch population

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Background and aims: Over the past years a tremendous growth of knowledge in FTD pathology has occurred, including the identification of novel TDP-43 molecular pathological subgroups. In addition, the diagnostic criteria for clinical subgroups of behavioural-variant FTD and primary progressive aphasia have been updated, providing a more accurate diagnostic framework for clinicians. However, due to the overlap in clinical symptoms with other dementia's and with psychiatric disorders, diagnosing FTD in sporadic patients remains challenging. Here, we aim to assess the agreement between clinical and pathological diagnoses over the past ten years, and explore clinical symptoms that concur within a pathological subgroup.
Methods: Donors with a clinical primary FTD diagnosis, or FTD diagnosis during their disease duration, were selected from the Netherlands Brain Bank Cohort (n=108). Extensive clinical information was available from all donors. Psychiatric and diagnostic clinical features were retrospectively scored, and pathological molecular subgroup was determined. Comparisons between pathological subgroups were made with chi-square test.
Results: The overall clinical-pathological agreement was 71%. Since the introduction of the new criteria diagnostic accuracy has improved (from 68% to 88%). Within our cohort 43 donors had FTD-TDP pathology and 30 FTD-Tau pathology. We found that hallucinations were more prevalent in donors with FTD-TDP pathology ($p<0,05$).
Conclusion: The current diagnostic criteria have improved the agreement between clinical and pathological diagnosis. In addition, in our cohort hallucinations were more frequent in FTD-TDP compared to FTD-tau , which suggests it can be used as a tool to differentiate pathological subgroups in patients with FTD.
Disclosure: Nothing to disclose

EPR3003

Peripapillary retinal nerve fiber layer thickness and macular ganglion cell layer volume are reduced in Alzheimer's disease

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Background and aims: Alzheimer's disease (AD) represents a great medical challenge in the Third Millennium. Great efforts have been produced to develop disease-modifying drugs. Reproducible, easy to handle progression markers are needed to monitor the response to treatment. Since AD pathological hallmarks were found in retinas of AD patients, OCT might reliably detect pathological changes occurring in AD retinas
Methods: 145 subjects were involved in this study (49 with AD, 39 with Mild Cognitive Impairment, MCI and 57 healthy controls, HC), receiving an OCT scan acquisition at baseline. CSF AD biomarkers (Aβ42, t-tau and p-tau) and neuropsychological assessment were available, as well. 19 AD and 23 MCI underwent a follow-up OCT scan
Results: At baseline, peripapillary RNFL, both global and in superior quadrant, was significantly thinner in AD and MCI patients than in HC (global: AD: 91.56±10.5, MCI: 93.26±9.8, HC: 98.44±8.36μm; superior: AD: 108±17.8, MCI: 113.96±14.8, HC: 124.3±12.99μm, $p<0.05$). Macular GCL volume was significantly reduced in AD (AD: 0.95±0.9; MCI: 1.03±0.87; HC: 1.05±0.68mm^3, $p<0.05$). Over time, AD patients showed a significantly higher decay in global RNFL thickness than MCI subjects (-2.28±2.99 vs. -0.72±1.94μm/year). RNFL, GCL and IPL thinning over time was positively associated with worsening in cognition
Conclusion: OCT might reflect the current disease stage in which patients are and seems to correlate with worsening in cognition. Therefore, OCT might be considered as a possible disease progression marker
Disclosure: Nothing to disclose

EPR3004

Cognitive impairment in patients with Parkinson's disease dementia and dementia with Lewy bodies in Slovenia (2010–2015)

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Background and aims: There is a considerable overlap in clinical presentation of Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) suggesting common disease spectrum. We aimed to describe and compare cognitive impairment (CI) and management in PDD vs DLB.
Methods: We reviewed the medical records of PDD and DLB patients who attended the movement disorders clinic at the UMC Ljubljana, Slovenia, in the period between 2010–2015, using a retrospective cross-sectional study design. Assessment of CI was based on Mini-Mental State Exam (MMSE) score. Demographic characteristics and risk factors for cognitive impairment were analysed.
Results: 204 PDD and 50 DLB patients were included in the study. Mean age for PDD was 77.9±7.9 years, DLB 78.1±6.3 years, disease duration: PD 12.2±6.1 years and 6.6±3.8 years for DLB. Duration of CI in PDD was 4.8±2.9 years, DLB 6.0±4.0 years. The first recorded MMSE score was 25.0±3.6 in PDD vs. 22.3±3.9 for DLB and the mean two years rate of cognitive decline for PDD was -1.2±3.9 points vs. -3.8±3.3 points for DLB. Acetylcholinesterase inhibitors were used in 86% of PDD and 92% of DLB patients. Antidepressants were used equally in 44% and antipsychotics in 44% of PDD vs 60% of DLB patients.
Conclusion: Patients with DLB have more rapid cognitive decline and are more commonly treated with antipsychotics than PDD patients. This was the first study to describe and compare the characteristics and management of cognitive decline in PDD and DLB patients in Slovenia.
Disclosure: Nothing to disclose

EPR3006

Retina changes in Alzheimer's disease: potential biomarker for dementia

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Background and aims: A relatively new concept in neurodegenerative diseases claims that the retina can be used as a window to look into the brain. Structural retinal imaging biomarkers are important for early recognition and monitoring of neurodegeneration in Alzheimer's disease (AD). With the introduction of Optical Coherence Tomography (OCT), a non-invasive approach, supervised segmentation of retinal layers is possible. We aim to investigate which retinal layers show atrophy associated with neurodegeneration in AD and the correlation with disease variants and other biomarkers.
Methods: Patients with diagnosis of mild AD, between 55 and 75 years, without ophthalmologic pathology, were selected. The protocol included: clinical assessment, neuroftalmologic evaluation (retinal and optic nerve structures evaluated by OCT), neuropsychological assessment, CSF biomarkers, C11 PiB-PET and alipoprotein E.
Results: We included 20 patients, mean age 66 years, 9 years of education. All patients were positive for amyloid deposits in C11-PiB-PET. Patients that recently converted to AD presented higher total retinal thickness than those with a longer evolution time, as well as in the IPL-OD, OPL-OD, ONL layers. There was no relationship between neuropsychological tests, apoE4 allel and retinal thickness. However, considering clinical subtypes, the visual forms presented Outer Segment thicker than mnesic forms. Regarding CSF biomarkers, higher p-tau correlated with smaller OPL thickness ($p<0.001$).
Conclusion: Retinal atrophy seems to be related with evolution time of AD. The mnesic variants showed a greater atrophy compared to visual forms of the disease, especially in the Outer Segment layer. OPL atrophy layer correlated with a greater evidence of CSF degeneration biomarkers.
Disclosure: Nothing to disclose

EPR3007

Clinical variability in Gerstmann-Sträussler-Scheinker syndrome with the P102L mutation - a study of 6 cases and retrospective analysis of 80 cases reported in the literature

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Background and aims: P102L Gerstmann-Sträussler-Scheinker syndrome (P102L-GSS) is a rare genetic prion disease caused mutation at codon 102 in the prion protein gene. Clinical presentation includes early ataxia with gait disturbance, sensory symptoms in lower extremities and late cognitive decline, but clinical presentation is highly variable.

Methods: We compared data from six Czech patients with neuropathologically confirmed P102L-GSS and retrospective data from 80 published P102L-GSS cases. We focused on gender, onset of disease, duration of disease, onset of dementia (in the first 2 years of disease, late, none), duration of cognitive impairment, ataxia (early, late, none), MRI brain abnormalities (basal ganglia, cortex, and cerebellum), polymorphism in codon 129 and 219, changes in deep tendon reflexes and sensory symptoms. We used descriptive statistics; Wilcoxon-Mann-Whitney parametric hypothesis test, principle component analysis, Mardia multivariate analysis of normality a DBscan cluster analysis to define typical phenotypes of GSS syndrome.

Results: GSS is probably far more common than previously estimated and cluster analysis of our patients and data from previously published cases suggest the existence of three GSS clinical phenotypes ("classical GSS", "GSS with areflexia and paresthesia" and "GSS with dominant dementia") with distinct disease duration and clinical manifestation.

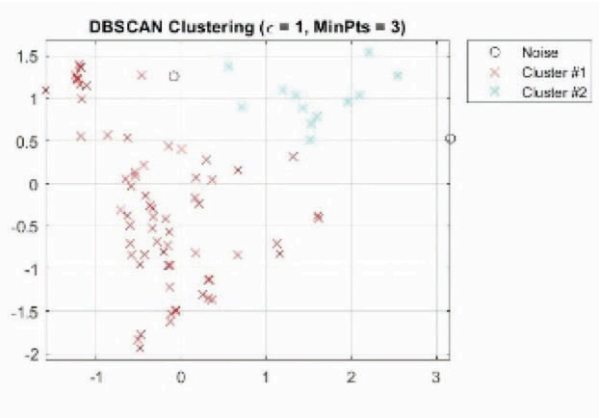

Figure 1. DBscan analysis of 3 PCA components, epsilon=1

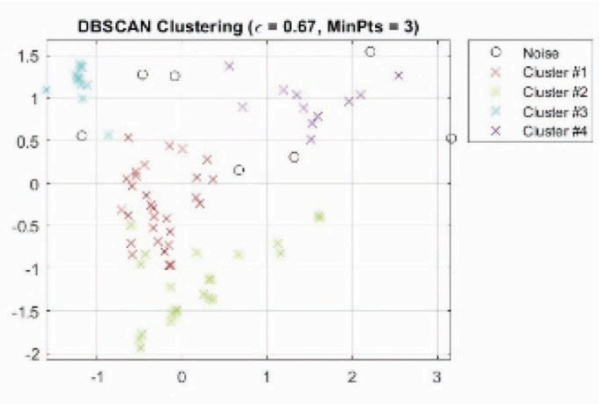

Figure 2. DBscan analysis of 3 PCA components, epsilon=0,67

Conclusion: GSS is a rare genetic disease with probably higher prevalence that previously estimated and despite its clinical variability, different phenotypical groups may be identified. Supported by program Progress Q27/LF1 (Charles University, Prague, Czech Republic)

Disclosure: Supported by program Progress Q27/LF1 (Charles University, Prague, Czech Republic)

Autonomic nervous system

EPR3008

Adrenergic hyperactivity: a missing link between multiple sclerosis and cardiovascular comorbidities?

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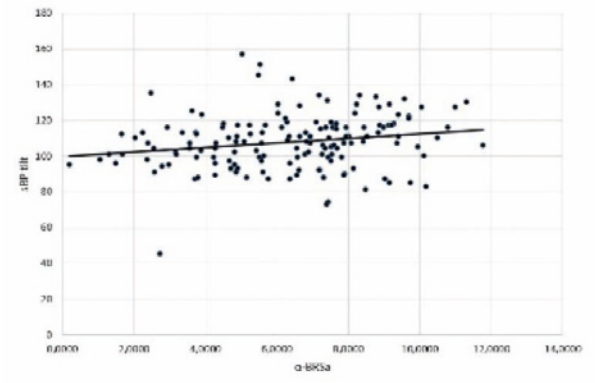
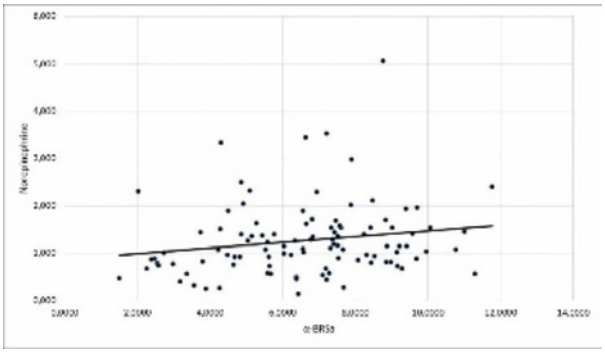
Background and aims: Impaired autonomic control of cardiovascular function has been reported in a large proportion of patients with Multiple Sclerosis (pwMS). The implications of this may be numerous, especially due to an increased risk of ischemic heart disease and congestive heart failure in pwMS. The aim of his study was to investigate differences in non-standard adrenergic baroreflex sensitivity (BRS) indices in patients with different phenotypes of pwMS and healthy controls (HC).
Methods: Retrospective analysis of types of systolic blood pressure (BP) curves during Valsalva maneuver (VM) (balanced (BAR), augmented (AAR) and suppressed (SAR) autonomic responses) and adrenergic baroreflex sensitivity measured with BRSa1, α-BRSa and β-BRSa in patients with clinically isolated syndrome (CIS), relapsing remitting Multiple Sclerosis (RRMS), progressive multiple sclerosis (PMS) and HC. We also investigated correlations between BRSa1, α-BRSa, β-BRSa and resting catecholamines levels.
Results: pwMS had higher α-BRSa compared to HC (p=0.02). There was no difference in BRSa1, α-BRSa and β-BRSa between patients with CIS, RRMS and PMS. There was no association between pwMS and HC and the type of sBP curve ($\chi(2)=4.332$, p=0.114). pwMS and BAR or AAR had higher supine systolic and diastolic BP compared pwMS and SAR. There was a significant correlation between α-BRSa and upright systolic BP (rp =0.194, p=0.017) (Fugure 1), α-BRSa and norepinephrine (rs =0.228, p= 0.021) (Figure 2) and BRSa1 and epinephrine (rs =0.226, p=0.040).



Correlation between α-BRSa and systolic BP in the tilted position.



Correlations between α-BRSa and norepinephrine.

Conclusion: pwMS and HC exhibit different alpha-adrenergic response to Valsalva maneuver. These results may explain the connection between MS and increased cardiovascular risk.

Disclosure: This study was funded by the Installation Research project 2622 of the Croatian Science Foundation and University of Zagreb research support for the academic years 2015/2016 and 2016/2017.

EPR3009

Joint hypermobility is related to pathological finding on tilt table testing

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Background and aims: Aim of this study was to evaluate the association of generalized joint hypermobility, expressed by Beighton score (BS), and pathological findings on head-up tilt table test (HUTT).

Methods: Prospective study that included consecutive patients referred for the HUTT. Generalised joint hypermobility was evaluated according to the BS system. Clinically significant BS was considered if ≥4.

Results: 115 patients met the inclusion criteria (91 females, mean age 34.35±14.11). BS was 0 in 65 (56.5%) and ≥1 in 50 (43.5%) patients. HUTT was normal in 58 (50.4%) patients, 15 (13.0%) patients fulfilled criteria for OH, 30 (26,1%) for syncope and 21 (18,3%) for POTS. Patients with pathological findings on HUTT had significantly higher BS compared to patients with normal HUTT (median 1 vs. 0, p=0.001). The same finding was observed for patients with OH, POTS and syncope (Table 1). We found significant association between participants with BS ≥4 and pathological HUTT and also with each type of pathology (Table 2). A multivariate logistic regression was performed in order to examine the influence of gender, age and BS on the likelihood that patients have HUTT pathology ($\chi 2(3)=18.009$, $p<0.001$) and it correctly classified 71.3% of cases. Increase in the BS was associated with increased likelihood of HUTT pathology (Exp(B) 1.44, 95%CI 1.084 – 1.922, p=0.012), while increase in age was associate with lower risk of HUTT pathology (Exp(B) 0.968, 95%CI 0.939 – 0.998, p=0.036).

HUTT		BS				
		Median	Range	Mean Rank	Sum of Ranks	p
HUTT pathology	No	0	0-5	49.10	2848.00	0.001
	Yes	1	0-9	67.05	3822.00	
OH	No	0	0-5	33.15	1940.00	0.001
	Yes	2	0-8	50.73	761.00	
POTS	No	0	0-5	36.95	2143.00	0.023
	Yes	1	0-5	48.13	1017.00	
Syncope	No	0	0-5	40.22	2332.50	0.012
	Yes	1	0-9	52.78	1583.50	

Table 1. Difference in the Beighton score regarding the HUTT pathology. HUTT – head-up tilt table test. BS – Beighton score. OH – orthostatic hypotension. POTS – postural orthostatic tachycardia syndrome.

		BS 0	BS ≥1	p
HUTT pathology	No	55	3	0.011
	Yes	45	12	
OH	No	55	3	0.012
	Yes	11	4	
POTS	No	55	3	0.015
	Yes	16	5	
Syncope	No	55	3	0.030
	Yes	24	6	

Table 2. Association between participants with BS ≥4 and HUTT pathology. BS – Beighton score. HUTT – head-up tilt table test. OH – orthostatic hypotension. POTS – postural orthostatic tachycardia syndrome.

Conclusion: Results of this study demonstrate an association of joint hypermobility features and pathological findings on HUTT.

Disclosure: Nothing to disclose

EPR3010

Evolution of dysautonomia in people with clinically isolated syndrome over two-year follow-up

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Background and aims: The Composite Autonomic Scoring Scale (CASS) has been validated for assessment of dysauotnomia in people with clinically isolated syndrome (pwCIS). Dysautonomia in pwCIS is restricted to sympathetic nervous system involvement. The aim of this study was to investigate the evolution of dysautonomia in pwCIS over two-year follow-up.
Methods: In 59 pwCIS (45 females, mean age 31.88±9.12) CASS was performed during the CIS diagnosis and 24 months later. Baseline Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite were performed at baseline and month 24 visit.
Results: Baseline median CASS was 1 (0-4) (adrenergic 0 (0-3), cardiovagal 0 (0-1) and sudomotor 0 (0-2)). At M24, median CASS was 1 (0-5) (adrenergic 0 (0-3), cardiovagal 0 (0-1) and sudomotor 0 (0-3)). Out of 47 patients with all data available for analysis, increase in CASS was identified in 22 (47%), improvement in 15 (32%) and 10 patients (21%) had no change in CASS. Baseline median EDSS was 2 (0-3.5) and median MSFC was 0.057 (-2.089-1.343). There was no difference in baseline EDSS in patient with and without progression of dysautonomia measured with CASS. However, those patients who progressed in CASS had higher EDSS at M24 (2 vs 1, p=0.012). Furthermore, patients who had progressed in CASS, had worse baseline MSFC (0.458 vs. -0.246, p=0.004). According to binary logistic regression model, baseline MSFC is statistically significant predictor for worsening in dysautonomica measured with CASS (Exp(B)=0.343, p=0.023).
Conclusion: Substantial proportion of pwCIS experience worsening of CASS over 24 months of follow-up.
Disclosure: Funded by the Installation Research project HRZZ UIP-11-2013-2622 of the Croatian Science Foundation.

EPR3011

Autonomic nervous system involvement in patients with neuromyelitis optica spectrum disorders

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Background and aims: Autonomic dysfunction (AD) occur in patients with multiple sclerosis (MS), and until now, it has not been investigated in patients with neuromyelitis optica spectrum disorders (NMOSD). Therefore, the aim of our study was to analyse its presence in patients with NMOSD.
Methods: 20 NMOSD (16 females, mean age 47.2±10.7 years, median EDSS 2.5, median disease duration 88.5 months, and 14 NMO-IgG positive) patients from two University hospital centers were enrolled. Dysautonomia was evaluated subjectively with the Composite Autonomic Symptom Score (COMPASS 31), and additionally, objectively, with the following autonomic tests: heart rate and blood pressure responses to the Valsalva maneuver, heart rate response to deep breathing (RSA), blood pressure response to passive tilt. All tests were interpreted in the form of the adrenergic and cardiovagal indices, parts of the Composite Autonomic Scoring Scale (CASS).
Results: All participants had COMPASS 31 score >0. Median value of the total score was 12.2 (orthostatic intolerance 2.0, vasomotor 0, secretomotor 1.1, gastrointestinal 3.6, bladder 1.1, pupillomotor 1.3). Pathological adrenergic and cardiovagal indices of the CASS were present in 8 (42.1%) and 10 (50.0%) patients, respectively. Median (range) of the adrenergic and cardiovagal indices was 0 (0-3) and 0.5 (0-1), respectively. There was no correlation between disease duration and EDSS with neither the COMPASS, nor the CASS variables. There was significant correlation between adrenergic index and bladder domain of the COMPASS 31 (r=0.559, p=0.015).
Conclusion: AD is frequent in patients with NMOSD and shows different pattern compared to patients with MS.
Disclosure: Nothing to disclose

EPR3012

Frequency of the invalidity of tachicardia pick in patients with peripheral sensory diabetic polyneuropatie

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Background and aims: Tachycardia at rest is often the first symptom of cardiovascular autonomic neuropathy and therefore has high diagnostic value in the early detection of serious cardiac dysregulation, including sudden death syndrome in type-2 diabetes mellitus (DM 2).
Methods: Surveyed 83 patients with type-2 diabetes (52 women and 31 men) aged 43 to 65 years (53,8±7.96 years) with an average duration of diabetes in the range of 7.04±3.73 years. All patients had various symptoms of peripheral sensory diabetic polyneuropathy (DPN) without active complaints of the cardiovascular system (CVS)
Results: The main sensory complaints were pain and burning sensation in the feet - in 56% of patients, numbness of the toes - in 47%, fast fatigue with minor physical exertion - in 58%. In a physical examination, tachycardia at rest (> 90 beats/min) was detected in 43% of patients with type-2 diabetes with sensory DPN without active cardiac complaints. Asymptomatic tachycardia at rest without cardiac arrhythmias was registered in 67% of patients. Such a high frequency of occurrence of diabetic autonomic neuropathy (DAN) in patients with sensory DPN is due to the failure of the small unmyelinated sensory sympathetic and parasympathetic fibers under the influence of chronic hyperglycemia
Conclusion: Thus, in patients with diabetes mellitus with sensory DPN, it is advisable to actively detect signs of autonomic cardiac dysfunction during routine clinical monitoring, as well as to conduct instrumental studies for early detection and intensive correction of cardiovascular risk factors to prevent fatal complications of type-2 diabetes.
Disclosure: Nothing to disclose

EPR3014

Hemodynamic changes during tilt table test: neurogenic orthostatic hypotension or vasovagal syncope? Towards improved hemodynamic criteria to distinguish between neurogenic orthostatic hypotension and vasovagal syncope during tilt-table testing

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Background and aims: Current criteria may not distinguish sufficiently well between neurogenic orthostatic hypotension (nOH) and vasovagal syncope (VVS) in tilt table tests (TTT). We explored additional criteria.
Methods: TTT data were gathered from our tertiary Syncope Unit. Inclusion criteria for VVS were a history of VVS and symptoms, complaint recognition, blood pressure (BP) drop and EEG changes during TTT. Inclusion criteria for nOH were a history of nOH and a BP decrease following the 2011 consensus. Clinical diagnoses were established prior to TTT. Exclusion criteria were incomplete data, age<16 years, concurrent nOH and VVS and additional diagnoses. We defined (1) the overall shape of systolic BP (i.e. whether the BP drop accelerated –convex- or decelerated –concave-; (2) when half the BP drop was reached, relative to tilt-up and tilt-back; (3) the direction of HR change at the BP nadir (up or down).
Results: We included 43 VVS and 42 nOH cases. For nOH, 83% had a concave BP pattern and for VVS 95% had a convex pattern ($p<0.0001$). Half the BP drop was reached shortly after tilt-up for nOH, but just before syncope/tilt-down in VVS ($p <0.001$). HR in nOH increased or remained unaltered in 88%, whereas HR dropped in 95% in VVS ($p <0.0001$).
Conclusion: Three criteria help differentiate nOH and VVS: the shape of BP decline (convex for VVS, concave for nOH; the rate of drop (late in VVS, early in nOH); the HR response to BP drop (down in VVS, up or no change in nOH).
Disclosure: Nothing to disclose

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EPR3016

Lung function, sleep-disordered breathing and incidence of stroke: a community-based longitudinal cohort study

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Background and aims: Impaired lung function is regarded as a risk factor for stroke in patients with chronic obstructive pulmonary disease. However, the association between reduced lung function and incident stroke in a community-based population with sleep-disordered breathing (SDB) remains unknown.
Methods: We performed a prospective study within the Sleep Heart Health Study cohort. Full montage home sleep testing and spirometry data on 2082 and 2072 individuals with and without SDB, respectively, were analysed. Cox proportional hazards regression models were used to estimate the association between lung function and incident stroke.
Results: During a median (interquartile range) follow-up of 11.7 (10.8–12.5) years, 183 cases of stroke were identified in participants without pre-existing cardiovascular diseases, including 112 and 71 with and without SDB, respectively. In the entire population, after all covariate adjustments, lung function was inversely associated with incident stroke (hazard ratio, HR: 0.913 [95% confidence interval (CI): 0.839–0.994] for every 10% increase in percentage of predicted forced vital capacity, FVCPP). In subgroup analysis, the association of lung function with incident stroke became stronger in individuals with SDB (HR: 0.899 [0.822–0.984] for every 10% increase in percentage of predicted forced expiratory volume in one second; HR: 0.881 [0.787–0.987] for every 10% increase in FVCPP) but not in individuals without SDB.
Conclusion: Lung function may serve as a risk factor for incident stroke in a community-based population, especially in those with SDB. Spirometry may improve the risk management for primary care in community-based populations.
Disclosure: Nothing to disclose

EPR3017

Correlation between occurrence of cerebral microembolic signals and characteristics of carotid plaques, inflammatory biomarkers, and lipid profile

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Background and aims: Microembolic signals (MES) are only detectable via transcranial doppler (TCD), and can occur in individuals with embolic origin of cerebral ischemia. Role of lipids and systemic inflammation in appearance of cerebral MES is not fully understood. Aim of our study is to investigate the correlation between occurrence of cerebral MES and characteristics of carotid plaques, inflammatory biomarkers, and lipid profile.
Methods: Retrospective study included 107 individuals, treated at Neurology Clinic CCS in Belgrade. MES were detected by TCD, whilst morphological and hemodynamic parameters were obtained via a carotid artery ultrasound (intima–media complex thickness; presence and character of carotid plaques; degree of stenosis). The erythrocyte sedimentation rate; C-reactive protein; fibrinogen; leukocytes; total cholesterol; HDL, LDL; and triglyceride were measured by appropriate tests.
Results: Out of entire sample, 54 were females and 53 males, with an average age of 52.96±14.25. A comparison was made between 34 MES positive and 73 MES negative individuals. Highly statistically significant MES positive individuals were those with migraines and/ tension headaches, whilst significantly higher frequency of plaques ($p=0.002$; $p=0.001$, left and right sides respectively) was noted in MES negative patients, who also had higher average value of right side carotid stenosis. MES positive patients depicted presence of more frequent statistically significant unstable left side plaques.
Conclusion: Detection of MES with carotid artery ultrasound, as well as adequate monitoring of specific biomarkers in the blood, can help in prevention of initial as well as recurrent cerebral ischemic events.
Disclosure: Nothing to disclose

EPR3018

Hospital management of acute ischemic stroke in dementia: a cohort study from the Swedish Dementia and Stroke Registries

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Background and aims: 10% of strokes occur in persons with pre-existing dementia. The aim of the study was to compare hospital management of acute ischemic stroke in patients with and without dementia.

Methods: Observational cohort study combining Swedish national registries SveDem, the Swedish dementia registry, and Riksstroke, the Swedish stroke registry. Patients with dementia and an acute ischemic stroke 2010–2014 (n=1356) were compared with matched non-dementia acute ischemic stroke patients (n=6755). Outcomes included length of stay in a stroke unit, total length of hospitalisation, and utilisation of diagnostic tests and assessments.

Results: Dementia patients were equally likely to be directly admitted to a stroke unit as their non-dementia counterparts, however, their stroke unit and total hospitalisation length were shorter (10.5 vs. 11.2 days and 11.6 vs. 13.5 respectively, $p<0.001$). Dementia patients were less likely to undergo assessments by the interdisciplinary team members (physiotherapists, speech therapists, occupational therapists; $p<0.05$ for all adjusted models). On the other hand, a similar proportion of patients received a swallowing assessment (90.7% vs. 91.8%, $p=0.218$) and CT imaging (97.4% vs. 98.6%, $p<0.001$).

Conclusion: Patients with dementia and acute ischemic stroke have equal access but shorter stay in a stroke unit, shorter hospitalisation, and are less likely to receive specific diagnostic tests and assessments by the interdisciplinary stroke team compared to non-dementia counterparts. In most aspects of stroke care (e.g. CT, swallowing assessment, longitudinal ECG) we found no or small differences. Diagnosis of dementia should not be the reason to exclude them from post-stroke investigations and rehabilitation.

Disclosure: This project was conducted with support from the Swedish Order of Saint John/Johanniterorden, the Swedish Stroke Association, Stiftelsen Dementia, the Swedish Research Council and the Swedish Associations of Local Authorities and Regions, and FORTE Swedish Research Council for Health, Working Life and Welfare.

EPR3019

Erythrocytes deformability in acute ischemic stroke and cerebral small vessel disease

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Background and aims: Erythrocyte deformability is rheological parameter that measures the ability of blood cells to change their shape in capillary tube. The pathogenesis of acute and chronic ischemia of the brain consist of a violation of cerebral circulation, associated with hemodynamic and rheological disturbantes, leading to diffuse and focal changes in brain tissue. The aim of study is observation of erythrocytes deformability in acute ischemic stroke (AIS) and small vessel disease (SVD).
Methods: The study included 47 patients with AIS, age 62 [53; 69] years, 48 patients with SVD, age 60 [53;65] years, and 20 control patients, age 55 [54,59] years. Erythrocyte deformability measured by laser diffraction in shear rates 90, 180, 360 and 890 s-1. Erythrocyte deformability was been measured in patients with SVD one time and with AIS - 3 times (in the first 12 hours, in 3-5 and 18 - 20 days).
Results: Erythrocyte deformability was significantly reduced in SVD: the index of deformability at shear rates 90-360 s-1 was been low, compared with the AIS and control group (Fig. 1). Was been found a significant deterioration of erythrocyte deformability during the acute phase of ischemic stroke in the measurement from the first hours after stroke to 18-20 days of the disease (Fig. 2).
Erythrocyte deformability in patients with AIS in 18-20 days after onset was significantly lower than in the control group.

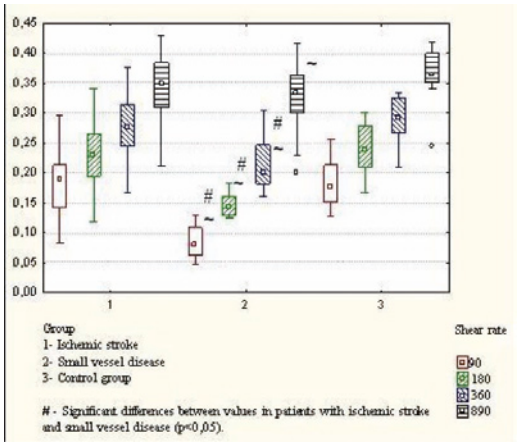

Figure 1. . Erythrocyte deformability at different shear rates in patients with ischemic stroke, small vessel disease and control group

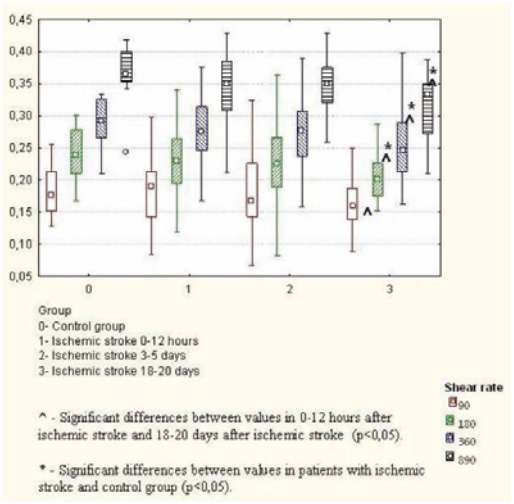

Figure 2. Erythrocyte deformability at different shear rates in patients with ischemic stroke in 12 hours, 3-5 days and 18-20 days

Conclusion: Persistent changes in erythrocyte deformability is important pathogenetic mechanism at the level of microcirculation in patients with chronic and acute cerebrovascular ischemic disorders.
Disclosure: Nothing to disclose

EPR3020

Treatment of acute ischemic stroke classified as lacunar with i.v. rtPA - systematic review and meta-analysis

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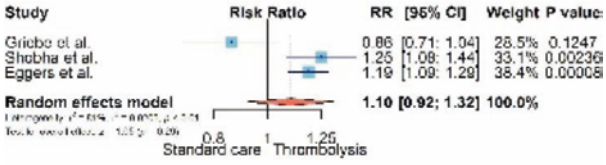
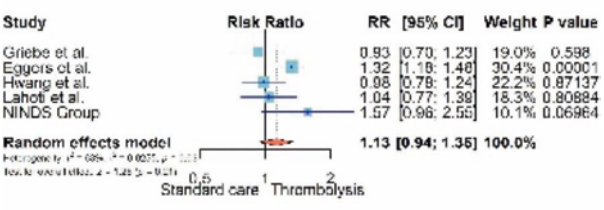
Background and aims: Small-vessel and large-vessel ischemic strokes are characterised by different structure of aetiologies and pathogenesis. Large clinical trials on intravenous thrombolysis (iv-rtPA) combined these groups in effect analyses. Thrombolysis in lacunar stroke (LS) is safe although it is unclear how large is the benefit from this therapy. We reviewed all original studies to determine the efficacy of iv-rtPA in LS.

Methods: Two of the authors have independently reviewed scientific databases using the search code ("lacunar"[Title/Abstract]OR"small vessel"[Title/Abstract]OR"small artery"[Title/Abstract]OR"minor stroke"[Title/Abstract]) AND("thrombolysis"[Title]OR"rtPA"[Title] OR"actilyse"[Title]OR"alteplase"[Title] OR"fibrinolysis"[Title]) for PubMed, and analogical for Scopus. They selected papers towards original comparative trials investigating the efficacy of iv-rtPA administration (vs placebo) in OCSP or TOAST or neuroimaging defined LS, covering as a minimum data on modified Rankin Scale (mRS) at discharge or 90-day. All search and analytical procedures have been based on PRISMA.

Results: Amongst 89 (Pubmed) and 97 (Scopus) initially identified studies, 6 fulfilled the criteria (three defining LS according to OCSP, two –TOAST, one –neuroimaging), and included five observational plus one randomised trial. The meta-analyses did not reveal any significant differences in mRS between thrombolysis and placebo. mRS 0-2 was more frequent in thrombolysed patients (RR=1.10, 95% CI:0.92-1.32, I^2:81%; Figure 1), similar effect was found for mRS 0-1 (RR=1.13, 95% CI:0.94-1.35, I^2:63%; Figure 2).



Forest plot of pooled risk ratio for mRS 0-2



Forest plot of pooled risk ratio for mRS 0-1

Conclusion: There are few trials showing the effects of iv-rtPA in LS. mRS is not an optimal measure of the outcome in these patients as many show initially only mild neurological deficit. Management of LS demands separate analyses and different therapeutic designs in future studies.

Disclosure: Nothing to disclose

EPR3021

Ten years of Stroke code: a retrospective review of diagnostic performance at a comprehensive stroke centre

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Background and aims: Stroke is one of the leading causes of morbidity and mortality in Portugal. Rapid recognition of stroke and timely therapy are the cornerstone of current treatment. The Portuguese stroke code program ensures a fast track for stroke patients recognised by emergency medical services (EMS) using the face-arm-speech criteria (FAST), or at triage using broader criteria (e.g. vision loss, altered consciousness). Our goal was to evaluate the diagnostic performance of both systems over 10 years at a single centre.
Methods: All stroke code activations from 2007-2016 were included. Demographic and diagnostic variables were analysed using descriptive statistics and compared using the chi-squared test.
Results: There were 5028 stroke code activations, of which 63.2% were strokes (83.8% ischaemic). A third (23.5% triage; 42% EMS $p<0.001$) of ischaemic strokes underwent thrombolysis and 12.7% had an endovascular procedure (2015-16). Activations progressively decreased until 2014 (range: 356-722). In 2015-16, there was a marked increase of activations (453 and 712, respectively) likely due to the introduction of mechanical thrombectomy (treatment window up to 6h or if onset unknown). Yearly false positive rates (stroke mimics) were significantly higher with broader triage criteria (EMS: 27.5%-41%, triage: 45-72.5% $p<0.001$). Functional neurological disorders, seizures, syncope and migraine accounted for 55% of total mimics.
Conclusion: Stroke code allowed timely treatment of a good proportion of stroke patients while maintaining a reasonable false positive rate. As expected, broader criteria correlate with higher false positive rates.
Disclosure: Nothing to disclose

EPR3022

Mild encephalitis/encephalopathy with reversible splenial lesion (MERS) in adults-a case report and literature review

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Background and aims: Mild encephalitis/encephalopathy with reversible splenial lesion (MERS) is a rare clinico-radiological entity characterised by the magnetic resonance imaging (MRI) finding of a reversible lesion in the corpus callosum, sometimes involved the symmetrical white matters. Many cases of child-onset MERS with various causes have been reported. However, adult-onset MERS is relatively rare. The clinical characteristics and pathophysiologiccal mechanisms of adult-onset MERS are not well understood. We reviewed the literature on adult-onset MERS in order to describe the characteristics of MERS in adults and to provide experiences for clinician.
Methods: We reported a case of adult-onset MERS with acute urinary retension and performed literature search from PubMed and web of science databases to identify other adult-onset MERS reports from Januarary 2004 to March 2016. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was followed on selection process. And then we summarized the clinico-radiological features of adult-onset MERS.
Results: 29 adult-onset MERS cases were reviewed from available literature including the case we have. 86.2% of the cases (25/29) were reported in Asia, especially in Japan. Ages varied between 18 and 59 years old with a 12:17 female-to-male ratio. The major cause was infection by virus or bacteria. Fever and headache were the most common clinical manifestation, and acute urinary retention was observed in 6 patients. All patients recovered completely within a month.
Conclusion: Adult-onset MERS is an entity with a broad clinico-radiological spectrum because of the various diseases and conditions. There are similar characteristics between MERS in adults and children, also some differences
Disclosure: Nothing to disclose

EPR3023

Cerebrospinal fluid analysis in acute stroke patients of noninflammatory etiology

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Background and aims: Cerebrospinal fluid (CSF) assessment is rarely performed in ischemic stroke, unless inflammatory etiology is suspected. Ischemic stroke initiates inflammatory response. CSF cellular response is reported in variable extent ranging from normal to pleocytosis. Consequently, there is often uncertainty in identifying stroke mimics or underlying inflammatory etiology. The aim was to assess CSF in acute ischemic stroke of noninflammatory etiology.
Methods: Retrospective monocentric analysis of ischemic stroke patients with CSF analysis. Inclusion criteria were complete evaluation of etiology, lumbar puncture in the first 30 days and acute infarction on CT/MR. Exclusion criteria were vasculitis, inflammatory vasculopathy or traumatic puncture.
Results: 127 patients out of 547 screened were included, 81 (63.8%) men, age 59.9 (22-89) years. Mean time of lumbar puncture was 8.0 (SD 5.7) days poststroke. Etiology was in 40 (31.5%) cardioembolic, 26 (20.5%) large vessel atherosclerosis, 11 (8.7%) small vessel disease, 39 (30.7%) undetermined and 11 (8.7%) other. Infarct on imaging was territorial in 22 (17.3%), lacunar 38 (29.9%), cortico-subcortical subterritorial 35 (27.7%) or peripheral emboli 28 (22.0%). Mean CSF leucocyte count was 1.56 (0-30, SD 2.98)/mm^3, erythrocyte 56.56 (0-1000, SD 151.04)/mm^3, total protein was 533.6 (230-1310, SD 217.6) mg/l. We have not found any significant differences depending on infarct size, etiology, age or delay of CSF analysis.
Conclusion: Noninflammatory ischemic stroke should have normal CSF values irrespective of etiology or size. Abnormal CSF should prompt further search for other etiology or stroke mimics.
Disclosure: The study was supported by grant project no. 15-33115A from Czech Health Research Council.

Cognitive neurology/neuropsychology 2

EPR3024

Post-stroke cognitive impairment in patients with metabolic syndrome

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Background and aims: Post-stroke cognitive impairment (PSCI) significantly influences professional, social adaptation, retards patient rehabilitation.
Methods: There were 100 patients after ischemic stroke (IS) in the anterior circulation area enrolled into the study. Cognitive functions 3 and 6 months after IS were evaluated, depending on the presence of metabolic syndrome (MS) and localisation of the ischemic lesion. Patients were divided into 2 groups: with MS (n=62) and without (n=38) and into 3 age subgroups: middle, elderly, senile age. Clinical and neuropsychological examinations, laboratory tests, MRI of the brain were done. Exclusion criteria were aphasia and severe paresis.
Results: The incidence of post-stroke dementia was significantly higher in patients with MS 3 months after IS ($p<0.05$), comparing with patients without MS. There was significant augmentation of PSCI severity with age in patients with and without MS. Comparing data of neuropsychological tests in patients without MS 3 and 6 months after IS we found significant improvement of immediate and delayed associated memory on the Paired Associates Learning Test, increasing of information processing speed on the Stroop Color-Word Interference Test, increase in the rate of psychomotor reactions on the Shulte tables ($p<0.05$), especially in patients with left hemisphere IS. In patients with MS we did not find significant improvement of cognitive functions comparing results of neuropsychological tests 3 and 6 months after IS in both hemisperes of the brain.
Conclusion: Patients with MS had significantly severe PSCI. Presence of MS worsened recovery of cognitive functions in patients with PSCI.
Disclosure: Nothing to disclose

EPR3025

Deficits in cognitive theory of mind are associated with self-perceived lack of social support in Parkinson's disease

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Background and aims: Theory of Mind (ToM) is defined as the ability to infer about other person's state of mind. It has been reported that patients with Parkinson's disease (PD) experience ToM deficits which may result in malfunctioning in day-to-day social relationships. The aim of the current study was to find out if deficits in cognitive ToM performance are associated with impaired social support quality of life (QoL).
Methods: We enrolled 51 non-demented patients with idiopathic PD according to UK Brain Bank Criteria (32 male, age 62.49±10.2, disease duration 6.28±4.78). ToM abilities were assessed using Comic Strip Task which challenges cognitive component of ToM. To assess the health-related QoL 39-item Parkinson's disease Questionnaire (PDQ-39) was used. For further analyses, it was divided into standard subdimensions (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and bodily discomfort). Non-parametric Spearman correlation was used to assess the relationships between the variables.
Results: The performance in Comic Strip Task did not correlate with the total score of PDQ-39. We found a negative correlation between Comic Strip Task and subscore reflecting social support ($r_s=-0.339$, $p=0.022$).
Conclusion: Patients with worse performance in cognitive ToM task reported more significant lack of social support. Deficits in ToM could be one of the underlying mechanisms of self-perceived lack of social support.
Disclosure: This study was supported by APVV grant nr. 15-055.

EPR3026

Epidemiology of functional cognitive disorders: prospective memory clinic study

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Background and aims: A previous retrospective study suggested functional cognitive disorders (FCD) account for >50% of referrals to a dedicated cognitive disorders clinic; age, referral source, and attended alone sign were suggestive of FCD.
Methods: A prospective study to examine clinical features which distinguish functional cognitive disorders (FCD) from traditional cognitive disorders was initiated.
Results: Initial data on 29 patients, seen November-December 2017, were analysed. 20 (69%) were diagnosed with FCD. Compared to patients with other cognitive disorders, a higher percentage of FCD patients was found to be younger (≤65 years: 75% vs 22%), attended alone (50% vs 11%), manifested la maladie du petit papier (15% vs 0%), had positive family history of dementia (40% vs 11%), and had markers of disturbed mood (two question screener for depression, 74% vs 44%) and sleep (dichotomised Jenkins Sleep Questionnaire, 74% vs 44%), but there was no difference in referral source (70% vs 77% from primary care). None of the comparisons reached statistical significance (chi-square test), unsurprisingly in view of the small patient numbers recruited thus far.
Conclusion: FCD are commonly encountered in dedicated cognitive disorders clinics. A positive diagnosis of FCD, rather than a diagnosis of exclusion, may be possible based on relatively simple, dichotomised, clinical observations.
Disclosure: Nothing to disclose

EPR3027

Structural and functional abnormalities underlying cognitive impairment in benign MS

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Background and aims: The definition of benign Multiple Sclerosis (BMS) does not take into consideration cognitive deficits. We investigated whether cognitive impairment in BMS patients is associated with specific patterns of structural and functional abnormalities using advanced MRI techniques.
Methods: High-resolution 3D-T1-weighted, diffusion tensor (DT), dual-echo, and resting state (RS) functional MRI were acquired from 38 BMS patients (EDSS score<3.0 and disease duration >15 years) and 50 matched healthy controls (HC). All patients underwent neuropsychological assessment. Regional GM atrophy was estimated using a voxel-based-morphometry analysis, WM microstructural abnormalities were investigated with tract-based-spatial-statistical analysis, and RS functional connectivity (FC) was assessed using independent-component analysis.
Results: 16 (42%) BMS were classified as cognitively impaired (CI). Compared to HC, cognitive preserved (CP) BMS patients had GM atrophy of thalami, left precuneus and left middle cingulum. In CI-BMS patients, GM atrophy in the anterior/posterior cingulate gyrus, left caudate nucleus, and right precentral gyrus was also found. Compared to HC, CP and CI-BMS patients had decreased fractional anisotropy of supratentorial/infratentorial WM tracts and increased mean (MD), axial and radial (RD) diffusivity of the main supratentorial WM tracts. CI-BMS patients had additional increased MD and RD of several infratentorial regions located in the cerebellum and brainstem. Compared to the other two groups, CI-BMS patients showed a widespread increase of RS-FC in fronto-temporo-parietal regions of the attention and executive functions networks.
Conclusion: Distinct patterns of structural and functional abnormalities relevant for cognitive processing are associated with CI in MS patients with a benign course.
Disclosure: Partially supported by Fondazione Italiana Sclerosi Multiple (FISM2013/S/1).

EPR3028

Divergent thinking and cognitive reserve in mild cognitive impairment

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Background and aims: In the last years, creativity and its potential role in terms of diagnosis and rehabilitation for patients with Alzheimer's disease (AD) has attracted the scientific interest. Research has demonstrated that divergent thinking (DT) usually begin early to decrease in non-artist AD patients but less is known about patients affected by Mild Cognitive Impairment (MCI). The present study aimed to preliminary evaluate the relationships between DT, cognitive reserve (CR) and neuro/psychological conditions in MCI patients.
Methods: 32 subjects, 12 MCI patients and 20 controls, has been recruited in this observational study. The main measures were general cognitive functioning (Mini Mental State Examination – MMSE; Montreal Cognitive Assessment -MOCA), CR index (CRIq), divergent thinking (Abbreviated Torrance Test for Adults - ATTA) and psychological conditions scales (i.e. perceived quality of life, depression, anxiety and apathy).
Results: MCI patients performed worse at MOCA ($p=0.05$). A significant positive correlation between ATTA total score and CRIq total score ($p=0.05$) and a negative correlation between AES (Aphaty Evaluation Scale) and ATTA total score ($p=0.01$) were found in the whole sample.
Conclusion: Despite the small sample of patients, our preliminary results showed that, in line with the current literature, there was a significant positive correlation between DT and CR. These results allowed us to hypotize that an early cognitive intervention focused on divergent thinking could enhance CR and subsequently slow down the cognitive decline of MCI patients. Our results suggested also the necessity for further investigations about the relationship between apathy and creativity.
Disclosure: Nothing to disclose

EPR3029

The effect of early-stage Alzheimer's disease on right-left discrimination and mental rotation

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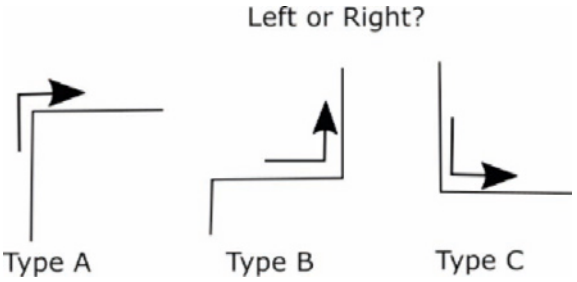
Background and aims: Alzheimer's disease (AD) is associated with gradual cognitive decline that may result in spatial disorientation. We aimed to evaluate two spatial abilities – right-left discrimination and mental rotation in early clinical stages of AD.
Methods: 152 participants – amnestic mild cognitive impairment (aMCI) due to AD (n=62), mild AD dementia (n=37) and cognitively normal (CN) older adults (n=53) underwent clinical and neuropsychological evaluation, MRI brain scan and Standardized Road-Map test of Direction Sense (RMTDS). In the RMTDS, the participants followed a pathway on a city map indicating a direction of turning (left or right) at each intersection. Group and gender differences in a total score (the higher the better) and three subscores – A) left-right discrimination without rotation, B) half-, and C) full- mental rotation were evaluated using non-parametric tests with Holm-Bonferroni correction.



Different turn types

Results: Both AD groups had lower RMTDS total score, B and C subscores than the CN group ($p<0.001$). AD dementia group had lower subscore A than the CN group ($p<0.001$). Men reached higher scores than women across all groups ($p<0.001$). The between-group differences were more pronounced among the women ($p\leq0.003$).
Conclusion: Patients in the early clinical stages of AD including aMCI due to AD and mild AD dementia were impaired in mental rotation, while right-left discrimination was impaired only in mild AD dementia. Gender differences in the RMTDS favoring men may be taken into account when evaluating the test. RMTDS may be a useful test to detect spatial cognition decline in the early stages of AD.
Disclosure: Nothing to disclose

EPR3030

Predictors of cognitive impairment in untreated Multiple Sclerosis: preliminary findings

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Background and aims: Cognitive impairment is frequent in Multiple Sclerosis (MS), but its natural history has still to be completely elucidated. This is partly due to the early treatment approach, which is able to modify neurodegeneration and brain volume, likely deflecting the natural trajectory of cognitive decline. On this background, the aim of our study is to assess the cognitive performance of MS patients who did not undergo early disease modifying treatment (DMT) and to correlate findings with well established clinical and imaging prognostic measures collected at disease onset.

Methods: Complete neuropsychological testing (T1) was administered at last follow-up consult (in 2017) to all MS patients who did not receive DMT over the first five years of disease. So far, we enrolled 22 patients, who were defined as cognitively healthy or impaired. We retrospectively collected clinical (sex, age, type and recovery from first attack, relapse-rate) and MRI (lesion load rated: ≤10 or >10) data at onset.

Results: Clinical features are presented in Table 1. We found a statistically significant association between current cognitive state and MRI lesion load at onset (chi-square=5.59, p=0.018). Conversely, we found no other statistically association with other prognostic factors (gender, severity or onset type, relapse-rate). Noteworthy, we found a trend of association with older age at onset (≥35year-old, p=0.09).

Demographic data and MS history N=22	
Female (N, %)	15 (68%)
Age at onset, years (mean value ± SD).	37 ± 10,6
Age at T1, years (mean value ± SD).	54 ± 8,6
Functional system at onset. N (%):	
-pyramidal	8 (36,3%)
-sensory	2 (9,1%)
-cerebellar	2 (9,1%)
-brainstem	2 (9,1%)
-visual	2 (9,1%)
-sphinteric	6 (27,3%)
Relapse-rate in the first 5years of disease. N (%)*:	
-high relapse-rate (>0,5)	10/20 (50%)
-low relapse-rate (<0,5)	10/20 (50%)
*2PPMS were excluded	
Lesion load MRI at onset. N (%):	
- <=10 lesions	13 (59%)
- >10 lesions	9 (41%)
MS type at T1. N (%):	
-RR	17 (77,3%)
-SP	3 (13,6%)
-PP	2 (9,1%)
Disease duration at T1, years (mean value ± SD).	16,7 ± 7,2

Table 1

Conclusion: Lesion load at onset may predict cognitive changes over time in MS patients who underwent delayed or no DMT. We plan to increase our sample size and collect MRI data on atrophy and grey matter lesions to strengthen our results.

Disclosure: Nothing to disclose

Epilepsy 3

EPR3031

Detection of motor seizures using wearable multi modal sensors

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Background and aims: This study aims to evaluate the detection of motor seizures using physiological parameters such as ictal movements, heart rate and audio signal with wearable multi-modal sensors that are available with smart watches.

Methods: 35 seizures (13 automotor seizures, 11 tonic-clonic seizures, and 11 hypermotor seizures) of 12 patients (5 F, 7 M, mean age 26±9.7) who were underwent continuous EEG-video-monitoring were included. Seizure detection included analysis of limb movements via four accelerometer (ACM) (418 hours of data), heart rate (HR) and audio data. One class non parametric probability density function classifier was used to identify seizures.

Results: Hypermotor seizures were detected with a sensitivity of 100%, a positive predictive value (PPV) of 76.8%, specifity of 99.5% and a false detection rate (FDR) of 0.025 per hour. Automotor seizures were detected with a sensitivity of 96%, PPV of 65.8%, specifity of 98.9% and a FDR of 0.088. Tonic-clonic seizures were detected with a sensitivity of 100%, PPV of 80.5%, specifity of 99.6% and a FDR of 0.025. Adding audio and HR data to movement data improved the sensitivity and PPV by 12%. Using four ACM sensors did not improve the seizure detection performance significantly compared to one sensor.

Conclusion: Motor seizures in epilepsy patients can be reliably identified using currently available wearable multimodal sensors such as smart watches.

Disclosure: Nothing to disclose

EPR3032

The therapeutic effect of repetitive transcranial magnetic stimulation (rTMS) combined with neuronavigation systems on non-lesional focal epilepsy

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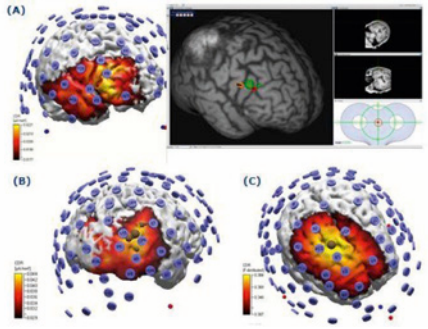
Background and aims: Repetitive transcranial magnetic stimulation(rTMS) is a non-invasive technique that changes excitability of different cortical areas. Our aim is to evaluate the number and duration of seizures in patients with focal epilepsy during and after 0.5Hz-rTMS.

Methods: Three patients with focal epilepsy were studied whose electrical sources of paroxysmal activity in neocortical regions were determined. They received standard pharmacological treatment without modification from at least 1-month before study.

rTMS was carried out at baseline, intervention, follow-up periods. The baseline period duration was 4-weeks and intervention with rTMS for 2-weeks, follow-up period for 8-weeks.

A high-resolution 120ch-EEG was used. The epileptic focus was determined with current source analysis of paroxysmal activity by sLORETA. Current sources are restricted to brain parenchyma by the use of a mask that prohibits solutions where the mask is zero, i.e., in the CSF (Figure1). rTMS session at 0.5Hz was carried out on the epileptogenic zone with total of 900pulses delivered at 100% intensity of the resting motor threshold (RMT) during 2-weeks. Using neuronavigation system improved the targeting of the epileptic foci (Figure1).



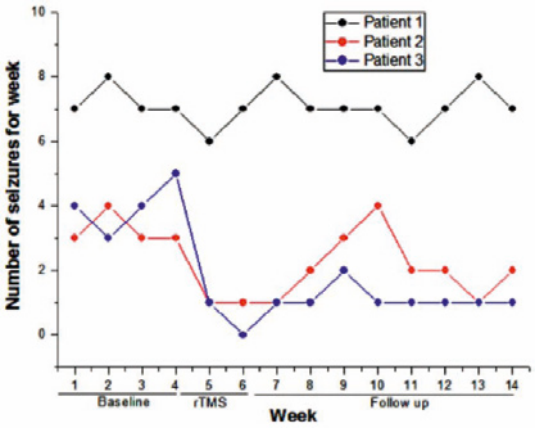
Localisation of the epileptic focus using sLORETA (A)Rt. inferior frontal region of patient No.1. A precise localisation of the epileptic focus combined with neuronavigation systems to place the coil over the head improved targeting of the epileptic foci (B)Rt. parietal region of patient No.2 (C)Rt. superior frontal region of patient No.3

Results: Seizure reduction

During the baseline, three patients had seizures, 7.25,3.25,4times/week. In patient 2&3, this frequency decreased during the intervention to 1,0.5/week respectively, which means 69%, 87% reduction. During follow-up period, this decreased to 2.13,1.13/week, corresponding to 34%, 72%(Figure2).

Patient	Gender	Years of evaluation	Age	Focus localization with sLORETA
1	M	21	24	Rt Inf. Frontal
2	F	10	26	Rt Parietal
3	F	13	28	Rt sup. Frontal

Clinical data of patients with focal epilepsy



Mean number of seizures per week during, baseline, rTMS and follow-up period.

Conclusion: We think that 0.5Hz rTMS over epileptic focus decrease the number of seizures in patients with focal epilepsy. rTMS for non-lesional focal epilepsy may be an alternative treatment for pharmoco-resistant patients, who have the identifiable seizure foci.

Disclosure: Nothing to disclose

EPR3034

Single-center long-term results of vagal nerve stimulation for epilepsy: a 10–17 year follow-up study

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Background and aims: We present a long-term follow-up study of VNS patients, analysing seizure outcome, the role of medication changes, and surgical aspects.

Methods: The study followed 74 adult patients with VNS for 10 to 17 years. The patients were evaluated yearly as: non-responder – NR (seizure frequency reduction<50%), responder – R (seizure frequency reduction ≥ 50% and<90%), and 90% responder – 90R (seizure frequency reduction ≥ 90%). Patients with delayed response (≥ 4 years after surgery) and patients with battery replacement or complete system replacement were identified.

Results: A markedly increasing R rate was evident up to study year 4, and the 90R rate rose to year 6; both then remained stable until the end of the study. During the study period, antiepileptic therapy was changed in 62 patients (87.9%). There were 11 delayed responders (categorised as R at or after study year 4) with associated antiepileptic medication changes in 9. There were four delayed 90R (categorized as 90R at or after study year 4) with associated antiepileptic treatment changes in three. At least one battery replacement was performed in 51 patients (68.9%), 49 of which were categorised as R or 90R. A complete system replacement was needed in seven patients (9.5%). The VNS system was explanted in seven NR (9.5%).

Conclusion: The study provides data on VNS patients over a long-term, complex follow-up period. After an initial steady increase for at least four years, the rate of R and 90R remained high and stable.

Disclosure: Nothing to disclose

EPR3035

Individual prediction of post-operative verbal memory decline in temporal lobe epilepsy: the contribution of post-ictal memory testing

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Background and aims: The prediction of verbal memory decline after temporal lobe epilepsy surgery remains difficult at individual level. We evaluated the prognostic value of post-ictal memory testing in predicting the post-operative verbal memory decline.
Methods: 74 consecutive patients were included, who underwent temporal lobe epilepsy (TLE) surgery in our center with preoperative interictal/post-ictal and post-operative memory testing. Verbal memory was evaluated using Rey's auditory-verbal learning task. Sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) were calculated to find the best threshold to predict a clinically significant post-operative verbal memory decline (20%). The analysis was performed for all TLE patients and for the subgroup with hippocampal sclerosis (HS).
Results: The L-TLE patients (n=39) had lower verbal memory scores than R-TLE at 3 months (59 vs 79%) and 12 months (54 vs 79%) after surgery. The interictal scores correlated with the post-operative decline (CC=0.415, $p<0.001$). The post-ictal verbal memory predictive value was not significant in the whole group ($p=0.25$). In HS patients, the post-ictal verbal memory predicted the post-operative VDR decline ($p=0.03$, AUC=0.694, CI [0.493-0.895]). The 40% posti-ctal decline had Sn of 46%, Sp of 90%, PPV of 63%, NPV of 82% and an AUC of 0.677 to predict a significant post-operative memory decline in patients with HS.
Conclusion: Post-ictal memory testing is a non-invasive bedside measure that can help predict the post-operative verbal memory decline in patients with HS with an overall accuracy of 78%.
Disclosure: Nothing to disclose

EPR3036

Is automated interictal epileptiform discharge detection sufficient to diagnose epilepsy from overnight EEG?

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Background and aims: In clinical practice, the detection of interictal epileptiform discharges (IED) in overnight EEG is the hallmark to diagnose epilepsy. Nevertheless, visual analysis to identify the IEDs in the EEG is a labor-intensive, objective and time consuming task. In this study, we investigate the usefulness of automated IED detection to diagnose epilepsy.
Methods: 38 patients had an overnight EEG recording at the University Hospital of Geneva, Switzerland. Epilepsy diagnosis based on visual inspection of the EEG, performed by expert electrophysiologist (MS), was compared to diagnosis made by a second blinded expert electrophysiologist (SV) based on the automatically detected IEDs that were summarised in a concise report (Epilog NV, Belgium). The blinded reviewer did not receive any clinical information about the patient.
Results: Visual interpretation of the overnight EEG led to a diagnosis of epilepsy in 12 of the 38 admitted patients had IEDs present in the overnight EEG. The diagnosis based on the report corresponded with the visual analysis in 33 of the 38 patients. The sensitivity of epileptic diagnosis was 75%, the specificity 92%, positive predictive value 82% and negative predictive value 89%, which corresponds to a diagnostic odds ratio of 36.
Conclusion: We showed that automated IED detection can help in the diagnosis of epilepsy from overnight EEG. It can help neurologists decrease the time spent for visual analysis of the EEG, but for now the achieved sensitivity should be augmented before using it in standard clinical practice. This could be achieved by adding clinical details about the patient to the reports.
Disclosure: Pieter van Mierlo is co-founder and shareholder of Epilog NV, Belgium.

EPR3037

Remodeling of morphology in temporal lobe epilepsy

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Background and aims: Medial temporal lobe epilepsy (TLE) is one of the most widespread neurological network disorders. Computational anatomy MRI studies demonstrate a robust pattern of cortical volume loss. The majority of statistical analyses provide information about localisation of significant focal differences in a segregationist way. Multivariate Bayesian modeling provides a framework allowing causal inferences about interregional dependencies. We adopt this approach to answer following questions: Which structures within a pattern of dynamic epilepsy-associated brain anatomy reorganisation best predict TLE pathology and do these structures differ between TLE subtypes?
Methods: 128 TLE patients were characterised dependent on laterality of epileptogenic focus and on MRI detected pre-/absence of mesial temporal lobe sclerosis (MTS/MRI-) and compared to 120 healthy volunteers.
Building upon classical inferences on mass univariate analysis of MRI data, we observed a pattern of structural reorganisation in TLE patients. Using MVB, we set the detected partitioned cortical regions as distinct regional models to estimate their predictive power for disease and TLE subtypes using Bayesian model selection.
Results: Corresponding ranking of predictive structures demonstrated that volume estimates in ipsilateral medial temporal lobe regions best predict disease-related cortical differences between TLE and healthy controls, independent of laterality and TLE subtype. Consequent ranking positions were located in ventromedial PFC for left TLE and bilaterally thalamic and ipsilateral temporal polar for right TLE.
Conclusion: Para-/hippocampal regions are the most predictive ones for disease-related remodeling whereas beyond medial temporal lobes, focal weightings are highly dependent on laterality of the epileptogenic focus and mesial temporal lobe pathology.
Disclosure: BD and ER are supported by the Swiss National Science Foundation (NCCR Synapsy, project grant Nr 320030_135679 and SPUM 33CM30_140332/1), Foundation Parkinson Switzerland and Foundation Synapsis. The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 604102 (Human Brain Project).

EPR3038

Efficacy and safety of different antiepileptic drugs in post-stroke epilepsy

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Background and aims: The proper choice of antiepileptic therapy is of a major importance for patients with post-stroke epilepsy (PSE). Interactions with cardiovascular therapy, attenuation of post-stroke depression or vascular cognitive impairment are possible side effects of antiepileptic drugs (AEDs). Data on efficacy and safety of AEDs in PSE are limited. The aim was to compare different AEDs in the treatment of PSE in terms of an observational study.
Methods: Data on patients with PSE on antiepileptic monotherapy were collected and analysed in terms of the Mainz Epilepsy Register (MAINZ-EPIREG) and the Marburger Stroke Register (MARSTREG).
Results: Overall, 88 patients with PSE on antiepileptic monotherapy were recruited. In this cohort, 25% of patients (N=22) were treated with levetiracetam(LEV), 22.7%(N=20) with eslicarbazepine (ESL), 22.7%(N=20) with lacosamide(LCS), 15.9%(N=14) with lamotrigine(LTG), 13.6%(N=12) with valproate. The mean annual seizure frequency was 2±4 on LCS, 2±3 on ESL, 3±5 on LEV, 4±8 on LTG and 5±7 on VPA. Among side effects, the most frequent were vertigo (25%), tiredness (15.9%) and headache (13.2%). Post-stroke depression was attenuated in 31.8% of patients on LEV. Other AEDs did not show association with depression. Insomnia was reported by 42.9% of patients on LTG. Weight gain was observed in 41.7% of patients on VPA.
Conclusion: Our analyses show the best efficacy and the most desirable safety profile for ESL and LCS in the monotherapy of PSE. One can speculate that AEDs facilitating slow inactivation of sodium channels have most favourable properties for the treatment of PSE. Farther studies with larger patient groups should replicated these findings.
Disclosure: Nothing to disclose

EPR3039

Cost savings and improved patient outcomes from best management of epilepsy

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Background and aims: Variability in access to epilepsy care results in delayed diagnosis and access to treatments. This results in poorer clinical outcomes and has economic consequences. As part of the European Brain Councils Value of Treatment programme we modelled the costs of 'better' management versus 'current' management, using the UK as an example.

Methods: Using the NICE-guidelines as the reference for better management, we constructed an economic model that considered patient pathways from first seizure through to epilepsy surgery, with a time horizon of 70 years. Costs and quality adjusted life years (QALYs) were considered from the perspective of the UK National Health Service and discounted at an annual rate of 3.5%. The model pathways, and the assumptions underpinning the model, were determined through consultation with EU clinical experts, reviews of the literature, and data from the SANAD study.

Results: For better compared to standard care, we estimate an incremental cost-effectiveness ratio (ICER) of £6,848 per QALY gained for people aged 20 with epilepsy. 97.6% of the monetary savings resulted from preventing seizures and hence complications and admissions. The overall incremental cost per person associated with better management was £7,321 with an incremental QALY gain of 1.069 per person.

Conclusion: Failure to provide good accessible epilepsy care results in poorer clinical outcomes. Our results indicate that it would be cost effective invest in services, with ICERs per QALY much lower than those typically estimated for new treatments and technologies. Our open access model is available in the public domain.

Disclosure: This case study on epilepsy is part of a series of case studies covering nine neurological and psychiatric conditions, conducted within the "Value of Treatment for Brain Disorders" research project of the European Brain Council and was supported by Livanova and UCB.

Headache and pain 3

EPR3040

Utilisation of acute neurological service during the European refugee crisis in Salzburg, Austria 2014-2016: high rate of chronic pain and psychiatric comorbidity

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Background: Between 2014 and 2016, the European Union experienced an unprecedented influx of refugees. Little is known about neurological emergencies during the arduous journey, which would be valuable to prepare health care providers for upcoming challenges.
Aim of the study: To analyse acute neurological health service utilisation among refugees and asylum seekers in a gateway city along the refugee route.
Material and methods: Retrospective chart review of refugees and asylum seekers treated at the neurological emergency ward of a tertiary care in Salzburg, Austria between 2014-2016. Demographics and diagnosis on discharge were extracted and compared with findings in consecutive non-refugee patients utilizing acute neurological service between Jan-Apr 2015.
Results: The refugee group consisted of 134 patients (77.6% men) with a median age of 30.2 years (range 15-70). The most frequent countries of origin were Afghanistan, Syria and Iraq (total 86.6%). Diagnosis on discharge were most frequently headache and back pain (47.8 and 38.1%, respectively), followed by psychiatric disorders (33.6%).
The patients in the non-refugee group (679 patients, 51.7% men) were significantly older (median 67.9 years, range 11-101, P<0.0001). Diagnoses at discharge in this cohort were headed by cerebrovascular disease (50.8%) and seizures (18.1%).
Discussion: Both demographics of patients and conditions leading to acute neurological consultations differ for refugees and asylum seekers. Health care provides need to take the high rate of pain syndromes and psychiatric disorders for future provision of adequate medical service into account.
Disclosure: Nothing to disclose

EPR3041

Comparing effectiveness of electrocatheter-mediated pulsed radiofrequency to epidural adhesiolysis for chronic lumbosacral radicular pain with neuropathic features: a randomised controlled study

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Background and aims: Objective of this study is to investigate the effectiveness of electro-catheter-mediated pulsed radiofrequency and epidurolysis (P+E) in comparison with epidurolysis alone (E) in chronic lumbosacral radicular pain with neuropathic features.
Methods: We evaluated 31 adult patients suffering from an unresponsive single leg-radiating neuropathic pain lasting for>6 months. 19 subjects were randomly assigned to P+E whereas 14 subjects underwent E. Mean changes in numeric rating scale (NRS), Italian Pain Questionnaire, Oswestry Disability Index (ODI) and DN4 questionnaire at pre-treatment, one and six months post-treatment. P values<0.05 were considered statistically significant.
Results: At one and six months respectively, a significant reduction in mean NRS (p=0.01, p=0.01), ODI (p=0.03, p=0.01) and DN4 score (p=0.03, p=0.02) was observed in the P+E compared to E group. The 58% and 53% in P+E but only the 29% and 21% of patients in the E group showed a radicular pain reduction in NRS>30% at one and six month respectively.
Conclusion: P + E appears to be more effective than E in the treatment of chronic lumbosacral radicular pain with neuropathic features.
Disclosure: Nothing to disclose

EPR3042

Evaluation of peripheral vascular alteration in migraine patients by using video capillaroscopy

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Background and aims: The aim of this study is to examine the nailbed capillaries of migraine patients with video capillaroscopy and to show the extracranial vascular changes.
Methods: 45 migraine patients and 50 control were included. Demographic data, migraine disability scale and numeric pain rating scale were noticed. Nailbed assessment was made on total of 8 fingers of both hands excluding the thumbs. Capillary architecture, tortuosity, avascular fields, hemorrhage, the presence of giant capillaries were evaluated. The largest diameters of apical capillaries, capillaries, veins and arteries detected in the measurements of all fingers were recorded and the average of the largest three measurements was accepted as the overall value of the patient.
Results: Capillary tortuosity and giant capillaries were seen more frequently in migraine patients ($p<0.05$). The apical diameter of the patient group was found to be significantly larger ($p= 0.045$). The severity of the headache was directly proportional with the incidence of giant capillaries ($p=0.015$). The severity of the headaches increased with the diameter of the capillaries ($p=0.024$).The effect of the length of headache history by means of years on the capillaroscopic findings was investigated. Migraine incidence was found to be directly proportional with the apical diameter ($p=0.005$).
Conclusion: Vascular pathology can be determine objectively by using video capillaroscopy.Increased tortuosity is a sign of tissue hypoxia. Increased tortuosity and giant capillaries were seen more frequently in migraine patients and migraine patients with old headache history also. These findings will be guide for understanding migraine pathophysiology.
Disclosure: Nothing to disclose

EPR3043

Headache intensity is associated with increased white matter lesion burden in CADASIL patients

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Background and aims: CADASIL (Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy) is the most common hereditary cause of vascular dementia in adults. Migraine is a major symptom of the disease.
Aim: To identify variables associated with increased cerebral lesion burden in a cohort of Portuguese CADASIL patients.
Methods: Cross-sectional study of CADASIL patients. Demographics data, vascular risk factors and headache characteristics were collected through a structured questionnaire. MRI (3-Tesla) was used to determine white matter hyperintensities burden - in terms of volume (WMH-V) and number (WMH-N).
Results: We included 32 patients with CADASIL. WMH-V was significantly associated with age ($\beta=1.266$, 95%CI=[0.805, 1.726], $p<0.001$), headache intensity ($\beta=5.143$, 95%CI=[2.362, 7.924], $p=0.001$) and female sex ($\beta=19.727$, 95%CI=[8.750, 30.075], $p=0.001$). WMH-N is best predicted by age, obesity and history of migraine, although not statistically significant.
Conclusion: Age, female sex and headache intensity are associated with increased white matter lesion burden in CADASIL.
Disclosure: Nothing to disclose

EPR3044

Gene expression of the endocannabinoid system components in peripheral blood mononuclear cells of subjects with migraine

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Background: Among the mediators involved in the modulation of the trigeminovascular system, the endocannabinoid system (ES) has recently attracted considerable attention. The ES interacts with the serotonergic system, NO synthesis and neuropeptides release, all of which are involved in migraine pain. Increasing experimental and clinical evidence suggests a link between dysregulation of this system and migraine.
Aim: To further investigate the possible changes in ES tone in episodic and chronic migraine.
Methods: The gene expression of cannabinoid receptors CB1 and CB2, and of two enzymes involved in the metabolism/catabolism of endocannabinoids - N-Acyl Phosphatidylethanolamine Phospholipase D (NAPE-PLD) and FAAH) - was evaluated by means of rtPCR in peripheral blood mononuclear cells (PBMCs) of patients with episodic or chronic migraine and age-matched healthy controls.
Results: We detected an increase in cannabinoid2 (CB2) gene expression in PBMCs of migraine subjects, compared to controls. The increase was more markerd in subjects with chronic migraine when compared to either episodic migraine and controls. CB1 and NAPE-PLD gene expression increased only in chronic migraine patients. A significant decrease in FAAH gene expression was found in all migraineurs compared to controls, with significantly lower levels in chronic migraine patients.
Conclusion: The present findings show significant transcriptional changes in ES components in PBMCs of patients suffering from migraine. These changes are more marked in the chronic subtype of migraine and, for their characteristics, they are likely to reflect ongoing compensatory mechanisms aimed at maintaining AEA levels.
Disclosure: Nothing to disclose

EPR3045

Role of the transient receptor potential ankyrin type-1 (TRPA1) channel in migraine pain: evaluation in an animal model

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Background and aims: To date, the pharmacological treatment of migraine remains somewhat unsatisfactory, partly because the pathophysiology of this disabling disease is still poorly understood. Clinical and experimental studies have pointed to the possible involvement of the transient receptor potential ankyrin type-1 (TRPA1) channels in migraine pain.
The aim of this study is to further investigate the role of TRPA1 in the pathophysiology of migraine pain in an animal model using a novel TRPA1 antagonist (ADM_12) as a probe.
Methods: The effects of ADM_12 on nitroglycerin-induced hyperalgesia at the trigeminal level were investigated in male rats using the quantification of nocifensive behavior in the orofacial formalin test. The expression levels of the genes coding for c-Fos, TRPA1, calcitonin gene-related peptide (CGRP) and substance P (SP) was evaluated in peripheral and central neuronal areas relevant for migraine pain.
Results: The findings show that ADM_12 inhibited the hyperalgesia induced by nitroglycerin treatment, in the second phase of the orofacial formalin test. This effect was associated to a significant inhibition of nitroglycerin-induced increase in c-Fos, TRPA1 and neuropeptides mRNA levels in medulla-pons area, cervical spinal cord and in the trigeminal ganglion.
Conclusion: The present findings support a critical involvement of TRPA1 channels in the pathophysiology of migraine, and show their active role in counteracting hyperalgesia at the trigeminal level.
Disclosure: Nothing to disclose

EPR3046

The efficacy of ergotamine-based combination antimigraine drug compared to sumatriptan in the treatment of migraine without aura

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Background and aims: The aim of the study was to investigate the efficacy of ergotamine tartrate + mecloxamine ciitrate + camylofine hydrochloride + caffeine + propyphenazone (Nomigren®) compared to Sumatriptan in the treatment of migraine without aura.

Methods: The study was designed as double-blind with double placebo (double dummy), parallel, randomised, multicentric. The study included patients aged 18-64 years with a diagnosis of migraine without aura according to the International Headache Society Criteria (ICHD-3 Beta). There were 201 respondents in four clinical centers (98 in the Nomigren® group and 103 in the Sumatriptan group). The efficacy was assessed on the basis of a complete cessation of pain two hours after administration of the drug and the need for additional analgesic therapy (diclofenac).

Results: The use of Nomigren® resulted in the complete cessation of pain in 51% of reported migraine headaches without aura (91/178), while Sumatriptan administration resulted in complete cessation of pain in 34% of migraine attacks (62/184) (p=0.0015). The use of additional analgesic therapy with diclofenac was observed in 21% of migraine attacks in the Nomigren® group and 35% in the Sumatriptan group (p=0.004). A complete failure of therapy was observed in 2 subjects in the Nomigren® group and in 9 subjects in the Sumatriptan group (p=0.0006). Approximately the same number of patients in both groups (70%) were willing to continue the therapy.

Conclusion: The study showed better effectiveness of Nomigren® in the complete cessation of migraine pain compared to Sumatriptan in the treatment of migraine without aura.

Disclosure: Nothing to disclose

EPR3047

Are clinical features of nummular headache different when precipitated by head trauma? Analysis of a series of 225 patients

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Background and aims: Nummular Headache (NH) is located in a sharply contoured rounded area of the scalp. Head trauma as a precipitating event has been described. We aimed to compare characteristics of idiopathic and post-traumatic NH.

Methods: Patients diagnosed of NH in a Headache Unit in a tertiary hospital (January 2008-January 2018), accordingly to ICHD criteria. We prospectively considered clinical and epidemiological data, comparing idiopathic cases with those triggered by a cranial trauma.

Results: We included 225 patients (145 women, 80 men) with NH. Among them 29 (23 women, 6 men) described a head trauma related to beginning of pain. In 27 there was a background pain of oppressive or burning character and rated as 5±1.9 (2-10) on a verbal analogical scale (VAS), and in 12 stabbing superimposed exacerbations rated as 6.6±1.3 (4-8) on VAS. In 15 post-traumatic patients, an oral preventative was considered necessary, usually gabapentin, achieving at least a partial relief in most cases. When comparing groups with or without previous trauma, age of onset was higher among post-traumatic patients (59.9±17.4 vs 48.1±18 years, p:0.002). Allodynia upon palpation was encountered more frequently in trauma triggered painful areas (53.3% vs. 32.7%, p:0.04). There was no difference between both groups regarding characteristics of pain, location of painful areas or requirement of preventatives and their efficacy.

Conclusion: Cranial trauma is not an uncommon trigger in our series of Nummular Headache. Patients with post-traumatic forms are older and the presence of allodynia is more frequent.

Disclosure: Nothing to disclose

EPR3048

Efficacy of erenumab for the treatment of patients with episodic migraine with aura

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Background and aims: Erenumab is a fully human monoclonal antibody that inhibits the calcitonin gene-related peptide (CGRP) receptor. In a Phase III study (NCT02456740), erenumab demonstrated a significant reduction in the mean monthly migraine days (MMD) compared with placebo. Here, we report a subgroup analysis assessing the efficacy of erenumab in episodic migraine patients with/without history of aura (self-reported).
Methods: Patients were randomised 1:1:1 to erenumab 70mg, 140mg or placebo monthly for 6 months. This subgroup analysis assessed changes in MMD, acute migraine-specific medication days (MSMD), and proportion of patients achieving ≥50% reduction in MMD averaged over months 4-6. Nominal p-values were presented without multiplicity adjustment and were not used for pre-planned hypothesis testing.
Results: Of 955 patients randomised, 52% had a history of aura. Baseline characteristics were similar among the groups. Compared with placebo, erenumab induced greater reductions in MMD in both the subgroups. In patients without history of aura, least-squares mean (SE) changes from baseline were −1.5 (0.3) for placebo vs −2.7 (0.3) for 70mg ($p=0.002$) and −3.8 (0.3) for 140mg ($p<0.001$). In patients with history of aura, changes were −2.1 (0.3) for placebo vs −3.8 (0.2) for 70mg ($p<0.001$) and −3.5 (0.3) for 140mg ($p<0.001$). In both the subgroups, treatment with erenumab 70 and 140mg resulted in more patients achieving ≥50% reduction in MMD and fewer acute migraine-specific medication days than with placebo (Table).
Conclusion: Erenumab was efficacious in migraine patients with and without history of aura.
Disclosure: This study was supported by Amgen Inc. USA

EPR3175

Pericranial nerve block for the short-term preventive treatment of refractory chronic migraine: a randomized, double-blinded, placebo-controlled study

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Background and aims: This study aims to investigate the efficiency of a single and repeated the greater occipital nerve (GON), the supraorbital (SON) and the auriculotemporal nerve (ATN) block using lidocaine in the treatment of refractory chronic migraine.
Methods: Patients between 18 and 60 years old with chronic migraine (modified ICHD-II as patients with > 10 days with consumption of acute medications were permitted into the study) were randomized to receive either 5 ml 1% lidocaine plus 5mg dexamethasone over pericranial nerve block application or 6 ml normal saline(placebo). Patients completed a one-month headache diary prior to and after the double-blind injection. The primary outcome measure was defined as a 50% or greater reduction in the frequency of days with moderate or severe migraine headache in the four-week post-injection compared to the four-week pre-injection baseline period.
Results: 50 patients received active and 50 patients received placebo treatment. In the active and placebo groups respectively, the mean frequency of at least moderate (mean 6.2 versus 9.5) and severe (2.6 versus 4.3) migraine days and acute medication days (5 versus 10.0) were statistically significant difference between the groups after treatment ($p>0.05$). The percentage of patients with at least a 50% reduction in the frequency of moderate or severe headache days was 45% for pericranial nerve block group.
Conclusion: These results show that repeated pericranial nerve blocks with local anesthetic can be an effective alternative treatment in migraine patients who are unresponsive to medical prophylaxis or who do not prefer to use medical prophylaxis.
Disclosure: Nothing to disclose

Miscellaneous

EPR3049

TK2-deficiency masquerading as critical illness neuromyopathy in an adult

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Background and aims: Critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) are common complications in patients undergoing intensive care treatment. They are usually diagnosed on clinical grounds and by neurophysiological findings.
Methods: A 37-year-old patient sustained hypoxic brain damage after resuscitation from cardiac arrest and required prolonged artificial ventilation. After developing a severe flaccid tetraparesis with bilateral ptosis, a diagnosis of CIP/CIM was made based on the neurophysiological findings of severe neuropathy and myopathy. A 53-year-old patient developed peritonitis with sepsis which necessitated long-term artificial ventilation. She developed a severe neuromyopathy with tetraparesis and cranial nerve involvement, and a diagnosis of CIP/CIM was assumed. In both patients, muscle biopsy was performed to confirm CIP/CIM. Mitochondrial DNA deletions were analysed by long-range PCR; sequencing of thymidine kinase 2 (TK2) was performed.
Results: In patient 1, muscle histology findings did not support CIM, instead ragged blue fibres were identified. Long-range PCR analysis revealed multiple deletions in mtDNA and sequencing of the TK2 gene revealed a known pathogenic homozygous mutation. In patient 2, muscle histology was in keeping with CIM, but also showed some multiple deletions of mtDNA. Sequencing of TK2 revealed a novel heterozygous mutation, which was predicted to be pathogenic.
Conclusion: Both patients were noted to have clinical features unusual for CIP/CIM (ptosis, cranial nerve involvement). Further testing eventually showed pathogenic mutations in TK2, expanding the phenotype of TK2 deficiency. Investigation for multiple mtDNA deletions and TK2 deficiency is warranted in patients who present with apparent CIP/CIM and unexplained additional clinical features.
Disclosure: Nothing to disclose

EPR3050

The PSH-AM is a valuable tool in diagnosing autonomic dysregulation: a cohort study and review.

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Background and aims: This study aimed to determine the clinical expression of autonomic dysregulation in patients with diffuse axonal injury (DAI) after traumatic brain injury (TBI) in comparison with the literature.
Methods: Patients clinically diagnosed with autonomic dysregulation were selected from a cohort study involving 116 patients with DAI. We studied the incidence, autonomic features, treatment, and outcome, and performed a systematic review.
Results: In 16.4% (n=19) patients autonomic dysregulation was diagnosed. In 58% (n=11) of these patients was a probable PSH scored according to the PSH-AM, only 5% (n=1) scored unlikely. Autonomic dysregulation was associated with age (OR 0.95), DAI grade (OR 7.2), and an unfavourable outcome (OR 5.6). Patients with autonomic dysregulation had a significantly longer ICU and hospital stay.
The review yielded 30 articles. The incidence of autonomic dysregulation after TBI varied from 7.7-32.6% (mean 13.5%). TBI patients with autonomic dysregulation had a longer ICU stay and poorer outcome.
Conclusion: Patients with DAI and autonomic dysregulation had a longer ICU stay and a poorer outcome compared to patients without autonomic dysregulation. The number of autonomic features is no prerequisite for diagnosing PSH. The PSH-AM is a valuable tool to determine the likelihood of autonomic dysregulation.
Disclosure: This work resulted from the TopCare Experiment which is supported by a grant of the Dutch organization for health research and care innovation (ZonMw, grant number 842004002), the authors alone are responsible for the content and writing of the article.

EPR3051

The use of continuous EEG-monitoring in intensive care units in Europe: an international survey

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Background and aims: For unclear reasons, there is variation in the use of continuous electroencephalographic monitoring (cEEG) between medical centers. In this study, we aim to describe the current practice of cEEG monitoring among European physicians.

Methods: An online survey was sent to 23 European national clinical neurophysiology societies for distribution amongst their members.

Results: The survey was completed by 62 physicians from 11 countries, corresponding to a response rate of 48%. More than half of respondents use cEEG (57%). The duration of cEEG monitoring is <24h (17%), 24 to 48h (45%), 49 to 74h (24%) and >74h (14%). Nonconvulsive seizures (NCS) or nonconvulsive status epilepticus (NCSE) detection is the most common indication for cEEG (42%). The majority of respondents do not comply to (inter)national guidelines to determine the indications and duration for cEEG (59%). There is general agreement on the impact of cEEG monitoring on clinical decison-making. Almost all participants refraining from cEEG use, perform routine 30 minutes EEG if NCS or NCSE is suspected. Limited technical and financial resources besides limited qualified personal are the most common obstacles for introducing or expanding cEEG.

Conclusion: More than half of respondents to this international European survey use cEEG. The primary indication for applying cEEG is NCS(E) detection. However, due to lack of consensus, significant variation exists among physicians who currently use cEEG at their institutions. Also, implementation of cEEG is hampered by technical, financial and personnel issues. Further multicenter prospective studies are needed to advance uniformity of cEEG utilisation.

Disclosure: Nothing to disclose

EPR3052

Lower limb neurological examination and interpretation by medical trainees

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Background and aims: Neurological symptoms account for one-fifth of admissions to the emergency department, yet the neurological examination is thought to be the hardest examination to learn by doctors.

Methods: We studied medical trainees attending a revision course in London for the clinical part of the Membership of the Royal College of Physicians examination. Candidates were observed during the lower limb neurological examination of people with four different neurological diseases including spastic paraparesis and peripheral neuropathy.

Results: One examiner observed 245 trainees over 3 years. Gait was assessed by 233 (95%) doctors, with tandem gait checked by 39 (25%) and Romberg's test by 100 (41%). Tone, power and reflexes were assessed fully by over 80% of candidates. Plantar response was checked by 86% of candidates. When reflexes were absent, 123 of 180 (68%) candidates attempted reinforcement manoeuvres. For sensation, 63% chose to use cotton wool first, 32% chose pinprick first, and 4% chose a tuning fork or tested proprioception first.

When presenting their findings, the proportion of candidates who correctly identified signs were: 54% for gait, 91% for tone, 66% for pattern of weakness, 59% for reflexes and 69% for plantar response. 64 out of 245 (26%) candidates correctly diagnosed the subjects.

Conclusion: This is the first study, to our knowledge, to observe neurological examination technique, detection of abnormal signs and interpretation of findings in a controlled setting. Trainees find certain parts of the neurological examination difficult and the majority of trainees have difficulty interpreting their findings and diagnosing conditions.

Disclosure: Nothing to disclose

EPR3053

A new form of martyrdom?

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Background and aims: Organ donation after euthanasia has been practiced in Belgium in some 25 patients. Transplant surgeons testify that organ donation often leads to a new sense of identity and meaning. The case presentation illustrates a problem confounding the decision-making process on euthanasia followed by organ donation.
Methods: A 34-year-old woman was being treated for a long-standing depression. As an adolescent, she had already made several suicide attempts. At one point in her life, she had promised her parents that she would not make another attempt. Now that both parents were deceased she requested euthanasia.
Results: The doctor who received her euthanasia request immediately presented organ donation as a possibility. A documentary film was made before her death, in which she stated that her 'suicide' provided a new meaning and sense of identity for her because she felt that she would be living on thanks to her organ donation. She claimed to have the right to self-determination in connection with others up to and beyond death.
Conclusion: Candidates for organ donation after euthanasia often suffer from neuropsychiatric disease. Patient's motivation in living altruistic organ donation has been thoroughly debated. No act is unmotivated and gratuitous and in patients with severe neurodegenerative disease the renewed sense of identity involved in organ donation would be acceptable. In patients with primary psychiatric diseases such as long-standing depression and intense death wish, the increased significance that is attached to the life-ending-act should be viewed with extreme caution. Dying for someone else seems to be a new form of martyrdom.
Disclosure: Nothing to disclose

EPR3054

What can mythology of Portuguese river Lima and ancient Greek and Roman goddesses Lethe and Mnemosyne tell us about ancient knowledge of memory and memory loss?

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Background and aims: Greek and Roman goddesses and rivers of memory (Mnemosyne) and oblivion (Lethe) may give us some insight into the common knowledge about memory and memory loss in the ancient times. The Portuguese river Lima was believed to be the mythological river of forgetfulness – Lethe.

Picture 1: Mnemosine enhancing the retrieval with her touch. Hatay Archaeology Museum, Turkey. Mnemosyne's symbol was luscious hair, representing many thoughts coming out the head. "If you had no memory you could not even remember that you ever did enjoy pleasure, and no recollection whatever of present pleasure could remain with you."(Plato)

Methods: We searched texts on ancient Roman and Greek mythology and artworks for symbols and descriptions of Menmosyne and Lethe and put them into the context of modern neurocientific knowledge.

Picture 2: The nine Muses - Roman sarcophagus, Louvre, Paris. Mnemosyne was mother of nine muses, that are personifications of different aspects of memory, from implcit to semantic. In culture based on oral tradition, people heavily depended on memory when passing knowledge through generation (muses represent music, law, dance, poetry, etc.)

Results: Knowledge on different memory stages (from imprinting to retrieving) could be identified. For example: "This is the gift of Mnemosyne...Whenever we wish to remember anything, we hold this wax under the perceptions and thoughts and imprint them upon it. Whatever is imprinted we remember and know as long as its image lasts, but whatever is rubbed out or cannot be imprinted we forget

and do not know."(Plato,Theaetetus 191d). Mnemosyne touch on a forehead, was believed to enhance memory retrieval (Picture 1).
Mnemosyne was also believed to be responsible for language processes, for invention of meanings of all the things (semantic memory) and controlling episodic and autobiographical memory (Picture 1).
As goddess, Lethe was also a mythological river, causing symptoms now closely associated with dementia. Drinking from Lethe induced symptoms such as fading of existing memories, daytime sleepiness and poor orientation in space (Picture 3).

Picture 3: Photography of Ponte de Lima. Legend says, Roman army was afraid to cross the Lima river, believing it is the mythological river Lethe: ''Romans believed that Lima River produced forgetfulness, and they feared to cross it, in doing so, they thought that they would forget Rome and remain in the area forever'' (Augusto Pino Lehal).

Conclusion: We found evidence on ancient awareness of different types of memory, memory stages and symptoms of memory loss. There was public awareness of dementia even 2500 years ago

Disclosure: Nothing to disclose

EPR3055

Patients with diffuse axonal injury can recover to a favourable long-term functional and quality of life outcome

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Background and aims: Functional outcome and quality of life are difficult to predict in patients with diffuse axonal injury (DAI) after traumatic brain injury (TBI). Primary aim of this cross-sectional cohort study was to assess long-term functional outcome in patients with DAI and to identify prognostic factors. Secondly health-related quality of life (HRQL) at long-term follow-up was assessed.

Methods: Patients aged ≥16 with TBI and DAI (admitted 2008-2014) were included. Clinical and imaging data were collected. The primary outcome parameter was the Glasgow Coma Scale Extended (GOSE) at long-term follow-up. Secondly HRQL was assessed with the Quality Of Life after Brain Injury (Qolibri) questionnaire.

Results: DAI was diagnosed in 185 patients. Long-term functional outcome was obtained in 134 patients (72%), median follow-up 54 months (range 14-100). 51% had a favourable outcome (GOSE 6-8). Independent prognostic factors were age, pupillary reaction, Hb, DAI grading, and return of consciousness ≤7 days. Sixty-two percent had a good HRQL, median follow-up 57 months (range 14-100) with age as an independent prognostic factor.

Conclusion: More than half of patients with DAI had a favourable functional outcome and a good HRQL at long-term follow-up. Also in patients with a DAI grade 3 a favourable outcome was seen. HRQL is a clinically relevant outcome measure since it reflects perceived outcome by patients. Independent prognostic variables for the functional outcome were factors obtained in the acute phase after injury whereas age was an independent prognostic factor for HRQL.

Disclosure: This work was supported by a grant of the Dutch organisation for health research and care innovation (ZonMW) section TopCare projects (grant number 842004002), the funding source had no role in design, collection, analysis, interpretation or publication of the data.

Motor neurone diseases 2

EPR3056

Oligogenic and discordant inheritance: a population based genomic study of Irish kindreds carrying the C9orf72 repeat expansion

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Background and aims: The C9orf72 repeat expansion is the most commonly identified genetic cause of ALS in Ireland and has known pleiotropic effects evidenced, in part, by higher rates of neuropsychiatric conditions in family members. In addition, oligogenic inheritance of C9orf72 with other risk variants e.g. knockdown of SUPT4H1 gene, may modify expression and thus perceived penetrance of the repeat expansion.
Methods: 151 individuals with familial ALS, identified through the Irish ALS Register, were screened for the presence of the pathogenic GGGGCC hexanucleotide repeat expansion by repeat-primed PCR.
Results: 47 patients with ALS from 40 families carried the C9orf72 repeat expansion. By analysing inheritance, we observed definite co-segregation in 2 of the 40 families. However, in 7 families co-segregation was absent. 8 C9orf72 positive patients carried one or more additional known or putative ALS risk variants: SETX (2), TBK1 (2), ATXN2 (2), TAF15 (1), SPG11 (1), NEK1 (1) and UNC13A (1).
Conclusion: Our findings demonstrate that the presence of a family history does not necessarily infer the presence of a common disease aetiology. Genetic pleiotropy, oligogenic inheritance, age dependent penetrance, variable tissue expression and the potential for laboratory error all have implications for counselling of patients and asymptomatic relatives.
Disclosure: Nothing to disclose

EPR3057

CSF Tau as survival biomarker in Amyotrophic Lateral Sclerosis

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Background and aims: Amyotrophic lateral sclerosis is a fatal neurodegenerative disease that still lacks of reliable diagnostic biomarkers. Aim of the study is to test the diagnostic and prognostic potential of CSF protein Tau, p-Tau and p-Tau/Tau ratio in ALS compared to other neurodegenerative and non-neurodegenerative diseases.
Methods: We included 66 incident patients with possible, probable and definite ALS. Control groups included 126 patients with Alzheimer's disease (AD) and 49 patients with other non-neurodegenerative diseases (ONND) (mainly polyneuropathies and some migraines). Patients were enrolled in a period from March 2009 to April 2016 and followed up till April 2017. Comparisons between groups were performed with Mann-Whitney test while correlations were evaluated with Spearman rank correlation test. Kaplan-Meier estimator was used for the analysis of survival.
Results: ALS patients had higher CSF Tau and pTau/tau than ONND, whereas AD patients had the highest levels of both the biomarkers. ROC analysis revealed a sensitivity of 80.3% and a specificity of 61.2% of CSF Tau in discriminating ALS patient from ONND. No relations were found between CSF Tau and p-Tau and clinical features. Survival analysis showed a shorter survival in ALS with higher CSF tau (p=0.03).
Conclusion: The increased levels of CSF Tau and p-Tau in comparison to ONND confirms the existing process of neurodegeneration in ALS. Nevertheless, the low specificity of CSF Tau makes it as an unreliable diagnostic tool for ALS. However, the shorter survival observed in patients with high levels of CSF Tau makes this biomarker a potential biomarker of survival.
Disclosure: Nothing to disclose

EPR3058

Microstructural correlates of Edinburgh Cognitive and Behavioural ALS (ECAS)

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Background and aims: ECAS has been designed for testing patients with amyotrophic lateral sclerosis (ALS) including tests sensitive to impairment of cognitive domains specifically involved in ALS (Language, Fluency, Executive functions), and an assessment of ALS non-specific functions (Memory, Visuospatial functions). Using whole-brain tract-based spatial statistics (TBSS) diffusion tensor imaging (DTI) we aim to explore the potential association between brain microstructural damage and ECAS scores.
Methods: 40 ALS patients (King's clinical stages 1 or 2), cognitively assessed by ECAS, and 35 healthy controls underwent 3T-MRI. DTI TBSS analysis was performed to measure fractional anisotropy (FA) and axial, radial and mean diffusivities (AD, RD, MD) for between-groups comparisons and correlations between DTI metrics and ECAS scores.
Results: ALS patients exhibited a decreased FA ($p<0.05$, corrected) in bilateral cortico-spinal tracts, corpus callosum (CC) and superior longitudinal fasciculi and an increased RD in the rostral part of the right cortico-spinal tract and in the midbody of CC. ECAS total score were significantly related to measures of FA, MD and RD ($p<0.05$, corrected). Regard ALS-specific scores, verbal fluency was significantly associated to RD in the splenium of CC. The total score from all ALS non-specific tests was significantly related to FA decrease in the right cortico-spinal tract, the body of CC, the fornix, the left inferior fronto-occipital fasciculus and bilateral superior longitudinal fasciculi, extended also to bilateral superior longitudinal fasciculi, considering the memory subscore alone.
Conclusion: Results point towards an early microstructural degeneration of brain areas, with significant relationships between DTI metrics and ALS-specific and non-specific ECAS scores.
Disclosure: Nothing to disclose

EPR3059

Molecular biomarkers associated with respiratory insufficiency in Amyotrophic Lateral Sclerosis

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Background and aims: Amyotrophic Lateral Sclerosis (ALS) is a devastating and fatal neurodegenerative disorder. Death typically occurs within 3–5 years after disease onset. ALS patients die mainly from respiratory failure (RF). No effective treatment is available and no molecular biomarker related to respiratory outcome and to early ventilatory dysfunction was described. The club-cell protein (CC-16) is a biomarker associated with respiratory distress and lung inflammation. We aim to explore CC-16 as a candidate biomarker for respiratory failure in ALS. Additionally, we intend to identify morphological and viscoelastic changes of the erythrocyte membrane and associate them with the clinical features.
Methods: Patients were compared with a control group of healthy blood subjects. CC-16 was quantified by ELISA. Morphological and viscoelastic properties of the erythrocytes were analysed by Atomic Force Microscopy (AFM).
Results: CC-16 was significantly higher in ALS patients and predictive of non-invasive ventilation within 3 months and death in the 18 months. It was observed higher erythrocyte maximum height, area and volume, decreased erythrocyte membrane roughness, increased membrane stiffness and fluidity, and lower membrane negativity (zeta potential), in the ALS population. This set of findings indicates abnormal erythrocyte the membrane structure and changed lipid composition.
Conclusion: Overall, our preliminary results are in favor of an increased lung inflammatory response related to respiratory distress. Moreover, erythrocyte abnormalities can enhance risk of tissue hypoxia. These results should prompt a larger study to confirm our preliminary results, since we urge to find biomarkers of respiratory dysfunction and tissue hypoxia in ALS.
Disclosure: Nothing to disclose

EPR3060

Do ALS motor phenotypes develop stochastically?

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Background and aims: Amyotrophic lateral sclerosis manifests with various motor phenotypes. Our aim was to assess whether these phenotypes are determined by detectable factors.

Methods: ALS incident patients (N=2,702) included in the PARALS (an Italian regional registry of ALS) from 1995 to 2014 were enrolled. Six motor phenotypes were considered: classic, prevalent upper motor neuron, flail arm, flail leg, respiratory, classic bulbar, prevalent upper motor neuron bulbar (Chiò, JNNP 2011). Logistic regression analysis was performed, adjusting for gender and age (ten-year age classes). The outcome was represented by dummy variables: spinal vs bulbar phenotypes as macro-categories; each spinal phenotype (classic, flail arm, flail leg, prevalent upper motor neuron, respiratory) vs bulbar phenotypes; each bulbar phenotype (classic and prevalent upper motor neuron) vs spinal phenotypes.

Results: Males showed a probability of developing a spinal form 72% higher than females (OR=1.72; p=0.000). Among patients over 60 years, the spinal onset was less frequent than the bulbar one (test for trend in subsequent ten-year age classes: p<0.0001). This finding was particularly strong in females, with ORs between 5.40 (60-69 years) and 9.10 (over 80 years). Respiratory and flail arm phenotypes were more common in males, with a probability more than ten-fold and more than two-fold than females respectively (OR=11.72 and OR=3.39). The likelihood of the pyramidal bulbar phenotype resulted more than two-fold in females compared to males (OR=2.20; p=0.0001), without differences among age classes.

Conclusion: ALS motor phenotypes seem to arise from a combination of patients' gender and age.

Disclosure: Nothing to disclose

EPR3061

Assessment and diagnostic utility of the upper motor neuron involvement in amyotrophic lateral sclerosis by 3T-MRI

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Background and aims: Clinical signs of upper motor neuron (UMN) involvement are important for amyotrophic lateral sclerosis (ALS) diagnosis, although often difficult to appreciate. Conventional MRI can identify abnormalities associated with UMN involvement, especially with high field scanners. We evaluated the diagnostic contribution of 3T-MRI in ALS patients.

Methods: We retrospectively evaluated MRI from 93 ALS patients (55 men, mean age 62.8±10.1) and 89 controls (56 men, mean age 60.2±9.5). All subjects performed 3T-MRI study including 3D-FSPGR-T1, FSE-T2, GRE-T2*, FLAIR-T2 and SWI sequences, visually assessed by two blinded neuroradiologists. A third rater resolved disagreements. Features of interest were cortico-spinal tract T2/FLAIR hyperintensity, motor cortex T2*/SWI/FLAIR hypointensity and selective motor cortex atrophy. Agreement was tested using Cohen's k statistics and differences between groups using $\chi 2$ test ($p<0.05$ corrected). Sensitivity, specificity, PPV, NPV, and accuracy of ALS diagnosis by MRI were calculated using clinical diagnosis as gold standard.

Results: Raters agreement was 83%-91% (kappa=0.53-0.75, p<0.001). All MRI features were significantly more prevalent in ALS patients, mainly cortico-spinal tract FLAIR hyperintensity (75% vs 32%; p<0.0001) and motor cortex SWI hypointensity (76% vs 39%; p=0.001). Diagnostic accuracy was 60%-72% considering single features. The highest accuracy was reached combining cortico-spinal tract FLAIR hyperintensity and motor cortex SWI hypointensity (sensitivity: 70%; specificity: 81%; PPV: 90%; NPV: 51% and accuracy: 73%).

Conclusion: 3T-MRI is able to detect specific changes related to UMN involvement with good accuracy and can be useful to support the clinical diagnosis of ASL.

Disclosure: Nothing to disclose

EPR3062

The natural course of dysphagia in ALS is different between patients with bulbar and spinal onset

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Background and aims: We aimed at evaluating the relationship between dysphagia and site of onset in amyotrophic lateral sclerosis (ALS) in terms of progression rate.
Methods: We enrolled 871 incident ALS patients (580 with spinal onset, 291 with bulbar onset), resident in Piemonte and Valle d'Aosta, Italy, from 2007 to 2013. Based on ALSFRS-R item 3, dysphagia was classified as "severe" (0-1), "moderate" (2-3), "absent" (4). The progression of dysphagia was considered as time-dependent variable and was reassessed at each visit. Progression rate of dysphagia was calculated separately among patients with bulbar and spinal onset (N=642). Time intervals ended with the date when dysphagia became severe. The starting date was the date of onset for bulbar patients (N=279) and the date of first bulbar symptoms (considering ALSFRS-R items 1 and 3<4) for spinal patients (N=363). 217 patients did not develop dysphagia during the follow-up.
Results: ALS patients showed moderate dysphagia after a median of 24.4 months (IQR=13.5-44.7) from the onset. Dysphagia became severe after additional 17.7 months (IQR=9.5-29.8); death/tracheostomy occurred after additional 6.9 months (IQR=2.6-14.7). The progression rate showed a median time interval of 17.4 months (IQR=8.9-29.5) between the first bulbar symptom and severe dysphagia. These time intervals were shorter in patients with spinal onset (median 11.9 months; IQR=5.5-24.1) than in cases with bulbar onset (22.9 months; IQR=16.0-31.8) (Wilcoxon test p=0.000).
Conclusion: The progression rate of dysphagia significantly differs between ALS patients with bulbar and spinal onset.
Disclosure: Nothing to disclose

Movement disorders 7

EPR3063

Changes in resting state cerebellar connectivity in cervical dystonia induced by botulinum toxin

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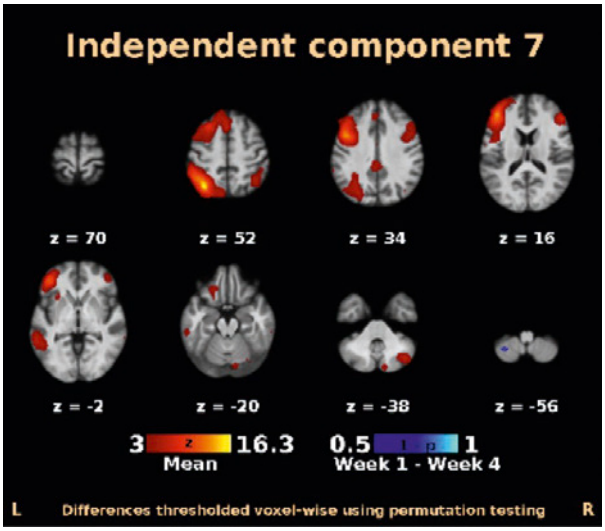
Background and aims: Administration of botulinum neurotoxin A (BoNT) injections is currently the preferred treatment of focal dystonia. The clinical effect of BoNT is assumed to be mediated by dynamic changes at multiple levels of the sensorimotor system. Recently, the role of the cerebellum in the pathophysiology of dystonia has been discussed. The aim of our study was to compare the connectivity between large-scale resting state networks and the cerebellum before and after treatment initiation.

Methods: 12 patients with cervical dystonia indicated for treatment with BoNT were enrolled (11 female, aged 50.8±8.1 years, range 38-61 years). Clinical and functional MRI examinations were carried out immediately before and 4 weeks after BoNT injection. Clinical severity of dystonia was evaluated using the TWSTRS. The functional imaging data were acquired using a 1.5 Tesla MRI scanner during an 8-minute rest. Pre-processed data from both sessions were decomposed into 30 group-wise independent components (IC's) using MELODIC from the FSL toolbox. Treatment-related changes in connectivity between the cerebellum and the whole-brain components were evaluated using dual regression analysis and non-parametric permutation testing. Results were thresholded at the corrected $p<0.05$.

Results: Clinical scoring demonstrated satisfactory clinical effect of BoNT. The only significant difference was detected in the left-sided fronto-parietal component (IC 7, Figure 1), which demonstrated a decrease of functional connectivity after the treatment in the left cerebellar lobule VIIIa (coordinates [x,y,z]: -34, -54, -56).



Independent component 7 and treatment-related difference. The red-yellow overlay shows the spatial representation of the IC 7. The blue overlay shows the significant connectivity decrease at Week 4.

Conclusion: Our data provide evidence for abnormal resting state connectivity between large-scale cortical networks and the cerebellum.

Disclosure: Research was supported by grants of the Agency for Healthcare Research of the Czech Republic (AZV MZ ČR) NV16-30210A.

EPR3064

Mutations of the VPS35 (PARK17) and FBXO7 (PARK15) genes associated with pathological finding of Lewy body pathology

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Background and aims: A 83-year-old man with positive family history of parkinsonism suffered from atypical parkinsonism with a clinical picture phenotypically correlated with PSP-P from his 66 years. Mutations associated with parkinsonism in this family have been identified in VPS35 (PARK17) and FBXO7 (PARK15) genes. The aim of this study was a description of a neuropathological finding associated with these PARK genes mutations.
Methods: Post-mortem histopathological examinations (formalin-fixed, paraffin –embedded blocks from the temporal, frontal, parietal and occipital cortex, hippocampus and parahippocampal regions, basal ganglia, thalamus, subthalamic nucleus, brain stem, substantia nigra and cerebellum) were performed by using H-E, Luxol blue, impregnation of silver salts, immunohistochemistry with monoclonal antibodies against: phospho-PHF-tau AT8, anti-tau 3-repeat isoform RD3, anti-tau 4-repeat isoform RD4, α-synuclein, b-amyloid, and antiphospho- TDP-43.
Results: The macroscopic finding was characterized by diffuse cerebral atrophy. The immunohistochemical examination confirmed the diagnosis of Parkinson's disease, Braak stage VI, neocortical type by McKeith. Lewy body pathology was also present in periaqueductal gray matter, in the rostral interstitial nucleus of the medial longitudinal fasciculus, interstitial nucleus of Cajal and nucleus Darschewitsch which are involved in the supranuclear control of gaze. Together with Lewy body pathology, low level Alzheimer's disease neuropathologic changes (A1B1CO) according to the ABC scoring system was present. Concomitant tauopathy and TDP-43 proteinopathy were excluded.
Conclusion: This case provides the first description of neuropathological correlation of Parkinson's disease associated with VPS35 (PARK17) and FBXO7 (PARK15) genes mutations. The clinical picture resembled PSP-P due to involment of the structures involved in eye movement control.
Disclosure: This work was supported by grans: AZV-Ministry of Health of the Czech Republic Nr. 15-32715A, IGA-LF-2017-023 and MH CZ – DRO (FNOL 00098892) – 2017.

EPR3065

Pharmacokinetic and safety characterisation of carbidopa/levodopa subcutaneous infusion (ND0612): Phase I studies in healthy volunteers and patients with fluctuating Parkinson's disease

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Background and aims: Improving the continuity of carbidopa/levodopa (CD/LD) delivery is desirable in Parkinson's disease (PD) patients experiencing motor fluctuations. As an alternative to oral LD formulations with pulsatile pharmacokinetics, ND0612 is under development as a drug-device combination to provide continuous delivery of CD/LD (without the need for surgical gastrostomy tube implantation for drug infusion).
Methods: Study 001 was a dose-escalating study conducted in healthy volunteers (n=54). Study 002 was a randomised, cross-over study in 8 PD patients experiencing motor fluctuations; both treatments (placebo/ND0612) were given with 2 doses of Stalevo® 100. CD/LD plasma concentrations at steady-state were assessed following continuous ND0612 subcutaneous delivery over 24 hours. Systemic and local skin safety were evaluated.
Results: Study 001: LD and CD plasma concentrations increased proportionally as a function of ND0612 infusion rate during testing of low (night-rate of 80µl/h) and a high (day-rate of 240 µl/h) delivery. Study 002: In PD patients, ND0612 demonstrated plasma concentrations that were markedly increased in the therapeutic range and steady-state plasma LD concentrations with substantially reduced (10-fold) fluctuations in LD plasma concentrations. In both studies, ND0612 showed good systemic tolerability. For some subjects, small, transient nodules were palpable at infusion sites.
Conclusion: Subcutaneous delivery of ND0612 in PD patients can achieve continuous therapeutic LD plasma concentrations, offering the potential for fewer motor fluctuations.
Disclosure: Funded by NeuroDerm

EPR3066

ND0612 infusion in fluctuating Parkinson's disease: a randomised, double-blind, placebo-controlled study

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Background and aims: ND0612 is being developed as the first non-surgical drug-device combination that provides continuous delivery of levodopa-carbidopa (LD-CD) to patients with fluctuating Parkinson's disease (PD).
Methods: iNDiGO is a multicenter, randomised, double blind, placebo-controlled clinical study. PD patients (Hoehn and Yahr ≤3) on ≥4 doses/day of LD-CD therapy, experiencing motor fluctuations (≥2h OFF time per waking day) that cannot be further improved with oral PD medications will be randomised equally to 4 treatment arms (Figure). Study treatment is added to standard-of-care oral LD-CD. Oral immediate-release LD-CD may be used as rescue therapy. The primary endpoint is change from Baseline to Week 16 in the mean percentage of OFF time during waking hours, based on patient home diary assessments on 3 consecutive days before the visit. The mean percentage of ON time without troublesome dyskinesia during waking hours will be assessed as the key secondary endpoint. Statistical analyses will use the combination of both placebo arms.
Results: The goal is to conduct the study at 85 sites internationally.
Conclusion: This will be the first Phase III trial of two dosing regimens (low and high) of ND0612 for establishing efficacy and safety of continuous subcutaneous levodopa delivery in patients with PD who experience motor fluctuations that are not satisfactorily controlled on conventional oral PD medications. Patients who complete the study will be offered open-label ND0612 for an extension period of additional 48 weeks of treatment.
Disclosure: Funded by NeuroDerm

EPR3067

Decreased amyloid-beta in patients with idiopathic Parkinson's disease and white matter hyperintensities

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Background and aims: Parkinson's disease (PD) is the fastest growing neurological disorder, surpassing Alzheimer's disease, and its incidence increases sharply with age. Cardiovascular disease and associated risk factors, including cerebral white matter hyperintensities (WMH), are also common among the elderly, and their association with PD has been debated. The aim of this study is to investigate the clinical and biochemical profile of patients with PD with and without WMH.
Methods: 91 patients were included in this pilot project. All participants had given written consent to recruitment in an academic study, at the movement disorders clinic in the Department of Neurology, Karolinska University Hospital Huddinge. WMH were assessed by a neuroradiologist according to Fazekas. Patients were divided in those with no or light WMH (Fazekas 0 or 1; n=66), and with moderate or severe WMH (Fazekas 2 or 3; n=25).
Results: Patients with light WMH were younger than those with severe WMH (median age 64.5 vs. 74; $p<0.0001$), had less often hypertension (29% vs. 56%, $p=0.02$), and had less severe motor symptoms assessed with MDS-UPDRS part 3 (22 vs 29 points, $p=0.03$). Glucose and HbA1c levels did not differ between the two groups. Amyloid-beta in cerebrospinal fluid was lower in patients with severe WMH compared to those with light WMH (558ng/L vs 994ng/L; $p=0.009$).
Conclusion: Lower amyloid-beta levels were observed in cerebrospinal fluid of patients with PD and severe WMH compared to patients with PD and light WMH. Further investigation of the impact of this association on development of dementia and all-cause mortality is ongoing.
Disclosure: Travel grant with application number 1057/17 has been awarded by Parkinsonfonden, for the presentation of this abstract in EAN Congress 2018.

EPR3068

A cross-sectional evaluation of health resource use in patients with functional neurological disorders referred to a tertiary neuroscience centre

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Background: Patients with Functional Neurological Disorder (FND) constitute approximately 30% of referrals to general neurology clinics. Analysis of this cohort's resource use is required for service reform and more efficient NHS planning.
Aim: To evaluate the health and social care costs over the preceding 6 months of FND patients attending a tertiary FND clinic.
Methods: Method: Health and social care resource use, in the 6 months preceding their consultation, were assessed through a modified version of the Client Service Receipt Inventory (CSRI) in the form of a postal questionnaire. The total cost was estimated by combining the number and frequency of health resource use with recognized sources of national unit costs.
Results: Results: 41.6% of the 77 participants returned the CSRI, 94% of which were sufficiently completed. Of the 30 CSRI respondents, the mean cost of NHS resource use was £2686.60 (±£4821.63) in the six-month period, with 16.67% of respondents costing over £7500 predominantly due to in-patient admission. Of the cohort's total outpatient costs, General practitioner appointments represented 51.87%, with a mean cost of £237.27 (±£272.49) per patient. The longer the duration of the patient's FND before diagnosis the greater the NHS costs in the previous 6 months ($p=0.028$, $r=0.372$).
Conclusion: Discussion: Patients with FND present significant costs to the NHS. The longer the duration of their disease, the greater their cost in the preceding 6 months. Adequate reform of the patient pathway and re-organization of NHS services to make diagnoses and initiate treatment more quickly would reduce direct NHS costs.
Disclosure: Nothing to disclose

EPR3069

Management of dyskinesia in COMT-naïve patients starting adjunctive therapy with opicapone: the BIPARK-I double-blind experience

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Background and aims: Elucidate which levodopa-treated COMT-naïve Parkinson's disease (PD) patients were at higher risk for developing dyskinesia when starting opicapone (OPC) 50mg or entacapone (ENT).
Methods: Double-blind, 14 to 15-week, placebo- and active-controlled study. In the emergence of dopaminergic adverse-events (AE) during the first 3-weeks of treatment, investigators could titrate the levodopa daily-dose. Dopamine-agonists (DA) and MAO-B inhibitors (MAO-Bi) for the treatment of PD were allowed provided their stable regimen for 4-weeks before and throughout the study. Dyskinesia-related AEs were defined as new or worsening of baseline dyskinesia. This subgroup analysis investigated the association of dyskinesia with a daily-dose of levodopa (<700mg; ≥700mg) as well as concurrent use of DA/MAO-Bi.
Results: 359 patients were randomised to placebo (PLC, n=121), OPC-50mg (n=116) or ENT (n=122). Patients taking OPC-50mg presented more frequently with dyskinesia (16%) compared to ENT (8%) and PLC (4%). Patients with concurrent use of DA and taking levodopa ≥700mg at baseline appeared to be at higher risk of developing dyskinesia. About 64% of all patients with dyskinesia-related AEs had a levodopa daily-dose reduction by ~25%. No new dyskinesia-related AEs were reported during maintenance period for patients on OPC-50mg who reduced their levodopa daily-dose during adjustment period.
Conclusion: High levodopa daily-dose and DA concomitant use were associated with a higher risk of developing treatment-emerging dyskinesia. Patients who develop dyskinesia after starting OPC may benefit from a reduction of their daily-dose of levodopa. An early follow-up during the first weeks of treatment may be warranted, particularly in patients taking high levodopa daily-dose (≥700mg) and DA concomitant.
Disclosure: Nothing to disclose

EPR3070

Electrocortical connectivity and non-linear quantitative analysis of EEG signal in PD-MCI

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Background and aims: To analyse electrocortical networks related with cognitive decline in Parkinson's disease (PD) patients with mild cognitive impairment (PD-MCI) compared to PD patients with normal cognition (PD-NC).
Methods: From the PaCoS (Parkinson's disease Cognitive Study) cohort of 659 PD patients, a sample of 102 subjects (46 PD-MCI and 56 PD-NC) was selected based on the presence of a comprehensive neuropsychological assessment and at least one artifact-free EEG recording. Diagnosis of PD-MCI was made according to the definition by Litvan et al. EEG signal epochs were analysed using Independent Component Analysis LORETA. The Power Spectral Density (PSD) of site-specific signal epochs was also obtained together with the power law exponent β to estimate fractal-like behavior of site-specific signal.
Results: LORETA analysis revealed significant differences in PD-MCI patients as compared to PD-NC, with a reduced network involving alpha activity over the occipital lobe, an increased network involving beta activity over the frontal lobe associated with a reduction over the parietal lobe, an increased network involving theta and delta activity over the frontal lobe and a reduction of networks involving theta and delta activity in the parietal lobe. Quantitative EEG analysis showed a significant decrease of alpha PSD over the occipital regions and an increase of delta PSD over the left temporal region, with a significant β increase over the frontal regions in PD-MCI as compared to PD-NC.
Conclusion: Results suggest reduced occipital resting-state alpha rhythms and enhanced frontal low-frequency electrocortical networks associated with non-stationary EEG signals in PD-MCI as compared to PD-NC.
Disclosure: Nothing to disclose

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EPR3071

Asymmetric neurostimulation to improve freezing of gate: a case report

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Background and aims: Freezing of gate (FOG) is usually one of the most disabling symptoms for patients with Parkinson's disease (PD) and may appear or persists after subthalamic nucleus (STN) deep brain stimulation (DBS). Recent studies suggest the use of low-frequency stimulation to improve FOG.We report a 68-year-old male with Parkinson's disease (PD) with asymmetric freezing of gate (FOG) who showed an improvement after reduce frequency stimulation asymmetrically.
Methods: We report a 68-year-old male who was diagnosed with PD 15 years ago. In the last year, he developed severe motor fluctuations, dyskinesias and gate disorders despite medical treatment. NST-DBS was considered and levodopa test was performed, obtaining a motor benefit of 63%.
Results: During the months following surgery, an asymmetric adjustment of the intensity stimulation was required and patient showed an improvement of parkinsonian syndrome but persistence of FOG. We observed the freezing disorder was more evident when patient turned to his left than to his right. In addition, it was decided to reduce frequency stimulation asymmetrically, 66 Hz in right STN and 79 Hz in left STN, and FOG improved considerably.
Conclusion: Low-frequency stimulation of NST seems to be useful in improving FOG in PD patients. It would be interesting to consider the use of different frequencies in patients with asymmetric freezing.
Disclosure: Nothing to disclose

EPR3072

Non-motor symptoms (NMS) improvement is positively correlated with baseline NMS burden and improved quality of life in advanced Parkinson's disease patients treated with levodopa-carbidopa intestinal gel: a post-hoc analysis from the GLORIA registry

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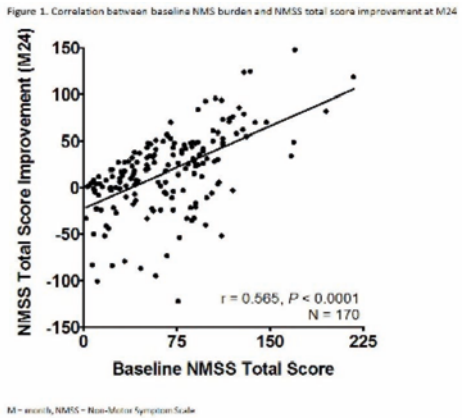
Background and aims: To evaluate the relationship between baseline (BL) NMS burden and NMS improvement in advanced Parkinson's disease (APD) patients treated with levodopa-carbidopa intestinal gel (LCIG, also known as Carbidopa/Levodopa Enteral Suspension) over 24 months (M).
LCIG, delivered via percutaneous gastrojejunostomy, significantly improved NMS and QoL in the GLORIA registry at 24M.
Methods: LCIG was administered over 24M to APD patients in routine clinical care (Gloria Registry). NMS were measured with the NMS Scale (NMSS); QoL was measured with the 8-item PD Questionnaire (PDQ-8). The relationships between BL NMS burden and NMSS total score improvement (TSI) at M24 and NMSS TSI at M24 and QoL were assessed (Pearson correlation coefficients). NMS responder rates with different changes from BL in NMSS total score were calculated at M24.
Results: BL NMS burden correlated significantly with NMSS TSI at M24 of LCIG treatment ($r=0.565$; $P<0.0001$) [Figure1]. Median NMSS total score improved by 35% (M24) compared to BL (median change from BL=-18.0; n=170/233). 47% (n=42/89) of patients with severe NMS burden at BL (> 80 BL NMSS total score) had NMSS TSI's ≥30 points (M24); as a group, these patients exhibited 42% improvement in median NMSS total score compared to BL (median change from BL=-45.0; n=64/89). NMSS TSI correlated significantly with PDQ-8 TSI at M24 ($r=0.464$, $P<0.0001$). Observed patient tolerability was consistent with established LCIG safety profile.



Conclusion: At M24, NMS improvement correlated strongly with BL NMS burden and associated with improved QoL and nearly half of patients with the highest BL NMS burden exhibited ≥30 points NMSS TSI.

Disclosure: Funding: 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.

EPR3073

Applying "5-2-1" diagnosing criteria for advanced Parkinson's disease to an observational study population treated with Levodopa-carbidopa intestinal gel

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Background and aims: 5- (times oral levodopa tablet intake/day) 2- (hours of OFF time/day) 1 (hour/day of troublesome dyskinesia [TSD]) criteria have recently been proposed by a Delphi expert consensus panel for diagnosing advanced Parkinson's disease (APD).

Methods: In this initial application of "5-2-1" criteria, patients were analysed post-hoc as subgroups meeting single or any or all criteria. ADEQUA was a 6-month, observational study assessing the effect of LCIG on quality of life (QoL) of Spanish patients. Assessments included the frequency of daily levodopa intake, hours of OFF time and TSD per day, and total scores of 39-item Parkinson's Disease Quality of Life Questionnaire (PDQ-39) and Non-motor Symptom Scale (NMSS).

Results: Of the 59 study patients, 93% met ≥1 of the "5-2-1" criteria, 15% met all. More patients had ≥5 times oral levodopa intake/day (56%) or ≥2 hours OFF/day (88%); whereas fewer patients had ≥1 hour TSD/day (31%). All subgroups with n>5 experienced significant (P<0.05) improvements in PDQ-39 and NMSS Total Scores from baseline to month 6 (Figures 1 and 2). The only significant difference between subgroups was on the NMSS Total Score between patients with <1 hour TSD/day (significantly greater reduction) and ≥1 hour TSD/day (p=0.039, Figure 2).

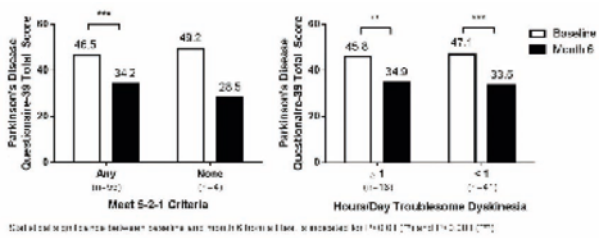

Figure 1: Parkinson's Disease Questionnaire-39 Total Score at Baseline and Month 6 for APD Patients in the Troublesome Dyskinesia and Any Vs. None Criteria Subgroups

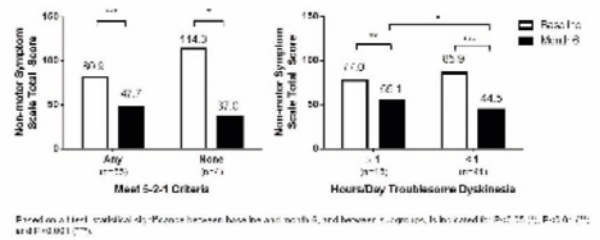

Figure 2: Non-motor Symptom Scale Total Score at Baseline and Month 6 for APD Patients in the Troublesome Dyskinesia and Any Vs. None Criteria Subgroups

Conclusion: In this first application of the "5-2-1" APD diagnosis criteria to an observational LCIG study population, most patients fulfilled ≥1 criterion and experienced QoL improvements, suggesting usefulness as a screening tool for APD and consideration of device-aided therapies.

1Antonini, A. et al., Movement Disorders. 2015;30:S1186

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.

EPR3075

Brainstem volumetry for separating progressive supranuclear palsy from other parkinsonian disorders

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Background and aims: Separating progressive supranuclear palsy (PSP) from Parkinson's disease (PD) and multiple system atrophy (MSA) is often challenging. An early diagnosis is important for prognostics and management. We aimed to retrospectively evaluate automatic volumetric brainstem measurements in distinguishing PSP from PD and MSA.

Methods: Clinical 3D T1-weighted magnetic resonance images were obtained from 30 patients with PSP, 28 with MSA and 146 with PD. At the time of MRI, 18 were probable and 12 possible PSP. All but one possible PSP converted to probable later on. Midbrain, pons, medulla oblongata and superior cerebellar peduncles were segmented using FreeSurfer. Metrics from these analyses were evaluated as biomarkers for disease using receiver operating characteristic curves. We calculated a brainstem index analogous to the midbrain-pons area ratio by dividing the midbrain volume by the pons volume.

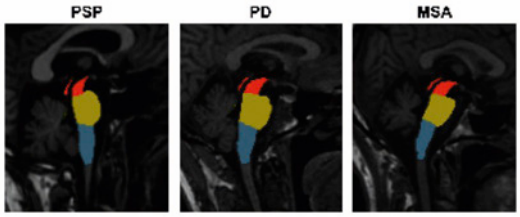

Figure 1. Visualisation of the segmentation process showing representative images from a 63 year old woman with PSP, a 45 year old man with PD and a 55 year old woman with MSA. Red=midbrain; yellow=pons; blue=medulla oblongata; green=superior cerebellar peduncles.

Results: We found that midbrain volume was most effective in diagnostically separating PSP from PD, with a sensitivity of 87% and a specificity of 79%. For separation between PSP and MSA, best results were seen with our brainstem index, with a sensitivity of 70% and a specificity of 71%. Discriminant analysis using all brainstem regions improved diagnostic separation PSP vs. MSA to sensitivity 83% and specificity 71% while separation PSP vs. PD was stationary.

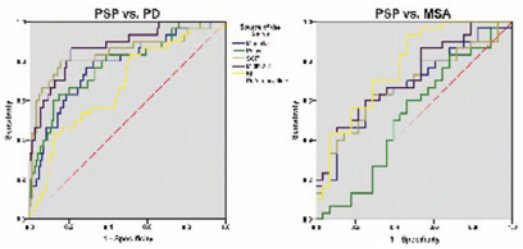

Figure 2. Receiver operating characteristic (ROC) curves depicting diagnostic separation PSP vs. PD and PSP vs. MSA. SCP=superior cerebellar peduncle; BI=brainstem index.

Conclusion: Automatic brainstem segmentation using FreeSurfer shows a promising diagnostic performance for separating PSP from PD and MSA. If further developed, automatic brainstem volumetrics could play a role in diagnosing PSP. A correct diagnosis is important in management and when considering treatment trials.

Disclosure: The study was funded by the Stockholm County Council through an ALF grant.

EPR3076

Longitudinal assessment of autonomic dysfunction in early Parkinson's disease

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Background and aims: Profile and clinical correlates of dysautonomia in early Parkinson's disease (PD) have been addressed in a cross-sectional way in previous studies.
Methods: We report longitudinal assessment of autonomic dysfunction in a cohort of early PD patients (Hoehn and Yahr stage 1 and disease duration <2 years at baseline) over 3-year follow-up. Autonomic dysfunction was assessed using SCOPA-AUT.
Results: A total of 112 PD patients and 79 healthy controls at baseline and 83 PD patients during longitudinal phase were included. PD patients had more overall symptoms of dysautonomia compared to controls. At least one dysautonomia symptom was present in 72% of PD patients at the baseline and in 93% of patients after three years. Nocturia was the most commonly reported symptom both at baseline and year 3. All gastrointestinal symptoms tended to worse during follow-up, except for dysphagia. Urinary dysfunction including urgency, increased frequency and incontinence, as well as lightheadedness, hyperhydrosis, cold intolerance, erection and ejaculation problems progressed over time. Age, depression, anxiety and apathy, but not motor impairment contributed to the autonomic dysfunction. Higher doses of dopaminergic medications and cognitive impairment were significant predictors of cardiovascular autonomic dysfunction over time.
Conclusion: Autonomic dysfunction affects the majority of patients with PD within the first 3 years from disease onset. Dysautonomia symptoms are usually mild, and progress independently from motor impairment.
Disclosure: This study was supported by a grant from the Ministry of Education and Science, Republic of Serbia (project No. ON175090).

EPR3077

Can a smartphone camera 'see' different tremor types?

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Background and aims: Computer vision refers to the processing of camera images or video to automatically extract useful information. The technology can recognise and track the human body from simple video, and this is used in multiple commercial applications. It has the potential to provide objective and automatic measurement of neurological signs, which currently rely on subjective visual estimation by a doctor. Crucially, no special hardware is required. Cameras and computers are ubiquitous and inexpensive (e.g. smartphones). There have been relatively few attempts to apply computer vision to neurology, but we report early findings using a smartphone camera applied to limb tremor.
Methods: Smartphone video of the upper limbs was recorded from healthy controls and also patients with three types of tremor disorder: Parkinson's, Essential Tremor, and Functional Tremor. The computing technique of Eulerian magnification was applied to these videos, to amplify small pixel movements. We then applied a computing method termed 'optical flow', to track and measure hand movement.
Results: We present striking videos that reveal hitherto invisible tremor in upper limbs (which could not be seen on the original video). Examples of this revealed tremor suggest the clinical appearance may differ across groups. Furthermore, we describe computer vision metrics derived from the tremor, such as motion vector distribution, which begin to allow characterisation of tremor types.
Conclusion: Our early findings (and remarkable videos) suggest that a simple smartphone camera may be able to detect and characterise tremor, including tremor that cannot be seen with the human eye alone.
Disclosure: Nothing to disclose

EPR3078

Sarcopenia and frailty in Parkinson's disease: a case-control study

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Background and aims: Sarcopenia and frailty are found in up to 1/4 of the general elderly and associated with major adverse health outcomes. Data on the frequency of both syndromes in Parkinson's disease (PD) is very limited. Thus, we aimed to screen for sarcopenia and frailty in PD patients and to assess potential demographic and clinical associations and the impact on QoL.
Methods: In this case-control study, we included 104 PD patients from a tertiary center and 330 non-PD controls from a population-based cohort aged >65 years. All groups were screened using the SARC-F score and the Clinical Frailty Scale of the Canadian Study of Health and Aging. Moreover, Prevalences were assessed in 18 PD patients from a population-based cohort. PD patients from the tertiary center were evaluated for motor and non-motor symptoms, QoL, and their level of dependency.
Results: Prevalence of sarcopenia was 55.8% (46.1–65.5%) in PD patients from the tertiary center and 8.2% (5.2–11.2%; $p<0.01$) in non-PD controls. Frailty was detected in 35.6% (26.2–44.9%), and 5.2% (2.8–7.6%; $p<0.02$). Prevalences for sarcopenia and frailty were 33.3% (9.2–57.5%; $p<0.01$) and 22.2% (1.0–43.5%; $p<0.02$) in the community based PD sample. Sarcopenia and frailty were significantly associated with longer disease duration, higher MDS-UPDRS-III scores, higher Hoehn and Yahr stages, decreased QoL, higher frequency of falls, higher non-motor symptom burden, and institutionalisation in PD patients compared to not affected PD patients (all $p<0.034$).
Conclusion: Sarcopenia and frailty are common in PD patients and are associated with a more adverse course of the disease.
Disclosure: Nothing to disclose

Movement disorders 9

EPR3080

Walking in orthostatic tremor – effects on tremor frequency, intensity and gait stability

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Background and aims: Primary orthostatic tremor (OT) is characterised by high-frequency lower-limb muscle contractions and a disabling sense of unsteadiness while standing. Patients consistently report a relief of symptoms when starting to ambulate. The objectives of this study were to systematically examine and link tremor and gait characteristics in patients with OT while walking.
Methods: Tremor and spatiotemporal gait features were examined in 9 patients with OT on a pressure-sensitive treadmill for one minute of continuous walking framed by two 1-minute periods of standing. Tremor characteristics (frequency, intensity, and coherence) were assessed by frequency domain and continuous time-frequency analysis of surface EMG-recordings from 4 leg muscles (tibialis anterior, gastrocnemius, biceps femoris, vastus medialis).
Results: All patients exhibited a coherent high-frequency tremor during standing (mean frequency: 15.29±0.17Hz). This tremor persisted during walking but was consistently reset to a higher frequency (mean frequency: 16.34±0.25Hz; $p<0.001$). Tremor intensity during walking was phase-dependently modulated, being predominantly observable during the stance phase of the gait cycle ($p<0.001$). Tremor intensity levels scaled with the force levels applied during stepping ($p<0.001$) and were linked to specific gait alterations, i.e., wide base walking ($p=0.019$) and increased stride-to-stride fluctuations ($p=0.002$).
Conclusion: Tremor activity in OT during walking persists but undergoes specific alterations indicating the influence of supraspinal centers (with respect to tremor frequency reset) and peripheral sources (with respect to tremor intensity modulations). High-frequency muscle contractions during walking are linked to gait alterations resembling a cerebellar and/or a sensory ataxic gait disorder.
Disclosure: Nothing to disclose

EPR3081

Unveiling the relationship between motor impairment, vascular burden and cognition in Parkinson's disease

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Background and aims: To determine frequency and type of cognitive disorders in cross-sectional analysis of a Parkinson's disease (PD) cohort, and explore its relations to motor symptoms, vascular risk factors and white matter lesions (WML) volume.
Methods: In a group of 133 PD patients, mild cognitive impairment (PD-MCI) and dementia (PDD) were diagnosed according to Movement Disorders Society task force criteria (level 2 for PD-MCI). Detailed motor measurements were applied, including rigidity, axial, bradykinesia, tremor and postural instability gait disorders (PIGD) scores. Vascular risk was estimated by the Framingham General Cardiovascular Disease risk-scoring algorithm and WML volume was measured for whole brain and frontal lobe.
Results: 61 (46.9%) patients fulfilled criteria for PD-MCI, and 23 (17.7%) for PDD. Non-amnestic multiple domain MCI was most frequent (52% of PD-MCI patients). Motor scores were significantly higher in cognitively impaired patients, but only axial score discriminated between MCI and dementia. High vascular risk was related to impaired cognition, bradykinesia, axial, PIGD and FOG score, while whole brain WML volume was associated with PDD, freezing of gait and attention deficits. Furthermore, high vascular risk was identified as a potential predictor of both MCI and dementia in PD. Additionally, age and bradykinesia score were independently associated with PD-MCI and age, axial score and whole brain WML volume with PDD.
Conclusion: Cognitive disorders in PD are associated with more severe motor deficits and probably aggravated by elevated vascular risk, thus opening an avenue for possible preventive strategies in PD.
Disclosure: This study was partially funded by a grant from the Ministry of Education and Science, Republic of Serbia (project 175090).

EPR3082

Are there two different forms of functional dystonia? A multimodal brain structural imaging study

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Background and aims: To investigate brain structural alterations in two diverse clinical forms of functional (psychogenic) dystonia (FD) – typical phenotype of fixed dystonia (FixFD) and recently recognized new phenotype "mobile" dystonia (MobFD) compared with controls.
Methods: 43 FD patients (13 FixFD, 30 MobFD) and 42 controls were recruited. All subjects underwent three-dimensional T1-wighted and diffusion tensor (DT) magnetic resonance imaging (MRI). We assessed cortical thickness with surface-based morphometry, subcortical volumes using FIRST, and DT MRI metrics using TBSS.
Results: Normal cortical volumes in both FD patient groups compared to age-matched controls were found. However, when compared with FixFD, MobFD patients showed cortical thinning of the left orbitofrontal cortex, and medial and lateral parietal and cingulate regions bilaterally. Compared with both controls and MobFD cases, FixFD patients showed a severe disruption of white matter (WM) tract architecture along the corpus callous, corticospinal tract, anterior thalamic radiations, and major long-range WM tracts. Additionally, compared to controls, MobFD patients showed reduced volumes of the left nucleus accumbens, putamen, thalamus, and bilateral caudate nuclei, while MobFD patients compared to FixFD demonstrated atrophy of the right hippocampus and globus pallidus.
Conclusion: These data showed different morphology patterns in two variants of FD. FixFD group was related to a global WM disconnection affecting main sensorimotor and emotional control circuits. On the other hand, MobFD had alterations in grey matter structures important for sensorimotor processing, emotional, and cognitive control. These findings may have important implications in understanding the neural substrates underlying different phenotypic expressions.
Disclosure: Study supported by the Ministry of Education and Science Republic of Serbia (Grant #175090).

EPR3083

Brain structural changes in focal dystonia – what about task specificity? A multimodal imaging study

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Background and aims: Brain abnormalities in the basal ganglia, thalamus, cerebellum and sensorimotor cortices were identified as common features of focal dystonia with heterogeneus phenotypic expression. However, task-specificity present in some forms of dystonia is still a poorly understood phenomenon. This study investigated grey and white matter alterations in patients with task-specific (TSD) and non-task-specific dystonia (NTSD), and defined common and group-specific brain changes.
Methods: 36 patients with TSD (spasmodic dysphonia and writer's cramp), 61 patients with NTSD (blepharospasm and cervical dystonia), and 83 healthy controls were included in the study. Participants underwent 3D T1-weighted and diffusion tensor MRI to study cortical thickness, basal ganglia volume, and WM tract damage.
Results: Compared to healthy controls, TSD patients had widespread, bilateral WM tracts damage including superior and inferior longitudinal fasciculi, cingulate bundle, anterior thalamic radiations, and corticospinal tracts. NTSD patients compared to healthy controls had more focal and right lateralised damage. Vertex analysis of cortical thickness showed cortical thinning in the right pars triangularis in NTSD group.
Conclusion: TSD is characterised by disruption of the main subcortical motor and cognitive controlling networks suggesting complex pathophysiology of task-specificity of dystonia.
Disclosure: Supported by: Ministry of Education and Science Republic of Serbia (Grant #175090).

EPR3084

The occurrence of dopamine-responsive and dopamine-resistant resting tremor in Parkinson's disease

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Background and aims: To investigate individual differences in the dopamine-responsiveness of Parkinson's resting tremor.

Parkinson's resting tremor has a variable clinical response to levodopa that can differ considerably between patients. However, it is unclear whether there are two distinct tremor phenotypes (dopamine-responsive and dopamine-resistant) or whether these groups are two ends of a normal distribution. Furthermore, it is unclear to what extent the dopamine response of resting tremor is different from that of bradykinesia.

Methods: We performed a standardised L-Dopa challenge in 76 tremulous Parkinson patients. Clinical scores (MDS-UPDRS part III) were collected OFF and ON 200/50mg levodopa-benserazide. In both sessions, resting tremor intensity was quantified during REST and during cognitive co-activation, using accelerometry. We calculated the distribution of dopamine-responsiveness for resting tremor and for bradykinesia.

Results: The dopamine response of bradykinesia, assessed clinically and using finger tapping speed, showed a unimodal (i.e. normal) distribution. In contrast, the dopamine response of resting tremor, assessed clinically and using accelerometry, significantly departed from a unimodal distribution and best fitted a bimodal distribution. This effect was present both at rest and during cognitive-stress. Comparison of the extreme groups revealed that the dopamine-responsive group schowed higher prevalence of women, a higher levodopa-equivalent-dose, and a higher prevalence of dyskinesia.

Conclusion: Our findings indicate that there are two partially overlapping tremor phenotypes, i.e. Parkinson patients with a dopamine-responsive and a dopamine-resistant tremor. This pattern sets tremor apart from bradykinesia, the core motor symptom of Parkinson's disease. Female gender and the presence of dyskinesia are associated with a better dopamine-response of resting tremor.

Disclosure: Nothing to disclose

EPR3085

Identification of a prospective rapid motor progression cluster of Parkinson's disease: data from the PPMI study

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Aim: The aim of our study is to phenotype PD motor progression, and to detect whether serum, cerebrospinal fluid (CSF), neuroimaging biomarkers and neuropsychological measures characterise PD motor progression phenotypes.

Methods: We defined motor progression as a difference of at least one point in the H&Y (H&Y) scale between the baseline (Visit 0, V0), 12 months (Visit 04, V04) and 36 months (Visit 08, V08) of the Progression Markers Initiative (PPMI) study. H&Y progression events were recorded at each milestone in order to be used as cluster analysis variables that would produce progression phenotypes. Subsequently, cross-cluster comparisons prior to and following (pairwise) propensity score matching were performed ito assess phenotype – defining characteristics.

Results: Four progression clusters where identified: SPPD: Secondarily Progressive PD, H&Y progression between V04 – V08; EPPD: Early Progressive PD. H&Y progression between V0 – V04; NPPD: Non Progressive PD, no H&Y progression; MIPD: Minimally Improving PD, i.e. Minimal H&Y improvement H&Y progression between V04 – V08;. Independent Samples Mann Whitney U tests determined CSF aSyn ($p=0.006$, adj p-value=0.036) and Semantic Animal fluency T-score (SFT, $p=0.003$, adjusted p-value=0.016.) as statistically significant cross-cluster characteristics. Following PSM, SFT, Hopkins Verbal Learning Test (Retention / Recall), Serum IGF1, CSF aSyn and DaT-SPECT binding ratios (SBRs) and the Benton Judgement of Line Orientation Test (BJLOT) were determined as statistically significant predictors of cluster differentiation ($p<0.05$).

Discussion: SFT, Serum IGF1, CSF aSyn and DaT-SPECT, basal ganglia SBRs warrant further investigation as possible motor progression biomarkers.

Disclosure: Nothing to disclose

EPR3086

Long-term course of progression of clinical ocular motor signs in progressive supranuclear palsy

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Background and aims: To investigate the natural course of progression of ocular motor signs in patients with progressive supranuclear palsy (PSP).
Methods: 114 patients with a possible or probable PSP following NINDS-SPSP criteria were included in this retrospective study. All patients underwent structured neuro-ophthalmological testing at initial diagnostic evaluation, 35 patients several times during their course of disease. The following ocular motor signs were analysed: Saccadic slowing/paresis in vertical/horizontal direction, up-/downward/horizontal ocular motility, square wave jerks, VOR-function. Ocular motor signs were investigated in relation to disease duration.
Results: In the whole group of PSP patients saccadic abnormalities showed the following distribution over time: at 1y of disease duration 10% showed only saccadic slowing on upgaze, 40% on up- and downgaze, 21% saccadic paresis on upgaze and 29% complete vertical saccade paresis; at 2y the proportion of vertical saccade paresis was 32%, at 3y 65% and at 4y 82%. Progression of horizontal saccade paresis was slower (1y: 6%, 2y: 9%, 3y: 21%, 4y: 41%). The subgroup of patients with longitudinal follow-up showed a similar tendency. Ocular motility in this group decrease by a mean of 1.5mm/y on upgaze, 1.6mm/y on downgaze and 1.4mm/y on horizontal gaze. The degree of motility loss on up-/downgaze over time showed a good correlation (R2=0.71).
Conclusion: Ocular motor examination can be used as a robust marker of disease progression. Variability between patients however is considerable. Prospective clinical and apparative quantification of ocular motor markers in well-characterized cohorts of PSP patients is needed.
Disclosure: Nothing to disclose

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EPR3087

Durable suppression of MRI disease activity and slowing of brain volume loss in alemtuzumab-treated patients with active RRMS: 7-year follow-up of CARE-MS I (TOPAZ Study)

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Background and aims: In CARE-MS I (NCT00530348), alemtuzumab (12mg/day, baseline: 5 days; 12 months later: 3 days) demonstrated significant improvements in MRI outcomes, and reduced brain volume loss (BVL) versus SC IFNB-1a over 2 years (y). Alemtuzumab efficacy was durable in a 4-y 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; NCT02255656). We present MRI lesion/BVL outcomes over 7 y (2 y core study plus 4 y extension, and TOPAZ Y1) in alemtuzumab-treated CARE-MS I patients.
Methods: Assessments: Annual MRI for disease activity (scored as new Gd-enhancing lesions; new/enlarging T2 lesions), new T1 hypointense lesions, and BVL (derived by relative change in brain parenchymal fraction [BPF]).
Results: 299 patients (93%) completed TOPAZ Y1. After the initial 2 courses, 59% received neither alemtuzumab nor another DMT. At Y7, patients were free of MRI disease activity (68%), new Gd-enhancing lesions (91%), new/enlarging T2 lesions (68%), and new T1 hypointense lesions (85%). Median BPF change from baseline was –0.59%, –0.87%, –0.98%, –1.13%, –1.37%, –1.43%, and –1.62% in Y1–7, respectively. Median annual BPF change was reduced versus SC IFNB-1a over 2 y, remaining low in Y3–7 (Y3: –0.19%, Y4: –0.14%, Y5: –0.20%, Y6: –0.17%, Y7: –0.16%).
Conclusion: Alemtuzumab durably reduced MRI disease activity and slowed BVL over 7 y in treatment-naive patients. Alemtuzumab provides a unique treatment approach for RRMS patients, offering durable efficacy without continuous treatment.

Disclosure: Study supported by Sanofi and Bayer HealthCare Pharmaceuticals.

EPR3088

Cladribine tablets produce selective and discontinuous reduction of B and T lymphocytes and natural killer cells in patients with early and relapsing Multiple Sclerosis

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Background and aims: Efficacy of cladribine tablets 3.5 mg/kg (CT3.5) has been demonstrated in patients with early MS (ORACLE-MS) and in patients with relapsing MS in the CLARITY and CLARITY-Extension studies. Here, we evaluate B and T lymphocyte and natural killer (NK) cell profiles after the first administration CT3.5 in ORACLE-MS, CLARITY and CLARITY-Extension.
Methods: Longitudinal evaluation of peripheral blood lymphocyte subtypes was conducted for patients receiving the first course of CT either as part of the initial 3.5 mg/kg active treatment groups (ORACLE-MS and CLARITY) or the placebo switched to active treatment groups (CLARITY-Extension). Absolute lymphocyte counts (ALC) and lymphocyte subtype dispositions were evaluated at baseline, and Weeks 5, 13, 24 and 48.
Results: Baseline distributions of ALC were similar across studies. Temporal profiles of CD19+ B lymphocytes and CD4+ and CD8+ T lymphocytes were consistent across studies. Rapid reductions were observed for CD19+ B-cells (~75% reduction at Week 5 in each study), with nadir at ~Week 13 (Figure 1). Reconstitution of CD19+ B-cells towards baseline value occurred from Week 24 to 48. Lesser, discontinuous reductions also occurred for CD4+ and CD8+ T-cells that had not fully returned to baseline by Week 48. CD16+/CD56+ NK cells were also transiently reduced with CT, with recovery evident at Weeks 24 and 48.
Conclusion: CT3.5 achieved an early and discontinuous reduction of peripheral blood B-cells, with rapid reconstitution to baseline, and a moderate, discontinuous reduction of T-cells. Treatment with CT is associated with early, transient NK cell reductions.

Disclosure: This study was sponsored by EMD Serono Inc, a business of Merck KGaA, Darmstadt, Germany (in the USA), and Merck Serono SA, Geneva, an affiliate of Merck KGaA Darmstadt, Germany (ROW).

EPR3089

Innate immune cell counts in patients with Relapsing-Remitting Multiple Sclerosis (RRMS) treated with cladribine tablets 3.5mg/kg in CLARITY and CLARITY extension

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Background and aims: In CLARITY and CLARITY Extension, lymphopenia was the most common adverse event, consistent with the mechanism of action of cladribine tablets (CT). Absolute lymphocyte counts (ALC) were shown to recover towards the normal range over time in these studies. Here we evaluate the effect of CT on innate immune cell counts.
Methods: Data from patients randomised to CT 3.5mg/kg (CT3.5; cumulative dose over 2 years) in CLARITY or CLARITY Extension (N=685) were pooled to provide long-term follow-up data. Data from patients randomised to placebo in CLARITY and followed up in PREMIERE are also reported (N=435). Neutropenia was graded by Common Terminology Criteria for Adverse Events v3.0.
Results: Neutrophil counts remained within the normal range (>2.03x10^9/L) over the 2 treatment years and beyond, this included the small decrease observed shortly after (2 to 5 weeks) each dose of CT. Grade 3 or 4 neutropenia was reported in ≤6 (<2%) patients treated with CT3.5 at any single time point. Median monocyte counts at the end of each year ranged from 0.34×10^9/L to 0.36×10^9/L for CT3.5 and 0.40×10^9/L to 0.42×10^9/L for placebo.
Conclusion: These data, together with the previously-reported data on ALC, support the concept that CT selectivity reduces adaptive immune cell counts, and that the impact on the innate immune system is relatively minor.
Disclosure: This study was sponsored by EMD Serono Inc, a business of Merck KGaA, Darmstadt, Germany (in the USA), and Merck Serono SA, Geneva, an affiliate of Merck KGaA Darmstadt, Germany (ROW).

EPR3090

Incidence and outcomes of varicella zoster virus (VZV) reactivation in the ozanimod phase-3 clinical program (SUNBEAM and RADIANCE) in relapsing Multiple Sclerosis (RMS)

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Background and aims: VZV rates of 4.47 versus 11.5/1000 patient-years in immunocompetent (general medical population) versus immunocompromised patients have been reported (Johnson 2015; Schroder 2017). In an MS patient survey, VZV reactivation was reported in 17% of respondents, with mean age at onset of 37 years (Manouchehrinia 2017). We report VZV incidence in SUNBEAM (patients treated for at least 12 months) and RADIANCE (treatment duration 24 months).
Methods: Pooled safety data from 2 completed phase-3 trials were analyzed for VZV adverse events (AEs) of herpes zoster and varicella zoster virus infection. Positive VZV IgG antibody status or VZV vaccination 30+ days prior to randomisation was required to enroll.
Results: 2659 patients (ozanimod 1 mg, n=882; 0.5mg, n=892; interferon beta-1a [IFN], n=885) were treated. Five (0.6%) VZV cases were reported with ozanimod 1 mg, 3 (0.3%) with ozanimod 0.5mg, and 2 (0.2%; one with multiple reactivations) with IFN. All cases were single-dermatome distribution, non-serious, and treated with acyclovir. No patient discontinued treatment due to VZV. None of the VZV AEs were associated with Common Terminology Criteria Grade 4 lymphopenia (<0.2 x 10^9/L). Mean age at VZV AE onset was 45, 41, and 45 years (ozanimod 1 mg, 0.5 mg, IFN, respectively). Incidence rates of VZV were 3.73, 2.24, and 1.51 cases/1000 patient-years (ozanimod 1mg, 0.5mg, IFN, respectively).
Conclusion: With required immunity, VZV reactivation in SUNBEAM and RADIANCE was low, with no serious or complicated cases.
Disclosure: Nothing to disclose

EPR3091

Quantitative manual pupillometry as a valuable tool to assess visual pathway function in MS: first results on potential association with fatigue

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Background and aims: To evaluate the potential usefulness of pupillometry for assessing magnitude of relative afferent pupillary defects, EDSS, number of previous optic neuritis attacks (PONAs), fatigue severity in RRMS patients.

Methods: We analysed pupillometry data (NeurOptics®NPi-200TM) including neurological pupil index (NPi), pupil size (PS), minimum size of pupil (MinPS), percentage change of pupil size (CH), Constriction Velocity(CV), Maximum of Constriction Velocity (MCV), and Dilation Velocity (DV) from 182 RRMS and 90 healthy controls. To assess the changes across case and control subjects, multiple regression with age and group as independent variable was run. To address the effect of PONAs, an ANCOVA was run. The eye with no PONAs was considered as covariate. To address EDSS and fatigue, we categorized eyes with no PONAs into two category of high and low scores. age-adjusted control group were compared by ANCOVA.

Results: In multiple regressions, dichotomous variable of group statistically significantly predicted just PS and MinPS ($P<0.005$) with Adj. $R2=0.17$, Adj. $R2=0.19$, respectively. In ANCOVA analysis of PONAs, there was statistically significant differences in NPI, PS, MCV, DV and CH between groups. The notable effect size belongs to CH, ($p<0.0005$, partial $\eta\ 2=0.105$). Statistical mean variations among control group and either groups of EDSS/MFIS was significant for PS and CH variable.

Conclusion: Our prospective study provides solid data that pupilometer is an easy to use, new technique to quantify the visual pathway function in MS. The results suggest that MS-related symptoms statistically affect pupillometry results, and thereby offers a new tool for measurements.

Disclosure: Nothing to disclose

EPR3092

withdrawn

EPR3093

Long-term, real-world effectiveness of natalizumab treatment in relapsing-remitting multiple sclerosis: data from ≥6 years in the TYSABRI® Observational Program (TOP) Portuguese, Spanish, and global cohorts

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Background and aims: TOP is an ongoing, global open-label study in relapsing-remitting multiple sclerosis patients treated with natalizumab in the real world. Country-specific data can provide information on natalizumab's effectiveness in local clinical practice.
Methods: Annualised relapse rates (ARRs) before and on natalizumab and the cumulative probability of 24-week confirmed Expanded Disability Status Scale (EDSS) worsening (score increase of ≥1.5 from 0.0, ≥1.0 from 1.0-5.5, or ≥0.5 from ≥6.0) or improvement (score decrease of ≥1.0 from ≥2.0) were analysed using data from study initiation to May 2016. Updated data (at November 2017) including pooled data from the Portuguese and Spanish cohorts will be presented.
Results: As of May 2016, Portuguese (n=67), Spanish (n=124), and global (N=5927) TOP patients had received a median (range) of 29 (1-77), 43 (2-84), and 34 (1-113) doses, respectively. ARR decreased from 1.51 pre-natalizumab to 0.14 on natalizumab (90.7% decrease; P<0.0001) in Portuguese patients, from 2.22 to 0.18 (91.9% decrease; P<0.0001) in Spanish patients, and from 1.99 to 0.22 (88.9% decrease; P<0.0001) in the global population. Through ≥6 years on natalizumab, ARR assessed annually remained ≤0.27 in all 3 cohorts. At year 6, cumulative probability of confirmed EDSS worsening was 30.6% (Portuguese patients), 26.7% (Spanish patients), and 24.2% (global), and cumulative probability of confirmed EDSS improvement was 39.9% (Portuguese patients), 37.4% (Spanish patients), and 32.4% (global).
Conclusion: Consistent with global TOP results, natalizumab ARRs and EDSS worsening rates remained low over ≥6 years in the Portuguese and Spanish cohorts. These results support natalizumab's long-term effectiveness in real-world settings.
Disclosure: This study is supported by Biogen. MJS: consulting fees from Bayer, Biogen, Merck Serono, Novartis, Sanofi Genzyme and Teva. LR-T: research grants and speaker honoraria from Bayer, Biogen, Genzyme, Merck Serono, Novartis, and Teva. KR, SL, P-RH, MK: employees of and/or hold stock and/or stock options in Biogen.

EPR3094

Teriflunomide use in european clinical practice in patients with relapsing forms of Multiple Sclerosis: an overview of regional real-world studies

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Background and aims: In Teri-PRO (NCT01895335), a global phase-4 study, patients reported high levels of treatment satisfaction and improvements in patient-reported outcomes (PROs) with teriflunomide treatment. Here, we present interim data from several European studies evaluating the effect of teriflunomide on PROs, including quality of life and treatment satisfaction.
Methods: TAURUS-MS I and II (Germany), TACO (Switzerland), Teri-LIFE (Nordics), AURELIO (Greece), and Teri-CARE (Spain) are multicentre, prospective, non-interventional, ≤2-year studies in patients with relapsing-remitting MS receiving teriflunomide 14mg, per local labelling. Target enrolment: TAURUS-MS I, n=1115; TAURUS-MS II, n=1080; TACO, n=70; Teri-LIFE, n=200; AURELIO, n=350; Teri-CARE, n=323.
Results: Most studies are ongoing; interim data are available for 733 patients who received teriflunomide for 1 year (≥9 months) in TAURUS-MS I (enrolment complete; n=1115), and for the first 57 and 200 patients enrolled in TACO and Teri-CARE, respectively. Interim baseline demographics were broadly similar across studies, with some differences (mean [SD] for TAURUS-MS I, TACO, and Teri-CARE, respectively): years since diagnosis, 8.6 (7.4), 11.7 (10.0), and 7.3 (7.5); EDSS scores, 2.4 (1.5), 2.4 (1.1), and 1.7 (1.6). In TAURUS-MS I, mean (SD) Treatment Satisfaction Questionnaire for Medication (TSQM; higher scores indicate greater treatment satisfaction)-9 scores at baseline/Month 12 were: Global Satisfaction, 64.7 (24.1)/74.6 (22.3); Convenience, 74.8 (24.2)/91.0 (11.2); Effectiveness, 62.1 (23.6)/69.0 (23.8); P<0.001 for all comparisons.
Conclusion: Interim results from TAURUS-MS I showed significantly improved treatment satisfaction with teriflunomide vs baseline. Data from these and other similar observational, regional studies will be pooled to further evaluate the real-world effectiveness of teriflunomide, and better inform treatment decisions.
Disclosure: Study supported by Sanofi.

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EPR3095

Efficacy of a fourth alemtuzumab course in RRMS patients with disease activity after three prior courses: analysis of CARE-MS I

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Background and aims: In treatment-naïve relapsing-remitting MS (RRMS) patients (CARE-MS I [NCT00530348]), alemtuzumab 12mg/day (baseline: 5 days; 12 months later: 3 days) improved clinical/MRI outcomes versus SC IFNB-1a over 2 years. In a 4-year extension (NCT00930553), patients could receive as-needed alemtuzumab retreatment (12mg/day, 3 days; ≥12 months apart) for relapse/MRI activity, or receive another disease-modifying therapy (DMT). Efficacy remained durable, despite 63% receiving neither alemtuzumab retreatment nor another DMT. Through Year 6, 325/349 (93%) remained on study; 42 (12%) received ≥4 alemtuzumab courses (13 [4%] received ≥5 courses). We evaluated efficacy of a fourth course (Course [C] 4) in CARE-MS I patients receiving ≥4 courses.

Methods: Assessments 12 months before and up to 3 years post-C4: annualised relapse rate (ARR); improved/stable Expanded Disability Status Scale (EDSS) score (versus core study baseline); 6-month confirmed disability improvement (CDI). Included patients (N=31 [9%]) received ≥4 courses by Month 60 (allowing for 1-year post-C4 follow-up), and received no other DMT. Data for patients receiving a fifth course (C5) were censored at C5 administration.

Results: ARR decreased post-C4 (12 months pre-C4: 0.65; 12 months post-C4: 0.42), remaining low (0.33) at Year 3 post-C4. EDSS scores versus core study baseline were stable/improved in 73.1% 12 months post-C4, compared with 58.1% at C4 administration. The percentage with CDI increased from 4.3% (12 months pre-C4) to 17.4% (12 months post-C4).

Conclusion: A fourth course reduced relapses and stabilised/improved disability in CARE-MS I patients receiving ≥4 courses due to disease activity after 3 prior alemtuzumab courses.

Disclosure: Study supported by Sanofi and Bayer HealthCare Pharmaceuticals.

EPR3096

Evolution of new lesions and its temporal patterns in patients with clinically isolated syndrome treated with subcutaneous interferon beta-1a

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Background and aims: Subcutaneous interferon beta-1a (scIFNbeta-1a) treatment improves standard imaging outcomes in clinically isolated syndrome (CIS) patients. We assessed whether scIFNbeta-1a reduced new lesion evolution and temporal patterns using MRI data from REFLEX.

Methods: In REFLEX, CIS patients were randomised to scIFNbeta-1a 44mcg three times weekly (tiw), once weekly (qw) or placebo for 24 months; upon clinically definite multiple sclerosis (MS) patients switched to open-label scIFNbeta-1a tiw. This analysis included patients with scans available at Month (M) 12 and ≥2 scans after M12 (tiw n=128; qw n=137; placebo n=128). New lesion intensity on T1-weighted images without contrast was assessed and classified with respect to the surrounding white matter at: first appearance (iso- or hypo-intense [black holes]); first appearance and M24 (iso-iso, iso-hypo, hypo-iso, hypo-hypo); and the majority of timepoints (mostly iso- or hypo-intensity). Data are median (IQR) lesion numbers, unless otherwise stated. Kruskal-Wallis tests were used to assess overall treatment effects and Mann-Whitney U tests for pairwise comparison treatments.

Results: Overall, numbers of new lesions at M24 were reduced vs placebo (Table 1). Numbers of iso-hypo and hypo-hypo lesions were reduced vs placebo (0.4 [mean] and 1 [0–3], respectively) with scIFNbeta-1a tiw (0.09 [mean], p=0.003; and 0 [0–4], p<0.001) but not with qw (0.13 [mean], p=0.052; and 1 [0–3], p=0.165). At the majority of timepoints, scIFNbeta-1a reduced the number of new lesions that were mostly iso- and hypo-intense (Table 2).

	Overall	New iso-intense lesions	New hypo-intense lesions
Placebo	5 [2–11]	4 [1–8]	1 [0–3.5]
scIFNbeta-1a			
tiw	2 [0–5] P<0.001	1 [0–3] P<0.001	0 [0–1] P<0.001
qw	3 [1–7] P<0.001	2 [0–4] P<0.001	1 [0–2] P=0.147

Table 1: The number of new iso- and hypo-intense lesions at M24

	New iso-intense lesions	New hypo-intense lesions
Placebo	2 [0–5]	4 [2–8.5]
scIFNbeta-1a		
tiw	1 [1–4] P=0.003	2 [1–4] P<0.001
qw	1 [0–3] P=0.273	2 [1–5] P<0.001

Table 2: The number of new iso- and hypo-lesions at the majority of timepoints

Conclusion: scIFNbeta-1a tiw treatment reduced evolution of new lesions into black holes in CIS patients.

Disclosure: Funded by Merck KGaA, Darmstadt, Germany

EPR3097

A systematic review of non-interventional studies reporting on humanistic and economic burden of cognitive decline in multiple sclerosis patients regardless of study design

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Background and aims: Prevalence of cognitive impairment (CI) varies across disease duration. A clinically meaningful change in CI may be of interest to clinicians. Our objective was to summarise humanistic and economic outcomes of cognitive decline (CD) in patients with multiple sclerosis (MS).
Methods: Medline, Embase and PUBMED databases were searched considering English language studies only. Paediatric studies were excluded. CD was expressed as either a change in CI over MS duration or comparing assessments between patients with MS and healthy controls.
Results: 55 studies from 11 countries (Canada, France, Germany, Hungary, Italy, Israel, Norway, Spain, Switzerland, The Netherlands, United States) were included. Assessment of MS diagnosis was not homogenous. Humanistic: Prevalence of CI increased between baseline and disease duration of >5 years. Frequently reported CI assessments: Selective reminding test (SRT), Spatial recall test (SPART), Symbol digit modalities test (SDMT), Paced Auditory Serial Addition test (PASAT) and Word List Generation (WLG). Weighted differences in test scores comparing MS patients to healthy controls: [mean (95% Confidence Interval)] SDMT: -8.1 (-2.3, -13.9); SRT. D: -2.3 (-0.5, -1.3); PASAT 2: -7.7(-6.0, -9.5) WLG:-4.2 (-2.2, -6.2). Economic: Studies reported employment status, caregiver burden, ability to drive car, resource use or burden of disease. SDMT, PASAT and poor episodic memory contributed to predicting employment status and work productivity. CI in MS patients negatively impacts caregiver quality of life.
Conclusion: Prevalence of CI increases with disease duration. Cognitive assessments in patients with MS show deteriorating scores when compared to matched controls. CI negatively impacts employment status and caregiver quality of life.
Disclosure: Craig: Employee of and holds stock/stock options in Biogen Christopher/Basil: paid by Thomas R. Einarson & Associates that received fees from Biogen to complete the analysis.

EPR3098

Anti-CD20 antibodies ofatumumab and ocrelizumab have distinct effects on human B-cell survival

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Background and aims: Ofatumumab is a subcutaneous, fully human anti-CD20 monoclonal antibody (mAb), currently in Phase-3 clinical trials for Multiple Sclerosis (MS), whereas ocrelizumab is an intravenous humanised anti-CD20 mAb. This study investigated the mode of B-cell cytotoxicity of these antibodies as a potential basis for clinical efficacy.
Methods: The human B-cell lines RAJI and RAMOS were used as target cells. The cells were coated separately with both anti-CD20 mAbs before washing and incubation for various time points. Human complement was added to initiate complement-dependent cytotoxicity (CDC) and cell lysis was analysed by fluorescence-activated cell sorting (FACS). Rituximab, another anti-CD20 mAb, was used as a control.
Results: All the tested anti-CD20 mAbs induced CDC. The degree of human RAJI B-cell lysis was a function of the mAb tested and the time of incubation prior to the addition of complement: cell lysis was more pronounced with ofatumumab compared with ocrelizumab when the cells were exposed to mAb and complement together for 2 hours. Similar results were obtained with the RAMOS B-cell line. The strongest difference was observed when complement was added 8 hours after washing. Under this condition, the extent of cell lysis was highest with ofatumumab, followed by rituximab and ocrelizumab. Ongoing studies in other B-cell cytotoxicity assays will provide deeper insights into relevant modes of action.
Conclusion: The strong complement-dependent B-cell lysis by ofatumumab may contribute to its high potency in vivo that enables a low-dose subcutaneous dosing regimen.
Disclosure: This study was supported by Novartis Pharma AG, Basel, Switzerland. All authors are employees of Novartis.

EPR3099

Subgroup analyses of NEDA re-baselined at week 24 in ocrelizumab recipients with relapsing Multiple Sclerosis receiving ocrelizumab in OPERA I and II

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Background and aims: The Phase III OPERA I/II studies (NCT01247324/NCT01412333) demonstrated the efficacy of ocrelizumab versus interferon-beta-1a (IFNβ1a) on a broad range of clinical and imaging outcomes in patients with relapsing multiple sclerosis, including no evidence of disease activity (NEDA; 47.7% vs 27.1%; p<0.001; pooled analyses). Benefit on NEDA was maintained across patient subgroups; magnitude varied. Re-baselining at Week 24 might provide a different perspective of treatment efficacy.
Methods: Proportions of patients at Week 96 with NEDA (no 12-week confirmed disability progression, protocol-defined relapse, new/enlarging T2 lesions or T1 Gd-enhancing lesions) re-baselined to Week 24 were compared (Cochran-Mantel-Haenszel test) using the pooled OPERA I/II modified intent-to-treat (mITT) population (OCR [600mg IV/24 weeks], n=745; IFNβ1a [44µg SC three times weekly], n=706; excludes patients discontinuing treatment for reasons other than lack of efficacy/death with NEDA prior to discontinuation).
Results: Treatment benefit for NEDA seen in the mITT population with OCR vs IFNβ1a (72.2% vs 41.9%; relative improvement, 72%; p<0.001) was maintained across subgroups (OCR/IFNβ1a): age (<40 years: 73.9%/36.1%; ≥40 years: 69.8%/50.2%), gender (male: 72.7%/36.7%; female: 72.0%/44.6%), prior [last 2 years] disease-modifying therapy (yes: 72.1%/35.8%; no: 72.2%/44.0%), prior relapses [last 12 months] (≤1: 73.3%/43.0%; ≥2: 69.6%/39.5%), baseline T1 Gd-enhancing lesions (none: 71.2%/51.5%; ≥1: 72.9%/27.6%) and baseline EDSS score (EDSS <2.5/<4.0: OCR 77.8%/76.5%, IFNβ1a 45.6%/42.9%; EDSS ≥2.5/≥4.0: OCR 68.9%/58.4%, IFNβ1a 39.4%/38.9%). All p-values (OCR versus IFNβ1a) <0.001.
Conclusion: The results of these NEDA subgroup analyses with re-baselining were consistent with those of the overall pooled population on NEDA with re-baselining.
Disclosure: Sponsored by F. Hoffmann-La Roche Ltd.

EPR3100

Pregnancy outcomes in patients with MS treated with teriflunomide: clinical study data

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Background and aims: Teriflunomide is a once-daily oral immunomodulator approved for treatment of relapsing forms of MS. Results from the clinical programme showed no signal for human teratogenicity in teriflunomide-exposed pregnancies. Additionally, no teratogenic signal has been reported in post-marketing surveillance of the parent compound, leflunomide (approved to treat rheumatoid arthritis since 1998). However, teriflunomide is contraindicated in pregnancy based on embryo-foetal toxicity in rats and rabbits. Despite the requirement to use reliable contraception, pregnancies have occurred in teriflunomide-treated patients.
Methods: Pregnancy outcomes are summarised for females treated with teriflunomide monotherapy in the clinical programme. Data cut-off was May 17, 2016.
Results: Overall, 62 pregnancies were reported: live birth (n=22), elective abortion (n=30), spontaneous abortion (n=8), and ectopic pregnancy (n=2). Of 22 live births, 3 (14%) were pre-term (<37 weeks). No malformations/abnormalities were reported with elective abortions. Mean (SD) treatment duration prior to pregnancy was 19.6 (19.1) months; an accelerated elimination procedure for teriflunomide was used in 82% of the cases with live births. In all pregnancies, the last dose of teriflunomide was administered pre-conception or in the first trimester (>0 to <14 weeks). One structural abnormality, ureteropyeloectasia, was reported in a pre-term infant. Patient-level data from individual pregnancies in the clinical setting will also be presented.
Conclusion: Current data from pregnancies exposed to teriflunomide show no teratogenic signal, consistent with observations from post-marketing surveillance of leflunomide. These data from the clinical setting, together with those from the International Teriflunomide Pregnancy Exposure Registry, will provide valuable information to healthcare providers and female patients of child-bearing potential.
Disclosure: Study supported by Sanofi.

EPR3101

CSF biomarkers do not associate to early disability in Multiple Sclerosis

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Introduction: Neurodegeneration occurs early in Multiple Sclerosis (MS), and caused clinical deterioration and disability. Biomarkers reflecting this phenomena, such as neurofilament light chain (NF-L), tau and β-amyloid (Aβ), could be measured easily in the cerebrospinal fluid (CSF).
Aim: To evaluate if CSF biomarkers of neurodegeneration predict early MS disability.
Methods: CSF NF-L, Aβ and tau levels were determined with commercial enzyme-linked immunosorbent assay in 48 newly-diagnosed MS patients (33 females). Baseline disease-courses were: three radiological (RIS) and 18 clinical isolated syndrome (CIS), 24 relapsing-remitting (RR) and 3 primary of secondary progressive (PR)-MS. Our disability outcome was the MS severity score (MSSS) at the last follow up (minimum 1 year after disease onset). We estimated differences between CSF biomarkers in baseline MS courses and disability with ANOVA.
Results: First, only CSF NF-L differed significantly among MS courses (p=0.002). In fact RIS showed the lowest levels (CSF NF-L mean 206 ng/ml±standard deviation 220) if compared to CIS (1158±511), RR (1616±741), and PR-MS (1714±27). On contrast, none of the CSF biomarkers was related to MSSS at last follow up. Of note, we excluded a correlation among tau or Aβ levels with NF-L.
Conclusion: NF-L are the unique biomarker of neurodegeneration related to MS forms. Their levels increased progressively with MS-course severity reflecting the higher axonal damage in PR-MS.
CSF NF-L, Aβ and tau failed to predict early MS disability: short-term outcome could not reflect the natural disease history.
Disclosure: Dr. Domizia Vecchio has been supported by a research felloship by Merck-Serono

EPR3102

Lack of apparent association between lymphocyte pharmacodynamics and clinical or MRI disease activity in alemtuzumab-treated relapsing-remitting Multiple Sclerosis patients through 6 years: CARE-MS extension

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Background and aims: In the CARE-MS studies (NCT00530348; NCT00548405), alemtuzumab (12mg/day, baseline: 5 days; 12 months later: 3 days) significantly improved clinical/MRI outcomes versus subcutaneous IFNB-1a over 2 years in patients with active relapsing-remitting MS. Durable efficacy was observed in a 4-year extension (NCT00930553) without continuous treatment; 53% of patients received no additional alemtuzumab or other disease-modifying therapy. The effects of alemtuzumab may be due to its selective depletion and distinctive repopulation of circulating CD52-expressing T and B lymphocytes. We examine the association between lymphocyte repopulation patterns and clinical/MRI disease activity through 6 years following alemtuzumab treatment.
Methods: Blood counts were performed monthly; lymphocytes were phenotyped by flow cytometry quarterly and at Months 1 and 13. Lymphocyte subset counts from the CARE-MS studies were pooled (CD4+/CD8+ T-cells: total/naïve/memory/regulatory [Treg]; CD19+ B-cells: total/immature/mature/memory). Further analyses examined ratios of CD19+ (total/immature/memory) to Treg (CD4+/CD8+) cell counts. Relationship between lymphocyte repopulation patterns and efficacy was assessed in patients with/without relapses, 6-month confirmed disability worsening (CDW; ≥1.0-point Expanded Disability Status Scale increase [≥1.5 points if baseline EDSS=0]), or MRI disease activity (new gadolinium-enhancing lesions or new/enlarging T2 lesions).
Results: Lymphocyte subset repopulation kinetics over 2 years did not differ in patients with or without relapses, CDW, or MRI disease activity through 6 years. No correlation was observed between any CD19+/Treg cell count ratio and relapse, CDW, or MRI disease activity.
Conclusion: Based on these analyses, lymphocyte repopulation kinetics were not associated with return of disease activity and likely cannot be used to predict need for further treatment.
Disclosure: Study supported by Sanofi and Bayer HealthCare Pharmaceuticals.

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EPR3103

A double-blind placebo-controlled study of satralizumab (SA237), a recycling anti-IL-6 receptor monoclonal antibody, as add-on therapy for neuromyelitis optica (NMO) and NMO spectrum disorder (NMOSD)

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Background and aims: NMO/NMOSD is a severe neuroinflammatory disorder associated with auto-antibodies to aquaporin-4 (AQP4). Interleukin-6 stimulates antibody production by plasmablasts and increases blood-brain-barrier permeability, thus permitting the penetration of pathological auto-antibodies into the central nervous system. Satralizumab is a recycling anti-IL-6 receptor monoclonal antibody with a long plasma circulation. We present the design and baseline demographics of a randomised, multicenter, international, double-blind, placebo-controlled study of satralizumab, the SAkuraSky study (NCT02028884).

Methods: The study is a randomised, double-blind, phase 3 study of satralizumab compared to placebo as add-on to baseline treatment (immunosuppressants or corticosteroids). The primary endpoint is time to first relapse. Main inclusion criteria: Adult (aged 18 to 74 years) and adolescent (aged 12 to 17 years) patients with NMO by 2006 Wingerchuk criteria (any serostatus), or NMOSD by 2007 Wingerchuk criteria with anti-AQP4 antibody seropositive status. At least 2 relapses in the last 2 years prior to screening, at least one of which occurred in the last 12 months.

Results: Adult enrollment is complete (76 patients). The enrollment of adolescents is ongoing (6 patients as of Oct 2017). 93.9% of total patients are females (77 patients). Baseline annual relapse rate was 1.0 for 39 patients (47.6%) and greater than 1.0 for the remainder. The number of patients with anti-AQP4 antibody seropositive status at screening is 55 (67.1%).

Conclusion: The SAkuraSky study is designed to evaluate the safety and efficacy of satralizumab compared with placebo in patients with NMO/NMOSD.

Disclosure: This study was funded by Chugai Pharmaceutical Co., Ltd., Tokyo, Japan. Detailed disclosures of each author will be included in the poster/oral presentation.

EPR3104

Patients switching to fingolimod from other oral DMTs and different treatment frequencies in daily clinical routine: results from PANGAEA 2.0

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Background and aims: Fingolimod was approved as first oral drug for the treatment of relapsing MS. Since 2011, treatment options highly increased. We analyse the effectiveness of fingolimod in patients switching from different pre-treatment frequencies and other oral disease-modifying therapies (oDMTs, dimethylfumarate and teriflunomide) to fingolimod.

Methods: PANGAEA 2.0 is an ongoing non-interventional study conducted in Germany. As of January 2018 it included app. 1800 patients. 15% of these patients switched from oDMTs to fingolimod.

Results: Baseline characteristics of all patients were comparable to patients switching from oDMTs. Patients switching after 1, 2 or 3 pre-treatments had an increasing mean age, time since diagnosis and EDSS but similar ARR at baseline. Patients were pre-treated with interferons (4.1±0.7; years±SD), glatiramer actetate (3.0±0.8), oDMTs (1.3±0.3); or other DMTs (3.2±0.6). For 41.1% of the patients fingolimod was the second therapy since diagnosis. The ARR (±95%CI) 12 months after switch to fingolimod was reduced by 88.0% from 1.58±0.25 to 0.19±0.07 for patients switching from oDMTs. Patients switching from 1 DMT to fingolimod had a significant lower relapse rate (0.07±0.02). compared to patients switching from 2 ($p<0.001$) or 3 ($p=0.038$) DMTs to fingolimod.

Conclusion: Independently of the treatment sequence before switching to fingolimod all patients benefit from the switch within twelve months of treatment. Patients treated with one DMT before switching to fingolimod had a significant lower ARR twelve months after switch in comparison to patients treated with more than one DMT or oDMTs before switch.

Disclosure: This study was supported by the Novartis Pharma GmbH, Nuremberg, Germany.

EPR3105

PANGAEA: 5 years safety of fingolimod in daily clinical practice

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Background and aims: Fingolimod (Gilenya®) is a sphingosine-1-phosphate receptor modulator approved for the treatment of relapsing MS. By June 2017 total patient exposure exceeded 453.000 patient years. PANGAEA (Post-Authorisation Non-interventional German sAfety of GilEnyA in RRMS patients) is a non-interventional study conducted in Germany to investigate long-term safety, effectiveness and patient reported outcomes.
Methods: PANGAEA included 4229 patients. By Jan 2018 over 800 patients finished the 5 year documentation period. Here we present safety and adherence data from 5 years fingolimod treatment in daily clinical routine.
Results: The mean observation period in PANGAEA was 3.75 (±1.62SD) years. Over a period of 5 years, the annual mean study discontinuation rate was 10-12%. 65% of the patients are continuing treatment 79% of patients discontinuing the study also discontinued fingolimod treatment. Most frequent reasons for study discontinuation were patient's decision (33%), adverse events (28%), switch of physician (12%) and disease progression (11%).
85% of the patients had no therapy interruption so far. Over 5 years, the safety profile of fingolimod in real-life is comparable to that observed in phase III clinical trials. Common adverse events are lymphopenia (11.3%), increase in liver enzyme values (5.3%), upper respiratory tract infections (e.g. nasopharyngitis (9.9%); bronchitis (2.4%); cough (2.2%)), fatigue (3.4%) and depression (2.6%). 28% of the patients experienced no adverse events so far. 5.0% of all adverse events were rated as serious.
Conclusion: The results of the 5 year interim analysis of PANGAEA support the positive benefit-risk profile that fingolimod demonstrated in phase III clinical trials with real-world evidence data.
Disclosure: This study was supported by the Novartis Pharma GmbH, Nuremberg, Germany

EPR3106

PANGAEA: 5 years effectiveness of fingolimod in daily clinical practice

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Background and aims: Once-daily fingolimod (Gilenya®, Novartis Pharma AG) is a sphingosine 1-phosphate receptor modulator approved for the treatment of relapsing MS. As of June 2017 total patient exposure exceeds 453.000 patient-years. PANGAEA is a non-interventional study, conducted in Germany, to investigate long-term safety, effectiveness and patient reported outcomes in daily clinical practice.
Methods: PANGAEA included 4229 patients. By Jan 2018 over 800 patients finished the 5 year documentation period of fingolimod treatment. In this interim analysis we present effectiveness data of fingolimod in daily clinical practice.
Results: The proportion of female patients was 71.6% and the mean age was 39.9 (±10.1SD) years. The mean annual relapse rate of PANGAEA patients improved from 1.6±0.12 (95%CI) to 0.28±0.07 in the third year of treatment and remained stable over the following two years. The mean baseline EDSS in PANGAEA was 3.0 (±0.03; 95%CI) and remained stable over 5 years. In each year of treatment app. 90% of the patients had a stable or improved EDSS. In each year of treatment between 60.4% (year 1) and 71.1% (year 5) of the patients were free of relapses and 6 months confirmed disability progression (CDP). 42.8% of the patients neither had a relapse nor a 6 months CDP over 4 years. Patient reported outcomes evaluated in a substudy (n=830) also confirmed the good effectiveness and convenience profile of fingolimod.
Conclusion: The results of the 5 year interim analysis of PANGAEA support the positive effectiveness profile of fingolimod demonstrated in phase III clinical trials with real world evidence data.
Disclosure: This study was funded by the Novartis Pharma GmbH, Nuremberg, Germany.

EPR3107

The change of the fingolimod patient profile over time: a comparison of two non-interventional studies PANGAEA and PANGAEA 2.0.

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Background and aims: Therapeutic options for Multiple Sclerosis (MS) have increased over the years. Treatment guidelines have changed from baseline and escalation therapies to the treatment of mild to active forms of MS. How did this influence the demographic and clinical profile of fingolimod patients over time?
Methods: PANGAEA and PANGAEA 2.0 are two non-interventional studies conducted in Germany that recruited patients switching to fingolimod between 2011-13 and 2015-18 respectively. PANGAEA included 4229 patients. PANGAEA 2.0 included app. 1800 patients and recruitment is still ongoing.
Results: The mean age of PANGAEA 2.0 patients is comparable (38.7±10.6 vs 38.9±10.1 years) to PANGAEA. 84.4% of patients were treated with at least one other disease modifying therapy (DMT) before entering PANGAEA 2.0 (PANGAEA 92.3%). 15.6% of patients were not pre-treated with any DMT (41.1% one pre-treatment, 24.6% two pre-treatments, 18.6% three or more). Patients included in PANGAEA 2.0 have a shorter disease history (7.2±6.6 vs. 8.2±6.3 years), a similar relapse rate (1.3±1.0 vs. 1.6±1.2), lower EDSS (2.2±1.6 vs. 3.0±1.7) and MSSS (3.5±2.5 vs. 5.1±2.6). 40.5% of PANGAEA 2.0 patients had an EDSS ≤1.5 at baseline (PANGAEA: 23.3%). MSSS score of 49.5% of PANGAEA 2.0 patients ranged within the first 3 deciles (PANGAEA: 29.5%).
Conclusion: Treatment guidelines have influenced demographic and clinical profiles of fingolimod patients. Patients included into PANGEA 2.0 (2015/16) switched to fingolimod earlier from a demographic and clinical point of view in comparison to PANGAEA (2011-13). This might indicate a change to earlier optimization of sub-optimally treated patients with MS between 2011 and 2016 in Germany.
Disclosure: This study was funded by the Novartis Pharma GmbH, Nuremberg, Germany

EPR3108

Extended interval dosing (EID) of natalizumab is associated with significantly lower progressive multifocal leukoencephalopathy (PML) risk: sensitivity and post hoc analyses from the TOUCH registry

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Background and aims: Natalizumab, approved for intravenous 300mg every 4 weeks dosing, is associated with a risk of PML. Previous analyses of US TOUCH registry data found that, in anti-JC virus antibody positive (JCV Ab+) patients, natalizumab EID was associated with significantly lower PML risk compared with standard interval dosing (SID; Table). Those analyses were limited to patients with known JCV Ab seropositive status and excluded patients with infusions at >12-week intervals (ie, dosing gaps). Sensitivity and post-hoc analyses were conducted to explore the robustness of these results.
Methods: In the previous primary analysis, SID was based on average dosing intervals (ADIs) of ≥3 to <5 weeks; EID was based on ADIs of >5 to ≤12 weeks. In prespecified sensitivity analyses, alternative EID definitions and inclusion of PML cases occurring pre-2012, prior to JCV Ab testing, was evaluated. A post hoc analysis included patients with dosing gaps. EID and SID PML hazard ratios (HRs) were compared with covariate (age, sex, prior immunosuppressant use, initiation calendar year, and infusion number)–adjusted Cox regression models and Kaplan-Meier estimates.
Results: Across all sensitivity and post-hoc analyses, HRs and 95% CIs were similar to those in the primary analysis.
Conclusion: In the US, natalizumab EID is associated with a statistically significant, clinically meaningful lower PML risk in JCV Ab+ patients compared with SID; changes in EID definition and inclusion/exclusion criteria did not reveal differences from the primary analysis. As TOUCH does not collect effectiveness data, EID's benefit-risk could not be evaluated.
Disclosure: Support: Biogen. LZR: personal compensation for speaking/advisory boards from Biogen, Teva; research support from Biogen. JF: personal compensation for consulting from Biogen, Genentech, Genzyme, Teva. IC, ER, KS, BY, ZR, CH, P-RH, NC: employees of and own stock and/or stock options in Biogen. IK: served on advisory boards for Biogen, Genentech. GC: compensation for consulting/advisory boards from Argenix, Atara Biotherapeutics, Bioeq GmBH, Genentech, Genzyme, Innate Therapeutics, Klein-Buendel, MedDay, Medimmune, Novartis, Opexa Therapeutics, Roche, Savara, Somahlution, Teva, TG Therapeutics, Transparency Life Sciences, CMSC (grant); president of Pythagoras, Inc. RM: owns stock in Biogen. JDG, XL: nothing to disclose.

EPR3109

Lack of apparent association between lymphocyte repopulation kinetics and autoimmune events in alemtuzumab-treated patients with relapsing-remitting Multiple Sclerosis through 6 years: CARE-MS extension

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Background and aims: Alemtuzumab 12mg significantly improved clinical and MRI outcomes versus subcutaneous IFNB-1a in patients with relapsing-remitting MS (RRMS) in the 2-year CARE-MS studies (NCT00530348; NCT00548405). Autoimmune adverse events (AEs), including thyroid events, immune thrombocytopenia (ITP), and nephropathies, were observed during the trials. Alemtuzumab selectively depletes CD52-expressing T and B lymphocytes; a distinct pattern of cellular repopulation then follows. This analysis tests the hypothesis that differential lymphocyte repopulation patterns following treatment with alemtuzumab create the environment for secondary autoimmunity.

Methods: Patients who completed the CARE-MS studies could enroll in a 4-year extension (NCT00930553). Autoimmune AE monitoring occurred at baseline and monthly (ITP; nephropathies) or quarterly (thyroid). Blood cell counts in the CARE-MS studies were performed monthly; lymphocytes were phenotyped by flow cytometry quarterly and at Months 1 and 13. Lymphocyte subset counts from the CARE-MS studies were pooled (CD4+/CD8+ T-cells: total/naïve/memory/regulatory [Treg]; CD19+ B-cells: total/immature/mature/memory). Further analyses examined ratios of CD19+ (total/immature/memory) to Treg (CD4+/CD8+) cell counts. The relationship between lymphocyte pharmacodynamics and autoimmune AEs over 6 years was assessed.

Results: There was no difference in either T or B lymphocyte depletion or repopulation patterns over 2 years in patients who did or did not experience autoimmune AEs through 6 years following alemtuzumab treatment. No correlation was observed between autoimmune AE occurrence and any CD19+/Treg cell count ratio.

Conclusion: The current analyses do not support the hypothesis that differences in lymphocyte subset count depletion or repopulation kinetics predict the occurrence of autoimmune AEs in alemtuzumab-treated RRMS patients.

Disclosure: Study supported by Sanofi and Bayer HealthCare Pharmaceuticals.

Muscle and neuromuscular junction disease 2

EPR3111

Ratio of creatine kinase to alanine aminotransferase as a biomarker of acute liver injury in dystrophinopathy

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Background and aims: To investigate the ratios of creatine kinase (CK) to aminotransferases as biomarkers of acute liver injury in dystrophinopathy.
Methods: We enrolled 658 male patients with dystrophinopathy and 378 male patients without muscle and liver injury as control. Patients were analySed for lower limb motor function, genotype, clinical phenotype, glucocorticoid management, and serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and CK. To examine whether CK-adjusted aminotransferase levels could indicate liver status in dystrophinopathy, the CK/ALT ratio was compared in mice treated or not with a hepatotoxic reagent D-galactosamine (D-GalN), as the number of patients with dystrophinopathy and acute liver injury were insufficient for analysis.
Results: In patients with dystrophinopathy, the correlations between CK and aminotransferases were significant ($P<0.05$). But only CK/ALT did not show association with factors related to muscle injury severity ($P>0.05$). Animal experiments indicated that D-GalN decreased the CK/ALT ratio both in C57 mice and mdx mice ($P<0.001$), suggesting that CK/ALT may also be decreased in patients with dystrophinopathy and acute liver injury. Lower reference limit of CK/ALT in patients with dystrophinopathy was determined as 22.16.
Conclusion: CK/ALT has potential clinical applicability for monitoring acute liver injury in dystrophinopathy.
Disclosure: The study was funded by the Natural Science Foundation of China (grant nos. 81771359, 81471280 and 81271401), the Guangdong Provincial Science and Technology Plan (grant nos. 2014A020212130), the Guangzhou City Science and Technology Plan (grant nos. 1561000153/201508020012), the National Key Clinical Department and Key Discipline of Neurology, the Guangdong Provincial Key Laboratory for Diagnosis and Treatment of Major Neurological Diseases (No. 2014B030301035), the Southern China International Cooperation Base for Early Intervention and Functional Rehabilitation of Neurological Diseases (No. 2015B050501003) and Guangdong Provincial Engineering Center for Major Neurological Disease Treatment, Science and Technology Planning Project of Guangzhou (No. 201604020010).

EPR3112

Study on the origin of the electromyographic spontaneous electrical activity in an ex vivo muscle model

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Background and aims: Spontaneous electrical activity (SEA) is the electromyographic record obtained from relaxed healthy muscles. In non-pathological muscles SEA consists of end-plate noise (EPN) and end-plate spikes (EPS). Even though SEA has been studied since the 1950s, its origin in the spontaneous neurotransmission of the neuromuscular junction (NMJ) is not proven in a reliable way. The objective of this study is to assess the participation of NMJ in the generation of SEA.
Methods: Muscle areas were recorded by using electromyography at 1mm and at 10mm of the intramuscular nerves in ex vivo diaphragm. The presence of EPN and EPS in each area was recorded and their amplitude was calculated. The amplitude of EPN was also evaluated before and after a quick incubation with ClK (30 mM).
Results: The number of areas with EPN and EPS and their amplitude decrease progressively from near the nerve to 10mm away. Moreover, 10mm apart from the intramuscular nerve, no EPN was recorded. Finally, 3 seconds after CIK exposure the EPN amplitude increases by 300%.
Conclusion: The spontaneous electrical activity recorded with electromyography is related to the spontaneous release of acetylcholine by NMJ.
Disclosure: Nothing to disclose

EPR3113

Myopathy in trunk muscles in Myotonic Dystrophy type-1: a case control study with MRI

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Background and aims: Myotonic Dystrophy 1 (DM1) is an inherited multisystem disorder caused by a CTG nucleotide repeat expansion in the Myotonic dystrophy protein kinase (DMPK) gene on chromosome 19. The motor impairments in DM1 are assumed to progress from distal to proximal in the extremities. Resently, we documented early and severe impairments in trunk muscles when measured by manual muscle strength tests (MMT). Whether these impairments are caused by DM1 myopathy is not clear. We therefore investigate trunk muscles with MRI and relate the findings to different motor function in a case control design.
Methods: 20 patients and 20 age and geneder matched controls included in a case control design. MR imaging was performed using a 1.5-T MR unit of trunk muscles (abdominal flexors and trunk extensors). MRIs were analysed for% of muscle fat infiltration, and muscle size measured in mm and mm^2. Trunk muscle strength, general mobility, balance and forced vital capacity (FVC) are measured by clinical tools and related to MRI findings.
Results: We show a clear difference in fat infiltration and muscle size between patients and matched controls. We find strong relations between the different MRI measures and impairments for both motor-performance and respiratory function. Certain patterns of fat infiltration and atrophy are present.
Conclusion: MRI document pathological levels of fat infiltration and atrophy in DM1. The two forms of myopathy have different relations to function. The findings are important for managing DM1 and future interventions studies.
Disclosure: Nothing to disclose

EPR3114

Ultrasound for assessment of diaphragm function in late-onset Pompe disease

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Background and aims: To evaluate the correlation between diaphragm thickness and mobility assessed by ultrasound and classical pulmonary function tests (PFTs) in patients with late-onset Pompe disease (LOPD).
Methods: 17 LOPD patients (M/F ratio: 9/8) were studied comparing classical PFTs with diaphragm thickness and mobility measured by ultrasound.
Results: The mean age was 46.7±4.7 yrs and with a mean disease duration of 12.3±8.5 yrs. Ultrasound studies of diaphragm thickness in full inspiration correlated with maximal inspiratory pressure (MIP) (r=0.69; p=0.004) and maximal expiratory pressure (r=0.57; p=0.024), forced expiratory volume in one second (FEV1) (r=0.59; p=0.016), forced vital capacity (FVC) both in seated (r=0.70; p=0.002) and supine position (r=0.63; p=0.026). Diaphragm thickness at functional residual capacity correlated with maximal expiratory pressure (r=0.58; p=0.021) and seated FVC (r=0.57; p=0.021). Diaphragm thickening fraction correlated with MIP (r=0.80; p=0.0003), seated (r=0.68; p=0.003) and supine FEV1 (r=0.65; p=0.020), seated (r=0.66; p=0.005) and supine FVC (r=0.61; p=0.034).
Conclusion: Diaphragmatic function assessed by ultrasound is a simple, noninvasive tool that correlates significantly with classical PFTs in patients with LOPD.
Disclosure: Nothing to disclose

EPR3115

Antifibrotic efficacy of nintedanib in in vitro and in vivo models of Duchenne muscular dystrophy

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Background and aims: Several growth factors have been involved in the process of muscle fibrosis in Duchenne muscular dystrophy (DMD). Nintedanib, a tyrosine kinase inhibitor targeting FGFR, PDGFR and VEGFR, is approved for the treatment of idiopathic lung fibrosis. To study whether nintedanib is effective in reducing fibrosis in DMD.

Methods: Effect of nintedanib on proliferation, chemotaxis and gene expression of human muscle fibroblasts was explored in vitro. Effect of nintedanib on muscle function and structure was assessed in 10 months old mdx-mice treated with 60 mg/kg nintedanib for one month compared to age matched mdx mice and C57BL/6N control mice using digigait, electromyography (EMG) and histological studies.

Results: Nintedanib significantly decreased human fibroblast proliferation ($p<0.001$) and chemotaxis ($p<0.05$) and reduced collagen I and III and fibronectin expression in vitro. EMG detected motor unit action potentials of bigger amplitudes and shorter duration in nintedanib-treated mice compared to non-treated. Histological studies showed a significant reduction in the fibrotic tissue area in muscle sections of diaphragm ($p<0.001$) and quadriceps ($p=0.03$) of nintedanib-treated compared to non-treated animals. Real Time PCR and WB studies showed a reduction in the expression of collagen I and III and fibronectin in muscles obtained from nintedanib-treated mice compared to controls.

Conclusion: Nintedanib demonstated antifibrotic efficacy in a murine model of DMD by reducing the fibrotic area and markers of fibrosis in muscles. A reduction of the proliferation of fibroblasts is the assumed mode of action. This promising result suggests a potential value of nintedanib in the treatment of muscle dystrophies.

Disclosure: This study has been partially sponsored by Boehringer and buy Fondos FEDER-ISCIII PI15/01822 to JDM

EPR3117

Phenotype variability in a large Spanish family with Hyperkalemic Periodic Paralysis associated with mutations in SCN4A gene

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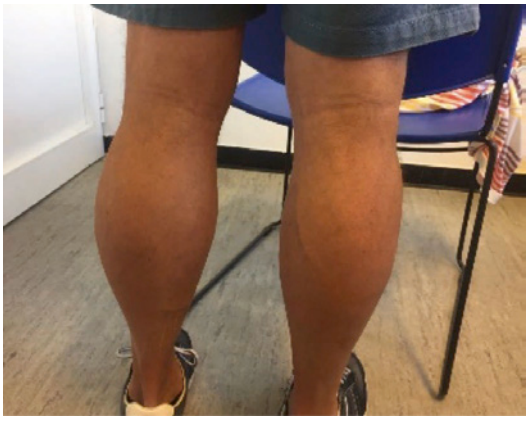
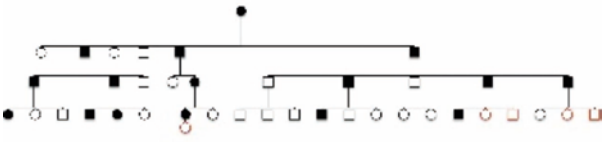
Background and aims: The Hiperkalemic Periodic Paralysis is a rare skeletal muscle channelopathy caused by mutations in the SCN4A gene, that encodes the a-subunit of the voltage-gated sodium channel. It's characterised by recurrent transient attacks of muscle weakness triggered by potassium-rich food, quick temperature changes, fasting and rest after heavy workload.

Methods: We report a case of a Spanish family with 16 affected members. They were all subjected to full anamnesis, physical examination and routine blood analysis, however, only 4 of them were studied genetically and were confirmed to have the mutation T704M.



Pseudohypertrophic calves on a patient that showed vacuolar myopathy on biopsy.



The family studied with 16 members affected. Healthy patients shown in red have been genetically selected.

Results: We observed two different clinical forms of presentation. A part of the family presents between 1-2 invalidating attacks per day of 30-180min; but the other part only presents 1-2 attacks every two weeks lasting for less than 120min, and with less severe weakness and better recovery with carbohydrates, despite that they all have the same mutation. Four of the patients that belong to the most severe clinical variant are over 40-50 years old and they all

have pseudohypertrophic calves and thighs, two of them with edema-like changes/fatty degeneration on MRI and vacuolar myophathy on biopsy. Prevention treatment with acetazolamide, hydrochlorthiazide and salbutamol has shown partial results, but the genetical selection of healthy embryos has proved to be the only way to avoid this disease in 5 members of the family.

Conclusion: Our findings are slightly different to cases reported previously as our patients have more attacks than described for this mutation and show a variable clinical presentation despite having the same mutation.

Disclosure: Nothing to disclose

Neuroepidemiology

EPR3118

Subacute neurological complications following living donor liver transplantation; Egyptian experience

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Background and aims: Liver transplantation (LT) is the only curative treatment in patients with end-stage liver disease. Of all the complications post-LT, the neurological complications (NC) are particularly relevant, since they affect up to a third of transplanted patients. The aim of this study is to assess the incidence, risk factors and clinical presentation of NC after liver transplantation in patients who underwent living donor liver transplantation (LDLT).
Methods: Between November 2011 and December 2013, 149 patients were admitted to ICU after LDLT and were evaluated by full general and neurological examination, full laboratory investigations including drug levels, brain CT and/or MRI, assessment of encephalopathy by West Haven classification, patients were observed after LT for one month.
Results: Of 149 transplanted patients 46 (30.9%) developed neurological complications. The most common neurological complications were Encephalopathy (14.1%) while the least were both Central pontine myelinolysis and Meningoencephalitis (0.7%). Out of the 149 patients, 146 (98%) patients were prescribed Tacrolimus (FK-506) 46 patients (30.9%) developed neurological complications, 30 of which (20.1%) developed side effects related to the drug administration. 29 patients (19.5%) prescribed cyclosporine, 2 patients (1.3%) developed side effects related to the drug administration.
Conclusion: There was a high incidence of neurological complications after LT, prolonging the patients stay in intensive care significantly and most common complications following LT were encephalopathy, delirium, hallucinations, delusions and seizures. Consequently, careful pre-operative and post-operative neurological evaluation and close observation and follow-up is important for early diagnosis of NCs and therefore their prompt treatment.
Disclosure: Nothing to disclose

EPR3119

Vitamin D supplementation in Multiple Sclerosis: time matters. A two-year observational study

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Background and aims: Consistent amounts of studies support the role of Vitamin D (vitD) in multiple sclerosis (MS) pathogenesis. This study investigates the relationship between time of beginning vitD supplementation and prognosis
Methods: We included consecutive MS patients who started vitD treatment, determining vitD blood levels before treatment initiation. We considered two groups according the time of treatment initiation: within the first three years from disease onset or later. We considered the following variables: age at MS onset, age at baseline, relapse rate, new MRI gadolinium enhancing lesions and T2/FLAIR lesions, EDSS at the end of follow-up (September 1st 2017). We used t test, Chi square analyses Kaplan-Meyer estimates to compare means or frequencies distribution between groups according to quartiles of vitD at baseline. We used Cox proportional analyses to calculate the effects of time to initiation of vitamin D on disease activity and progression.
Results: We included 231 MS patients. Patients starting vitD within the first three years from onset had a significantly lower mean EDSS score at the end of follow-up and a lower risk to reach an EDSS score of 3.5 (HR 0.86; CI 0.75-1.00; p=0.05). Trends were similar dividing patients according to quartiles of vitD distribution at baseline. Patients had a lower probability to develop new MRI lesions when they started vitD earlier (p=0.001).
Conclusion: Our study suggests that a time window opportunity could exists for vitD supplementation in MS patients. If confirmed, these results would add relevant information about the time and use of vitD among MS patients.
Disclosure: Nothing to disclose

EPR3120

Prevalence of Parkinson's disease – a repetitive epidemiological study in Estonia

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Background and aims: A previous epidemiological study on Parkinson's disease (PD) in the county of Tartu, Estonia found the adjusted prevalence rate to be 152/100,000. This study aimed at determining the PD prevalence almost twenty years later as well as evaluating the dynamic changes in the disease frequency compared to the first study.
Methods: This cross-sectional, community-based study was conducted in 2010-2016 in the county of Tartu, Estonia. Multiple case-finding sources including information from neurologists, family doctors, local PD Society, nursing institutions and the database of Estonian Health Insurance Fund were used to identify patients in all ages with PD.
Results: The total age-adjusted prevalence rate (standardized to the age structure of 2014 Estonian population) of PD was 314/100,000. After age-adjustment to the European 2011 standard population, the overall prevalence rate was 324/100,000. The adjusted prevalence rate was significantly higher for women compared to men (rate ratio [RR]=1.51; p=0.00003). No significant differences were found between PD prevalence in urban and rural areas (RR=1.09; p=0.40). After adjustment to the same standard population as used in the previous prevalence study, the overall age-adjusted prevalence rate was found to be 197/100,000. Patients in the current study were older, had more often a severe disease and a longer disease duration compared to those reported in the first epidemiological study.
Conclusion: The age-adjusted prevalence has moderately increased in past decades in Estonia. We believe that the substantial aging of the Estonian population and the improved diagnosis have the biggest contribution to the increase in the disease frequency.
Disclosure: The study has been supported by the Grants PUT1239, the IUT2-4 of the Estonian Research Council, and the Liisa Kolumbus Memorial Scholarship 2017 of the Tartu University Foundation.

EPR3121

Severity of impulsive compulsive behaviors in patients with Parkinson's disease

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Background and aims: Impulsive compulsive behaviors (ICBs) are clinically complications of Parkinson's disease. However, the clinical characteristics of ICBs in the Siberian population of patients with Parkinson's disease (PwPD) were rarely reported. We aimed to explore the prevalence and the clinical profile of ICBs in Siberian PwPD.
Methods: December, 2017, 819 patients were registered in movement disorders electronic database in Siberian region (women:men=346:473, mean age 66.3±8.4, PD mean duration 7.5±5.6, mean H&Y stage 2.89±2.63, mean UPDRS III 33.1±16.3). Each PwPD were examined by extended clinical and neuropsychological study with qualitative and quantitative analysis. Clinical assessments were carried out using UPDRS, H&Y Scale and Questionnaire for Impulsive-Compulsive Disorders in PD-Rating Scale. From all patients 293 of them were investigated using Montreal Cognitive Assessment (MoCA-test), Beck depression inventory-II, Hospital Anxiety and Depression Scale, Apathy Scale, PD Sleep Scale, Epworth Sleepiness Scale, PD Questionnaire-39 (PDQ-39), Bristol stool scale, Scale for Outcomes in PD for Autonomic Symptoms, Sniffing Stix Test.
Results: 19.8% PwPD were affected with ICBs. ICBs was negatively correlated with onset age (r=0.430; p<0.0001), illness duration (r=0.334; p<0.0001), quality of life (pain/discomfort, r=0.430; p<0.0001), UPDRS-III scores (r=0.025; p=0.025) and positively associated with anxiety score (r=0.436; p<0.0001), LEDD (L-Dopa) (r=0.177; p=0.011), apathy (r=0.201, p=0.004), sleepiness (r=0.203; p=0.003), ICBs score weren't associated with H&Y Stage, olfactory dysfunction and constipation.
Conclusion: This study demonstrates that ICBs are common in PwPD. Subsequent studies should consider syndromal and subsyndromal symptoms.
Disclosure: Nothing to disclose

EPR3122

eMSQOL-29: Prospective validation of the abbreviated, electronic version of the MSQOL-54

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Background: We recently devised a shortened version of the 54-item Multiple Sclerosis Quality of Life (MSQOL-54) in paper (MSQOL-29) and electronic format with integrated scoring routine (eMSQOL-29). MSQOL-29 consists of 25 items forming 7 subscales, and 4 single items; one filter question for 3 'sexual function' items.

Aims: To prospectively assess eMSQOL-29 psychometric properties, and its acceptability/equivalence vs. paper version.

Methods: MS patients (n=623; mean age 44 years; median Expanded Disability Status Scale, EDSS 2.5, range 0.0–9.0) from 5 Italian centres completed eMSQOL-29, Hospital Anxiety and Depression Scale, Functional Assessment of MS (FAMS), European Quality of life Five Dimensions-3L, and received EDSS and Symbol Digit Modality Test (SDMT). We assessed eMSQOL-29 reliability (Cronbach's alpha), factorial (confirmatory factor analysis, CFA) and concurrent validity (Pearson's r). Equivalence vs. paper MSQOL-29 was assessed in 242 patients (randomized cross-over design, two-week administration interval).

Results: 'Sexual function' items were filtered out by 273 patients (47%). No multi-item scale had floor effect, while 5 had ceiling effect. Cronbach's alpha range was 0.88–0.90. CFA (multi-item subscales) showed good overall fit, and the two-factor solution for composite scores was confirmed. Concurrent validity was sub-optimal for 'cognitive function' (vs. SDMT, r=0.25) and 'social function' (vs. FAMS social function, r=0.38). eMSQOL-29 equivalence was confirmed, and multivariate model found no version, order or sequence effect; its acceptability was good.

Conclusions: eMSQOL-29 showed good internal consistency, factor structure, no floor effect, while most subscales had some ceiling effect. Concurrent validity was sub-optimal for 2 subscales. Equivalence and acceptability were good.

Disclosure: This study is supported by the Fondazione Italiana Sclerosi Multipla (FISM, grant 2013/R/20 to RR).

EPR3123

Consumer involvement in formulation of the questions to be answered: findings from the EAN Guideline on Palliative Care of People with severe Multiple Sclerosis

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Background and aims: Consumer involvement in clinical practice guideline development is warranted through all stages to increase guideline trustworthiness and relevance. We aimed to engage Multiple Sclerosis (MS) patients and caregivers in definition of the key questions to be answered in the EAN Guideline on Palliative Care of People with severe MS.

Methods: We used a mixed approach: 1) International online survey launched by the national MS societies, after pilot testing/debriefing on 20 patients and 18 caregivers. 2) Focus group meetings (FGMs) of MS patients and caregivers.

Results: 1) Of 1199 participants, 951 (79%) completed the whole survey, and 934 from seven countries with above-threshold figures were analysed: 751 (80%) were MS patients (74% women, mean age 46.1) and 183 (20%) caregivers (36% spouses/partners, 72% women, mean age 47.4). Participants agreed/strongly agreed on inclusion of the nine pre-specified topics (from 89% for 'advance care

planning' to 98% or 'multidisciplinary rehabilitation'), and <5% answered 'I prefer not to answer' to any topic. Free comments were 569: 182 (32%) on pre-specified topics, 227 (40%) on additional topics (16 guideline-pertinent), and 160 (28%) on outcomes. 2) Five FGMs (three of MS patients, two of caregivers, overall 35 participants) corroborated survey findings, and helped to identify patient-important outcomes.

Conclusion: Consumer involvement was resource and time intensive, but rewarding. It was key for the formulation of the guideline questions, and for the identification of patient-important outcomes. Importantly, free comments from several participants concerned sensitive issues which were purposely excluded from the pre-specified topics.

Disclosure: This guideline is a joint initiative of the EAN, the European Association for Palliative Care (EAPC), the European network for best practice and research in MS Rehabilitation (RIMS), and has been endorsed by the European Committee for Treatment and Research in MS (ECTRIMS). This guideline has been granted by the EAN, and by the Foundation of the Italian MS Society (FISM grant 2017/S/2).

EPR3124

Correlation between vascular risk factors, arterial remodeling and systolic function in patients with leukemia

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Background and aims: The aim of this study was to assess if there is an impact of vascular risk factors in patients with leukemia on hemodynamics parameters before and after chemotherapy by determining the arterial remodeling Intima-Media-Thickness (IMT) using Extracranial-Doppler (ECD) and the systolic function by Left Ventricular Ejection Fraction (LVEF) calculation using echocardiography.

Methods: We enrolled 15 patients with leukemia aged between 33 and 79 scheduled for chemotherapy. The ECD and echocardiography were performed prior and 3 months after the treatment. Systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate, IMT and LVEF were measured before and after chemotherapy and correlated with vascular risk factors.

Results: Out of the study patients, 3 (20%) had dyslipidemia, 2 (13,3%) had heart coronary disease, 6 (40%) had hypertension and 8 (53,3%) were smoking patients. IMT(mm) significantly increased from 0.64±0.08 to 0.76±0.09 ($p<0.05$) in left carotid artery. SBP(mmHg) significantly increased from 122±10.98 to 132.6±9.29 ($p<0.05$). LVEF(%) significantly decreased from 60.46±9.67 to 56.53±8.57 ($p<0.05$) post chemotherapy with slightly worse values in smoking and hypertensive patients ($p<0.05$). In smoking patients IMT(mm) significantly increased from 0.61±0.08 to 0.73±0.09 ($p<0.05$) and in hypertensive patients IMT(mm) significantly increased from 0.66±0.05 to 0.78±0.09 after chemotherapy.

Conclusion: Carotid and cardiac functions should be assessed at baseline with ECD and echocardiography before onset of chemotherapy. During and after treatment, repeated assessments should also be considered. Calculation of arterial remodeling- IMT and systolic function- LVEF and correlation with vascular risk factors are very useful in patients with leukemia in assessing the strategy for adherence to chemotherapy treatment.

Disclosure: Nothing to disclose

EPR3125

The prevalence of neuropsychiatric symptoms in Parkinson's disease on a nationwide level in Hungary

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Background and aims: Neuropsychiatric and cognitive symptoms are frequent in Parkinson's disease (PD) and may precede and exceed motor symptoms as major factors impacting disease course and quality of life. Neuropsychiatric symptoms (NPS) in PD are various and are attributed to pathologic changes within multiple brain regions, to psychological stress, and to adverse effects of dopamine replacement therapy. Our aim was to assess the prevalence of NPS in PD, analysing the whole Hungarian population.
Methods: In Hungary, a country with 10 million inhabitants and a single payer health insurance system we have set off the NEUROHUN 2004 – 2017 project. In the framework of the Hungarian Brain Research Program we created a database from medical and medication reports submitted for reimbursement purposes to the National Health Insurance Fund (NHIF) from all hospitals and outpatient services throughout the country in a ten-year period of time, between 2004–2013. For the current analysis, ICD-10 codes for PD and NPS were used from the database for patient selection.
Results: 96 874 patients were reported to the NHIF with PD between 2004 and 2013 out of which 56% had at least one NPS. Following the PD diagnosis, 60% of the NPS appeared within 2 years on average. The most common NPS were dementia, mood disorders and anxiety.
Conclusion: PD is a complex disease in which the prevalence of NPS is high. Therefore early and routine screening for a range of prevalent NPS is important and a multidisciplinary, personalised care is needed to initiate optimal treatment.
Disclosure: Nothing to disclose

EPR3126

Profile of Syrian Refugees from Neurological Outpatient Clinic in Turkey

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Background and aims: Turkey hosts the largest number of registered Syrian refugees – currently 3,424,237. Obstacles in the utilisations of medical services in this disadvantageous group may be viewed as financial, structural, and personal. We aimed to find out the sociodemographic and clinical profile of Syrian refugees who admitted to our clinic, changes in patient number across years, and the percentage of the patients on follow-ups.
Methods: Syrian patients who admitted to the our neurology outpatient clinics, neurology emergency department, and hospitalised in the neurology clinics were included in the study. Age, gender, number of admissions, year of admissions, chief complaints, diagnoses, and follow-up percentages of the patients were recorded retrospectively.
Results: Total number of patients who admitted to our hospital and consulted from other clinics were found to be 763. 547 (74%) of these patients did not come to the follow-ups even though their conditions required regular follow-ups. New admissions started in 2011 (0.3%), gained a momentum and peaked in 2014 (28.6%), continued to stay high in 2016 (27%), and decreased significantly in the year 2017 (9.2%). The most common diagnoses were primary headaches (22.9%), cerebrovascular diseases (20.6%), mental health problems (11.7%), and epilepsy (10.2%).
Conclusion: Most of the patients who admitted to our hospital did not come to the follow-ups and information regarding their treatments could not be obtained. Even though Turkish Republic provided the Syrian refugees with free medical care, utilization of these resources may be limited because of socioeconomic issues. Studies investigating why the people are not coming to the follow-ups are required.
Disclosure: Nothing to disclose

Neurogenetics 4

EPR3127

Spastic paraplegia 52 – a new AP4S1 variant?

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Background and aims: The identification of homozygous or heterozygous variants in highly preserved DNA regions by arrayCGH or whole exome sequencing is associated with interpretation difficulties.
Methods: We present a 2-year-old boy born of nonconsanguineous parents. He had a full term gestation with intrauterine growth restriction. In the first months of life he had poor weight gain, hyperammonemia, elevation of glutamine and ornithine, low citrulline and negative orotic acid. Weight recovery and normalisation of aminoacid profile occurred with hypoproteic diet and mantained with normal diet. Genetic study for NAGS, CPS and OTC were normal.
By nine months developmental delay, hypotonia and strabismus were evident. Brain MRI showed delayed myelination, polymycrogyria, corpus callosum dysgenesis and dysmorphic ventricules. Spectroscopy was normal. At fifteen months he had one episode of status epilepticus. Currently he has pyramidal signs in both legs.
Results: Exome revealed a splicing variant in homozygoty in AP4S1, c.294+1G>T. Additional genetic and metabolic studies were normal.
Conclusion: AP4S1 gene encodes a subunit of an adaptor-related protein that mediates vesicle formation and sorting of integral membrane proteins. Mutations in homozygoty in this gene were associated with spastic paraplegia 52. This is a very rare condition described in 11 children and consisting of dysmorphic features and neonatal hypotonia progressing to hypertonia, loss of ambulation, seizures and cognitive deficit without spoken language. Imaging abnormalities include aqueductal stenosis, hypomyelination, absent corpus callosum and lack of differentation of white/grey substance in basal nuclei ganglia. We present this case for discussion of the pathogenicity of the variant and genotype-phenotype correlation.
Disclosure: Nothing to disclose

EPR3128

Clinical whole-exome sequencing for the diagnosis of Mendelian neuromuscular disorders

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Background and aims: Whole-exome sequencing has recently become a widely used diagnostic test for individuals with rare Mendelian disorders. Its use for the diagnosis of neuromuscular disorders is promising, given the high genetic and clinical heterogeneity of this disease group. Previous data report a broad range of diagnostic yields between 25 and 50%, depending on the selected patient group and the used diagnostic approach.
Methods: We retrospectively selected all patients that were seen in the neuromuscular clinic of the Department of Neurology of the Medical University of Vienna (Austria) receiving whole-exome sequencing for a diagnostic purpose between 2014 and 2017. Whole-exome data were generated at the Institute of Human Genetics, Technical University Munich (Germany).
Results: Whole-exome data from 44 patients with various neuromuscular disorders including primary muscle diseases (n=20), motor neuron disorders (n=20) and peripheral neuropathies (n=4) were analysed. Likely or definite disease-causing variants were found in 20 of the 44 patients, leading to an overall diagnostic yield of 45.5%. This was similar for all analysed subgroups with 50% for primary muscle diseases (10/20) and peripheral neuropathies (2/4) and 40% for disorders affecting the motor neurons (8/20). Among the 20 patients with a genetic diagnosis, 10 had an autosomal recessive, 7 an autosomal dominant, 1 an X-linked and 2 a potential digenic inheritance pattern.
Conclusion: Diagnostic whole-exome sequencing is a useful and cost-effective tool in the clinical management of neuromuscular diseases with a suspected Mendelian aetiology.
Disclosure: Nothing to disclose

EPR3129

Distinct frontal lobe transcriptomes of FTLD and ALS phenotypes

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Background and aims: Fronto-Temporal Lobar Degenerations (FTLD), associated or not with amyotrophic lateral sclerosis (FTLD/ALS), have strong genetic component. Mutations in 3 genes are responsible for most genetic cases: MAPT, PGRN and C9orf72. Genetic or sporadic FTLDs share common neuropathological features such as neuronal TDP43 or TAU inclusions. Thus, independently of the genetic origin and because of the global and significant neurodegeneration, mostly frontal and temporal, it seems highly probable that the different subtypes share some similar molecular mechanisms. On the other hand, either due to the different genetic origin or to the nature of the protein aggregates we can also expect some specific molecular mechanisms to be involved in each disease subtype.
Methods: We analysed frontal cortices of FTLD patients by high-throughput RNA sequencing with a coverage sufficient to analyze transcriptome and splicing profiles. The samples were sorted according to the genetic mutation they carry, to their phenotype and to subtype.
Results: Hierarchical clustering revealed that the mutations in MAPT have a homogenous RNA metabolism response. Interestingly, some transcriptomic and splicing profiles are linked to the pathology (FTLD, FTLD/ALS) or to the subtype (TDP43 or TAU aggregates). Additionaly, less than 10% of the changes in RNA maturation lead to modification of RNA expression. Therefore, the newly processed mRNAs could escape from surveillance mechanisms.
Conclusion: Misregulation of pre-mRNA processing could lead to the synthesis of many aberrant proteins in FTLD patients, so these proteinopathies can be due to an accumulation of RNA processing defects. As such, FTLD are not only proteinopathies but also general RNAopathies.
Disclosure: Nothing to disclose

EPR3130

A family-based approach to identify genetic modifiers of the age at onset in Frontotemporal Lobar Dementia

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Background and aims: Frontotemporal-lobar dementia (FTD) is a rare neurodegenerative disease associated with behavioral changes, language dysfunctions and may be associated with amyotrophic lateral sclerosis. The clinical variability, in particular the variability of Age at Onset (AAO) is largely unexplained.
Through family-based approaches, the objective of this work was to quantify the effect of genetic factors influencing the AAO and identify modifier genes in families with FTD due to C9ORF72 hexanucleotide repeat expansions and GRN mutations, two major genes responsible for FTD and/or ALS.
Methods: We studied 504 affected individuals from 133 families with C9ORF72 repeat expansion and 90 FTD families with mutations in GRN. Intra-familial correlations of AAO were analyzed and variance component methods were used for heritability estimates.
Forty-four pairs of relative with highly concordant (<2y) or discordant (>10y) AAO were selected for linkage and association analyses.
Results: The heritability of AAO was high in FTD caused by C9ORF72 repeat expansions, and to a lesser degree in GRN families. Intra-familial correlation analyses revealed significant level of correlations in C9ORF72 families according to the degree of kinship. Pattern of intra-familial correlations also suggested potential X-linked modifiers acting on AAO. Non-significant correlation values were observed in GRN families.
Linkage and association analyses identified 3 new candidate loci with suggestive scores. In particular, an X-linked locus has been highlighted.
Conclusion: Upcoming analyses with additional families will be held to confirm linkage/association signals. The most robust loci will be explored in depth to find causal variants and their functional effects will be tested as well.
Disclosure: Nothing to disclose

EPR3131

Genetic predisposition, modifiable riskfactor burden and the risk of dementia in the general population

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Background: Dementia prevention trials are increasingly recruiting high-risk individuals based on genetic or clinical information, but it remains unclear whether these targeted interventions can offset this increased risk.
Methods: Within the Rotterdam Study, we determined APOE-related risk in 6353 individuals aged ≥65 years for whom allele status and covariate data were available. We also determined adherence to a healthy lifestyle based on six modifiable riskfactors: smoking, depression, diabetes, physical activity, social isolation, and diet. We subsequently stratified individuals on both APOE-related risk and lifestyle categories. Instead of APOE, we also stratified individuals based on the presence of memory complaints.
Results: During a median follow-up of 13.2 years, 867 individuals developed dementia. Dementia risk was higher among individuals in high compared to low APOE-related risk (HR: 3.17, 95% CI: 2.45;4.09). An unfavorable lifestyle, defined as ≤2 protective factors, was associated with higher dementia risk (HR: 1.31, 95% CI: 1.05;1.63). These associations were also found among low and intermediate, but not in high APOE-related risk individuals. These findings correspond to a 15-year dementia risk reduction from 27.8% (95% CI: 5.7;50.0) for an unfavorable to 12.0% (7.9;16.2) for a favorable lifestyle in low, and from 23.8% (15.0;32.6) to 13.9% (12.3;15.6) in intermediate APOE-related risk categories. Riskreductions across lifestyle categories were similar for individuals with and without memory complaints. External validation of these findings in cohort studies is ongoing.
Conclusions: A favorable lifestyle during late-life offsets an increased risk based on memory complaints, but cannot offset high genetic risk based on APOE-carriership.
Disclosure: Nothing to disclose

EPR3132

High diversity of MJD haplotypes in Eastern China: result of an ancient lineage or signature of new mutational origin(s)?

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Background and aims: Machado-Joseph disease is a dominant spinocerebellar ataxia (SCA) caused by a (CAG) n expansion in ATXN3. De novo expansions from the polymorphic normal range seem rare, since only two ancestral MJD origins (Joseph and Machado) had been identified. MJD is spread worldwide, China showing its highest relative frequency (62.1% among SCAs). Our aim was to study MJD origins in families from Eastern China.
Methods: We analysed 69 individuals from 16 MJD families from Shanghai, Zhejiang and Fujian. The Sequenom MassARRAY® system was used to genotype 16 SNPs, within a region of 15 kb encompassing the (CAG)n. More distant flanking STRs were genotyped by capillary electrophoresis. Allelic phases were inferred by familial segregation and PHASEv2.2.
Results: At least two different SNP backgrounds segregated with the MJD expansion in these Chinese families, but none shared the full haplotype with the Joseph lineage, of Asian origin. All families differed in SNPs rs10146519 and rs10467858, when compared to Joseph families. Interestingly, 9 of them showed another variant in rs56268847, the SNP that differentiates the Joseph-derived lineage present in Australian aboriginal MJD families. STR flanking-haplotypes confirmed a closer phylogenetic distance among families of similar SNP lineages.
Conclusion: Two novel SNP backgrounds were identified in MJD families from Eastern China, differing from the Joseph lineage at two or three SNPs. Only one of these SNPs was shown to distinguish the Joseph-derived lineage in other Australasian MJD families, implying either a scenario of rare recurrent SNP mutations on a very ancient lineage, or new mutational origins for MJD.
Disclosure: Nothing to disclose

EPR3133

No evidence for host-pathogen genetic interaction in Neisseria meningitidis causing meningitis

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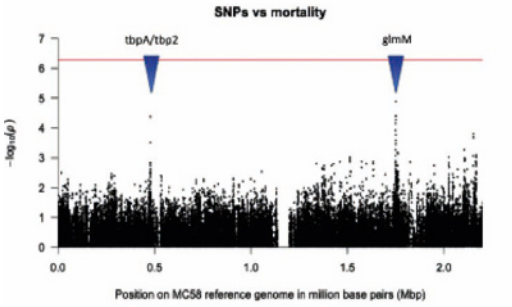
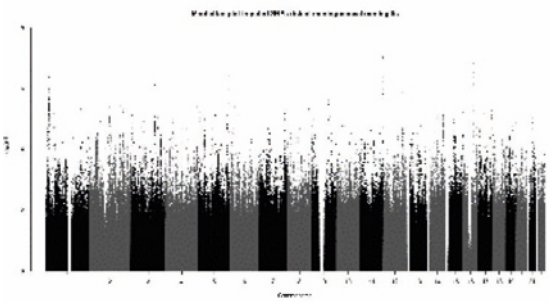
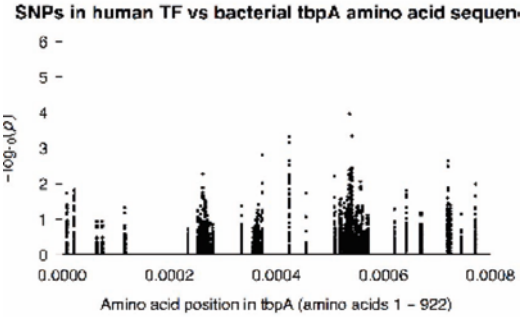
Background and aims: Neisseria meningitidis is a cause of severe sepsis and meningitis with a mortality of approximately 7%. While certain bacterial subgroups defined by a 7 gene locus typing scheme have been associated with poor disease outcome in patients, no specific genetic variants have emerged as virulence factors. Here we sequenced genetic data from 486 Neisseria meningitidis isolates causing meningitis, performed a genome wide association study on 103 patients with meningococcal meningitis and 4836 controls and analysed 82 paired patients and bacteria to discover new genetic risk factors and performed interaction analyses to search for evidence of epistasis.
Methods: Bacterial genomes were sequenced by whole genome sequencing on Illumina platforms. SNPs were called after mapping to a reference strain. In patients and controls, SNPs were determined with Illumina genotyping array after quality control and imputation.
Results: Bacterial whole genome SNP analyses in isolates reveal a region near phosphoglucosamine gene glmM and the transferrin binding protein gene tbpA/B to be suggestively associated with poor disease outcome, while not reaching statistical significance after correcting for multiple testing. A genome wide association study in patients reveals no genome wide hits for meningococcal meningitis. No evidence for host-pathogen genetic interaction emerges when probing SNPs near the human transferrin gene hTF with amino acid sequence variation in bacterial tbpA for overrepresentation.



SNPs in meningococci associated with mortality in patients



Manhattan plot for SNPs in patients associated with meningococcal meningitis



SNPs in human transferrin gene associated with bacterial tbpA

Conclusion: There is no evidence for host-pathogen genetic interaction in patients with meningococcal meningitis and causative Neisseria meningitidis isolates. A limitation of this study is the relatively small sample size; therefore this study might be underpowered to detect variants.
Disclosure: Netherlands Organisation for Health Research and Development (NWO), European Research Council and Wellcome Trust

Neuroimmunology 2

EPR3135

Autoantibodies to KCTD16 mark the presence of a tumor in patients with GABAb receptor encephalitis

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Background and aims: We report detailed clinical features of patients with anti-GABAB receptor (GABABR) encephalitis and optimise laboratory methods for the detection of GABABR antibodies. Also, we identify a novel auto-antibody that indicates the presence of an underlying small cell lung carcinoma (SCLC).
Methods: 2500 patients were tested for the presence of anti-GABABR antibodies using cell based assays (CBA), immunohistochemistry (IHC) and live hippocampal neurons (LN). Clinical data were obtained retrospectively. Antibodies to GABABR-accessory subunit potassium channel tetramerization domain 16 (KCTD16) were identified by immunoprecipitation, mass spectrometry analysis and CBA.
Results: Anti-KCTD16 antibodies were identified in 19/27 patients with anti-GABABR encephalitis and 1/26 patients with SCLC and anti-Hu antibodies. Of anti-GABABR encephalitis patients, 14/15 patients with KCTD16-antibodies had a tumor versus 2/8 anti-GABABR encephalitis patients without (p=0.0017). Patients presented with cognitive and/or behavioral changes (96%) and prominent seizures (93%). Twelve patients developed status epilepticus with ICU admittance (44%). Strikingly, 3/27 patients had rapidly progressive dementia (RPD). An underlying tumor was found in 16/23 patients, most commonly a SCLC (13 cases). IHC and LN were 100% sensitive for GABABR antibodies, while commercial CBA and in house fixed CBA had a lower sensitivity. The addition of KCTD16 to the GABABR-CBA improved sensitivity, without loss of specificity. Low and high titer anti-GABABR antibodies show functional effects on the GABABR in vitro.
Conclusion: GABABR encephalitis is a limbic encephalitis with prominent, severe seizures, but can also present with RPD. The co-occurrence of KCTD16 antibodies points towards a paraneoplastic origin. The addition of KCTD16 improves the sensitivity of the CBA.
Disclosure: Dr. Maarten Titulaer owns a patent for KCTD antibody CBA.

EPR3136

Retrospective study of patients with autoimmune encephalitis at a tertiary center

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Background and aims: Autoimmune encephalitis is an inflammatory disease with a complex differential diagnosis. Although the most frequently recognized causes are infectious, in the last years an increasing number of cases of autoimmune etiology have been identified. We aimed to characterize the patients diagnosed with probable and definitive autoimmune encephalitis in our center according the criteria proposed by Graus et al. (2016) and identify possible differences between the two groups.
Methods: Retrospective review of all cases diagnosed with probable and definitive autoimmune encephalitis at a tertiary center between January 2014 and August 2017. We review the clinical records and used descriptive statistical analysis, chi-square and t-student tests.
Results: We included 20 patients, 65% male, mean age 55 years. Six patients had positive autoantibody against extracellular neuronal antigens and definitive autoimmune encephalitis. The two groups did not differ in age or sex. The CSF study, was normal in 35% of the cases, but most frequently presented mild pleocytosis and increased protein levels. Brain MRI was positive in 27% of patients of the probable diagnosis group and in 83% with positive autoantibodies (p=0.026). All patients received intravenous methylprednisolone, while 4 patients in the negative autoantibodies study group and 5 in the positive autoantibody group received intravenous immunoglobulin (p=0.024).
Conclusion: The results suggest that patients with definitive autoimmune encephalitis had an history of more severe disease, requiring more intense immunotherapy. Brain MRI is more often positive in those patients.
Disclosure: Nothing to disclose

EPR3137

Autoimmune epilepsy in drug resistent and in new onset refractory epilepsy

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Background and aims: Autoimmune epilepsy (AE), is a rare condition, more responsive to immune treatments than to antiepileptic drugs (Graus et al 2016; Bien et al 2005), whose incidence and prevalence and frequency of anti-neuronal autoantibodies (AN-Abs) is unknown.
Methods: Adults with New Onset Refractory Epilepsy (NORE) of unknown etiology showing more than 4 seizures per month and Drug Resistant (DR) focal epilepsy with known (controls) and unknown etiology (DRUE) were recruited between 2014- and 2016. In these patients the diagnostic workup included search for AN-Abs in sera and CSF analysis with AN-Abs when indicated. Follow up was at least one year.
Results: Patients recruited, n=31. 29 gave consensus to the study: 13 DRUE, 9 NOE and 7 controls. 11 patients (6 NORE, 5 DRUE) received diagnosis of AE (6 autoimmune, 2 paraneoplastic, 3 Rasmussen encephalitis), resulting in an incidence of 75% and prevalence of 55%. Sensitivity of AN-Abs was 36,36%, while specifity 94,11%.
Inflammatory MRI abnormalitis1 ($p=0.036$) and neuropsychiatric symptoms at onset ($p=0.00034$) and at follow up ($p=0.017$) were associated with AE, but not infectious prodromes, autoimmune diseases, new onset refractory status epilepticus. DR was similar between groups. Positive AN-Abs or an early immunosoppressive treatment did not result in different long-term outcome.
Conclusion: High incidence and prevalence of AE was observed in this cohort with respect to other studies (Dubey et al, 2017). AN-Abs presence was not mandatory for the diagnosis of NORE or of DRUE, did not exclude other possible diagnosis and was not associate with longterm outcome.
Disclosure: Nothing to disclose

EPR3138

Olfactory and gustatory dysfunction in patients with Autoimmune Encephalitis

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Background and aims: We tested the hypothesis that olfactory (OF) and gustatory function (GF) is disturbed in patients with Autoimmune Encephalitis (AE).
Methods: In 32 AE patients and 32 age and sex matching healthy controls (HC), the orthonasal OF was tested with the standardized Threshold Discrimination Identification test (TDI). The GF was assessed with the Taste Strip Test (TST). Patients with olfactory dysfunction due to an alternative primary etiology were excluded.
Results: 75% of the AE patients were hyposmic and none of the HC ($p<0.001$). The results of the Threshold subtest, the Discrimination subtest and the Identification subtest were significantly reduced in AE patients compared to HC (all $p<0.001$). The GF was significantly limited in 26.3% of AE patients and in none of HC ($p<0.001$). Neither age, sex, disease duration or disability (assessed with the modified ranking scale) were associated with the olfactory or gustatory capacity.
Conclusion: This is the first study investigating olfactory and gustatory function in AE patients. AE patients showed a significantly reduced olfactory and gustatory capacity compared to HC. Further studies that perform imaging of the olfactory pathway are needed to investigate the reasons for olfactory and gustatory dysfunction in these patients.
Disclosure: Nothing to disclose

EPR3139

Serum and CSF neurofilament light chain as possible biomarker in anti-neuropil antibody-associated encephalitis

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Background and aims: A correlation between disease activity and neurofilament light chain (NfL) levels has been recently described in several inflammatory conditions reflecting ongoing axonal damage. High cerebrospinal fluid (CSF) levels of NfL have been observed in the acute stage of autoimmune encephalitis, while significantly lower values were noted after clinical improvement. However, a comparison between serum vs CSF NfL concentrations and the evaluation of these results vs clinical data has never been performed in anti-neuropil antibody-associated encephalitis.

Methods: We enrolled well-characterised subjects with anti-neuropil antibody-mediated encephalitis referred to the Neuropathology Laboratory, University of Verona in the last 5 years. Clinical, radiological, CSF, and follow-up data were collected. Serum and CSF samples obtained at onset were analysed for NfL levels using a high sensitive technology (Simoa, Quanterix) and compared with a group of healthy controls.

Results: 12 patients with anti-neuropil antibody-mediated encephalitis were studied (NMDAR-IgG, n=7, LGI1-IgG, n=3, CASPR2-IgG, n=1, and GABAbR-IgG, n=1). NfL concentration was higher in the CSF (median 509.85pg/ml, range 337.25-4274.04), than in serum. Serum NfL levels were higher in subjects with autoimmune encephalitis (median 9.87 pg/ml, range 4.48-61.41) than in healthy controls (median 6.62pg/ml, range 3.76-11.54) and in patients with LGI1/CASPR2-antibodies (median 1112.185 pg/ml in the CSF, and 23.64pg/ml in serum) compared to those with NMDAR-antibodies (median 400.67pg/ml in the CSF, and 8.92pg/ml in serum).

Conclusion: NfL levels are increased in subjects with anti-neuropil antibody-associated encephalitis, and in particular in cases with LG1/CASPR2-antibodies. Future studies will be useful to determine their prognostic value.

Disclosure: Nothing to disclose

EPR3140

IVIg long-term treatment in CIDP: a non-interventional, prospective study to assess safety, tolerability, fatigue and depression (GAMEDIS-2)

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Background and aims: Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare progressively disabling, relapsing immune-mediated disorder of the PNS. Though there is broad clinical experience in long-term treatments, real world evidence from systematic prospective studies is sparse. Therefore, an observational study to collect real world data on CIDP patients treated with IVIg (Gamunex® 10%, Grifols) has been designed.

Methods: GAMEDIS-2 is a multicentric, prospective, open-label, non-interventional study conducted on a large cohort of adult CIDP patients treated with Gamunex® 10% in Germany. Functional impairment (Inflammatory Neuropathy Cause and Treatment INCAT disability scale), fatigue (Fatigue Severity Scale, FSS) and depression (Beck Depression Inventory II, BDI) have been systematically documented at baseline and quarterly during an observational period of 96 weeks (8 visits). Safety and tolerability have been assessed. Descriptive statistics of baseline data have been performed. Analyses of efficacy and safety data are in progress.

Results: A total of 158 patients have been recruited in 46 centers throughout Germany (147 evaluable; 66.7% male). The mean age is 64.6±12.4 years (median: 66; range 24-89); 68% older than 60); At enrollment, the mean time since CIDP diagnosis was 5.2±4.7 years; 15% of the patients had no pre-treatment with IVIg, 85.0% received IVIg, 46.3% corticosteroids and 21.8% immunosuppressants. The mean baseline INCAT, FSS and BDI scores were 2.4±1.8, 4.0±1.7 and 8.7±7.7, respectively.

Conclusion: GAMEDIS 2 describes the real world, long-term treatment of a large cohort of CIDP patients with Gamunex 10%. Safety and tolerability findings and longitudinal changes in functioning measured in this real world setting will be reported.

Disclosure: This study was funded by Grifols.

EPR3141

A first phase of seizures characterizes paraneoplastic encephalitis with GABA B receptor autoantibodies.

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Background and aims: To report the clinical features and long term outcome of 22 newly diagnosed paraneoplastic patients with GABAB receptor antibodies (GABABR-Abs).

Methods: Retrospective clinical study of CSF-confirmed cases of GABABR-Abs encephalitis.

Results: We identified 22 patients (4 female) with GABABR-Abs, with a median age of 64 years (range: 55-85). All were paraneoplastic: 20 small-cell lung cancer, one malignant thymoma and one uncharacterised lung mass. The most frequent first symptom was isolated recurrent seizures without cognitive or affective inter-ictal impairment in 17 patients (77%). In the other, 3 presented first behavioral disorders and 2 de novo status epilepticus. After a median delay of 10 days (range: 1-30), the recurrent seizures phase was followed by an encephalitic phase characterized by confusion in 100% of cases and status epilepticus (SE) in 81% (n=17) with 53% (n=9) non-convulsive SE. During the encephalitic phase, dysautonomic episodes were frequent and killed 3 patients. First-line immunotherapy was initiated after a median delay of 26 days (range: 6-65) after disease onset and a partial response was observed in 10 out of 20 patients (50%). No complete response was observed. Two years after onset, a massive anterograde amnesia affected all still alive patients but all of them were able to live autonomously at home. 9 patients died from cancer progression (median survival: 1.2 years).

Conclusion: Paraneoplastic GABABR Abs encephalitis is characterised by a stereotype presentation with an epilepsy phase of a few days in duration without inter-ictal impairment before an encephalitic phase with dysautonomia. The functional prognosis is poor.

Disclosure: Nothing to disclose

Neuro-ophthalmology/ neuro-otology

EPR3143

Ocular motor palsies in the emergency room

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Background and aims: Double vision due to isolated ocular motor nerve palsy represents a common presenting symptom in the emergency room. However, no clear consensus regarding urgency and scope of required diagnostic work-up has emerged. In a majority of cases, no specific etiology is identified and a presumptive diagnosis of diabetic/microvascular ischemic or idiopathic etiology is finally made. Consequently, a recent case series suggested that under certain conditions, imaging may be dispensable in patients older than the age of 50.
Methods: We retrospectively analyzed records of patients presenting in the emergency room of a large tertiary care center with ocular motor nerve palsies as main presenting complaint.
Results: In approximately half of patients, a benign diagnosis of diabetic, idiopathic or microvascular ischemic etiology was made. In the other half of patients, a specific underlying etiology of ocular palsy was identified (e.g., autoimmune etiology, brainstem ischemia, neoplasm). MR imaging displayed pathological results directly related to underlying etiology in approximately 40% of patients with VI and III palsies. In IV palsies, this number was significantly smaller. In VI cranial nerve palsy, a central brainstem pathology represents a relevant differential diagnosis. Frequency of aneurysms was between 3 and 6% and thus less frequent than reported previously.
Conclusion: Cerebral MR imaging in ocular motor palsies seems warranted obligatorily, independent of patient's age. On the other hand, CT scans in the emergency room are probably dispensable in most patients without clinical red flags.
Disclosure: Nothing to disclose

EPR3144

Vertical one-and-a-half syndrome accompanying contralateral abduction and incomplete depression palsy due to thalamo-mesencephalic infarction

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Background and aims: Vertical gaze palsy is usually associated with lesions of the rostral midbrain and thalamo-mesencephalic junction. We describe a case of vertical one-and-a-half syndrome accompanying contralateral abduction and incomplete depression palsy due to thalamo-mesencephalic infarction.
Methods: A 79-year-old man visited to neurology department with sudden onset of dizziness, dysarthria, and diplopia. He was on treatment for hypertension and diabetes for 15 years and was taking aspirin for five years with right cerebellar infarction.

Fig.1.

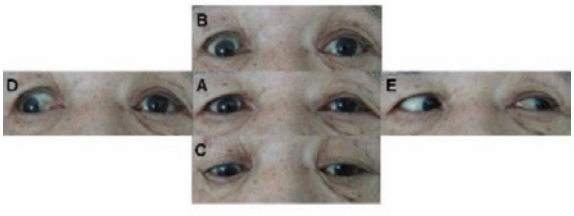
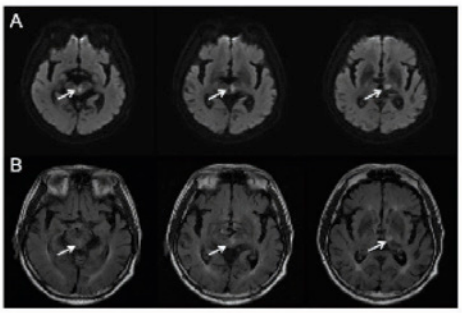


Fig.2.



Results: On neurological examination the size of the pupil was 2.5 mm on the right side and 3.5 mm on the left side. There was no strabismus or spontaneous nystagmus at the primary position. Vertical eye movements showed bilateral upward gaze paralysis, left paralysis of the left eye, and incomplete right paralysis of the right eye. The left eye was normal in the horizontal eye movement, but there was an adduction paresis of the left eye and an incomplete abduction of the right eye in the right eye. Horizontal vestibuloocular reflex was normal. Oculocephalic movements in vertical plane were absent. Convergence was absent. Electrocardiogram showed atrial fibrillation. On admission, the diffusion-weighted MRI revealed an infarct in the left thalamomesencephalic junction and the left paramedian midbrain. He was treated with anticoagulant. Three months later, bilateral upper gaze paralysis did not improve but downgaze paralysis partially recovered.
Conclusion: These vertical eye movement abnormalities are presumed to be caused by damage to the ipsilateral riMLF, interstitial nucleus of Cajal, and oculomotor fascicles.
Disclosure: Nothing to disclose

EPR3145

Vestibulo-ocular deficits without otolithic dysfunction in Machado-Joseph disease: a neurophysiologic biomarker of the disease?

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Background and aims: Although ocular motor abnormalities are frequent in all forms of Spinocerebellar ataxias (SCAs), vestibulo-ocular reflex (VOR) deficit seems to be a characteristic of SCA-3 (Machado-Joseph disease - MJD). However, all previous studies were focused on lateral semicircular canals function without information regarding the anterior and posterior canal responses and the otolithic function. We evaluated all canals VOR and otholithic functions in Jew Yemenite patients with SCA-3 in a search for a better neurophysiologic biomarker of the disease.

Methods: 16 MJD patients underwent a detailed clinical and laboratory neuro-otological evaluation including VOR recordings with the video head impulse test (vHIT) system and eight of them cervical vestibular evoked myogenic potentials (cVEMP) by bilateral tone burst stimulation measuring saccular function.

Results: All MJD patients had significant angular VOR gain decrease (about 50% of normal values) in both horizontal and vertical planes. cVEMP responses (latency of P13 and N23) were normal in all eight examined patients. Ataxia severity evaluated by the Scale for the Assessment and Rating of Ataxia (SARA) was mildly correlated with the degree of VOR impairment.

Conclusion: Angular VOR impairment in all semicircular canals seems to be a characteristic of MJD and could be explained by rostral vestibular nuclei degeneration. We suggest that quantitative VOR measures could probably be a neurophysiologic biomarker for detecting the appearance and progression of neurodegeneration in MJD.

Disclosure: Nothing to disclose

EPR3146

VPA induced sensorineural hearing loss; a case report of partial reversible hearing loss in a patient treated with valproic acid (VPA)

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Background and aims: Valproic acid (VPA) is a frequently used anti-epileptic drug (AED) with several common neurological side effects. Ototoxicty is a less frequent but serious side effect

Methods: Case report

Results: A 34-year-old woman with mental retardation and congenital microcephaly of unknown etiology was treated with VPA since several years because of epileptic seizures. Hearing loss was reported after she started using VPA. The audiogram showed mild to moderate sensorineural hearing loss (SNHL). Fletcher index: right ear 45 (H), air 40 bone 35 dB. Left ear 42 (H) air 50 bone 45 dB. After replacing VPA by levetiracetam the hearing loss resolved partially. Fletcher index: right 35 (H) air 35, left: 42 (H) air 43 bone 40. VPA induced reversible sensorineural hearing has been described in 5 patients previously. All these patients had prior hearing loss and therefor this is suggested to be a risk factor for VPA induced SNHL. In our patient hearing was never examined before. The neurotransmitter GABA and sodium channels are suspected to be involved because SNHL is also described in carbamazepine, gabapentin and vigabatrin. VPA is one of the most commonly used AED's but only 5 cases have been described. We assume the actual incidence of VPA induced sensorineural hearing loss may be underreported.

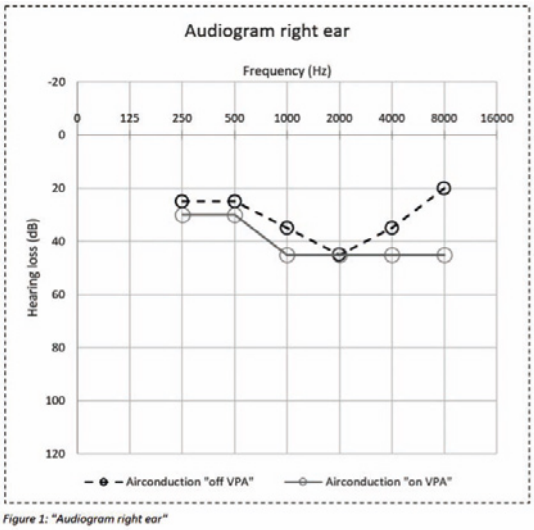

Figure 1: "Audiogram right ear"

Figure 1

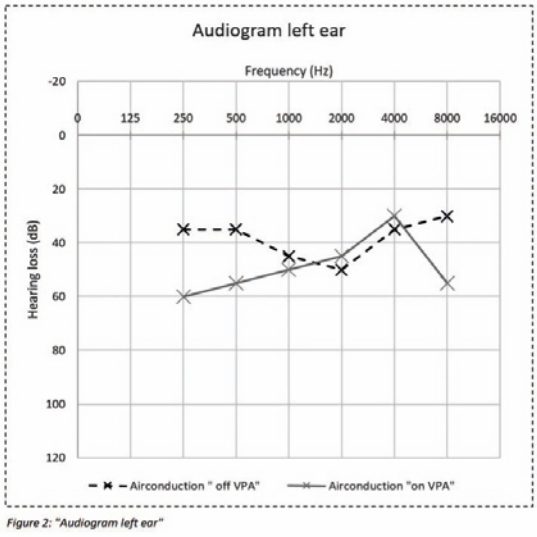

Figure 2: "Audiogram left ear"

Figure 2

Conclusion: It is recommended to ask for the existence of hearing loss before VPA is prescribed as pre-existent hearing loss seems to be an important risk factor. Further research is needed for better understanding of VPA related ototoxicity and to determine the actual incidence.

Disclosure: Nothing to disclose

EPR3147

Suppression of downbeat nystagmus during active motion

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Background and aims: Patients with downbeat nystagmus (DBN) – the most common form of acquired fixation nystagmus – typically suffer from oscillopsia and postural instability. Postural imbalance is reduced during active locomotion; hence, also ocular motor symptoms are likely to improve. We thus investigated the frequency and timing of downbeats nystagmus events during quiet standing compared to walking at different velocities.

Methods: Eye movements of DBN patients were recorded using video-oculography during standing and treadmill walking at slow, preferred and fast speeds. Angular and linear components of the vestibulo-ocular reflex (VOR) were analysed to assess general gaze stabilization performance. The occurrence of DBN events was determined and related to the phase of gait cycles.

Results: Walking significantly lowered the frequency of DBN occurrence in all patients compared to rest, indicating a re-weighting of the involved vestibulo-cerebellar pathways during active motion. This reduction became larger with increasing locomotor speeds and in some subjects the nystagmus was fully suppressed during fast walking. Furthermore, DBN events were phase-coupled to distinct periods of the gait cycle, predominantly occurring at the start of the swing phase. Whereas angular VOR gains of patients were comparable to those of healthy subjects, linear VOR gains were significantly decreased.

Conclusion: These findings suggest that a phase-coupled locomotor feedback (e.g. spinal motor efference copies) influences the brain networks linked to downbeat nystagmus. Deficits in compensating linear head motion during locomotion further point to a specific impairment in pathways processing otolithic inputs.

Disclosure: Nothing to disclose

EPR3148

An Algorithm as a diagnostic tool for ocular motor disorders

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Background and aims: To create an algorithm which can assist physicians as a "digital expert" with the diagnosis, particularly of rare diseases associated with central ocular motor disorders.
Methods: The algorithm's input consists of a maximum of 60 symptoms. The output is a list of the most probable diagnoses out of 14 alternatives and the most likely topographical anatomical localisations out of 8 alternatives. Positive points are given for disease-associated symptoms and negative points for symptoms unlikely to be found in a specific disease. The algorithm was evaluated using the two diagnoses and two brain zones with the highest scores. A dataset of 102 patients (56 males, age 48.0±22yrs) was used for developing the algorithm. After this the algorithm was validated with a dataset of 104 patients (59 males, age 46.0±23yrs).
Results: For 12/14 diseases the algorithm showed a sensitivity between 80 and 100% and the specificity of 9/14 diseases was between 82 and 95%. For instance, it showed 100% sensitivity and 75.5% specificity for Niemann Pick type C and 80% specificity and 91.5% sensitivity for Gaucher's disease, both of which are rare diseases. In terms of a topographic anatomical diagnosis, the sensitivity was between 77 and 100% for 4/8 brain zones, and the specificity of 5/8 zones ranged between 79 and 99%.
Conclusion: This algorithm using our knowledge on the functional anatomy of the central ocular system and possible underlying diseases is a useful tool, in particular for the diagnosis of rare diseases which are otherwise often overlooked.
Disclosure: M. Strupp is Joint Chief Editor of the Journal of Neurology, Editor in Chief of Frontiers of Neuro-otology and Section Editor of F1000. He has received speaker's honoraria from Abbott, Actelion, Auris Medical, Biogen, Eisai, GSK, Henning Pharma, Interacoustics, MSD, Otometrics, Pierre-Fabre, TEVA, UCB. He acts as a consultant for Abbott, Actelion, AurisMedical, Heel, IntraBio and Sensorion.

EPR3149

Slow vertical saccades as a hallmark of hereditary spastic paraplegia type-7

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Background and aims: Hereditary spastic paraplegia (HSP) is a rare autosomal recessive disorder, resulting from homozygous or compound heterozygous mutations in the HSP7 gene (16q24.3), coding the paraplegin protein. Clinically it can present as pure HSP or as complicated phenotype including supranuclear palsy with ophthalmoparesis. However, there is still a paucity of data on the spectrum of oculomotor disorders in HSP7. Thus, this study aimed to investigate oculomotor and vestibular dysfunction in patients with verified mutation of HSP7 gene.
Methods: 4 patients with HSP type-7 were included in this study and investigated using video-oculography and rotational chair testing. 2 patients were siblings harbouring c.1552+1G>T homozygote splice variant. The third patient harboured c.233T>A homozygote mutation and the fourth patient harboured two heterozygous mutations (c.1450_1458del9 and c.1529C>T). We analysed saccadic eye movements, smooth pursuit, the vestibulo-ocular reflex (VOR) and VOR suppression during fixation.
Results: All four patients exhibited slow velocities of vertical saccades. Three patients additionally exhibited slow velocities of horizontal saccades. The fourth patient with compound heterozygote mutation showed borderline slowed horizontal saccades. Both siblings (c.1552+1G>T) exhibited prolonged latencies of horizontal and vertical saccades. Furthermore, the two siblings showed saccadic smooth pursuit movements and impaired VOR-suppression during fixation. In these two patients, the VOR was elicited with regular gain at 0.32Hz, contrasting patients three and four.
Conclusion: Slowing of vertical saccades might be a hallmark of the HSP7. The range of horizontal saccade velocities and cerebellar oculomotor disturbance might be dependent on the mutation type.
Disclosure: Nothing to disclose

EPR3150

Imaging neuroinflammation along the vestibular nerve and nucleus in acute unilateral vestibulopathy by [18F]GE180-PET

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Background and aims: The aetiology of acute unilateral vestibulopathy (AUV) is unknown. Some histological findings suggest that it may originate from inflammation of the peripheral vestibular afferents, e.g. vestibular neuritis. In the present study a novel PET-based approach was used to show neuroinflammation along the vestibular nerve and brainstem entry zone in patients with AUV in vivo.

Methods: 5 patients with an AUV were included in the study. All patients underwent detailed neuro-ophthalmological and vestibular testing to confirm the clinical diagnosis. MRI was done to exclude a central aetiology. Glial activation as a marker of neuroinflammation was visualised by [18F]GE180-PET within the first 8 days after symptom onset.

Results: All patients showed signs of an AUV including spontaneous nystagmus, pathological video-head impulse test and caloric asymmetry towards the affected side, ipsilesional SVV deviation and falling tendency; no ear symptoms. Central ocular motor and vestibular signs were absent. Cranial MRI was unremarkable in all patients. [18F]GE180-PET depicted glial activation in the ipsilesional vestibular nerve and /or vestibular nucleus in 4 patients with typical AUV. During follow-up the one patient without [18F]GE180 uptake developed additional clinical signs indicative for Meniére's disease (i.e. transient tinnitus, acute and recurrent hearing loss), challenging the initial diagnosis of an acute unilateral vestibulopathy.

Conclusion: In the majority of patients with AUV it was possible to visualize in vivo tracer uptake in the ipsilesional vestibular nerve and nucleus during the acute and subacute stage of symptoms by [18F]GE180-PET. This points towards primary or secondary neuroinflammatory processes involved in the pathophysiology of AUV.

Disclosure: Research was supported by the German Federal Ministry of Education and Research (grant code 01EO1401).

Neurorehabilitation 3

EPR3151

32-contacts spinal cord stimulator

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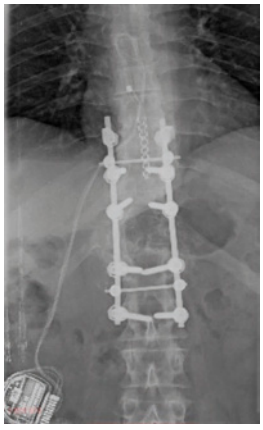
Background and aims: Spinal cord stimulation (SCS) is one of the most advanced interventional treatments available and many thousands of devices are universally implanted each year. We report a SCS case of successful treatment of chronic neuropathic pain following an old spine injury with a new 32-contacts surgical lead neurostimulator.

Methods: A 46-year-old wheel chaired male presented with five years history of neuropathic pain following a car accident with a burst T12 fracture eight years ago. Patient was in a Frankel's grade C and underwent a T9 – L2 stabilization procedure. During last years he developed a severe neuropathic pain not relieving by standard methods. After a detailed discussion, he underwent a successful placement of one 32-electrode (4x8) paddle lead that was caudally positioned at T9 – T11 connected to a Precision Spectra™ generator.



32-contacts paddle lead at T9 - T11 connected to a Precision Spectra generator

Results: After implantation, the neurostimulator was programmed according to desirable programming parameters. During early postoperative period, patient reported greater than 70% improvement of the pain syndrome and was gradually able to decrease oral pain medications. Later, he reported other positive outcomes including the ability to return to some social activities with improved family relationships.

Conclusion: SCS may be a therapeutic alternative for patients with an intractable neuropathic pain that exhausts conservative treatments. New paddles of 8 + 8 + 8 + 8 – poles provide better an complex coverage and are less prone to migration in comparison to percutaneous leads. Surgical experience and proper preoperative planning are useful when technical difficulties and singularities are present.

Disclosure: Nothing to disclose

EPR3152

Stimulation of the frontoparietal network using tDCS in patients with disorders of consciousness: a double blind sham controlled randomised clinical trial

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Background and aims: Patients in disorders of consciousness (DoC) lack of effective treatment options. In the present study we aimed to assess the behavioral effect of bilateral frontoparietal transcranial direct current stimulation (tDCS), targeting the external consciousness network, in severely brain-injured patient with DoC.

Methods: In this double-blind sham controlled randomised cross-over study we included 23 adult patients in vegetative state (VS; n=8) and in minimal conscious state (MCS; n=15), from traumatic and non-traumatic etiologies. Two sessions of tDCS were delivered, using either anodal or sham stimulation in a randomised order. Frontoparietal areas (F3-F4 & CP5-CP6) were stimulated. Level of consciousness was assessed with the Coma Recovery Scale-Revised (CRS-R) before and after each stimulation session.

Results: At the group level, no treatment effect was identified between the active and sham tDCS sessions. When looking at the subgroup of MCS patients from traumatic etiology, we did observe a treatment effect along with a significant increase in CRS-R total scores after the active tDCS session as compared to baseline, while no changes were found for the sham session. Finally, we did not identify any tDCS related side effect.

Conclusion: Our results showed that bilateral frontoparietal tDCS seems to be a safe technique to improve the level of consciousness of MCS patients from traumatic etiology. This non-invasive brain stimulation technique represents a promising tool to improve the recovery of severely brain-injured patients with disorders of consciousness.

Disclosure: Nothing to disclose

EPR3153

Efficacy and feasibility of home-based cooperative hand movement training in chronic stroke patients

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Background and aims: Cooperative hand movements (e.g. opening a bottle) are controlled by a task specific neural coupling mechanism which is partly preserved in chronic stroke subjects. Thus, cooperative hand movement training could be a promising tool for upper limb recovery in stroke rehabilitation. We developed a novel therapeutic device (ARCO) for cooperative hand movements which is supposed to be used not only in a clinical setting but also at the patients' home to increase training accessibility and dose. The study addresses (i) if cooperative hand movement training improves upper limb recovery in chronic stroke patients and (ii) if training with the ARCO is feasible for an unsupervised use at the patients' home.
Methods: Four chronic stroke patients trained with the ARCO for 2 weeks in our facilities followed by 6 week of unsupervised training at their home. Clinical and electrophysiological assessments of the upper limbs were performed before and after the training period. The feasibility of the device as well as the home training was assessed with questionnaires.
Results: After the training period, patients showed functional improvements and an enhancement of the neural coupling. The evaluation of the questionnaires indicated that our device was rated as easy to use, highly motivating and beneficial for health. Furthermore, all patients declared that they would continue the home training.
Conclusion: Due to its benefit in recovery, easy handling, transportability, and motivating design we suggest cooperative hand movement training with the ARCO to be a promising tool for the use at the patients' home.
Disclosure: This work was supported by the Swiss National Foundation (PMPDP3_164464/1) and the European Institute of Innovation & Technology- Health (17518).

EPR3154

Computerised cognitive rehabilitation improves executive functions in benign Multiple Sclerosis patients

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Background and aims: Although benign Multiple Sclerosis (B-MS) patients display preserved somatic neurological functions, they may nevertheless develop cognitive dysfunction. Our aim was to explore the impact of computerized cognitive rehabilitation (CCR) on cognitive functions of B-MS patients.
Methods: Age-gender matched 21 B-MS (EDSS£3.0 at 10 years of disease duration), 22 conventional MS (C-MS, EDSS>3.0 at 10 years) and 38 healthy individuals were recruited. CCR was administered to 10 B-MS patients and a panel of neuropsychological tests were employed to B-MS patients with (n=10) and without (n=11) CCR at baseline and at 6 months. CCR was based on a mental exercise software containing attention, memory, reasoning, visual and verbal task modules. Patients supervised with program's institutional interface every week and were assessed by a psychologist every month.
Results: Both B-MS and C-MS patients showed significantly impaired selective reminding, spatial recall, symbol digit modalities (SDM), controlled oral word association (COWAT) and paced auditory serial addition (PASAT) tests. Stroop, 9-hole peg and timed 25-foot walk test results of B-MS patients were comparable to healthy controls. B-MS patients with CCR showed significantly improved SDM, COWAT and Stroop test results than those without CCR. CCR also had a moderate positive effect on selective reminding and spatial recall tests, albeit without attaining statistical significance.
Conclusion: Several cognitive domains including memory and executive functions are impaired in B-MS patients. CCR has an ameliorating impact particularly on executive functions of B-MS patients.
Disclosure: Nothing to disclose

EPR3155

Mobile accelerometry for assessment of changes in body position in early neurorehabilitation

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Background: Verticalisation and mobilisation in early neurorehabilitation are most important to improve function in severely affected immobile patients, e.g. after stroke, traumatic brain injuries or peripheral neuropathy. However, optimal mobilisation frequencies, both during in-patient and out-patient treatment, are not sufficiently known. Therefore, the aim of the current study was to investigate whether accelerometers on upper trunk can reliably detect changes in body position in immobile patients during early neurorehabilitation.

Methods: 30 patients in early neurorehabilitation (Barthel Index ≤ 30) were enrolled. Two ActivPAL micro™ tri-axial accelerometers were placed on upper trunk and on thigh. Accelerometer data on position changes were compared to care documentation over 24 hours. Frequencies and duration of different body positions (supine, side lying, sitting) were measured. Data are presented as mean±SEM. Groups were compared using one-way ANOVA followed by Kruskal-Wallis-test. Differences were considered significant if $p<0.05$.

Results: Trunk recording (99.5±0.4%) was significantly better able to detect changes in body positions compared to thigh sensors (92±4.7%) or care documentation (81.8±4.4%) ($p<0.0001$). Trunk sensors detected 100% and thigh sensors 66% of position changes.

Conclusions: Mobile accelerometric trunk sensors are suitable to record position changes during neurorehabilitation. Our findings are the prerequisite for the use of mobile accelerometry in severely affected patients after discharge from hospital. Follow-up studies are needed to gain insights into mobilisation frequencies after discharge. This again helps to understand if and how effects of early neurorehabilitation carry over to care after hospital discharge.

Disclosure: Nothing to disclose

EPR3156

Cerebrolysin after stroke leads to spontaneous motor recovery in the absence of reduced stroke volume in a mouse model of stroke

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Background and aims: Most functional upper extremity motor recovery occurs in the first 4 weeks after ischemic stroke both in humans and in rodent models. The majority of recovery in humans is spontaneous (i.e. occurs as a result of endogenous repair processes rather than rehabilitative interventions). However, in rodents models, spontaneous recovery is rare. In a mouse model of stroke, we tested the hypothesis that Cerebrolysin, a polypeptide preparation shown to enhance neuronal plasticity, can act early after stroke to enhance motor recovery, either spontaneous or training-associated recovery.

Methods: Adult mice were trained to perform a skilled prehension task to an asymptotic level of performance after which they underwent photocoagulation-induced stroke in the caudal forelimb area. The mice were then retrained after a 7-day delay in the presence or absence of Cerebrolysin injected IP daily.

Results: We have previously shown that training-associated recovery of prehension is complete if training is initiated after a 1-day delay but incomplete if training is initiated after a 7-day delay, even with additional training days. However, daily Cerebrolysin administration beginning 24 hours after stroke was associated with complete recovery of prehension by day 8 even in the absence of training. Stroke volumes were similar across all groups.

Conclusion: We conclude that Cerebrolysion administration beginning during an early time window can lead to spontaneous recovery of motor function (independent of rehabilitative interventions) and that this recovery is independent of a protective effect on stroke volume. This is the first demonstration of spontaneous motor recovery in a mouse model of stroke.

Disclosure: This research was paid for by a grant from EVER Pharma pharmaceuticals.

EPR3157

Transcranial direct current stimulation in post-stroke aphasia rehabilitation: bilateral vs unilateral online stimulation

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Background and aims: Aphasia is the most common post-stroke cognitive disorder and it severely impacts activities of daily living and social interactions. Transcranial Direct Current Stimulation (tDCS) recently showed good results in post-stroke aphasia rehabilitiation, even if no agreement at now exists about the stimulation parameters to employ to achieve the best rehabilitative outcome. Our aim is to evaluate the efficacy of repeated sessions of tDCS as additional treatment to standard behavioural rehabilitation in post-stroke aphasic patients, comparing bilateral with unilateral left-sided and sham-tDCS.

Methods: We enrolled 22 patients with single left-brain lesion. Aphasia was investigated through selected subitems of Aachener Aphasie Test (AAT), used as outcome measures. Patients were randomly assigned to 3 groups: bilateral-tDCS(7); unilateral-tDCS(8); sham-tDCS(7). Anode was placed on the left inferior frontal gyrus (IFG), while cathode was positioned over contralateral supraorbital area (unilateral-tDCS) or over the right-IFG (bilateral-tDCS). The direct current (1.5mA for 20 min) was delivered online in daily sessions during two consecutive weeks for a total of 10 stimulations.

Results: A repeated measures ANOVA showed as both dual and single-tDCS lead to significant improvements in outcome measures as compared to baseline evaluation and sham-tDCS. A Post Hoc Duncan's test highlighted how the most significant AAT score improvement concerned naming subitem, followed by the others.

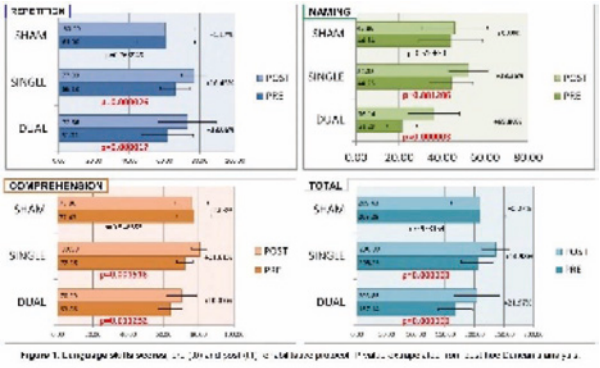

Figure 1. Language skills scores, pre (t0) and post (t1) rehabilitative protocol. P value extrapolated from post hoc Duncan's analysis.

Conclusion: tDCS over IFG showed to be an effective and safe tool to improve aphasia symptoms with no difference between the two montages, so it is worth to be further explored as additional rehabilitative tool for post stroke aphasic patients.

Disclosure: Nothing to disclose

Peripheral nerve disorders 5

EPR3158

Morvan's syndrome: A case report and literature review

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Background and aims: Morvan's syndrome is a rare autoimmune disorder characterised by peripheral nerve hyperexcitability (neuromyotonia), encephalopathy and dysautonomia. We present the case of a 75-year-old male patient who was diagnosed with this condition and made a dramatic improvement following treatment. The clinical presentation, investigation and management of our case alongside a literature review of this rare neurological disorder are discussed.
Methods: A previously well 75-year-old male presented with a six-month history of progressive weakness, unintentional weight loss and muscle twitching. Further questioning demonstrated a disturbed sleep cycle alongside periods of confusion. Neurological examination demonstrated a fluctuating level of consciousness associated with cognitive impairment. Physical examination demonstrated widespread muscle wasting and visible twitching of muscles. Tendon reflexes were preserved and there was no sensory impairment.
Results: Investigations included NCS/EMG which demonstrated evidence of peripheral nerve hyper-excitability. Serum voltage gated potassium channel antibody was positive for both LGI-1 and CASPR2 subtypes. MRI brain demonstrated subtle increased signal intensity and swelling within both limbic systems. A malignancy was excluded following investigation.
The patient was managed with high dose intravenous methylprednisolone over 3 days and made a dramatic improvement with improvement.
Conclusion: Morvan's syndrome is characterised by neuromyotonia, weight loss, hyperhidrosis and sleep disturbance. This rare autoimmune disorder is associated with antibodies to voltage-gated potassium channels which are implicated in the pathophysiology of this condition. There are a limited number of publications in the English literature regarding this disorder. Our case, supplemented by patient video provides a valuable reminder of this rare disorder.
Disclosure: Nothing to disclose

EPR3159

The diagnosis of carpal tunnel syndrome using sonography, sensitivity of this method

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Background and aims: Sonography of carpal tunnel syndrom (CTS) has recently been presented as a diagnostic method comparable with electromyography. The study's aim was to determine normative data and sensitivity of sonography in the diagnosis of CTS.
Methods: We included 40 limbs with CTS confirmed by EMG. Patients were divided into subgroup with mild lesion (MCTS) and severe lesion (SCTS). The threshold between MCTS and SCTS was sensory velocity of 38m/s and distal motor latency of 5.3ms in EMG. Control group included 61 limbs. Sonography of median nerve was conducted at the wrist and elbow and area, circumference, vertical and horizontal diameter were measured. The data of patients were statistically compared with control group and correlated with EMG.
Results: Normative data in sonography: area 12.84mm^2, circumference 16.42mm, vertical diameter 2.95mm, horizontal diameter 7.03mm. At the wrist for all parameters there was statistically significant difference between patients and controls ($p<0.002$). But no difference between MCTS and SCTS.
However sensitivity of parameters was different in MCTS and SCTS. The most sensitive was area – patients had abnormalities in 50% of MCTS and 73% of SCTS. The dependence of parameters at the wrist with EMG was very strong, the strongest correlation being to sensitive amplitude.
Conclusion: The sensitivity of area is 73% for severe carpal tunnel syndrome, but is much lower for mild carpal tunnel syndrome and result can often be false negative according to our data. The border of normal value for area at wrist is 12.84mm².
Disclosure: Nothing to disclose

EPR3160

A novel LITAF mutation (Charcot-Marie-Tooth type 1C) in a patient with chronic sensory-motor demyelinating neuropathy

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Background and aims: Charcot-Marie-Tooth (CMT) diseases are a heterogeneous group of inherited peripheral neuropathies. Mutations in LITAF gene are causative for CMT type 1C disease, a rare demyelinating CMT form characterized by weakness of distal limbs and panmodal sensory loss, sometimes with upper limbs tremor.
Methods: In this study we present the case of a patient affected by a sensory-motor demyelinating neuropathy resembling a chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) who carried a novel variant in LITAF gene.
Results: A 43-year-old man presented with a 12-year history of paresthesias and weakness of limbs, followed by involuntary tremor both upper limbs. Family history was unremarkable. Previously he had received CIDP diagnosis and treatment with corticosteroids, intravenous Immunoglobulins and plasma-exchange were ineffective. On our admission, neurological examination revealed gait imbalance, upper limbs muscle weakness, postural and kinetic tremor, areflexia, hypopallesthesia, distal pin-prick hypoesthesia in the four limbs. Antibodies against gangliosides, human neurofascin-155 and contactin-1 were absent. Electrophysiological study revealed a sensory-motor demyelinating neuropathy with conduction blocks. Genetic testing for CMT revealed a new mutation in LITAF gene (c.44C>T, p.S15L), located in the exon 2.
Conclusion: Herein we report on a patient with a chronic demyelinating neuropathy, with a clinical picture similar to a neurofascin antibodies-related CIDP, that carried a novel LITAF mutation. The pathogenic role of the LITAF c.44C>T, p.S15L variant is uncertain. Genetic tests to other five asymptomatic family members are ongoing to confirm the pathogenic role of this mutation.
Disclosure: Nothing to disclose

EPR3161

Glyphosate-based herbicide, but not pure glyphosate, affects peripheral nervous system myelination

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Background and aims: Glyphosate-based formulations comprise the world's most commonly used herbicides. While glyphosate is the active ingredient, it is often provided as isopropylamine salt and in combination with undisclosed auxiliary agents. Although glyphosate has long been considered safe for use in humans and animals, several studies have implicated glyphosate and/or auxiliary agents and surfactants in cytotoxicity, carcinogenicity and endocrine disruption. However, it remains unclear whether pure glyphosate or glyphosate-based formulations may have detrimental effects on myelin integrity in the peripheral nervous system.
Methods: We assessed the impact of pure glyphosate and a glyphosate-based herbicide (Roundup LB Plus, Monsanto) on myelination and demyelination in an ex vivo model of the peripheral nervous system. Dorsal root ganglia (DRG) cultures were treated with pure glyphosate or Roundup corresponding to 0.005 or 0.0005% glyphosate content in the culture medium. The glyphosate concentration in the Roundup formulation was 36% as isopropylamine salt. Controls were treated with equal volumes of vehicle adjusted for pH.
Results: Whereas pure glyphosate did neither affect myelination nor cause demyelination, Roundup exerted a concentration-dependent demyelinating effect. While there were no specific effects of Roundup on markers for oxidative and nitrosative stress or cell death, we recognized Roundup to cause the induction of TNF-alpha expression in Schwann cells. In line with its demyelinating effect, TNF-alpha expression appeared to depend on the concentration of Roundup.
Conclusion: These findings raise the possibility that not glyphosate itself, but isopropylamine or undisclosed additives in herbicide formulations may impact myelin integrity via a mechanism involving inflammatory Schwann cell activation.
Disclosure: Nothing to disclose

EPR3162

Post-occlusive Reactive Hyperemia in Diabetic Polyneuropathy

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Background and aims: Diabetes mellitus (DM) is hugely increasing worldwide, type 2 diabetes (T2DM) is prevalent among diabetics, and the most common complication is diabetic polyneuropathy (DPN) associated with microcirculatory disorders. The aim of the study was to investigate microcirculatory alterations and post-occlusive reactive hyperemia responses in patients with T2DM and polyneuropathy.
Methods: 79 patients with T2DM fulfilled the criteria for DPN and were included in the study with 44 sex and age matched healthy controls. The nutritious skin vessels were investigated by nailfold videocapillaroscopy. The skin perfusions of the big tiptoe were monitored by laser Doppler flowmetry (LDF) in arbitrary perfusion units (PU) as initial values (PUi) in supine position, during and after toe arterial occlusion by inflation of a blood pressure cuff. Vasodilator indices were calculated and assessed by SPSS software package.
Results: Reduced capillary density and spastic capillaries were found in most of the patients (89.87%) while the initial LDF perfusions (67.23±50.37 PU vs 39.29±25.31 PU) were higher compared with the controls ($p<0.001$). The postocclusive reactive hyperemic peak (102.54±62.7 PU vs 170.1±153.8 PU) was lower in T2DM patients ($p<0.05$). The post-occlusive hyperemic perfusion responses and vasodilator indices differed significantly between DM patients and healthy controls.
Conclusion: Decreased number and spasm of dermal capillaries but increased global skin blood flow at rest were established. The microvascular post-occlusive vasodilator capacity and reactive hyperemic indices were significantly reduced. Laser-Doppler flowmetry is an easy non-invasive method for investigation of skin microcirculation and vasomotor reactivity.
Disclosure: Nothing to disclose

EPR3163

Inotersen improved Norfolk quality of life–diabetic neuropathy (Norfolk QOL-DN) measures in patients with hereditary transthyretin (hATTR) amyloidosis treated in the phase-3 study NEURO-TTR

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Background and aims: hATTR is a rare, progressive, fatal disease caused by systemic build-up of transthyretin (TTR) protein, which causes significant morbidity and progressive decline in quality of life (QOL). The effects of inotersen, an antisense oligonucleotide inhibitor of TTR protein production, on QOL in patients with hATTR are described.
Methods: NEURO-TTR (NCT01737398) is a global, randomised, double-blind, placebo-controlled phase-3 study. Adults (n=172) with hATTR (stage 1 or 2) were randomized (2:1) and received 300-mg weekly subcutaneous inotersen or placebo for 15 months. QOL was evaluated using the Norfolk QOL-DN questionnaire and the SF-36v2 Health Survey (SF-36v2). Norfolk QOL-DN includes 136 points (higher score indicates worse QOL) derived from 5 domains (physical functioning/large-fibre neuropathy, symptoms, activities of daily living [ADL], small-fibre neuropathy and autonomic neuropathy).
Results: Statistically significant improvement in least-squares mean change from baseline [95% CI] in Norfolk

QOL-DN total score favouring inotersen-treated subjects compared with placebo was observed at week 35 (–6.14 [–11.77 to –0.52]; P=0.032). At week 66, significant improvement in favour of inotersen compared with placebo was observed in Norfolk QOL-DN total score (–11.68 [–18.29 to –5.06]; P=0.0006), physical functioning/large-fibre neuropathy (–6.33 [–10.03 to –2.62]; P=0.001), ADLs (–2.10 [–3.34 to –0.85]; P=0.001), and symptoms (–2.80 [–4.47 to –1.13]; P=0.001), as well as SF-36v2 Physical Component Summary score. Key safety findings of thrombocytopenia and renal events were monitorable and manageable.

Conclusion: Inotersen-treated patients demonstrated rapid, significant and sustained improvement in QOL measures compared with placebo-treated patients.

Disclosure: This study was sponsored by Ionis Pharmaceuticals (Carlsbad, CA, USA).

EPR3164

Chemotherapy-induced polyneuropathy in patients treated with vinca-alcaloids

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Background and aims: Chemotherapy-induced peripheral neuropathy (CIPN) represents one of the most worrisome and common long-term adverse effects of chemotherapy treatment of cancer. In patients treated with vinca-alcaloids (V-A), the clinical manifestation is mainly sensory and may affect predominantly small sensory fibers. The aim was to assess the incidence of CIPN in patients treated with V-A and compare diagnostic validity of quantitative sensory testing (QST) reflecting the function of both small and large sensory nerve fibers with routinely used electromyography/nerve conduction studies (EMG/NCS).

Methods: A group of 20 patients (12 men, 8 women, median age 39; range 23-72 years) with malignant lymphoma underwent detailed clinical examination, evaluation of medical history, pain status, EMG/NCS and comprehensive QST before and 6 months after the end of administration of anti-cancer V-A chemotherapy.

Results: At the follow-up examination, twelve patients (60%) reported some sensory symptoms and/or neuropathic pain in lower (11 cases) and/or upper (7 cases) extremities. The symptoms were usually of mild to moderate intensity. In upper extremities, the symptoms mostly corresponded with clinically symptomatic carpal tunnel syndrome. The EMG/NCS examination confirmed polyneuropathy in 10 patients (50%) (7 symptomatic, 3 asymptomatic). Eighteen patients (90%) displayed at least one new QST abnormity in feet (and 8 in hands), most frequently in thermal sensation and thermal pain modalities.

Conclusion: Symptoms of CIPN persist at least 6 month after the end of V-A chemotherapy in about 60% of treated patients, and relevant QST abnormities (mainly suggesting small nerve fiber dysfunction) can be found even in 90% of the treated patients.

Disclosure: Nothing to disclose

Sleep disorders

EPR3165

Timing and patterns of nocturnal melatonin secretion in Alzheimer patients at an early stage of the disease.

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Background and aims: Circadian dysfunction plays a crucial role in the intricate, biunivocal relationship between Alzheimer's disease (AD) and disordered sleep. Our study focused on melatonin secretion timing with calculation of dim light melatonin onset (DLMO) as a biological marker of the circadian phase in patients with mild to moderate forms of AD.
Methods: 21 patients with a diagnosis of AD according to McKhann criteria (2011) were consecutively enrolled. 22 healthy subjects comparable for age and sex served as controls. Nocturnal sleep parameters, subjective measures of chronotype and the social jet lag (SJL) were determined. DLMO and quantitative aspects of the initial nocturnal melatonin secretion were calculated by means of a five-point melatonin salivary test.
Results: Subjective sleep quality did not differ between groups. Sleep onset on workdays and freedays ad midsleep on freedays used to occur earlier in patients. The subjective chronotype distribution by global MEQ score did not differ between groups. The mean DLMO time in AD patients occurred significantly later respect to controls ($p=0.028$). The post-DLMO melatonin measures were significantly lower in AD patients. This result was confirmed by evaluating the single and global melatonine AUC semicurve between groups ($p=0.003$).
Conclusion: AD patients present a delay and impairment of melatonin secretion, despite sleep parameters and subjective chronotype similar to those of healthy controls. This data indicate that, subclinical, peculiar patterns of melatonin secretion exist in subjects with AD at an early stage of the disease.
Disclosure: Nothing to disclose

EPR3166

REM-Sleep Behavior Disorder (RBD) in Anti-IgLON-5 disease

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Background and aims: To evaluate the presence of RBD and its characteristics in 5 cases with IgLON5 disease.
Anti-IgLON-5 disease is associated with IgG4 antibodies to IgLON5, a neuronal surface cell adhesion molecule, and deposits of tau in the brainstem and hypothalamus. It is characterised by a parasomnia involving NREM and REM-sleep. Obstructive sleep apnea syndrome (OSA) with stridor is often observed. Other symptoms involve gait- instability, bulbar, oculomotor and autonomic symptoms, and cognitive impairment.
Methods: 5 patients (4 male, age 62.6±11.65) underwent video-polysomnography. REM sleep without atonia (RWA) was defined according to SINBAR criteria. RBD was diagnosed when RWA combined with abnormal movements during REM sleep occured. To rate the severity of RBD the RBD Severity Scale was used.
Results: 2 were diagnosed with bulbar syndrome, 2 with PSP-like-syndrome and 1 with sleep-disorder. Anti-IgLON5 antibodies were positive in 5/5. Sleep related breathing disorders were present in all patients (2/5 OSA), OSA+hypoventilation 2/5, 1/5 tracheostomy). REM sleep without atonia was present 5/5. REM sleep behavior severity range was 1.0 to 2.1. Complex behaviors during NREM sleep were observed in 2/5.
Conclusion: All patients showed RBD. RBD seems to be "mild" in Anti- IgLON5 disease. In these case series, Non REM behaviors were not present in patients with the PSP like syndrome. If this is a characteristic of a typical subtype of IgLON5 disease has to be determined in the future. The combination sleep disorder with REM and NREM abnormalities accompanied by of multifocal neurological symptoms Anti-IgLON5 disease should be considered.
Disclosure: Nothing to disclose

EPR3167

Movement disorders during sleep in children with Narcolepsy type-1 after treatment with sodium oxybate

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Background and aims: Recently, the occurrence of a severe and peculiar motor disorder occurring mainly during REM sleep in pediatric NT1 has been pointed out (Antelmi et al, 2017). Here, we aimed at assessing the effect of stable treatment with Sodium Oxybate (SO) on motor events occurring during nighttime in children with NT1.
Methods: 15 children with NT1 (40% females; mean age 12.8±2.86) were followed up after the at least three months of stable treatment with SO. All patients repeated video-PSG and the recordings were then reviewed by two independent experts in the field in order to analyse motor events. These latter were classified as previously reported (Antelmi et al, 2017) in elementary movements and complex behaviors. Baseline and follow-up data were confronted (within-subjects).
Results: When compared to baseline evaluation, NT1 patients taking SO showed a significant decrease of the pentad of NT1 symptoms, but for sleep paralyses. When analyzing motor patter during nighttime, it emerged that elementary movements emerging from NREM sleep were significantly increased after the start of treatment. Conversely, complex behaviors could be detected in a decreased number of patients and showed also a decrease in frequency. There was a concomitant increase of atonia index.
Conclusion: Motor events/behaviors emerging during REM sleep decreased after treatment with SO. The concordant increase in REM atonia index leads to infer on a direct role of the drug in modulating motor control during REM sleep.
Disclosure: Nothing to disclose

EPR3168

Different response to CPAP in man and women with chronic insomnia disorder and OSAS

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Background and aims: Obstructive Sleep Apnea Syndrome (OSAS) and insomnia are pathologies that frequently co-occur. Few studies have documented that CPAP (continuous positive airway pressure) may improve insomnia symptoms.
The objective of this study was to evaluate the response to CPAP in patients with chronic insomnia disorder (CID) with OSAS.
Methods: Retrospective study of patients with OSAS and CID, from an outpatient sleep clinic. OSAS and CID were diagnosed according ICSD-3. OSAS was considered mild/moderate if Respiratory Disturb Index (RDI) was 5-30 and severe if RDI $\geq$30. The main outcome was insomnia clinical improvement following CPAP. Other variables were gender, sex, PSG variables, CPAP compliance, insomnia subtypes, OSAS type, anxiety/depressive disorder and use of sedative pharmacological. Differences between responder and non-responders were evaluated with T test, Qui2 or Fischer test, $p<0.05$.
Results: From a database of 827 patient, 90 were identified with OSAS and CID (53.3% women). Middle/moderate OSAS was diagnosed in 68.9% and severe in 31.1%. Most patients (61.1%) improved insomnia after CPAP. Responders to CPAP were more frequently women (women 61.8%, men 38.2%, $p=0.035$), and there was no other difference between responders and non-responders. On subgroup analysis, this difference was significant only in severe OSAS ($p=0.013$).
Conclusion: Our study re-inforces that CPAP therapy improves CID, irrespective of insomnia type, across all OSA categories and in patients with psychiatric symptoms. This response is more frequent in women. Our results suggest that in men with severe OSA, the insomnia phenotype is less dependent on the respiratory symptoms and further studies are needed to understand this.
Disclosure: Nothing to disclose

EPR3169

Orexin and beta-amyloid pathologies in Obstructive Sleep Apnea Syndrome

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Background and aims: Obstructive Sleep Apnea Syndrome (OSAS) is an increasingly frequent sleep disorder. OSAS pathologically changes cerebral beta-amyloid dynamics and orexin may interfere with beta-amyloid metabolism.
On these bases, the aim of this study was to investigate beta-amyloid and orexin CSF levels in OSAS patients.
Methods: We evaluated OSAS patients compared to patients affected by Alzheimer's Disease (AD) and controls. All patients and controls underwent: lumbar puncture for CSF levels of beta-amyloid 40 (AB40) and 42 (AB42) and orexin; polysomnography (PG) to evaluate nocturnal sleep architecture.
Results: We include 20 OSAS patients, 10 AD patients, and 10 controls. We documented higher orexin levels in OSAS patients compared to AD and controls; moreover, AD patients showed higher orexin levels than controls. Considering beta-amyloid, OSAS showed lower AB40 levels compared to AD and controls, whereas AD patients showed lower AB42 levels than OSAS, who showed lower AB42 levels than controls.
Sleep macrostructure was similarly altered in OSAS and AD patients compared to controls. Finally, CSF beta-amyloid proteins levels correlated with PSG parameters in the OSAS group, while CSF orexin levels correlated with CSF beta-amyloid levels in the AD group.
Conclusion: This study documented the alteration of orexinergic system and beta-amyloid metabolism in OSAS patients. Sleep fragmentation and apneas correlated with CSF orexin and beta-amyloid levels in OSAS patients. Conversely, orexin CSF levels correlated with beta-amyloid CSF levels in AD patients. Hence, we suppose that orexinergic system impairment, sleep impairment, and beta-amyloid pathology may be present in OSAS patients as a possible preclinical stage of AD neurodegeneration.
Disclosure: Nothing to disclose

EPR3170

Diagnostic accuracy and validity of the swiss Narcolepsy Scale and a short-form version for the diagnosis of type-1 and type-2 narcolepsy against other central disorders of hypersomnolence

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Background and aims: The Swiss Narcolepsy Scale (SNS) was previously reported in two independent studies to have a sensitivity-specificity of about 80-90% for the diagnosis of narcolepsy with cataplexy. We aim 1) to assess the validity of the SNS and the Epworth sleepiness scale (ESS) in detecting type 1 (NT-1) and type 2 (NT-2) narcolepsy against other central disorders of hypersomnolence (CDH), 2) to develop a simplified form of the SNS.
Methods: Data from the Bern Sleep-Wake Registry were used. A two-item simplified form (sf-SNS) was created from the SNS based on the discriminative capability of the models.
Results: There were 299 individuals with CDH who completed the SNS scale, including 69 with NT-1, 16 with NT-2 and 214 with other CDH. For the diagnosis of NT-1 the sensitivity and the specificity of the SNS was 86% and 88%. The Hosmer-Lemeshow goodness of fit test indicates sufficient calibration (p=0.700) but the Brier score was relatively high (0.87), indicating relatively high disagreement. Therefore, we recalculated the model coefficients for scoring SNS and improved sensitivity (93%), but reduced specificity to 82%.
The sensitivity and specificity of the sf-SNS in identifying NT-1 were 80% and 92% respectively. For the diagnosis of NT-2 the following sensitivities and specificities were found: SNS 63% and 70%, sf-SNS 44% and 83%. For the diagnosis of narcolepsy the sensitivity and specificity of ESS was 53% and 70% respectively.
Conclusion: The updated SNS and its simplified form sf-SNS are useful and valid screening tools for NT-1 and superior to the ESS.
Disclosure: This work was financially supported by Jazz Pharmaceuticals

EPR3172

Sleep pattern and day time sleepiness in patients with mild cognitive impairment and mild Alzheimer's dementia

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Background and aims: Previous studies suggest that patients with advanced Alzheimer's dementia (AD) suffer from sleep disorders more frequently, however results are less conclusive for patients with mild cognitive impairment (MCI) and mild AD. Aim of our study was to evaluate sleep pattern and excessive daytime sleepiness in patients with mild AD dementia.
Methods: 61 healthy controls, 41 MCI and 44 mild AD patients were included. Cognitive status of patients was evaluated with Mini-Mental State Examination (MMSE). Excessive daytime sleepiness and sleep pattern were evaluated with Epworth scale and Insomnia Severity Index (ISI). Means between groups were compared with 1-way ANOVA. At the end, we correlated Epworth, ISI and MMSE scores.
Results: All three groups were age matched. MCI patients had significant higher MMSE score than AD patients (27±3 vs. 22±3; $p<0.001$). Mean Epworth Scale score did not differ between groups (healthy controls 5.9±4.6; MCI 5.9±4.3; mild AD 6.1±4.9). Insomnia Severity Index was the highest in healthy controls (8.1±6.0), followed by MCI (7.1±5.4) and mild AD (6.2±6.3), however differences were not statistically significant. There were no correlation between MMSE and Epworth or ISI score.
Conclusion: Our results indicate that patients with MCI and mild AD had similar excessive daytime sleepiness and sleep pattern as age-matched controls. No group have reached threshold for excessive daytime sleepiness and clinical significant insomnia. Disturbed sleep pattern may be a clinical sign of progression of AD as part of complex behavioral changes in addition to memory impairment.
Disclosure: Nothing to disclose

EPR3173

Narcolepsy-cataplexy and Sydenham's chorea

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Background and aims: Sydenham's chorea (SC) results from a post-streptococcal autoimmune process targeting basal ganglia neurons. In narcolepsy type-1 (NT1) streptococcal infection as potential trigger of the disorder was reported and clinical features in children include SC-like features (hypotonia, dyskinesias). The association SC-NT1 was reported only once in the literature (Natarjan, JCSM 2013).
Aim: To analyse the association between NT1 and SC in 3 tertiary sleep centers.
Methods: Retrospective international study in 3 large tertiary sleep centers.
Results: We report 3 patients with NT1 and SC.
Patient 1 (female, 22y, HLA DQB1*0602+) had an acute hemichorea followed within weeks by excessive daytime sleepiness (EDS), low CSF hypocretin (125pg/mL), and no SOREM with a mean sleep latency (MSL) of 2.8min on MSLT. EDS severely increased within 3 month accompanied by a further decrease of hypocretin (24pg/ml), MSL of 1.4min and 3 SOREM at subsequent MSLT.
Patient 2 (female, 10y, HLA DR15+) had acute hypotonia and dyskinetic movements followed within few weeks by EDS, typical cataplexy, disturbed nocturnal sleep, and 3 SOREM with a MSL of 3.5min on MSLT.
Patient 3 (female, 11y) had acute chorea followed within months by EDS, typical, cataplexy, undetectable CSF hypocretin and a mean latency of 1min on MSLT (without SOREM).
Conclusion: Further studies are needed to clarify the clinical and etio-pathophysiological implications of the reported rare association.
Disclosure: Nothing to disclose